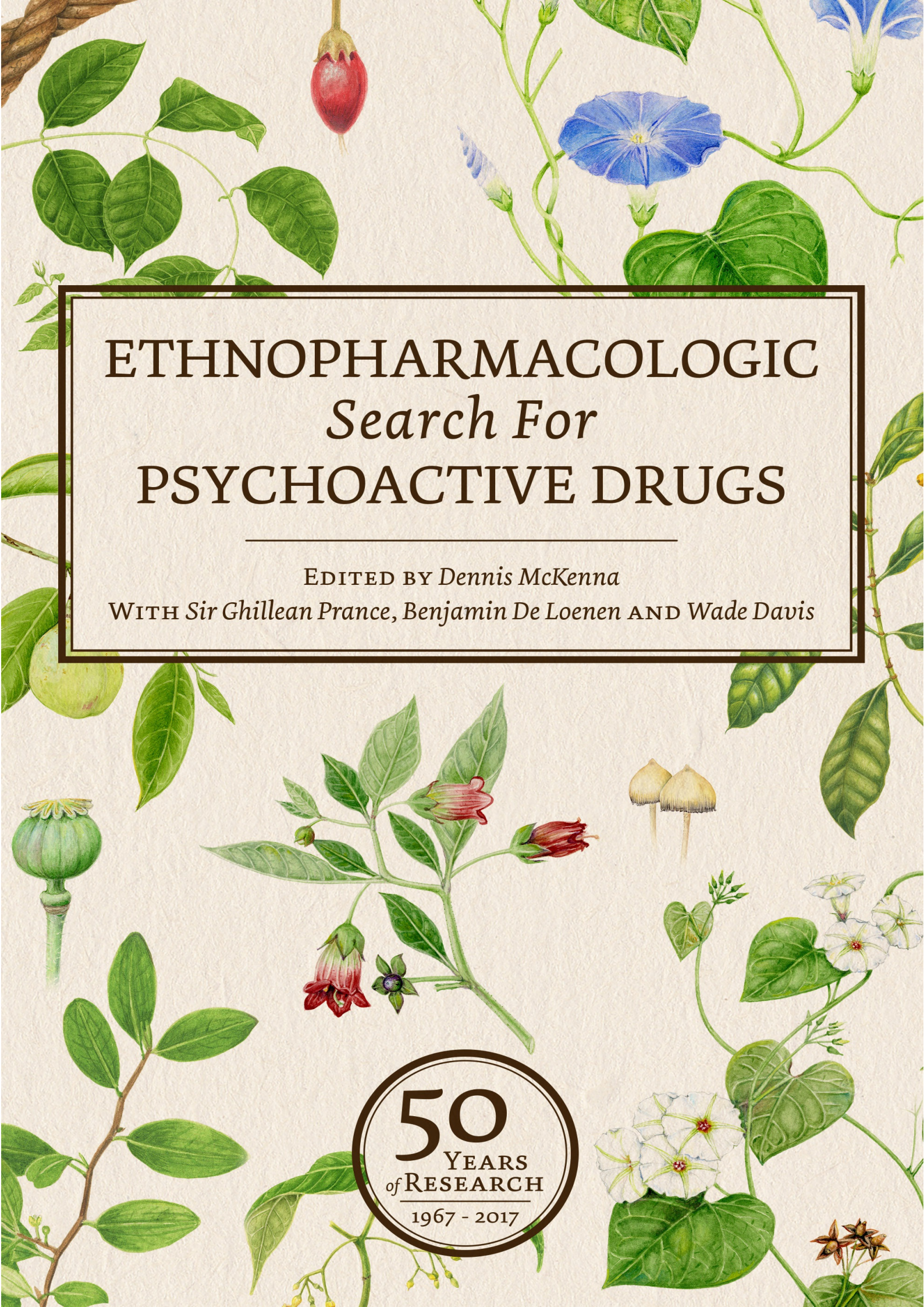


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# ETHNOPHARMACOLOGIC *Search For* PSYCHOACTIVE DRUGS

EDITED BY *Dennis McKenna*  
WITH *Sir Ghilleen Prance, Benjamin De Loenen AND Wade Davis*

50  
YEARS  
of RESEARCH  
1967 - 2017



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# ETHNOPHARMACOLOGIC SEARCH for PSYCHOACTIVE DRUGS • 2017

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Vol. II

50th Anniversary Symposium › June 6 – 8, 2017

ESPD50.com



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# ETHNOPHARMACOLOGIC SEARCH for PSYCHOACTIVE DRUGS • 2017

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50th Anniversary Symposium › June 6 – 8, 2017

ESPD50.com

EDITOR IN CHIEF

Sir Ghilleen Prance

[FRS, FLS, FRSB] Director (ret.), Royal Botanic Gardens, Kew

MANAGING EDITOR

Dennis J. McKenna

[PhD, FLS] Director of Ethnopharmacology Heffter Research Institute

ASSOCIATE EDITORS

Benjamin De Loenen,  
Wade Davis

[PhD, O.C.] Professor of Anthropology and BC Leadership Chair in  
Cultures and Ecosystems at Risk, University of British Columbia.  
Formerly Explorer in Residence, National Geographic Society

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# DEDICATION

The 2017 ESPD 50th Anniversary Symposium and The Symposium Proceedings are respectfully dedicated to Dr. Stephen Szára, MD DSc.

For his many contributions to Psychopharmacology and to the early days of NIMH and NIDA. His pioneering and courageous investigations definitively established for the first time the psychedelic properties of DMT (N,N-dimethyltryptamine) in humans

We would also like to recognize and honor some other pioneers of Ethnopharmacology, who presented at the 1967 ESPD conference, for their dedication to the science and the inspiration they provided for a younger generation.

|                                                                             |                                                                                 |
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Proceedings of a commemorative Symposium held at Tyringham Hall, Buckinghamshire, UK, in the spirit of, and in honor of, the first ESPD Symposium which took place at the San Francisco Medical Center, University of California, on January 28-30, 1967.

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- Pharmacology Section, Psychopharmacology Research Branch
- National Institute of Mental Health
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- U. S. Department of Health, Education, and Welfare

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This Anniversary Symposium and the 2017 Symposium Proceedings are an affirmation of our belief that many significant discoveries in this field took place in the five decades since the first ESPD symposium; and that the future holds great promise for many more to come. The 2017 ESPD Symposium and the Symposium Proceedings could not have been done without the generous support of our sponsors and donors. Additionally, the Symposium and the Proceedings reflect the hard work and dedication of many volunteers and support staff.

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To the chefs, housekeeping, and hospitality staff of Tyringham Hall – for keeping us well-fed, comfortably housed, and well-lubricated from beginning to end of the conference.

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To the 50,000 to 60,000 people who followed our conference on the Facebook Live Stream (at least occasionally), you have helped make “Ethnopharmacology” a household word.

To all members of the psychedelic community and beyond, who recognize the power of plant medicines, and believe in the importance of their scientific investigation, and in the preservation of traditional knowledge.

## ESPD50 2017 — SYMPOSIUM SPEAKERS —



FRONT ROW, L TO R:

Jean-Francois Sobiecki; Dr. Jeanmaire Molina; Jerry D. Patchen;  
Dr. Dennis McKenna; Dr. Glenn Shepard; Dr. Manuel Torres;  
Dr. Stacey Schaefer; Dr. Mark Plotkin

SECOND ROW, L TO R:

Keeper Trout; Dr. Luis Eduardo Luna; Snu Voogelbriender; Dr.  
David Nichols;  
Dr. Evgenia Fotiou; Dr. Christopher McCurdy

BACK ROW, L TO R:

Dr. Kenneth Alper; Dr. Nigel Gericke

NOT SHOWN:

Dr. Stephen Szára; Dale Millard; Dr. Michael Heinrich

## **Kenneth Alper, MD**

Associate Professor of Psychiatry and Neurology at the New York University School of Medicine. He is internationally recognized as an authority on the chemistry and pharmacology of Iboga and Ibogaine, and the clinical use of Ibogaine in the treatment of substance use disorders.

## **Evgenia Fotiou, PhD**

Assistant Professor of Anthropology, Kent State University. She is recognized for her work in cultural anthropology and Amazonian shamanism, in particular the ayahuasca tourism phenomenon.

## **Nigel Gericke, MD**

South African medical doctor, botanist, ethnopharmacologist and entrepreneur has published many peer-reviewed scientific papers on ethnobotany and ethnopharmacology; he is co-author of books on S. African ethnobotany including *Medicinal Plants of South Africa* and *People's Plants: A Guide to Useful Plants of Southern Africa*. He is the world's foremost authority on Kanna, an indigenous psychoactive plant used by the San and Khoi peoples.

## **Michael Heinrich, PhD**

Professor of Ethnopharmacology and Medicinal Plant Research (pharmacognosy) at the UCL School of Pharmacy, London, UK. He is Specialty Editor-in-Chief of *Frontiers in Pharmacology* (Ethnopharmacology section), and Review Editor of the *Journal of Ethnopharmacology*. He is co-editor with Anna Jaeger of a textbook, *Ethnopharmacology*.

## **Luis Eduardo Luna, PhD**

Director, WasiWaska Research Center for the Study of Psychointegrator Plants, Visionary Art and Consciousness. ([wasiwaska.org](http://wasiwaska.org)) Dr. Luna is internationally recognized as an authority on the ethnography of ayahuasca.

## **Christopher R. McCurdy, PhD, BS Ph, FAAPS**

Professor of Medicinal Chemistry, College of Pharmacy, University of Florida, Gainesville, FL. Dr. McCurdy is Director of the UF Translational Drug Development Core and the 2017-2018 president

of the American Association of Pharmaceutical Scientists. He is internationally recognized as an authority on Kratom, *Mitragyna speciosa*.

### **Dennis J. McKenna, PhD**

Director of Ethnopharmacology, Heffter Research Institute; Assistant Professor, University of Minnesota. He has studied the botany, chemistry and pharmacology of ayahuasca and other South American shamanic plants over the last forty years.

### **Dale Millard**

Ethnobotanist, naturalist and biodiversity explorer, with research interests ranging from herpetology to the study of plants used to treat tropical diseases and immune disorders. He has traveled and collected extensively in South Africa, Brazil, and Indonesia.

### **Jeanmaire Molina, PhD**

Assistant Professor of Biology, Long Island University. She specializes in plant systematics, ethnobotany, and in the flora of the Philippines, including the giant-flowered *Rafflesia*, and uses phylogenetic and genomic tools in her research.

### **David E. Nichols, PhD**

Distinguished Professor Emeritus of Medicinal Chemistry and Molecular Pharmacology, and former Robert C. and Charlotte P. Anderson Chair in Pharmacology, Purdue University. Founder and President of the Heffter Research Institute ([heffter.org](http://heffter.org)). He is recognized as a world authority on the chemistry and pharmacology of psychedelic medicines.

### **Jerry D. Patchen**

Texas attorney and trial lawyer who has represented the Native American Church (NAC) to help secure access to their sacrament, peyote, and to preserve their rights to religious freedom. He was also on the legal team that secured the right of the União do Vegetal (UDV) to use ayahuasca in U.S. religious services.

### **Mark J. Plotkin, PhD, LHD**

Ethnobotanist, educator, filmmaker co-founder and President of the Amazon Conservation Team ([ACT.org](http://ACT.org)). He is widely recognized

for his advocacy for the protection of indigenous knowledge and Amazonian ecosystems. Plotkin was a protege of Richard Evans Schultes, and gave a unique and insightful look at his mentor as part of ESPD50.

### **Stacy B. Schaefer, PhD**

Stacy B. Schaefer is Professor Emerita, Department of Anthropology, California State University at Chico. Her expertise from long-term ethnographic fieldwork with the Huichol people of Mexico includes their ritual use of peyote. She has also studied peyote and its importance in the Native American Church.

### **Glenn H. Shepard, PhD**

Staff Researcher at Goeldi Museum, Belem, Brazil. His writing, research and photography on shamanism, traditional environmental knowledge and indigenous rights has appeared in Nature, Science, National Geographic and The New York Review of Books, among other prestigious publications. He has participated in several TV documentaries including an Emmy Award-winning Discovery Channel film.

### **Jean-Francois Sobiecki, B.Sc. Hons.**

Ethnobotanist, Research Associate at the University of Johannesburg & founder of the Khanyisa Healing Gardens project, specializing in African psychoactive plants.

### **Stephen Szára, MD, DSc**

Dr. Szára has had a long and distinguished career as a psychiatrist, medicinal chemist, and pharmacologist. He began his career as an Assistant Professor of Biochemistry at the Medical University in Budapest. After he emigrated to the U.S., he held several positions as scientist and section chief at NIMH and NIDA, as well as Associate Professor of Clinical Psychiatry at George Washington University. He has received numerous honors and awards. He is perhaps best known for his determination, through self-experiments, to ascertain whether DMT is a psychedelic in humans.

### **Constantino Manuel Torres, PhD**

Professor Emeritus, Art and Art History Department, Florida International University. Dr. Torres specializes in the art and



iconography of ancient cultures of the Central Andes. He is recognized for his excavations of shamanic burial sites in the Atacama Desert, and is a recognized expert on the use of Anadenanthera snuffs in ancient South America.

### **Keeper Trout**

Self-taught ethnobotanist, scholar and photographer. Author of Trout's Notes series of ethnobotanical references, formerly technical editor of The Entheogen Review. He is active in the Cactus Conservation Institute and the Shulgin Archives Project.

### **Snu Voogelbriender**

Ethnobotanist, an authority on the Australian Acacias and author of The Garden of Eden: Shamanic Use of Psychoactive Flora and Fauna and the Study of Consciousness.

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# *Foreword*

---

The contents of this book and the ESPD50 symposium from which these papers are derived shows that the investigation of psychoactive drugs is now a serious scientific endeavour. It is no longer the playground of a few adventurers. The indigenous peoples of the world have been fantastic explorers of the properties of the plants and fungi around them. They have discovered and used many psychoactive compounds, and often these plants are central to their cultural and religious life. But these discoveries have also been significant in a broader context, in that they have provided leads to the development of significant therapeutic medicines. The preservation of this knowledge under the stewardship of indigenous cultures has been an invaluable contribution to the advancement of science and medicine. This book clearly shows that this is a worldwide phenomenon, as it reports discoveries from the Amazon to Australia and from Mexico to South Africa. It also shows the broad range of organisms that contain psychoactive compounds, from Mexican fungi to tall Amazonian trees or desert Acacias of Australia. Many of us involved with this volume owe much to the encouragement or tutelage of Richard Evans Schultes, who was the pioneer who could justifiably be recognized as the founder of the interdisciplinary field of psycho-ethnopharmacology. Schultes' role as an explorer, an ethnobotanist extraordinaire, and a scientist who encouraged his colleagues to investigate the biodynamic compounds in the plants he discovered, opened a new frontier in the study of naturally-occurring psychoactive compounds. Without his encouragement to publish a paper about a visit to the Yanomami where I reported on their hallucinogenic snuff, I might never have followed this up in many other places and with several other tribes.

The rich ethnomedical heritage of indigenous peoples is now being scientifically studied and applied in many different ways, as is apparent from chapters of this volume. As someone who has spent much time with the tribal peoples of the Amazon and studied many different psychoactive compounds, it is my hope that those of us involved in research do all we can to maintain the cultures and the knowledge of these indigenous pioneers. Their discoveries would

never have come to the attention of science had it not been for their role as guardians of this knowledge. In return for these inestimable gifts, it is our responsibility to be active in the preservation of the habitats in which tribal people live. But our responsibilities as members of the scientific community do not end there. We must also become strong advocates for the recognition and protection of the intellectual property rights of indigenous peoples. The sort of research reported here is leading to a much wider application of these indigenous discoveries, potentially yielding novel medicines worth billions of dollars to the global pharmaceutical industry. We must make sure that our indigenous friends also benefit for their role in making these discoveries and preserving this knowledge as part of their intellectual and cultural heritage. We must make sure that indigenous peoples and their knowledge are recognized and preserved. At the same time, we must encourage them to develop at their own pace and make their own choices when it comes to the decision to share (or not) their ethnomedical treasures.

*Sir Ghilleen Prance, FRS, FLS, FRSB*

Director (Ret.), Royal Botanic Gardens, Kew

Currently: Scientific Director of the Eden Project

## [ INTRODUCTION ]

# What a Long, Strange Trip it's Been: Reflections on the Ethnopharmacologic Search for Psychoactive Drugs (1967- 2017)

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*Dennis McKenna, PhD*

Director of Ethnopharmacology,  
Heffter Research Institute

### THE FIRST ETHNOPHARMACOLOGIC SEARCH FOR PSYCHOACTIVE DRUGS — SAN FRANCISCO, 1967

In 1967, a landmark symposium in the history of psychedelics was held in San Francisco, California, under the sponsorship of the National Institute of Mental Health, which was part of the U.S. Department of Health, Education, and Welfare (HEW). This agency is now called the Department of Health and Human Services (HHS). The title of the invitational symposium was the Ethnopharmacologic Search for Psychoactive Drugs, and a volume of the proceedings was published under the same name and sold through the U.S. Government Printing Office. The symposium volume, now rare, has become a classic reference in the ethnobotanical literature.

This was the first time that an interdisciplinary group of specialists, ranging from ethnobotanists to neuroscientists, gathered in one place to share their findings on a topic of widespread interest at the time: the use of psychoactive plants in the context of indigenous and non-Western societies. In 1967, the word “psychedelic” had not yet become stigmatized. There were still expectations in the psychiatric and neuroscience communities that these little-known and curious agents, used for centuries in the

ethnomedicine and rituals of more traditional cultures, might yield new healing materials that could be used therapeutically in our own troubled society, as well as being important tools in the exploration of the human mind.

The roster of those attending the original 1967 symposium reads like a who's who of ethnopharmacology: John Daly, Richard Schultes, Bo Holmstedt, Gordon Wasson, Alexander Shulgin, Andrew Weil, Stephen Szára, Nathan Kline, Daniel Efron, Daniel X. Freedman, and many others lesser known, and now all but forgotten. Only a few of the researchers who attended the original symposium are still alive, and of those, even fewer remain active in the field. Their work contributed to making the first ESPD symposium one of the most unusual and interdisciplinary scientific convocations ever organized.

Originally, follow-up symposia were planned to be held about every ten years; that time frame, it was thought, was sufficiently ample to accommodate the stately progress of scientific research, yet frequent enough to enable researchers in various specialties to come together in a collegial environment to share research results in a timely fashion.

Following the summer of 1967, the prevailing political winds shifted, and psychedelic substances soon after became demonized, feared, and banned. There was no further interest on the part of the federal government to sponsor any similar symposia. In fact, their sponsorship of the original symposium, as valuable as it was for the dissemination of research findings, became an embarrassment, and as a result, no follow-up symposia were ever held. The Symposium Proceedings, available for a time from the U.S. Government Printing Office (U.S. Public Health Service Publication #1645), eventually went out of print, closing that particular chapter in the history of psycho-ethnopharmacology.

In the fifty years that have passed since that first symposium, numerous federal administrations have come and gone. Our recent past and current administrations, along with most of their affiliated institutions, remain as far from developing a viable, realistic drug policy today as they were then. In the decades since, a new generation of researchers, many inspired by the giants represented at that first conference, has continued to investigate the outer limits



of psycho-ethnopharmacology. Some outstanding discoveries have been made, and the work continues. At the same time, there has been a sea change in public and medical perception of psychedelics. There is now a renaissance in research around the world, and the therapeutic potential of some of these agents is being reinvestigated. While psychedelic substances have become less stigmatized than in the past, they remain controversial. Much work in this field remains unfinished, and the most significant discoveries may still lie in the future.

## HOW ESPD CHANGED MY LIFE — SUMMER 1968

When the first ESPD symposium was held in 1967, I was 16 years old, a bored teenager living in a small town in Western Colorado. More than anything, I longed to escape my dreary life and travel to San Francisco, the Mecca for the counterculture, the epicenter of the psychedelic revolution. My brother, Terence, a lifelong friend and mentor, had escaped our soft prison a few years earlier and was a student at Berkeley at the time. We were both just beginning to discover the wondrous world of psychedelics, and we agreed that they were the most fascinating things that we had encountered in our young lives. The fascination we felt then continued to guide our interests and even careers for the rest of our lives.

Terence passed on in 2000 after a long fight with brain cancer. I have continued the quest for understanding on my own, grateful to him for introducing me to psychedelics, and for the passionate curiosity we shared. I do the best I can, but every day I miss having his wisdom and humor in my life. He was, as he kindly said of me in his book *True Hallucinations*, “my brother and a colleague of long standing.”

In 1967, while we were fascinated by psychedelics and wanted to immerse ourselves in the counterculture, neither of us had much of a clue about them. Terence was living in Berkeley, and I managed to get away from my small town and visit him during the height of the Summer of Love. Neither one of us was aware of the obscure private symposium that had taken place in San Francisco just a few months earlier.

Like most of our like-minded contemporaries, we had no context from which to understand the emergence of these ancient

compounds into mass consciousness in the 1960s. Timothy Leary had transformed from a mild-mannered Harvard researcher to the Messiah of LSD, and although we resonated with much of his message, we were slow to plunge full tilt into the hippie movement. Part of the reason for this is because we identified as intellectuals, and were put off to some degree by the distinctly anti-intellectual trappings of hippie culture. We felt there had to be more to psychedelics than their superficial depictions in the mass media, but we had no idea where to find a more in-depth and balanced perspective.

Sometime in 1968, while we were busy trying to sort all this out, two books surfaced in our world; these works were able to provide for us a deep background context in which psychedelics made sense. One of these was *The Teachings of Don Juan*, Carlos Castaneda's first book of many, detailing his apprenticeship with a Yaqui shaman (Castaneda, 1968). Although subsequent events have shown that much of Castaneda's work is highly fictionalized, if not a complete fabrication, we did not know that at the time. For me at least, that first book was influential because it provided a cultural context for psychedelics, based on traditions older and richer than anything I had encountered in mass media sources. It made clear that there was nothing new about psychedelics; in fact, these sacred plants and fungi had been used in indigenous shamanic practices for hundreds, if not thousands, of years. While Castaneda's book was not scientific or even accurate, it gave me insights into shamanism, a set of practical technologies and beliefs involving the use of these materials for healing and the exploration of consciousness. Terence gave me a copy of the first edition of the *Teachings of Don Juan* for my 18th birthday in 1968; it was a very special gift. I still have it, and I still cherish it.

The proceedings of the first Ethnopharmacologic Search for Psychoactive Drugs were published some months after the symposium, in 1967. The volume was issued by the U.S. Government Printing Office as U.S. Public Health Service Publication #1645, published under the sponsorship of the Pharmacology Section, Psychopharmacology Research Branch of the National Institute of Mental Health (Efron et al., 1967).

I have no recollection of how this volume first came into my

hands. All I remember is that somehow a rather well-used copy came into my possession sometime in the summer of 1968. I dropped whatever else I was reading and devoured the book from cover to cover! This book provided the perfect balance to the *Teachings of Don Juan*. While that work had made me aware of the cultural contexts related to the indigenous uses of psychedelics, the *Ethnopharmacologic Search for Psychoactive Drugs* was even more influential, because through it I became aware that this discipline – ethnopharmacology, or more accurately psycho-ethnopharmacology – was a real field of scientific investigation. Moreover, it was my first introduction to the people working in this field, people like R. E. Schultes, Bo Holmstedt, Alexander Shulgin, R. Gordon Wasson, and others, who became iconic figures in my personal pantheon, and in some cases, as with Schultes and Shulgin, mentors and friends.

The realization that real science was being pursued in this field was a revelation to me, not least because it opened up the possibility that one day I, too, might be able to achieve a place in this exclusive fellowship. And eventually I did, but when it first came into my hands, I thought at least I would be able to prove to my parents that I was serious about psychedelics, and not just a confused hippie in search of cheap thrills. They were not very reassured, but over the years they came to recognize the merits of my chosen career in science.

## TWO DECADES LATER ...

The shabby volume of that first edition resides on my shelf to this day. While I don't remember exactly how it came into my hands, I remember very well how my second copy came to me, in 1986. I had completed my PhD at the University of British Columbia in 1984 under the supervision of Dr. Neil Towers, another one of my lifelong mentors and friends. My thesis was an ethnopharmacological investigation of the ethnobotany, chemistry, and pharmacology of *ayahuasca* and another hallucinogen, a relatively more obscure preparation known as *oo'koey*, derived from *Virola* species. Though derived from entirely different botanical sources, both *ayahuasca* and *oo'koey* were orally active tryptamine hallucinogens, and my thesis was a comparative study of their active constituents and

pharmacology.



Following the completion of my thesis in early 1984, I moved to San Diego and began the first of three post-docs. About a year after I had moved, my thesis publications came out, and one attracted the attention of Dr. Juan Saavedra, a researcher at NIMH. When Dr. Saavedra requested a reprint of my publication on *ayahuasca* in the *Journal of Ethnopharmacology*, (McKenna et al., 1984), I was surprised. I recognized his name from an early paper he had published with Julius Axelrod on the endogenous synthesis of DMT in rabbit lung (Axelrod later won the Nobel Prize for his work on mechanisms of neurotransmission).

Figuring it was a long shot, I enclosed a letter with my signed reprint, timidly enquiring if there might be a chance I could come to NIMH and work with him on endogenous tryptamines. A few weeks passed (things moved slowly in those days), and one day I received a kind reply. He thanked me for my reprint, and mentioned that he had been in the Amazon in 1979 with Schultes and my mentor, Dr. Towers, along with a dozen other researchers on the R.V.<sup>1</sup> *Alpha-Helix*, operated by the Scripps Institute of Oceanography. He informed me that there was a fellowship program at NIMH, the Pharmacology Research Associate Traineeship (PRAT), that was targeted to young investigators wanting to expand their scientific training outside their field of specialization. He said it was a perfect fit for me, and encouraged me to apply. I did so, was accepted into the program, and began my second post-doc in the fall of 1986, in the hallowed environs of the Laboratory of Clinical Pharmacology at NIMH.

1. R. V. = Research Vessel

I had been in the lab for less than two weeks when Dr. Saavedra pointed to an upper shelf in a cabinet in the lab. He said there was a box up there containing some research chemicals that he and Axelrod had used in their research on endogenous tryptamines. He suggested I go through it and see if there was anything useful, and to send the rest to the hazardous waste disposal center on the NIH campus. I didn't waste any time; I stayed late one afternoon until most of my fellow workers had called it a day, then got up on the

bench and retrieved the box. And something more: a mint-condition copy of the *Ethnopharmacologic Search for Psychoactive Drugs*! How many years it had languished on the shelf next to that box of chemicals I had no idea, but it had clearly never been opened.

Here I was, just beginning my post-doctoral studies in the heart of NIMH, the very institution where the original ESPD had originated, and suddenly the book that had so enthralled me as a curious teenager magically, reappeared. How cool was that? I took it as a very good omen. It quietly disappeared into my library, where it sits beside my first copy from 1968. Some of those research chemicals turned out to be interesting as well. Along with a couple of vials of DMT and 5-methoxy-DMT, there was an interesting assortment of other derivatives such as 5,7-dihydroxy-DMT, 6-methoxy-DMT, and so on. I kept those for many years, but never found the courage to bioassay them.

### ESPD RETURNS: FIFTY YEARS LATER

So that is the story of my own personal history with this book. It has haunted most of my professional career. It opened my eyes to the science of ethnopharmacology, and later, I was fortunate to meet and befriend some of the people who presented at that 1967 symposium. Though its contents are dated now, that book influenced my life and career in profound ways, and I am sure that my career in ethnopharmacology, such as it has been, would never have happened had I not encountered that obscure tome in the summer of 1968.

I have wanted to organize a follow-up symposium for many years. In fact, I first drafted a proposal about it in 1995, hoping to stage it in 1997, the 30th anniversary of the San Francisco symposium. It never happened for various reasons, mostly due to lack of funds, time, and an appropriate venue. Now it is 2017, the 50th anniversary of the ESPD, and all of those necessary elements have come together almost miraculously.

I hope that this commemorative symposium and the publication of both symposium volumes, 1967 and 2017, will attract the attention of younger investigators working in the field of ethnopharmacology, and will inspire them to continue this valuable work. There is still more – much more – to be discovered. I hope that the quest

represented in the book's title – *Ethnopharmacologic Search for Psychoactive Drugs* – will be carried on by a new generation, who one day will report their discoveries to the world at a future ESPD symposium. I also hope that it will not take another 50 years!

## SIGNIFICANT DISCOVERIES OF THE LAST FIFTY YEARS

Psycho-ethnopharmacology has not stood still over the last fifty years. Significant discoveries have been made, and are still being made. The ESPD50 anniversary conference in June 2017 included presentations on some of the most interesting discoveries made in those decades, but this volume must necessarily omit many others that are just as worthy. Though it's not my intention to discuss them in any detail, a few are worth mentioning in brief:

**Ayahuasca Admixtures** – The importance of the many admixtures to *ayahuasca* had not received much attention in 1967. Some of Schultes' students were reporting on the use of admixtures including the DMT-containing admixtures that give *ayahuasca* its psychedelic properties, but most of this work was not published until 1968 or later (Pinkley, 1969). Interestingly, the word "*Psychotria*," the genus that includes the most widely utilized admixture, *Psychotria viridis* R&P, occurs only once in the entire 1967 edition. In the 1980s, Eduardo Luna and I also published research on the many other species that are occasionally used as admixtures (McKenna, Luna, and Towers, 1986, 1995<sup>2</sup>). Many of these remain poorly investigated both as to their chemistry and their pharmacology. In a later publication (McKenna et al., 2011), I screened many of these species using neuroreceptor-binding assays as part of a broad sampling of purported CNS-active plants with potential anti-dementia and anti-schizophrenic activity. I have contributed a condensed version of that paper to this volume.

<sup>2</sup>. This paper was originally published in Spanish in the journal, *America Indigena* in 1995; an English translation was published as a chapter in an anthology, *Ethnobotany: Evolution of a Discipline*. See bibliography for details.

**Salvia divinorum Epling & Játiva and Salvinorin A** – Although ethnographic reports of the use of this member of the



mint family (Lamiaceae) in Mazatec shamanism had been reported in the '30s (Johnson, 1939a, 1939b), it was not discussed in the '67 symposium. The primary active constituent, the diterpene Salvinorin A, was isolated and characterized in the '90s (Valdés, 1994), and its potent activity as a highly selective kappa-receptor agonist was described in 2002 (Roth et al., 2002). This initial discovery has led to a flurry of research on the chemistry and pharmacology of Salvinorin A and its analogs. Over 30 papers on Salvinorin A have been published since (for a review, cf. Cunningham et al., 2011). Dr. Michael Heinrich and his student, Ivan Casselman, contribute a retrospective on this interesting plant in this volume (Heinrich and Casselman, 2017).

**Kava - *Piper methysticum* (G. Forst)** – Kava, known under many names, is a mildly psychoactive beverage prepared from the roots of this member of the pepper family. It was reported on in the first ESPD symposium in 1967 (cf. Session II, ESPD 1967), but much additional work has been done on this plant in subsequent decades. It is now widely available as a dietary supplement; and its anxiolytic, muscle-relaxant, and sedative properties have made it a popular alternative to pharmaceuticals such as benzodiazepines (for review cf. LaPorte et al., 2011).

***Mitragyna speciosa* (Korth) Havil.** – Known by its folk name of kratom, this Rubiaceous tree is the source of mitragynine and related alkaloids that are potent mu-receptor agonists. The plant can cause addiction like any opiate, but in traditional contexts it is often used as an alternative to opium, and as a way to gradually end dependence on opium and heroin. The *Mitragyna* alkaloids do not cause respiratory depression, unlike heroin and other opiates, and hence show promise as less toxic, and less addictive, analgesics. It is not illegal in the U.S. at the time of this writing, but has been identified as a “drug of concern” by the DEA, and may be scheduled in the near future. At the same time, some investigators, such as Dr. Christopher McCurdy, have urged that it not be prohibited as it may enable many opiate addicts to overcome their habits, as a kind of herbal methadone (Ward et al., 2011; Babu et al., 2008). Dr. McCurdy has reported on his research and the current “state of the art” with respect to *Mitragyna* in this volume.

**Iboga – *Tabernanthe iboga* Baill. and Ibogaine** – Iboga,

sometimes spelled eboga, is used in traditional initiation rites among the Bwiti peoples of Gabon. In those rites, young men and women of the tribe, coming of age as adults, undergo an initiation in which they consume large – sometimes nearly lethal – amounts of iboga root. They experience a deep trance, sometimes lasting up to 36 hours, during which they are visited by their ancestors and are initiated and given the ancestral wisdom. Ibogaine, the major alkaloid, has received recognition and notoriety, as it is effective for the treatment of opiate and other addictions (Alper, 2001). Although a Schedule 1 controlled substance in the U.S., it is unregulated in many countries, and is used in treatment centers in various parts of the world, especially Mexico (Brown, 2013). Dr. Kenneth Alper, a leading authority on the chemistry and pharmacology of ibogaine, reports in this volume on The Ibogaine Project: Urban ethnomedicine for opioid use disorder.

**Kougoed – *Sceletium tortuosum* (L.) N.E. Br.** – Kougoed, also called canna or kanna, is a succulent in the family Aizoaceae whose roots contain a spectrum of alkaloids with CNS activities. Some, such as mesembranone, mesembrine, and mesembranol, are potent 5HT-uptake inhibitors and phosphodiesterase 4 inhibitors. These are only 3 of more than 30 alkaloids that have been isolated; the pharmacological properties of most have not been thoroughly characterized (Gericke et al., 2008). In this volume, Dr. Nigel Gericke reports on his research with *Sceletium tortuosum* that has led to the commercial development of Zembrin™, a natural herbal anxiolytic and antidepressant sold as a dietary supplement (Gericke, 2017).

**Jurema – *Mimosa hostilis* (C. Mart.) Benth.<sup>3</sup> and yuremamine** – This species has long been known as the source of Vinho de Yurema, a psychoactive beverage that has DMT as its main active constituent. However, it has been an ethnopharmacological enigma because DMT is not orally active unless potentiated by a monoamine oxidase inhibitor. Yet there are no admixture plants with MAOI activity that have been reported to be added to the mixture. Recently, a novel compound, yuremamine, was isolated from the roots of *M. hostilis* at about the same concentration as DMT (Vepsäläinen et al., 2005). This compound has an interesting structure in that the structure of DMT is “caged” within the larger

molecule, which may be a prodrug that is converted to DMT *in vivo*. The initially proposed structure has been challenged, and total synthesis has so far been elusive (Calvert and Sperry, 2015). It may also be an MAO inhibitor itself, and thus could potentiate the DMT. So far, there have been no human bioassays of this compound, so its pharmacological properties in a pure form are unknown.

3. Note: *Mimosa hostilis* (C. Mart.) Benth. is considered a synonym of the currently accepted name, *Mimosa tenuiflora* (Willd.) Poir. cf. <http://www.theplantlist.org/tpl1.1/record/ild-20760>

**Acacia spp. and tryptamines** – The large genus *Acacia* (Fabaceae) has proven to be an unusually rich source of DMT and other psychoactive tryptamines. At the time of the first ESPD conference in 1967, the tryptaminic *Acacias* were unknown to science. The earliest reference in Pubmed is Wahba and Elkhier (1975). Since that time, tryptamines have been detected in over 60 *Acacia* spp. world-wide, with about 40 species native to Australia, as documented in the review paper in this volume by Snu Voogelbreinder, *Australian Psychoactive Acacia Species and Their Alkaloids* (2017). Many more *Acacia* spp. contain unidentified alkaloids, and phenylethylamines,  $\beta$ -carbolines, tetrahydroisoquinolines, pyridines, and still other structural classes have been reported. Interestingly, much of what science knows about the chemistry of psychoactive *Acacia* spp. is due to investigations by amateur scientists who have conducted research outside conventional academic channels, and as a result, much of it does not appear in the peer-reviewed literature.

**Frog and Toad medicines** – Psychoactive and psychedelic amphibians – frogs and toads – have attracted attention recently as potentially being therapeutic. Among these are the so-called sapo medicines, more properly termed kambô, from *Phyllomedusa bicolor* (Giant Leaf Frog), a frog containing a variety of neuroactive peptides in their skin secretions. This species is used by the Matsigenka tribe as hunting magic, and taking “sapo” is becoming a popular pastime among tourists in Peru. So far the peptides identified include phyllocaerulein (a hypertensive), phyllomedusin (tachykinin, potent vasodilator, and secretagogue), phyllokinin (a potent arterial smooth muscle dilator), and several delta-selective

opiate peptides (the deltorphins), as well as mu-active peptides (the dermorphins). Many of these compounds may have therapeutic potential, and the neuroactive peptides are only a part of this rich peptide cocktail. For reviews and more information, see: Erspamer et al., 1993; Daly et al., 1992; den Brave et al., 2014.

In addition to the *Phyllomedusa* peptides, the venom of *Bufo* species contains psychedelic tryptamine derivatives, either bufotenine or 5-Methoxy-DMT, and its use has gained popularity in various neo-shamanic practices. Although the subjective effects of *Bufo* venom were first reported by Weil and Davis (1994), there is little evidence that these species were ever utilized as psychedelic medicines in any ethnomedical or shamanic tradition. A comprehensive review of the use of *Bufo* spp. as psychedelics, and an unpacking of some of the controversies surrounding this practice, can be found in Lyttle et al. (1996).

**Old yet new: Harmine and related  $\beta$ -carbolines** – Harmine is the major  $\beta$ -carboline in *Banisteriopsis caapi* (Spruce ex Griseb.) Morton, and is the primary MAO inhibitor in *ayahuasca*. Harmine is an “old” alkaloid. By that, I mean that it’s been around for a while, having first been identified in the seeds of Syrian rue, *Peganum harmala* L., in 1847 by chemist J. Fritsch, over ten years before *ayahuasca* came to the attention of science as a result of Richard Spruce’s discovery in 1858. However, recent investigations have shown that even old alkaloids can still harbor secrets; new research has shown that harmine and some of its derivatives can display a diverse array of biological activities. It has been shown to have antimicrobial, anti-diabetic, anti-depressant, anti-cancer, neuroprotective, and other effects. It interacts with a number of neuroreceptors including 5-HT<sub>2A</sub>, 5-HT<sub>2C</sub>, imidazoline, and DAT. Significantly, it has recently been shown to be a potent inhibitor of DYRK1A, a kinase involved in a variety of intracellular signaling functions related to cell proliferation and neurogenesis, and has been shown to potently stimulate proliferation of neural cell progenitors, an effect linked to its inhibition of DYRK1A (Dakic et al., 2016). For recent reviews on the pharmacology of harmine and other  $\beta$ -carbolines, see Cao et al., 2007; Patel et al., 2012; and the paper in this volume by Dale Millard (2017).

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I want to express my profound thanks to those who have made contributions to this 50th Anniversary ESPD symposium volume, and the website and e-book, as well as to the many individuals who saw and shared my vision, and stepped up to help make it happen in so many ways.

The idea may have been mine; the time and effort that made it happen came from all of us.

- *Dennis McKenna*

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[ FROM THE ARCHIVE ]

# A Scientist Looks at the Hippies<sup>I</sup>

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*Stephen Szára, MD, DSc*<sup>II, II</sup>

**I.** Report to the Director, SMHRP, NIMH.

**II.** Chief, Section of Psychopharmacology, Laboratory of Clinical Psychopharmacology, SMHRP, NIMH, Saint Elizabeth's Hospital, Washington, D.C.

## PRELIMINARIES

On the suggestion of the Director, SMHRP, NIMH, I agreed to take a visit to the San Francisco (SF), Los Angeles (LA) and New York City (NYC) hippie centers in order to obtain firsthand acquaintance with the “hippie” movement and with the role hallucinogenic drugs play in this psychedelic cult. I was to consult medical, psychological and sociological authorities well acquainted with this cult, as well as obtain personal impressions during the site visits. The main goals were:

1. To check on the validity of sensational newspaper and magazine stories on the “hippie” movement and drug usage associated with it.
2. To formalize scientific hypotheses on the possible biochemical, psychological or social mechanisms involved.
3. To suggest possible lines of approach for research relevant to handling the public health problems associated with this cult.

My credentials include over twenty years of experience in research, discovery of the hallucinogenic activity of a series of tryptamine derivatives (including DMT) and supervision as well as participation in over one hundred administrations of these drugs to



volunteer subjects for research purposes.

At first my intention was to contact psychiatrist friends, and through them get acquainted with drug-taking youngsters who came to them for help. But I realized very soon that the psychedelic culture has widespread social and psychological manifestations and the drug usage is only a part, although probably a significant part, of it. To approach it from the psychiatric side would be similar to an attempt by a visiting foreigner to learn about the role of automobiles in American life today by interviewing victims of accidents in the hospitals.

The picture obtained this way would obviously be a lopsided one, ignoring positive aspects, which might perhaps be important. Because of limitations of time, (four days each in San Francisco, Los Angeles and New York City) I decided to meet only a few personal acquaintances in each city (psychiatrists, psychologists and sociologists) and see as many manifestations of the psychedelic culture in each location as possible. In addition, I kept a close watch on the Washington, DC psychedelic scene throughout the summer of 1967.

In the following report, I shall use primarily the observations made on these trips and my personal experience with the hallucinogenic drugs discussed, but I shall also use, whenever it is necessary, the information obtained from interviews with knowledgeable persons and from material published by the Underground Press Syndicate (U.P.S.) collected on my visits to the various "hippie" areas in San Francisco, Los Angeles, New York City and Washington, DC.

My observations and comments are organized around five basic questions about the hippies:

1. Who are they?
2. What are they doing which is of public concern?
3. Where and when are they active?
4. Why are they doing what they are doing?
5. What can or should be done about potential problems?

Finally, as a scientist I shall suggest certain areas of research to be explored if we are to cope with the problems arising from the activities of the hippies.

## WHO ARE THE HIPPIES?

Time Magazine gives the etymology of the word “hippie” as deriving “from the pre-World War II jitterbug adjective ‘hep’: to be with it; hep became ‘hip’ (in noun form, ‘hipster’) during the bebop and beatnik era of the 1950’s, then fell into disuse, to be revived with the onslaught of psychedelia” (Brown, Time, July 7, 1967).

I did not find a concise definition of a hippie, but a good approximation seems to be *a person who has the subjective feeling of being aware of reality and all that is taking place about him in nature, in life and society, and who is seeking a better world where an ethic of individual freedom, love and personal honesty prevails.*

The definition given above would exclude pseudo-hippies, such as hangers-on who move into a hip community, grow long hair, wear psychedelic garb and identify with the action, but do not have a serious commitment to the hippie ethic or to its social consequences and secretly receive sustenance from their parents, knowing that they can return to their security any time.

The real hippie is an idealist, continually and sincerely reaching for eternal matters of ultimate concern such as love, beauty and liberation, is deeply committed to an enlightened existence and has nothing to escape to. As the outside reflection of his conviction, he grows long hair and a beard, wears psychedelic clothing and joins a hippie community to participate in communal living aimed at the complete realization of these ideals. (A lucid discussion of this “hang-loose ethic” is by Simmons and Winograd, 1966).

The part-time, or “plastic” hippie, who may “drop out” for a night or two each week but would hold onto their job or go to school during the rest of the time might be covered by the given definition if they have the “awareness” and are sincere about the ethical ideas of the hippies, but for some reason they wouldn’t join the hippie community full time.

It is my conviction that the use of hallucinogenic drugs like LSD, marijuana, DMT, mescaline and STP are instrumental in producing the subjective feeling of awareness of reality which, in turn, is

probably playing an important part in changing the value system of the individual and inducing them to seek a better world by joining the hippie movement. The frequent use of hallucinogenic drugs also creates a number of legal, social and medical problems which will be touched upon later.

H. G. Shane, Professor of Education at Indiana University, calls attention to the variety of groups associated with the “hang-loose” movements (Shane, 1967):

1. Beatniks of the 1950's with a new label and minor changes in garb.
2. A strongly dedicated activist subgroup believing in and seeking social change.
3. A dedicated but more passive group seeking reforms.
4. Some misfits who feel less conspicuous amidst a cluster of people with unconventional beliefs.
5. The “synthetic” hippies who seem to think that psychedelic drugs are just another fad.
6. Racketeering types who, through the sale of drugs and other psychedelic items, prey upon the gullible or maladjusted.

This grouping seems to be related to my proposed categories in the following ways: Groups 1 and 4 are pseudo-hippies, according to my categorization. The second group, partially, and the third group, totally, cover the real hippies. The rebellious “new” leftists, the so-called “peaceniks,” are essentially different from the followers of “flower power.” The real hippies do seek social change through reform. Group 5 can be considered as a transitory stage between the “plastic” and “real” hippies.

I prefer to call “plastic” those hippies who have taken psychedelic drugs and are open to and aware of the psychedelic message, and who are ready to change their lifestyle if the situation permits. The “real” hippies use the term “plastic” in a derogatory sense to refer to those who lack the stamina and/or courage to give up the affluent life, but occasionally enjoy indulging in what the hippie way of life promises: love, compassion and the taste of the eternal “now,”

mainly by means of the drug experience. Shane's group 6 consists of an economic stratum composed of real, pseudo and plastic hippies.

The magazines and newspapers stress the almost exclusive white, middle-class origin of the hippie youngsters as opposed to the fairly mixed, integrated "beat" generation of the 1950's. As far as I can tell, the visible hippie population is an integrated community, reflecting the cross section of the area's ethnic population. In San Francisco, I saw quite a few Asian-American descendants among them, while in Los Angeles a proportional number of African-American, and in New York African-American and Puerto Rican hippies, were mingling freely with the white hippies.

## WHAT ARE THEY DOING WHICH IS OF PUBLIC CONCERN?

The American sociologist W. I. Thomas set forth a theorem for his professional associates: "If men define situations as real, they are real in their consequences (Thomas and Thomas, 1929)." Time has proven the validity of this theorem and it is clearly applicable to the hippies. If they have the subjective feeling of being aware of certain "truths" about themselves or about the world around them, they will act according to this newly-found "reality" and the consequences of their actions should be regarded as real. Many of these actions do affect other people; therefore, they are of public concern. I shall review here only two types of activities which I have paid close attention to: the drug taking and the artistic activities.

### A. DRUG TAKING

The drug taking, which seems to be a central activity by hippies, is clearly of the foremost public concern.

Practically all the drugs they are taking have been declared illegal to manufacture, sell or possess. Many of the problems have actually been created by this illegality, and the evidence is plentiful in the daily press. Besides this, many medical dangers (hepatitis, malnutrition, sexually transmitted infections, upper respiratory infections, possible chromosome damage, etc.), possible psychological dangers (temporary panic reactions known as "bad trips" or "freak-outs," longer-lasting psychotic breakdowns, vivid

recurrences of the drug experience long after the acute drug effect has worn off (“flashbacks,” permanent personality changes, etc.), and social problems (creation of an isolated subculture, the group activities in public places during “love-ins,” association between hippies and “peaceniks,” etc.) are related to the drug-taking activity, and many of them are of serious public concern.

Since talking about the drug experience is not illegal, much valuable information can be obtained through direct or indirect personal contacts with drug-taking individuals and from the pamphlets and “Underground” newspapers circulating in the hippie communities.

It is not my purpose to go into a detailed discussion of the drugs, since I reviewed them recently (Szára, 1967), but I would like to authenticate the evidence of widespread illegal drug-taking by the hippies in all the sites I visited.

In the rooms of the “Hippie Clinic” at Haight and Clayton in San Francisco, I saw some 30 to 40 hippies either waiting for medical attention or sleeping off a bad trip. The manager of the clinic explained that they see some 70 to 100 patients a day, but they have difficulties obtaining and retaining the services of the volunteer physicians and nurses. One of the attending pharmacologists, Dr. Frederick Meyers<sup>4</sup>, drops in frequently to supervise the legal drug supply (donated mostly by the pharmaceutical houses themselves) and to pick up samples of illegal drugs submitted by hippies for analysis and purity checks. He stressed the significance of the existence of the clinic as the only link in San Francisco between illicit drug users and the Establishment, in the sense that straight society can keep a finger on the pulse of illegal drug commerce.<sup>5</sup>

**4.** Note: Dr. Frederick Meyers was a Bay Area physician and pharmacologist who played a key role in the founding of the Haight Ashbury Free Clinic. (SF Gate, 1998)

**5.** The clinic has been temporarily closed for about a month due to financial difficulties, but it is open again.

### MARIJUANA: “POT”

In Berkeley, I met a graduate student who is working on his thesis about the commercial aspects of marijuana (pot, grass, weed) traffic. He has interviewed over 200 students and other marijuana

users. The major conclusions of his survey were that marijuana traffic has the typical characteristics of individualized, part-time, small business merchandizing patterns, and in spite of this, the volume of the illegal marijuana trade is tremendous, estimated to be about 10 times as large as the amount seized by the narcotics authorities. In New York City alone, the Narcotics Bureau seized 1,680 pounds of marijuana in 1966. One pound yields as many as 1,000 joints, or cigarettes. The West Coast traffic is even heavier; in California and Arizona during the three summer months of July, August and September 1967, about 16,000 pounds of pot was seized by US Customs authorities (*Washington Post*, November 18, 1967). The price of marijuana depends on the quantity bought and upon the momentary market situation. One kilo (= 2.2 pounds) usually sells between \$20-80, which is then retailed usually at \$.25 to \$1.00 per joint (cigarette).

The use of marijuana does not seem to be limited to 17-25 year olds, but has also spread to younger high school children (13-15 years of age). It is difficult to measure the significance of this. College students can go back to school after a week, month or year of "dropping out," if they have had enough "expansion" of their minds or for some other sobering reasons. But younger high school kids don't go back to school once they drop out; they are lost to society. Dr. William Soskin of the University of California at Berkeley has a group-therapy project exploring the problems these high school children have and in which he tries to lead them back to normal life. He had only four or five boys and girls coming in regularly at the time I visited him, but he would not have had a problem recruiting 100-200 similar young hippies from the San Francisco and Berkeley area.

### LSD-25: "ACID"

Lysergic acid diethylamide (LSD-25, or acid) is the second major drug on the hippie scene. While marijuana is widely and frequently used for short-lasting mood manipulation and for its mild hallucinogenic effect, LSD is taken much less frequently (usually more than a week apart if taken regularly) and produces 10 to 16-hour "trips" consisting of profound perceptual and emotional experiences. In the setting it is taken, the major psychological effect

seems to be a temporary suspension of the primacy of one's habitual perceptions of the self, environment, beliefs, values and a subjective feeling of freedom, awareness and insight. The bodily changes are the usual pupillary dilation, paresthesia, feeling of floating, etc.

All black-market LSD is produced illegally (the original Sandoz LSD-25 is not available anymore), and there is a wide variation in the quality of "acid" circulating in Hippiedom. "Owsley's Acid" is considered the best-quality material, but after police raids it tends to disappear and be replaced by poorer-quality LSD, often mixed with methedrine or even heroin, as Dr. Meyers of San Francisco explained.<sup>6</sup>

<sup>6</sup>. Augustus Stanley Owsley III, with four alleged associates, was arrested and an amount of psychedelic drugs (LSD and STP) potentially worth \$11 million was seized by federal agents on December 21, 1967 (*New York Times*).

Dr. Sidney Cohen at the V.A. in Los Angeles has no problem recruiting subjects who are regular users of LSD. His project involves testing the subjects for organic brain damage; and they are glad to cooperate in order to find out whether or not any harmful effect has occurred.

*Washington Post* staff writer Nicholas von Hoffman, who spent three months with the hippies in San Francisco and described his experiences about the "Acid Affair" very vividly in the columns of his newspaper (October 15 through 31, 1967), conservatively estimates the monthly acid market in the Haight area to be 200,000 doses, selling at not less than 50 cents (usually \$2.00 to \$2.50) apiece.

#### METHAMPHETAMINE: "SPEED"

The third major drug in the hippie scene seems to be methamphetamine (methedrine, "meth," "speed"). It is a stimulant which is usually taken intravenously, hence its significance in the incidence of hepatitis. Since it is also an anorectic agent, the lack of food and nourishment leads to avitaminosis, general debility and wasting. The subjective feeling produced by "meth" is distinctly different from that produced by the hallucinogens. The elevation of mood and feeling of well-being comes on very fast (therefore the name "speed"); the feeling induced of tremendous energy has been compared to trying to drive a Ferrari with the gas pedal stuck to the

floor all the time. There is no feeling of awareness or insight, just a “coming of power ... this churning cloud of light with sparks shooting off” and “a continuous orgasm without a lover” until the drug effect wears off. A recent *Time* article estimates the “meth” users in San Francisco to be about 4,000 in number (October 27, 1967).

#### DANGERS OF MAJOR DRUGS QUOTED

All three drugs have been characterized by the WHO Expert Committee on Addiction-Producing Drugs (1966) as:

Moderate or variable psychic dependence.

Absence of physical dependence.

Development of tolerance is practically none in the case of marijuana, slow and considerable in the case of amphetamines, and greatly manifested with LSD, in which it develops rapidly and disappears rapidly.

The dangers of the hallucinogenic drugs LSD and marijuana are described by the same committee as follows:

1. The impairment of judgment can possibly lead to dangerous decisions or an accident.
2. The subjective feeling of increased capability with corresponding failure might lead to psychotic episodes or to development of depression and even suicide.
3. Society is harmed by the economic consequences of the impairment of the individual's social functions.

The dangers of the use of drugs of the amphetamine type are:

1. Facilitates the transition to the physically addicting “hard” narcotics, such as heroin and morphine.
2. Increases the incidence of hepatitis.
3. May lead to malnutrition, avitaminosis and wasting.
4. May precipitate paranoid psychosis (often indistinguishable from schizophrenia).



5. May lead to aggressive and dangerous antisocial behavior.

### THE MINOR DRUGS

The other hallucinogenic drugs seem to play a minor role in the whole movement. N, N-dimethyltryptamine (DMT) is available, but is more expensive than LSD. DMT, also called the “businessman’s lunchtime psychedelic” because of its short duration of action, is usually smoked in the form of dried parsley leaves soaked with the drug.

It seemed to me to be significant that the grocery store in the small rural community of Topanga Canyon, outside of Los Angeles, had a brisk business in dried parsley leaves at the time I visited.

DMT seems to be accessible in New York also. I received several calls from doctors at Bellevue Hospital requesting information about DMT on occasions of admission of patients with a history of having taken DMT.

In the middle of last summer, about 10,000 doses of a drug called STP were distributed among the West Coast hippies, which created some unusual problems. The drug (identified by the FDA as 4 methyl – 2,5 dimethoxy amphetamine) produced an unusually long effect lasting for 3-4 days, and attempts to “bring down” the subjects with thorazine seemed to aggravate the anxiety rather than to diminish it. The *East Village Other*, the U.P.S. paper for New York hippies, suggested “Tranquinol” as “the new come-down for STP freakouts” (Vol. 2/17, p. 7, August 1-15, 1967).<sup>7</sup>

7. Snyder, Faillace, and Hollister (1967) recently reported that STP is not as active as the hippies reported it to be (the effect of up to 10 mg of STP on volunteers lasted for about 12 hours), and chlorpromazine did not seem to aggravate the psychological effects.

A variety of STP seemed to create other problems in the East Village at the end of August 1967. Posters in hippie shop windows warned:

“Don’t Do Blue STP

It’s Belladonna

And makes you sick

Like s..t.”

On one of these posters, a P.S. in pencil added, “It’s fatal, too.”

## B. PSYCHEDELIC ART

Another important aspect of the hippie subculture is the close relationship between the drug-produced psychological state and so-called psychedelic art.

This relationship is mutual, in the sense that on the one hand, the drug state seems to inspire many individuals to express their experience in various artistic forms – paintings, drawings, poetry, music, etc.—but on the other hand, many of the products of this “psychedelic” art are used to recreate or facilitate the production of a psychological state similar to the drug-induced state, but without taking drugs.

The importance of this positively reinforcing feedback effect on the social level is nowhere more visible than in the history of the development of the hippie subculture itself, and in the role the popular media, newspapers, magazines, TV, radio and especially rock music groups have played in spreading the psychedelic message and in reinforcing the subjective beliefs of the hippies.

I shall touch upon the history of the hippie subculture a little later, but now I would like to describe my experience in the so-called psychedelic theaters or dance halls.

My first experience of this type was in the Avalon Ballroom in San Francisco on a Sunday evening. The setting seems to be typical for most of the other so-called Total-Environment entertainment places I have visited subsequently, so I am going to describe it in detail.

The ballroom is dimly lit, and has projection screens on three walls around the room. Onto these about a dozen slide projectors project various abstract color patterns inspired by hallucinations experienced under LSD, or faces, or pictures of statues or paintings (usually of a religious character).

Superimposed on these occasionally changing patterns are constantly dancing patterns from six overhead liquid projectors. These project the image from large watch glasses filled with an oil-water mixture, dyed with a non-mixing single color and moved by hand, or squeezed by another watch glass on the surface of the liquid, creating single or multiple amoeba-like images moving and

dancing to the rhythm of the music.

In some corners of the screen, still superimposed on the slide-projected images, there is a continuous, repeated projection of a short sequence from an old movie, a Mickey Mouse cartoon or some other, usually sexually suggestive, sequence of animated or real scenes.

As an additional visual stimulus, a flickering strobe light is turned on occasionally, under which the dancing people appear mechanized, their movements as jerky as in old-time movies.

The type of music called “acid rock” is played continuously by two or sometimes three orchestras, alternating with each other. It is called “acid” not only because many of the song lyrics allude to “acid” (LSD) and to “pot,” but also because it employs a monotonous, harshly amplified drone-like sound which can act as a psychedelic stimulus. In the midst of a routine rock-and-roll number for instance, the players may focus on a particular pattern which is repeated again and again, louder and louder until the limit of the human eardrum is reached, upon which it suddenly stops.

Only part of the audience is actually dancing on the floors. A large portion of youngsters (mostly teenage girls) are lying in front of the screens and orchestras, practically “stoned” under the barrage of visual and auditory bombardments.

I saw similar arrangements and “happenings” in the “Magic Mushrooms” and “Genesis IX” of Los Angeles, in the “Electric Circus” in New York and in the “Ambassador Theater” in Washington, DC.

More sophisticated and artistic shows suggested by and suggestive of the psychedelic experience are being put together by young artists. I saw one of them at Cinema Discothèque in New York, entitled “After the IIIrd World Raspberry,” by Al Rubin. The reference to “pot” by the projected pictures was unmistakable and the audio-visual manipulation was clearly aimed at the reproduction of the perceptual aspects of the psychedelic experience. When it was over (it lasted a little more than one hour), the audience seemed to be stunned. I was the first one to stand up and start walking out. Behind my seat there were two hippie girls sitting in a trance-like state, seemingly unaware that the show was over. It was not unusual to see about half of the audience in a

similar reverie for minutes after the show had ended.

I have described these experiences in detail not only because the acid rock music seemed to be an essential part of the hippie scene, but also because it is likely to be the main carrier of the psychedelic message into the future, even if the hippie subculture as we know it today passes. The Beatles turning to Asian mystical meditation and changing their style, adapting Hindu raga music to acid rock, is clearly a sign of searching for new ways of expressing the same message and carrying it into the future. And the audience at these shows are not the typical hippies (they could not afford the whopping [in 1967] \$3.50-\$4.50 admission fee), but the college and high school kids who can afford it. The significance of this is that they, due to their higher educational development, might be more successful in formulating a convincing social philosophy and integrating the psychedelic experience with ongoing life.

### WHERE AND WHEN ARE THE HIPPIES ACTIVE?

It seems to be most convenient to follow the ecological approach in answering these questions together about hippie communities. Human ecology is concerned with the influences of the environment on the structural pattern of a community, and with the forces behind its constant change. It helps to describe the development in space and time of a social movement in terms of five major processes, i.e., concentration, centralization, segregation, invasion and succession.

**A.** The pleasant climate, permissive atmosphere and local situations were probably important factors in inducing youngsters to concentrate in the Haight-Ashbury area of San Francisco in order to follow Timothy Leary's advice to "tune in, turn on and drop out" and form their own community to pursue these goals. In other cities, it is also possible to point to an already existing artistic or bohemian district to serve as points of concentration. Hollywood in the LA area, Greenwich Village in New York and the Georgetown area in Washington, DC clearly provide this type of permissive social climate.

**B.** The second process is centralization, i.e., the tendency to form a "Main Street" or perhaps several central areas, and this is clearly visible in all the places I visited.

- Haight Street in San Francisco, California
- Telegraph Avenue in Berkeley, California
- Sunset Strip in Hollywood, California
- N. Fairfax Avenue in Los Angeles, California
- St. Mark's Plaza in East Village, New York
- McDougal Street in West Village, New York
- “M” Street in Georgetown, Washington, DC
- DuPont Circle in Washington, DC

These are the focal points where the “action” takes place in psychedelic shops, coffee houses, print and button shops, psychedelic theaters and “meditation rooms.” The action consists of meeting other hippies, buying or selling marijuana and other drugs, finding a pad where drugs can be taken undisturbed and, in general, participating in the activities of the hippies’ subculture.

**C.** Segregation is the third process and it is not along racial lines, but is rather determined by the hippie’s age, educational background and type of drug preferred.

- The Haight-Ashbury hippies clearly segregate themselves from the high school-age teeny-boppers from Berkeley.
- The N. Fairfax Avenue hippies in LA do not mix with the lower educational-level, hard narcotic user, homosexual hippies (pseudo-hippies) from the Sunset Strip area.
- The St. Mark’s Plaza-area hippies in New York seemed to be the more committed, genuine types, while the West Village hippies were mostly the pseudo- or plastic-type, engaged more in exploiting the busy tourist business than pursuing an enlightened hippie existence.

**D.** The fourth process, invasion, is the tendency of a socio-economic group, usually of lower status, to move into the territory occupied by another. The attempts of gangster-type elements to move in and disrupt the hippie community could probably be considered such an invasion. The signs of this were the flooding of the black market with LSD and methedrine mixed with heroin in an obvious attempt to “hook” hippies on hard narcotics (Dr. Meyers), and the murders of a hippie called “Superspade” in San Francisco in the summer, and Linda Rea Fitzpatrick and James (Groovy)

Hutchinson in New York's East Village hippieland in the fall of 1967.

E. An obvious and visible result of this invasion is the process of succession, as the original inhabitants of the areas are completely displaced by another type of group.

This process seemed to be in the making as news came about the symbolic "Funeral of the Hippie" in San Francisco's Golden Gate Park on October 6, 1967. A gray casket labeled "Summer of Love" and filled with beads, charms, peacock feathers, bread, flags, crucifixes and a marijuana-flavored cookie was set on fire as a shout went up: "Hippies are dead; now the Free Man will come through" (*Time*, October 13, 1967).

The hippie population, at least as of this writing (November, 1967), seems to be gradually disappearing from the center scenes. The pseudo-hippies went back to their parents and to school, and the plastic hippies went back to work or to study, but the real hippies, especially the artistic types, have begun to move out since the middle of the summer to the countryside to establish hippie communities in Marin, Sonoma and Mendocino Counties to the north and Big Sur to the south in California, and to the Santa Fe area in New Mexico, as well as to other areas of the country.

Other hippies, the "searchers," have started to establish their own psychedelic churches, partly as a means of keeping the movement alive, but mainly to avoid legal problems by declaring the psychedelic drugs to be sacraments. As of this writing, there are at least seven such groups: The League for Spiritual Discovery, Kerists, The Water Brothers, The Neo-American Church, The Church of the Awakening and the oldest of all in America, the Native American Church. The seventh was established by hippies who have moved to Kathmandu, Nepal (newspaper and magazine sources).

## WHY ARE THEY DOING WHAT THEY ARE DOING?

It seems that there are as many answers to this question as there are subgroups or even individuals in the hippie movement. I would like to offer only some random psychological and philosophical notes on the origin of the hippie.

The hippie's crucial claim of greater "awareness of reality and all that is taking place about him in nature, in life and society" after a "transcendental" experience with LSD or the other psychedelic

drugs brings up the validity of their awareness in relation to the generally-accepted concepts of “reality.”

The definition and meaning of objective reality has been a major epistemological controversy for many philosophical schools from Descartes through Kant, Bergson, Berkeley, James and others to Whitehead, Carnap and today’s existentialists.

For science, however, the most general definition of reality is that “it is the universe of discourse of a conceptual system that serves to correlate and predict, deterministically or statistically, the data of experience” (Lenzen, 1956).

The development of this scientific concept of objective reality is a long way from the “blooming, buzzing confusion” of the sense perception of a newborn by means of a long learning process to separate it from the subjective realities of dreams, visions, play and aesthetic realities which are mingled with objective realities in childhood and in primitive cultures (James, 1950; Piaget, 1959; Werner, 1961).

It has been borne out from several studies that LSD and similar drugs produce a regression of mental functioning to a primitive, childlike level, and I would like to examine some notions about the role of this naive thinking in the hippie movement.

Primitive thinking has been characterized as subjective, concrete and diffuse (Werner, 1961). I would like to elaborate on the concrete as opposed to the abstract of this type of thinking, because I feel it is very crucial in the immediate and perhaps lasting action of psychedelic drugs used so widely by the hippies.

Concrete reality is the three-dimensional outside world with which we are in contact through our five senses. We, as human beings, have learned to cope with this concrete reality by forming concepts and communicating with each other by a written or spoken system of symbols which constitute a language.

Thus, man created a conceptual world, which helped him to conquer nature, to fight his enemies, to search for happiness, and to discover the laws of nature, the nature of his fellow beings and of himself. Language, thereby, has become his second and foremost reality (Cassirer, 1955; Langer, 1948).

At the same time, language acts as a socially conditioned filter, meaning that experience can enter into awareness only if it can

penetrate the filter of language, logic and the socially conditioned content of experience (Fromm, 1960).

It is interesting to speculate on how this development from concrete to abstract has occurred, and how much of a role the ubiquitous physiological process of habituation plays in decreasing our awareness of three-dimensional concrete reality to the point where we perceive it only to the extent it fits into our abstract world of concepts and socially accepted norms.

Habituation is a very general phenomenon in the biological world and refers to the decreased responsiveness of the organism to monotonously repeated stimuli if they are not rewarded (Jasper, 1966).

Since this perception of the concrete world is rewarded (reinforced) primarily through our thinking process, which is entirely in the conceptual sphere of reality, the first will be habituated (suppressed until we become unresponsive to it) and the abstract conceptual world becomes our main reality.

Science and philosophy have evolved during our struggle for survival into our foremost abstract reality, comprising the organized set of laws, values and formal solutions to recurrent problems which probably has a very practical purpose: It shows us the way to act in order to decrease our anxiety. Art, religion and love have remained in our lives as the main links to concrete, three-dimensional reality, giving us delight, spiritual lift and happiness.

There seems to be ample evidence that psychedelic drugs block the process of habituation, making even repeated stimuli appear to have special significance and meaning to the user.

At the animal level, Key and Bradley have shown this with LSD rather conclusively (1960). At the human level, we can quote a series of observers, professional and otherwise:

During the drug state, awareness becomes intensely vivid while self-control over input is remarkably diminished; customary boundaries become fluid and the familiar becomes novel and portentous. Events take on a trajectory of their own; qualities become intense and gain a life of their own; redness is more interesting than what is specifically meant; connotations balloon into cosmic allusiveness; the limits of sobriety are lost. The very definition of the importance of the



external world shifts when most mental activity is absorbed either in monitoring the novelty of experience or in maintaining the integrity of the self. (Freedman, 1967)

The effect of LSD ... was ... to remove certain habitual and normal inhibitions of the mind and senses, enabling us to see things as they would appear to us if we were not so chronically repressed. Little is known of the exact neurological effects of LSD, but what is known suggests that latter possibility.” (Watts, 1967)

The same author, talking about “cosmic consciousness,” notes:

All that I have been describing is a subjective feeling. It gives no specific direction as to what is or is not a proper use of intelligence in varying the course of nature which must always be a matter of opinion and of trial and error. What it does give is what I feel to be a correct apprehension of the continuum, of the context, in which we are working, and this seems to me to be prior to, basic to, the problem of what exactly is to be done. Much as we discuss the latter question, is it really sensible to do so until we are more aware of the context in which action is to be taken? That context is our relationship to the whole so-called objective world of nature—and relationship as something concrete, as more than an abstract and theoretical positioning of billiard balls, is practically screened out of consciousness by our present use of intelligence.” (Watts, *ibid*)

An hour and a half after taking mescaline, Aldous Huxley (1954) found himself looking intently at a small glass vase:

The vase contained only three flowers – a full-blown Belle of Portugal rose, shell pink with a tint at every petal’s base of a hotter, flamier hue; a large magenta and cream-colored carnation; and, pale purple at the end of its broken stalk, the bold heraldic blossom of an iris. Fortuitous and provisional, the little nosegay broke all the rules of traditional good taste. At breakfast that morning I had been struck by the lively dissonance of its colors. But that was no longer the point. I was not looking now at an unusual flower arrangement, I was seeing what Adam had seen on the morning of his creation –

the miracle, moment by moment, of naked existence ... My eyes travelled from the rose to the carnation, and from that feathery incandescence to the smooth scrolls of sentient amethyst which were the iris. The Beatific Vision, Sat Chit Ananda, Being-Awareness-Bliss – for the first time I understood, not on the verbal level, not by inchoate hints or at a distance, but precisely and completely what those prodigious syllables referred to.” (Huxley, *ibid*)

When college kids read and hear reports like the ones quoted above, no wonder they sincerely feel they should confront an experience advertised to be so important. Some of them see the drug as an emotional fitness test, somewhat analogous to physical fitness. A “need to feel” – to gain access to themselves and others – and a pervasive sense of being constricted seems to characterize some of the college takers of LSD whom Dr. D. X. Freedman studied.

Anyone who has experienced this intense episode must come to deal with it, to integrate it somehow into the normal fabric of living. Some will borrow stability from ready-made explanations. Others will isolate the experience or set it aside in an attempt to master it, but they may end up with various pathological symptoms of a traumatic neurosis, delayed panic, depression or anxiety and be finally forced to seek professional help.

However, quite a few do not isolate the experience, but do search for synthesis either in various self-help groups, which appear to be peer groups, or in various religion-oriented groups which use the psychedelic drugs as sacraments.

In the hippie movement, there are quite a few self-help groups and religious groups which seem to fill the need for synthesis with more or less success. It is illuminating to read Dr. William McGlothlin’s comments on the role psychedelic drugs and certain social forces played in the development of the hippie movement:

The reason why the hippie movement has had such a sudden spurt in the last few months is that it has reached the point (particularly in California) where the subculture provides effective reinforcement of the drug-induced alterations of beliefs and values. The LSD trip provides a common ground on the experiential level which serves as the unifying principle for

hippie communities, and for thousands of otherwise strangers at hippie gatherings. In turn, the subculture both suggests and sustains the new beliefs, and acts as a buffer against the faith-eroding forces of the dominant culture. The advent of large-scale communities and gatherings has turned the phenomenon of isolated drug use into a full-fledged, self-reinforcing movement.” (McGlothlin, 1967)

## WHAT CAN OR SHOULD BE DONE ABOUT POTENTIAL PROBLEMS?

Several possibilities seem to be open:

**A.** Ignore them. Every century and every land has had its hippies, but by different names. There have always been way-out non-conformists, whirling dervishes, bohemians and beatniks living on the fringes of society, and they constitute but a very small fraction of the population.

But we cannot easily ignore today’s hippies for at least four reasons:

1. There is a segment of the hippie society which is clearly visible because of their unorthodox clothing and behavior, and because they often manage to stir up headlines (c.f. the recent Dame Margot – Nureyev – affair in San Francisco)<sup>8</sup>. Although they are peaceful, they are very much in evidence in most of our great cities.

<sup>8</sup>. Editor’s Note: This refers to an incident that took place in San Francisco in 1967 in which the famous ballet dancers, Rudolf Nureyev and Dame Margot Fonteyn, got ‘caught up’ in a hippie party-cum-riot outside the War Memorial Opera House following a performance of *Romeo and Juliet*. The incident was humorously recounted in the *San Francisco Chronicle* in April, 2016: The Great Haight Ballet Bust of 1967, authored by Bill Van Niekerken, library director of the *San Francisco Chronicle*. <http://www.sfchronicle.com/thetake/article/The-great-Haight-ballet-bust-of-1967-7230386.php#photo-9749248>

2. The visible segment – like that of an iceberg – is only a small portion of the large-city college and even high-school students (the estimates vary between 10% and 35%) who have experimented with psychedelic drugs.

Only a few of them have joined the ranks of the openly defiant hippies. The parents seem to have a certain feeling of guilt and continue supporting them.

3. The drug usage leads very often to medical and psychiatric emergencies which cannot be ignored by society.

Major emergencies are:

- Spread of venereal diseases.
- Frequent “freakouts,” or bad trips.

Minor in number but still serious emergencies are:

- Hepatitis from the use of unclean needles for injecting amphetamine-type drugs.
- Turning to “hard” narcotics (heroin).
- Occasionally longer-lasting psychotic reactions requiring hospitalization.

4. The usage of drugs might contribute to criminal negligence, e.g., driving an automobile under this influence. The gross distortion of perception may lead to accidents which would add to the already high rate of traffic fatalities.

**B.** There are several possibilities at the legal level which could be pursued to face the problems drug abuse by hippies creates, but it is not my duty to comment on these here.

**C.** More research is needed along the following lines if society is to meet the challenge of the hippies:

1. The uncontrolled use of drugs creates medical problems. More research is needed in toxicology and into the mechanisms of psychotropic drug action at the basic biochemical, physiological and psychological levels. Particularly promising would be the exploration of the biochemical and physiological mechanisms for the process of habituation, which may be specifically affected by the drugs used and could be the basis for the observed behavioral and psychological phenomena.

2. Research into the mechanisms of non-drug means by which people are being turned on. The induction of a trance-like state akin to hypnosis, apparently by “driving” subcortical structures with rhythmic sensory stimuli, may be a reflection of an effect upon the abovementioned habituation mechanism. There are potential medical dangers to which people should be alerted, for instance, deafness (due to the high volume of music) and psychological damage via distorted perception, etc.
3. Research in social psychology on the significance of changes in personality, changes in value systems and their role in making adjustments to the existing social order.

## OUTLOOK

Since hippies are a minority of the younger generation and are peaceful non-militants who do not want to overthrow the government but want to change its value system, they represent no immediate threat to society. They are mostly young, defiant members of the mainstream middle class society; and where there is serious concern, it is at the individual level.

Drug taking is a basic part of the hippie movement; consequently, there should be serious concern about the medical, psychiatric and possible genetic dangers which may result from careless drug usage. The obvious medical dangers will only slowly penetrate this subculture because of its deliberate isolation from the dominant culture and the essentially irrational mode of their thinking. It will take some time until the biological and economic necessities of life will force them to integrate into the mainstream of society. Nevertheless, a subtle, almost imperceptible change does seem to result from even occasional drug taking, which may have some significance.

One of the results of drugs like LSD is that a tremendous array of possibilities present themselves, which first overwhelm the subject and give a powerful subjective feeling of freedom in terms of choices

available. Since most of these possibilities have been suppressed by the traditions of culture, it is understandable that an impatience with traditional ways and values arises and a revolutionary, rebellious attitude emerges. However, a sober re-evaluation of the potential damage versus the potential gain after the drug wears off could convince many of the subjects about the time-proven wisdom of tradition and convince them to return to the fold of society.

A long way lies ahead in creating and disseminating information through research and education before intelligent decisions can be assured at the individual level. In the meantime, the widespread illegal and mostly uncontrolled use of psychedelic drugs creates some non-medical problems as well. A subtle rearrangement of the subjective value system of these young people might remain, and might play a part in future decision-making affecting both the individuals and the society.

It is within this changing system of values where the impact of the drug movement can best be seen, and it is very hard to predict the effects this change may have on the final outcome of the hippie movement itself and on the future of our established society.

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# AYAHUASCA & THE AMAZON

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# *Ayahuasca*: A Powerful Epistemological Wildcard In a Complex, Fascinating and Dangerous World

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*Luis Eduardo Luna, PhD*

Wasiwaska Research Center for the Study of Psychointegrator Plants, Visionary Art and Consciousness  
Florianópolis, Brazil

## INTRODUCTION

*Yagé* and *ayahuasca* are the best-known preparations made of *Banisteriopsis caapi* Spruce ex. Griseb (Morton), a giant Malpighiaceae vine, which in the wild can climb through the forest up to 40 meters or more. It flowers in the canopy among other climbers and epiphytes. The terms *yagé* and *ayahuasca* are used to refer both to the preparations and to the *Banisteriopsis* vine itself. *Yagé* is made by adding the leaves of another Malpighiaceae vine, *Diplopterys cabrerana* (Cuatrecasas) B. Gates. This combination is used in the Colombian and Ecuadorian Amazon. *Ayahuasca* is prepared by adding the leaves of *Psychotria viridis* Ruiz & Pav., of the coffee family (Rubiaceae), to *B. caapi*, and is used in the Peruvian, Brazilian, Bolivian and Ecuadorian Amazon, where it coexists with *yagé*. In fact, indigenous and *mestizo* practitioners consider *P. viridis* the principal ingredient, with the other plants such as tobacco being possible additions. Some indigenous groups use the vine by itself. Anthropologists working in various areas of the Amazon have reported myths of origin of this plant, but not of the admixture plants (cf. Luna & White, 2016), probably indicating that the use of *Banisteriopsis caapi* alone is the most ancient one. In some areas, the vine is used as a tool to learn the properties of other plants, or ‘to get to know their spirits’ (Bristol, 1965; Luna, 1984). Indigenous and *mestizo* practitioners also recognize several “kinds” of the main vine, using taxonomic distinctions not yet

studied by Western ethnobotanists.

This chapter is mainly focused on *ayahuasca*, although the preparation has to be understood within a much larger historical context of South American visionary plant knowledge and experimentation. Constantino Manuel Torres presents convincing evidence for this in his chapter in this book. It is also important to take into account that the pre-Columbian Amazon had larger populations than was previously thought, organized in great part through societal networks of diverse complexity, with extraordinary plant and soil knowledge (Heckenberger & Góes Neves 2009; Erikson 2014). Amazonians were the creators of *terra preta*, the extremely rich, charcoal-based, anthropogenic soils found in many areas. Contrary to other civilizations, Amazonians actually improved their environment, probably contributing to its biological diversity (cf. Tindall, Apffel-Marglin & Shearer, 2017).

During the last three to four decades, *ayahuasca* has moved from being almost hidden among indigenous and *mestizo* healing rituals to becoming the central player in a burgeoning number of religious, spiritual and therapeutic centers with worldwide distribution (cf. Labate & Jungaberle 2011). Few who take it remain indifferent to it, provided that the setting is safe, that the brew is well prepared and that enough of it is ingested. This explains the attention *ayahuasca* is getting in the media, the many popular and scientific publications and the conferences and symposia in full or part dedicated to this preparation. *Ayahuasca* is also embedded within a larger contemporary resurgence of interest in plants, fungi and substances that possess remarkable effects on human cognition. Depending on one's own cosmology, *ayahuasca* may be conceived as an intelligent entity, a gift of nature conveying messages from the biosphere, a portal to spiritual dimensions, or an agent of cognitive shamanic transformation. It is at least a complex alkaloid cocktail with extraordinary physiological, perceptual, emotional and cognitive properties, an astonishing tool for the study of the human mind-body connection. The phenomenology of the *ayahuasca* experience, similar to other psychedelic agents, challenges our ideas of identity, consciousness and reality itself. For some, it amounts to revelations of dormant unsuspected visionary worlds. For others, it may elicit significant insights, bring vivid memories, enhance perception or

improve performance. Some may find resolution to mental or physical ailments, yet others may plunge into confusion – particularly if it is taken under poor guidance – or succumb to narcissistic behavior. The experiences may reinforce one's beliefs or shatter them. They may intensify the feeling of awe at the mystery of temporality, or may be rendered nearly ineffective due to repetition and dogma. *Ayahuasca* experiences may also increase fully-sensed body-and-mind awareness of the current perils of environmental destruction, nuclear disaster and social turmoil.

## GLOBALIZATION OF AYAHUASCA:

### POINTS OF DISPERSION

There have been two main areas of dispersion of *ayahuasca*: the Peruvian Amazon, especially around the cities of Iquitos, Pucallpa, Tarapoto and Lamas, in the so-called vegetalista tradition (Chevalier, 1982; Luna, 1984ab, 1986, 2011; Beyer, 2009; Barbira-Freedman, 2014); and the Amazonian states of Acre and Rondônia in Brazil, where highly syncretic religious organizations, created by leaders originally from the Brazilian Northeast, adopted *ayahuasca* as a sacrament. A third, less well-known point of dispersion has been the Putumayo area in southern Colombia. Indigenous practitioners of various ethnic groups (Kamentsá, Inganos, Siona, Kofán, Coreguaje) at some point started to travel and work as healers among the *mestizo* and white population via the Sibundoy Valley and the city of Pasto.

My own discovery of *yagé* is linked to this tradition. Apolinar Yacanamijoy, an Ingano originally from the Putumayo, moved to Yurayaco, about sixty kilometers from Florencia, the capital of the Department of Caquetá in the Colombian Amazon, where I was born. As he used to go to the city from time to time, I had seen him since my childhood. In 1971, when on holiday in Colombia after an absence of seven years in Spain and Norway, I met Terence McKenna and his partner at that time, Erica Nietfeld, both Americans. Through Hans Herbert Mosler, a German citizen who had a restaurant in town, we met Kálmán Zsabó, whom we all called “Carlos,” a Hungarian living in the Colombian Amazon. He was in contact with Don Apolinar, who gave him some *yagé*. The four of us

took it in my family's humble country house (cf. Luna, 2016).<sup>9</sup> This meeting was one of the early stages of the globalization of *yagé/ayahuasca*.

**9.** I wish to express here my gratitude to Mr. Mosler, still living in Caquetá, who provided me with Carlos' full name. He also mentioned Frans Wolloch, another Hungarian interested in *yagé* at that time. According to Mr. Mosler, he had been with the Hungarian Olympic team in Berlin in 1936, escaping as a refugee when the games were over. Both Hungarians are now deceased.

Peruvian psychologists and psychiatrists had written about *ayahuasqueros* operating in the Amazon region of their country, but their work was not translated into English and thus had little international impact (Del Castillo, 1982; Chiappe & Costa, 1979; Lemlij & Millones Santa Gadea, 1985). American anthropologist Marlene Dobkin de Rios wrote about *mestizo* practitioners living in Iquitos (1970ab, 1971ab, 1972, 1973), but her early work remained mostly confined to anthropological circles. Something similar happened with my own early work (Luna 1984, 1986) until 1991, when *Ayahuasca Visions: The Religious Iconography of a Peruvian Shaman*, which I co-authored with Peruvian painter and former *vegetalista* Pablo Amaringo, was published. Some researchers claim that this book is largely responsible for the initial international surge in interest in *ayahuasca* (Beyer, 2012; McKenna, 2013), and the subsequent flow of foreigners to the Peruvian Amazon.<sup>10</sup> Amaringo's paintings were presented in the book within a cultural context that included the basic Amazonian ideas of diet and isolation in order to "learn from the plants," which became part of the subsequent assimilation of *ayahuasca* by Westerners.

**10.** I am referring here only to the anthropological literature concerning *mestizo vegetalismo*. There were, of course, publications of anthropologists working with indigenous groups using *yagé* or *ayahuasca*, such as the Tukano (Reichel-Dolmatoff, 1970, 1972, 1975, 1978), the Yagua (Chaumeil, 1983), the Siona (Langdon, 1979ab), the Kofán (Robinson, 1976), the Matsigenka (Baer, 1984), the Aguaruna (Brown, 1978), etc.

The second most important point of dispersion of *ayahuasca* is located in the Brazilian Amazon. Three religious leaders who arrived in this area from the Brazilian Northeast created syncretic Brazilian religious organizations in which *ayahuasca* was incorporated as a sacrament. Raimundo Irineu Serra (1892–1971) in the thirties, and Daniel Pereira de Matos (1904– 1958) in the

forties, created in Rio Branco, the capital of the State of Acre, organizations that called the brew *Santo Daime*. José Gabriel da Costa (1922–1971) created in the sixties, in Porto Velho, capital of the State of Rondônia, the UDV (*União do Vegetal*). He called *ayahuasca Vegetal*, a term that shows its link to the Peruvian *vegetalista* tradition.

These religions present an amalgam of elements from various traditions. Afro-Brazilian components are particularly evident in the religions created by the first two leaders, especially in the case of Daniel Pereira de Matos, who created a *Barquinha* (the small boat), a new religious organization mostly restricted to the State of Acre. He was heavily influenced by *candoblé* and *umbanda*, Afro-Brazilian religions with mediums that incorporate entities: *pretos velhos* (spirits of black slaves), *caboclos* (Indians), *erés* (children), and *encantados* (princes and princesses incarnated in plants and animals). Popular Catholicism is also a very important element, with the profusion of images of Jesus, Mary and various saints, and the recitation of hymns and prayers. In the case of José Gabriel da Costa, who created the UDV (*União do Vegetal*), Afro-Brazilian elements as well as those from popular Catholicism have been eliminated. All of these religions have been influenced by *kardecism*, a religion based on the books of French spiritualist Alan Kardec (born Léon Denizarth Hippolyte Rivail) (1804–1869), and also by various organizations linked to European esoteric traditions cultivating meditation and telepathy. All of these religions believe in reincarnation. Amazonian elements, apart from the use of *ayahuasca*, are minimal. The standing of Amerindians in the church's understanding of its history is either practically ignored or, in the case of the UDV, relegated to an inferior position in its mythology. Dancing is a prominent element in some of the rituals of the organizations that use *Santo Daime*. This is not so at all in the UDV, in which “the power of the word,” the oral discourse of the religious leader under the effects of *Vegetal*, has predominance. In terms of organization, regarding those using *Santo Daime*, political power is based on the charisma of their leaders, with the succession going to their kin, while in the UDV, leadership is elected. The UDV is organized across a four-tier hierarchical structure, the upper level not accessible to women.

Disagreement about secession arose after the death of Irineu Serra, resulting in a split and the formation of a new congregation led by Sebastião Mota de Melo (1920–1990). This is the branch of *Santo Daime* that has expanded most, with communities in Europe, North and South America and Japan. The UDV is also present in many countries worldwide. According to Alex Polari, one of the main leaders of the branch that follows the doctrine of Sebastião Mota, there are now around 10,000 members drinking *Santo Daime*, not including transient participants that take the brew here and there (personal communication). Without having access to clear data, he believes that the members of the UDV should be around twice this number.

The third most important point of dispersion of the *Banisteriopsis* complex is linked to the healing activities of various indigenous practitioners, or *taitas*<sup>11</sup>, of the Putumayo-Caquetá in the Colombian Amazon. They worked first among the lower classes of the Putumayo and other areas, and from the nineties also among educated middle-high-class people, especially university students of the city of Pasto (capital of the Department of Nariño) and other Colombian cities. White and *mestizo* practitioners initiated by indigenous shamans, such as Pacho Francisco Piaguaje (Siona) and Martín Agreda (Kamentsá), created *malocas* near Pasto in which a growing number of Colombians as well as foreigners participate in rituals, some heavily influenced by Catholicism, but stressing always their indigenous roots (cf. Pinzón & Suárez, 1991; Taussig, 1987; Weiskopf, 2004; Caicedo Fernández, 2014).

<sup>11</sup>. A Spanish colloquial term meaning ‘Dad’ or ‘uncle’. A term of respect and endearment.

Engineer and prominent politician Antonio José Navarro Wolf, Governor of Nariño during 2008-2011 and currently a senator, took *yagé* with *taita* Querubín Queta Alvarado (Kofán). One of the results of his experience was the motivation to organize in 2009 the First International Encounter of Andean Cultures, with the active participation of numerous representatives of various ethnic groups. This was dedicated in great part to Amerindian traditional medicine, including the use of *yagé*. Well-publicized subsequent meetings took place in 2010, 2011 and 2014, all with the presence of *taitas* and shamans from various countries, as well as high-ranking

official representatives. The program included not only academic presentations and exhibitions, but also ceremonies with *yagé*, *yopo* (*Anadenanthera peregrina* (L.) Speg.), *peyote* and sweat lodges, or *temazcals*, from North American indigenous traditions.

## AMAZONIAN ANIMISM AND EVOLUTIONARY COGNITION: AN APPROACH TO CLOSING AN EPISTEMOLOGICAL GAP?

In Amerindian cosmology from Alaska to Tierra del Fuego, and especially in Amazonian cultures, humans are not the only persons on this planet. They share personhood with certain animals, plants and non-living objects and processes (winds, whirlpools, etc.) endowed with intention, volition and therefore subjectivity. Humans are not unique or special: They have to establish complex social relationships with other subjects, such as the master of animals, the master of fish, the master of the plants in a garden, or the “soul” of any particular species. There is therefore no clear distinction between nature (“out there”) and culture, the world of the human and their institutions and symbols. Moreover, these subjectivities see themselves as human, appearing to us – or to other species – in their animal (or *vegetal*) clothes. At the same time, they see us as animals (predators or prey). Eduardo Viveiro de Castro (2005) calls this “perspectivism,” which includes the idea that non-humans see their world as humans see their own world. Instead of multiculturalism, Amerindians would think in terms of multinaturalism.

A shaman has a special relationship with non-human entities: he/she is able to perceive them as they perceive themselves, as anthropomorphic. He/she is even able to transform into one of them, for instance a jaguar, an idea found not only in the Amazon, but also in the whole of Central and South America (Reichel-Dolmatoff, 1975; Stone, 2011). In mythic time, all animals were humans. The process of speciation was a process away from humanity, although the humanity of plants and animals is still perceptible through certain epistemological techniques – that is, through trance, dreams or illness. If, from the point of view of evolutionary biology, humans share with animals their animality, in

Amerindian thought animals share with us their *humanity* (Viveiro de Castro, 2005). This is a radically different way of dealing with other species: Amazonian hunters, for example, often refer to their prey as “brother” or being other kin, and their relationship with the animals they hunt is one of respect (Descola, 2005). The disruption of the life-energy flow for no reason is a transgression: Killing an animal and not eating it, or cutting a tree and not using it, may result in illness (cf. Reichel-Dolmatoff, 1971, 1976).

Form seems to be fluid in Amazonian thought. A certain animal may appear as another one; it may take “different clothing” to deceive humans or other animals. A forest spirit may take the shape of a hunter’s relative to attract him and trick him into getting lost. As Evgenia Fotiou points out in her chapter in this book, plants are taken to imbue the body with certain properties, to “construct” the body. Plants are taken to strengthen and refine perception, and to transfer to the body certain qualities from non-human persons. Shepard (2011), for example, reports that the Matsigenka take a certain mushroom-infected *Cyperus* to transfer to the hunter the predatory abilities of a harpy eagle (chemicals in the fungi may have physiological effects, such as giving the hunter sharper vision, or other properties). Fotiou gives other relevant examples in her chapter in this book. Don Emilio Andrade Gómez, my *mestizo ayahuasquero* teacher, said that *ayahuasca* is among the plants one should take in order to become strong, *para ser fuertes y mantener la mente despejada* (“to be strong and keep the mind clear”). Another expression often used by *ayahuasqueros* is to *limpiar y cerrar el cuerpo* (“cleanse and protect the body”), so that no illness gets through. Interestingly, a physical and visual motif many people report is that of being “scanned” with invisible hands, and of spirits, small serpents or other animals going through the body, stopping at specific parts and taking away illnesses. In the Amazon, dieting with plants, often in isolation, is equivalent to getting allies, to maintain a strong body and mind and to be able to learn from them through songs that need to be sung perfectly in order to later use them in healing ceremonies. For practitioners this is especially important, given that illness is believed to always be caused by an agent – be it human or spiritual. Healing requires either a confrontation with this agent or an arduous inner journey to restore the soul(s) of



his/her patient.

In some cases, the invocation of plants and animals would suffice for this transferral. A shaman may summon an armadillo to transfer the strength of its legs to a child having difficulties with starting to walk; slippery animals or plants may be called to transfer this quality to a woman giving birth (Luna, 1992). Claude Lévi-Strauss, in his analysis of an indigenous ritual, attributes the efficacy of healing to a *psychological manipulation* of the symbols, an *inductive property* by which “formally homologous structures, built out of different materials at different levels of life – organic processes, unconscious mind, rational thought – are related to one another. Poetic metaphor provides a familiar example of this inductive process, but as a rule it does not transcend the unconscious level. Thus, we note the significance of Rimbaud’s intuition that metaphor can change the world” (Lévi-Strauss, 1949:225).

Western science tries to totally disengage the subject from the object he is studying, even when that object is his own brain. The Amerindian way is to approach the subjectivity of the object, even identifying or transforming (cognitively) into it (the basis of shamanism). The idea that *ayahuasca*, other plants (especially large trees like the giant *Ceiba*) and animals are sentient is found in the three main areas of diffusion of *ayahuasca*. In the Peruvian Amazon, where I conducted fieldwork in the early eighties, animistic ideas are very much present (Luna, 1982, 1984, 1986). Don José Coral, another one of my teachers, pointed one day at the bubbles boiling on the surface of the *ayahuasca* being cooked. He said to me: “These are people.” One may hear practitioners asserting: “The plants are our university.” I found similar ideas in the Sibundoy Valley, where a young *mestizo* refers to the medicinal garden of his Kamentsá teacher Miguel Sibundoy as *el jardín de la ciencia* (the garden of science). In the *Santo Daime* tradition created in the State of Acre in the Brazilian Amazon, the sacrament is called *o professor dos professores* (the teachers’ teacher). Former *vegetalista* and painter Pablo Amaringo excelled in making extraordinary depictions of all these motifs in his astonishing creation of inner realms.

One may wonder if any of these cosmological ideas are absorbed

by Westerners – informed as they are by their individual cultural and personal histories and with no common coherent worldview – when they go to the Amazon to take *ayahuasca*, or when they take it in various settings all over the world. Surprisingly, the idea that *ayahuasca* is a sort of “mother,” “grandmother,” or “grandfather” is quite common, as one can see in reports of various kinds in the media. Often one hears statements such as “*ayahuasca* told me.” I personally have gathered hundreds of statements after ceremonies from people from many countries and professions. I am amazed how many of them spontaneously and without apparent indoctrination refer to *ayahuasca* and other plants as volitional subjects, as teachers. Of course, people trained with indigenous or *mestizo* practitioners often accept at least some of the views of their teachers. But even therapists working with this medicine openly refer to *ayahuasca* as kin, or as a spiritual entity (cf. Harris, 2017).

There is no doubt the states of consciousness elicited by this preparation predisposes one to animistic ideas. This may of course have practical consequences. From a purely cognitive point of view, it is perhaps difficult to fully accept the rights of plants and forests as sentient beings. But emotionally-charged experiences with psychedelic plants or substances can do the trick. Given our current state of the world, with impending ecological disasters nearly everywhere, and with little comfort in the idea that we are alone as a conscious species, it is not surprising that some may have the urge to seek company, as our ancestors did, and invoke Gaia, Pachamama, Mother Earth, etc. as an entity that protects us and that also needs respect and protection. It is existentially uplifting to “feel” the world as one teeming with intelligence.

This is what prominent biologists in the field of evolutionary cognition are saying. The study of nonhuman intelligence is gradually coming to the fore, thanks to the work of scientists like Frans De Waal, who titled his latest book *Are We Smart Enough to Know How Smart Animals Are?* (2016). Only people who have never had pets or any close contact with animals may have difficulty assigning “personality” to them. The same is true not only of animals, but also of plants, as plant-behavioral biologists and ecologists are discovering: Plants are able to learn; exhibit memory; take decisions; react to the environment, nutrients and predators;

show neighbor avoidance and plant competition; communicate with other plants through mycorrhizal networks; interact with the soil; and even take care of their offspring or transfer nutrients to plants of different species. This has been proved through experiments, for example giving radioactively labeled carbon to a tree and detecting it in independently growing saplings around them. (cf. Simard, 2009; Mancuso & Viola, 2013; Wohlleben, 2015; Gagliano, 2015; Vieira et al., 2017). It is, of course, difficult to recognize behavior in plants in our everyday experience, because plants operate at a different time scale than we do: We are not wired to recognize minute or extremely slow movement, and anyway much of it takes place out of our sight, whether under the ground or in the canopies. Plants move slowly and communicate through chemistry or even acoustically, processes mostly undetected by us (Gagliano 2012, 2013). Might it be true that not only animals but also plants have some sort of internal horizon? Could shifts in consciousness affect our perception in such a way as to make us sensitive to such signaling? This is what some indigenous societies say happens under appropriate conditions (cf. Callicott, 2013).

Philosophers, scientists of various disciplines, artists and religious leaders are increasingly discussing animism, posthumanism, panpsychism, the priority of consciousness and related ideas. Animism may have been the original cosmology of most cultures, and still is in some parts of the world. World religions have been fighting it fiercely. Going back to animistic thinking is perhaps a necessity, as most of humanity has been severed from direct contact with these other *persons* with whom we share this precious and limited planet. In any case, animistic ideas are pragmatically much better than the current radical separation of nature and culture, with nature being simply instrumental to our own needs and composed of objects to be exploited commercially. In this critical situation, we need to look without arrogance into the philosophical repository of ideas of the past and of other cultures and to try and find solutions.

### AYAHUASCA, A MIND-BODY PUZZLE

The extraordinary visionary and cognitive effects of *ayahuasca* have taken precedence in the general public over its physiological

ones. However, recent research is concentrating on the physiological effects not only of the brew as a whole, but also on the alkaloids present in it: DMT (Frecska et al., 2013), and various beta-carbolines (cf. Riba et al., 2002, 2003, 2004, 2006). Dale Millard in this book makes a detailed review of the extraordinary multifunctional effects of harmine, the main alkaloid in *Banisteriopsis caapi*. It is intriguing that the same molecules that have such an important role in the immune system are also responsible for such powerful cognitive effects, an indication of the deep body-mind relationship.

Shanon (2000: 18), working mostly with non-indigenous people (and with himself), was the first to point out that *ayahuasca* seems to “improve performance”: technical agility, accuracy, motor coordination and aesthetic delicacy, something I have also heard from practitioners and regular users of the brew in various settings. If *ayahuasca* improves your talents, whatever they are, then there must be a common underlying neurophysiological or psychological mechanism that needs to be investigated.

One area in which clear improvement is often felt is musicality. Many claim to have developed their musical capacities, or at least to have increased their musical sensitivity. A great number of current practitioners of *ayahuasca* sessions sing and play instruments. This is interesting, taking into account that learning *icaros*, magical songs or melodies to communicate with nonhumans and to exercise healing or malevolent power, is one of the essential elements in the process of becoming a shaman among indigenous and *mestizo* practitioners (Luna, 1986, 1992b, 1995; Beyer, 2012; Callicott, 2013; Bustos, 2016), who strive to establish performative ontological relationships with nonhuman persons (Brabec de Mori, 2011, 2015). Also of great importance are the *hinos* and *chamadas*, the songs “received” by members of the Brazilian organizations that have *ayahuasca* as a sacrament, in which doctrinal aspects and teachings are embedded (Labate & Pacheco, 2009).

Enhanced perception and observation may also play a role in the diagnosis of illnesses by practitioners, perhaps in the form of a greater capacity to receive factual information – as good doctors and therapists do – from small visual and psychological clues. *Ayahuasca* facilitates mental associations and the creation of

symbols and metaphors during the exchange with the patients, a language “by means of which unexpressed, and otherwise inexpressible, psychic states can be immediately expressed,” as Lévi-Strauss (1958: 198) wrote, referring to shamanic healing in general.

Perhaps one of the roles of contemporary Western *ayahuasca* facilitators is to help participants generate and interpret their own mythology and to identify with the appropriate archetypes, in order to regain strength and restore order and meaning to their lives. The cause-effect mode of healing, perceived as external, is in many cases less effective than the emotionally-charged mythopoeic process that affects the body and the mind simultaneously.

An area of great potential is to use *ayahuasca* as a tool for problem solving, whatever the problem’s nature. The “afterglow” of the *ayahuasca* experience – around 3-4 hours after ingestion – is particularly interesting. It is a time in which the spirit is calm and the mind receptive to active imagination and creativity, a time propitious to cement the insights one has received during the session. Most people report a remarkable feeling of well-being after the ceremonies, which may last for some time. A recent study shows that *ayahuasca* reduces anxiety and promotes mindfulness even two weeks after a session (Sampedro et al., 2017).

It is almost unthinkable today, given the view of most people about these matters, to use these particular states of consciousness to discuss matters of great political and international importance. Yet I envision groups of people working on specific problems, symposia taking place, in the afterglow of *ayahuasca* experiences. Political leaders, religious and medical authorities, powerful business people, artists and philosophers could use their transcendent experiences to try to solve the impending problems humanity is facing in our times. It is perhaps unrealistic to imagine that this will happen soon, or naïve to expect that automatic consensus would be reached simply by taking the brew (a proof that this is not so is manifested in the various competing Brazilian religious institutions that share *ayahuasca* as a sacrament). But if attention is shifted from the strictly “visionary” aspects of *ayahuasca*, of which many are afraid, to the medicinal and psychological ones, a better understanding of the possibilities of this

extraordinary preparation will gradually emerge. More and more influential people, although it seems so far only in the Western countries, are having extraordinary experiences and insights with *ayahuasca* and other such preparations and substances. Some of them are trying hard to show its many positive aspects and making a difference.

## NATURE

Many people claim to rediscover their connection with nature during *ayahuasca* sessions, the deep realization of our commonality with the rest of life. This is especially so with urban dwellers, who may have forgotten the magic of the night and the miracle of the breaking of dawn. Adopting environmental practices, raising ethical questions related to animal food consumption, getting involved in sustainable projects and the feeling of bonding with other people or with life in general (biophilia) are some of the results for those who are deeply touched by their experiences with the brew, often described in mystical or spiritual terms. In many cases, people say they feel as if they had gone “home,” as if these astonishing unsuspected inner realms were somehow totally natural, something forgotten, something that we may have experienced when we were children.

While humankind is making extraordinary advances in understanding the nature of the physical world and the depth of time, we are under the imminent threat of total annihilation of higher complex life due to environmental degradation and the permanent risk of nuclear cataclysm. Like the frog being heated slowly and not realizing that she is being cooked alive, we witness the gradual destruction of our environment as if it were a totally natural process. More than ever, we need creative thinking and imagination to determine ways we might come out of the terrible mess that our proud “civilization” has put us in.

Experiencing unity with other human beings, with the Earth or even with the cosmos may give a higher perspective on the mystery of existence, enhance solidarity and help to overcome the limitations of cultural identifications. When describing their experiences with *ayahuasca*, many use the word “love” to express them, extending to other human beings and the whole of nature.

Within religious communities, the concept of “brotherhood” or “sisterhood” is often uttered. This may also happen in nonreligious therapeutic or exploratory circles. Bonding is perhaps one of the most striking consequences of taking *ayahuasca* within a group, something often more effective than with isolated experiences.

## INNER WORLDS AND CREATIVITY

In our mostly urban and technical contemporary world, exploration of the natural environment is generally limited. However, the positive exploration of inner worlds is open to nearly anyone if the circumstances are right (appropriate set, setting and integration), and may be a source of awe and inspiration. *Ayahuasca* is one of the instruments that may open the gates of the “imaginal,” that cognitive aspect of consciousness beyond simple cognition and “imagination.” Jeffrey Kripal, not referring specifically to psychedelic experiences, conceives “the possibility that, in very special moments, the human imagination somehow becomes temporarily empowered or ‘zapped’ and functions not as simply a spinner of fantasies (the imaginary) but as a very special organ of cognition *and* translation (the symbolic) as a kind of supersense that is perceiving some entirely different, probably inhuman or superhuman order of reality but shaping that encounter into a virtual reality display in tune with the local culture” (Streiber & Kripal 2016).

*Ayahuasca* experiences are to a great extent the product of co-creation (Shanon, 2002; Luna, 2016). Our personal experiences and memories (at times extremely vivid), our aspirations and desires, interplay with something in us of which we are mostly unaware, and which may emerge effortlessly from a hidden dimension in a swift, elegant way, independent of our own volition. During the *ayahuasca* experience, the person is navigating between insights and projections, mind-wandering and mindfulness. Information stored in the mind seems to be at times readily available for reappraisal and integration, and rich narratives unfold while we try to make sense of them by trying to recognize and interpret their various components. Even if the process is interrupted by putting the attention onto the external world or by letting the mind wander into normal thinking, when the attention goes back to the inner

world, a new narrative may unfold.

*Ayahuasca* may provide states of consciousness in which things lose their boundaries. The person may enter a fluidity in which the borders between the individual and the social, the inside and the outside, between wakefulness and dreaming, are eroded. Elements from normal reality may be embedded in the vision, or our fears of war and ecological disasters may play out. Indigenous people may see cities, pharmacies, doctors and so on; and Westerners may see Indian villages, jaguars and serpents. Idiosyncratic worlds may be constructed with repetitive experiences, or when the sessions are embedded within particular worldviews (Luna, 2016:261). On the other hand, it may happen that during the *ayahuasca* experience, perceptions may go undetected by the “central” ego-mind, so that at the end only dim memories of the experience may remain.

Humor, “a gentle form of transcendence” (Jeffrey Kripal, personal communication), seems to be embedded in some of the *ayahuasca* experiences. I can attest to it. On one occasion during a session, I was seeing the usual extraordinary visions. I was wondering, “What is behind it all?” My point of view then shifted. I was taken gently behind a huge screen on which “my visions” were projected, held up with great effort by small, strange creatures. On another occasion, I was in one of those extraordinary worlds. I lifted my gaze and I could see small windows up high from where I was being watched, like a guinea pig, by what looked like scientists. In yet another session, after another fantastic display of visions, credits played like in a film, moving from bottom to top, although too faint to be able to read the names. These are the kinds of jokes my mind is playing with me.

## DANGERS AND PITFALLS

So far, I have presented a rather rosy picture of *ayahuasca*. But like everything that is of value, there are also problems involved. First of all, the growing demand for *ayahuasca* may lead to overharvesting of the plants. Michael Coe, working on his doctoral dissertation for the University of Hawaii, now in the field in the Peruvian Amazon, sent me the following provisional report:

There is anecdotal evidence to suggest that there has been



increasing scarcity of both *Banisteriopsis* and *Psychotria*, notably around the city of Iquitos, where prices are increasing for both plants due to demand linked to an estimated 200 retreat centers in the area and to its export out of the Amazon. In addition, it has been suggested that within a 130-mile radius of both Iquitos and Pucallpa, it has become more difficult to find wild populations of *Banisteriopsis* and *Psychotria*, indicating that harvest regimes are likely focused in areas further into the jungle. There is the concern by communities who have adopted a management plan that unauthorized harvest is occurring due to settlers in the area and to increased economic interests associated with *ayahuasca*. There is also potential for collateral damage with respect to *Banisteriopsis* harvests, as the companion plants (often large trees) have sometimes been cut down in order to gain access to the vine. It can take anywhere from 5 to 10 years before the vine is mature enough to harvest for preparation of *ayahuasca*, depending on soil, water and light conditions. Potential for sustainability is, on the other hand, likely to occur if mindful management practices are employed by *ayahuasca* retreats/centers, planting enough *Banisteriopsis* and *Psychotria* to meet the demands of harvest pressure and consumption. In addition, relationships built on reciprocity (i.e., living wages) with respect to working with communities who actively manage, grow, and harvest these plants are essential to long-term sustainability, especially when these cultural communities may provide *Banisteriopsis* or *Psychotria* for practitioners that live in areas where the plants may not grow due to biotic and abiotic factors.

*Banisteriopsis* is on the other hand an ideal high-value agro-forestry species, although not suited to be a monoculture. It is best planted in association with fast-growing pioneer species of trees. It has enormous potential to produce large amounts of biomass for recuperation of poor soils through falling leaves and twigs. The large root system is composed of fine roots that bind the soil and prevent erosion. It is capable of growing in many different soil types and therefore could grow in deforested and eroded areas damaged by cattle (Dale Millard, personal communication).

A second problematic area regarding *ayahuasca* is, of course, how it is used. Among indigenous and *mestizo* communities, a long and arduous apprenticeship is required to deal with this preparation. But as Peluso (2014, 231) points out, the globalization of *ayahuasca* is bringing together individuals with very divergent epistemologies and experiences, with the possibility of contradictions and misunderstanding. There are now probably hundreds of practitioners – Amazonian and non-Amazonian and with very different backgrounds – leading ceremonies of some kind, often without having undergone proper training or having acquired sufficient personal experience. For some, the experiences are such that they feel the urge to tell others about it, take practitioners to their countries or even take the great responsibility of dispensing the medicine themselves. It is easy to yield to the temptation to “initiate” other people without enough personal experience and basic pharmacological and psychological know-how. I know examples of young people who, after having spent a relatively short time in the Amazon, call themselves “shamans.” They may have followers eager to experience and learn from them, but they are unaware of how delicate it is to deal with the peculiar states of consciousness elicited by the brew. Facilitators need continuous training and a broad education to be able to more effectively help others in their explorations. One is dealing with the innermost depths and heights of other people, and with the mysteries of the human mind. That is sacred. Hopefully, there will be a gradual integration of psychotherapy and pharmacology (Sessa, 2012; Lattin, 2017; Richards, 2015), but no academic or religious qualification guarantees that *ayahuasca* will not be misused by some. Integrity and a humble attitude are needed, as well as sufficient personal experience (“flight hours,” in the language of pilots).

There are, unfortunately, also cases of people who need urgent therapy after participating in *ayahuasca* ceremonies that have minimal reintegration procedures. Regardless of setting – religious, therapeutic or “shamanic” – ego inflation is always one of the greatest dangers when dealing with this preparation (Luna, 2016:275-7).

There are external dangers as well: misunderstandings, prejudices,

ignorance and persecution, as *ayahuasca* is still illegal in some countries due to its DMT content. An exemplary negative case is that of France, in which all the components of *ayahuasca* and *yagé* have been made illegal, both the plants and the alkaloids. On the other hand, because *ayahuasca* is such a powerful substance, there is the danger of a rush towards trying to control it, either in the name of religion or through strict medicalization. What is most needed is interdisciplinary education so that we can all learn from many sources, from indigenous practitioners as well as from therapists, scientists, artists and philosophers. This is already happening, as proved by the many meetings either totally dedicated to *ayahuasca* and other psychotropic plants or substances, or at conferences where *ayahuasca* has also found a niche.

### FINAL REMARKS

*Ayahuasca* experiences are, for many, epistemologically challenging, obliging one to accommodate within one's worldview the evidence that reality seems to be much more intricate than had previously been deemed possible. Such fundamental concepts as time and space are perceived in a different way. Experiences of multidimensionality are common. There are many anecdotal reports of such phenomena as precognition and apparently telepathic episodes by seemingly "down-to-Earth" people that are impossible to comfortably ignore. One of the main indigenous uses of *ayahuasca* is for divination: locating game, seeing faraway places, finding the cause of illnesses, etc. In the past, it was even used to learn about the plans of the enemy in times of war. This amounts to obtaining information from the outside via the inside (Frecska & Luna, 2007). It is necessary to go beyond traditional scientific (and religious) paradigms. We need a radical empiricism that has no qualms about dealing with alternate states of consciousness, regardless of how awkward it is to write or talk about such things. We are really navigating in unknown – perhaps unknowable – waters, but we have to make an effort to know, with the best of our scientific tools as well as with introspective and meditative techniques developed by other cultures. We need to have the courage to investigate first-hand, with our own consciousness as part of a variety of methods, the vast inner universe of which we are

most of the time unaware.

I remember well the stir and enthusiasm caused, especially among young people, by the film *The Matrix* (1999), an indication that this film seemed to have touched something deeply, felt by many. There is a suspicion that there must be something beyond the fascinating, but ultimately not totally satisfying world presented to us by academic science (which is, to a certain extent, a new religion). There seems to be something not quite right in the way we conceive and perceive reality. We experience small hints here and there, dreams and synchronicities, that seem to point towards something other, but to which we commonly pay little attention or dismiss as mere curiosities or coincidence. These kinds of phenomena seem to happen (or perhaps are perceived) more often around psychedelic experiences. This is puzzling and disconcerting and cannot be ignored. One of the most important consequences of psychedelic experiences is the suspicion that reality seems to be much more complex than we had imagined, that the mind is intrinsically intermingled with the material world. *Ayahuasca* expands our ideas of what is possible. It enhances the senses, heightens emotions, produces visions and elicits particular ways of cognition that point towards something other than phenomenological reality. It is a tool for which we must be profoundly thankful to the Amerindian cultures that discovered it and preserve its use. In the crucial moment in history in which we are immersed, anything that expands our creativity and our imagination, anything that connects us with all that exists, is a sacred instrument which we need to cherish and deeply respect.

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# From Beer to Tobacco: A Probable Prehistory of *Ayahuasca* and *Yagé*.

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*Constantino Manuel Torres, PhD*

Professor Emeritus, Art and Art History Department, Florida International University

*Origin, although an entirely historical category, has, nevertheless, nothing to do with genesis. The term origin is not intended to describe the process by which the existent came into being, but rather to describe that which emerges from the process of becoming and disappearance. Origin is an eddy in the stream of becoming, and in its current it swallows the material involved in the process of genesis.*

*The Origin of German Tragic Drama*, p. 45, Walter Benjamin.  
Verso, 2009.

## INTRODUCTION

The iconography related to ancient South American snuff powders obtained from the seeds of trees of the genus *Anadenanthera* has been the primary focus of my research. These seeds, rich in bufotenine (5-OH-DMT) and related tryptamines, were reported by early Spanish chroniclers as an additive to fermented drinks. In the course of my studies on *Anadenanthera*, I began to inquire whether these drinks could be analogous to *ayahuasca* and *yagé*, and whether these could be linked to the origins of these complex beverages. The recipes for these potions presently available include plant combinations that provoke synergy between diverse alkaloids present in the component plants. It should be stressed that these are not fixed or standardized recipes, but rather are distinct beverages that adapt to regional demands, including plant availability and culturally determined methods of administration (e.g., smoking,

snuffing, drinking, enemas and/or unguents). Consequently, instead of a fixed recipe, a construct related to plant synergy and modulation becomes apparent.

*Ayahuasca* and *yagé* share a basic potion composed of *Banisteriopsis caapi* (Spruce ex. Griseb.) Morton stems to which different plants are added (Beyer, 2009; Labate and Cavnar, 2014; América Indígena, 1986; Ott, 1994; Schultes, 1957). The *Banisteriopsis* (Figure 1) vine contains several  $\beta$ -carboline alkaloids – harmine, harmaline, and tetrahydroharmine – which are potent inhibitors of the enzyme monoamine oxidase (MAO). Frequently, *ayahuasca* and *yagé* are combined with the leaves of *Psychotria viridis* Ruiz & Pav. (Figure 2) or *Diplopterys cabrerana* (Cuatrec) B. Gates (Figure 3), respectively. The leaves of these two species contain N,N-dimethyltryptamine (DMT), which is not orally active. However, its combination with the MAO-inhibiting harmala alkaloids allow for its activity. Solanaceous additives are also common, and include *Nicotiana*, *Brugmansia*, and *Brunfelsia* species (Figure 4). Approximately 100 species from 40 plant families are reported as *ayahuasca/yagé* admixtures, many of them also psychoactive plants (Ott, 1994). Several other beverages, distributed throughout South America, employ similar notions of plant interaction. Among these, *vinho de jurema* (Samorini, 2016), *yaraque* (Reichel-Dolmatoff, 1944), *vino de cebil* (Califano, 1976), and *chicha* with an admixture of *Anadenanthera* seeds (Ondegardo, 1916), are of importance and are indicative of indigenous knowledge of plant synergy (Map 1, Table 1).



**Fig. 1** *Banisteriopsis caapi* (Spruce ex Griseb) Morton (Malpighiaceae). Watercolor drawing courtesy of Donna Torres.

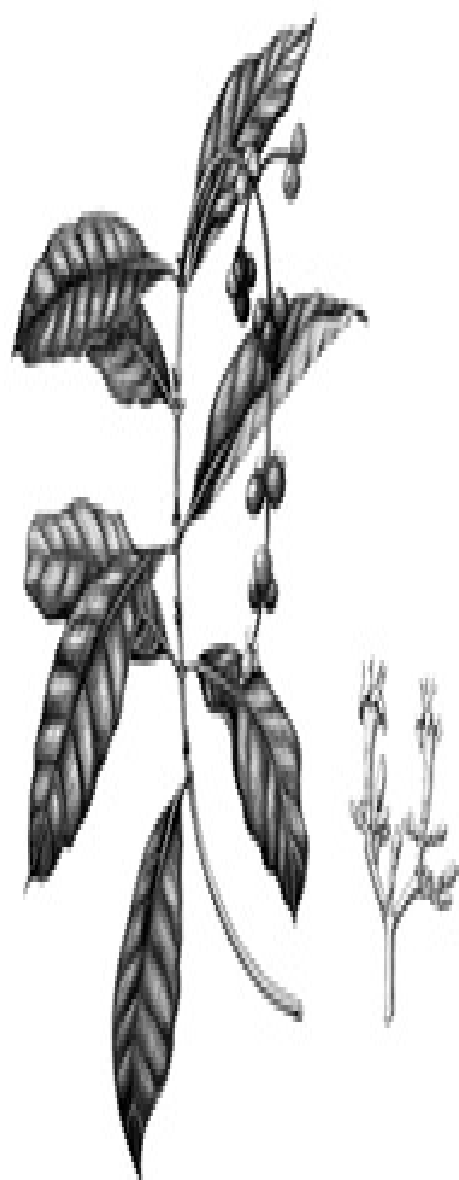


**Fig. 2** *Psychotria viridis* Ruiz & Pav. Watercolor drawing courtesy of Donna

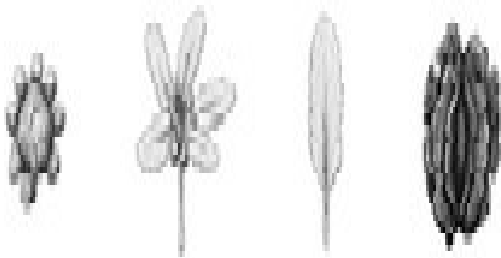


**Fig. 3** *Diplopterys cabrerana* (Cuatrecasas) Gates. Watercolor drawing courtesy of Donna Torres. Photo courtesy of Kathleen Harrison.

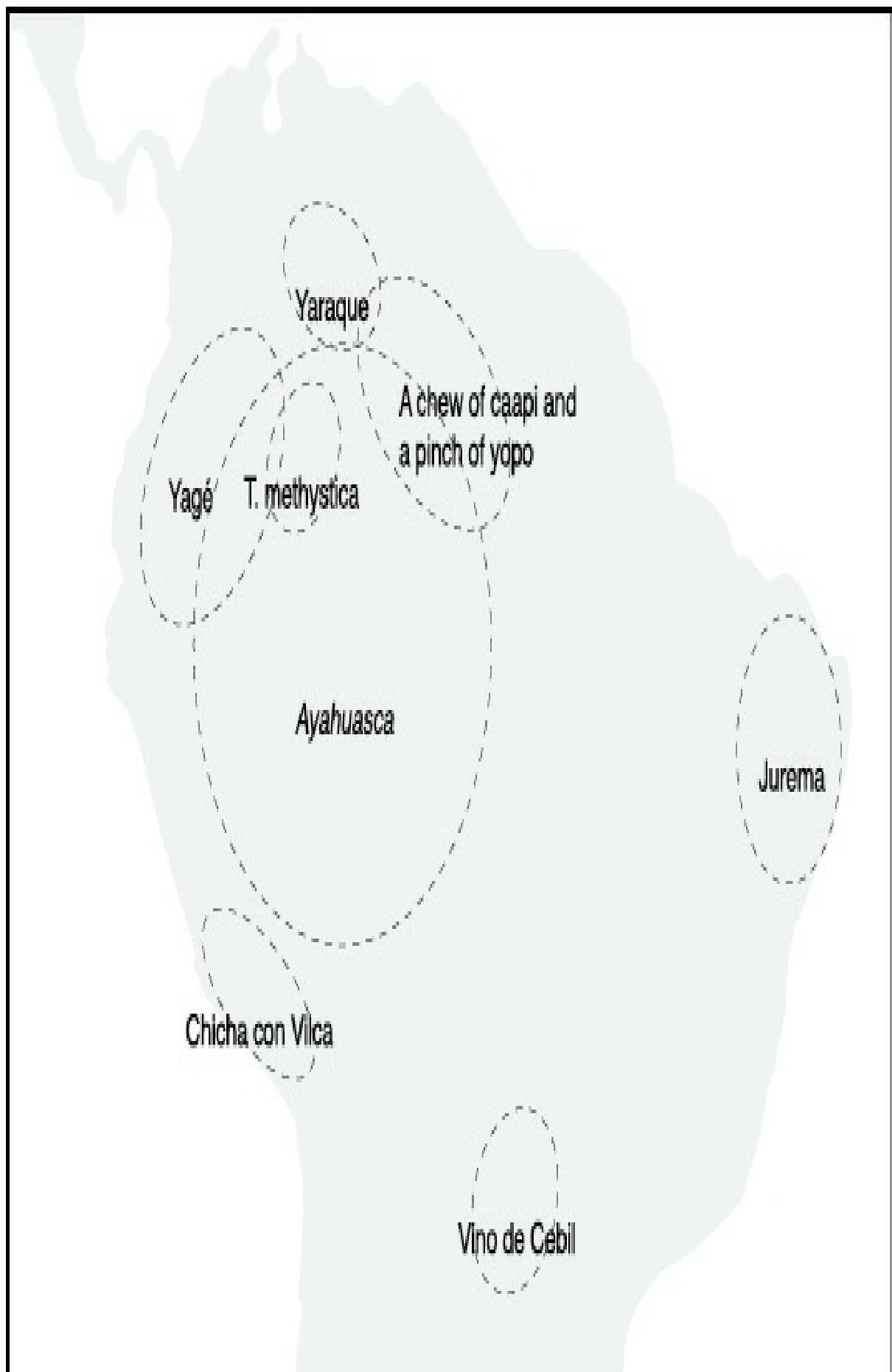




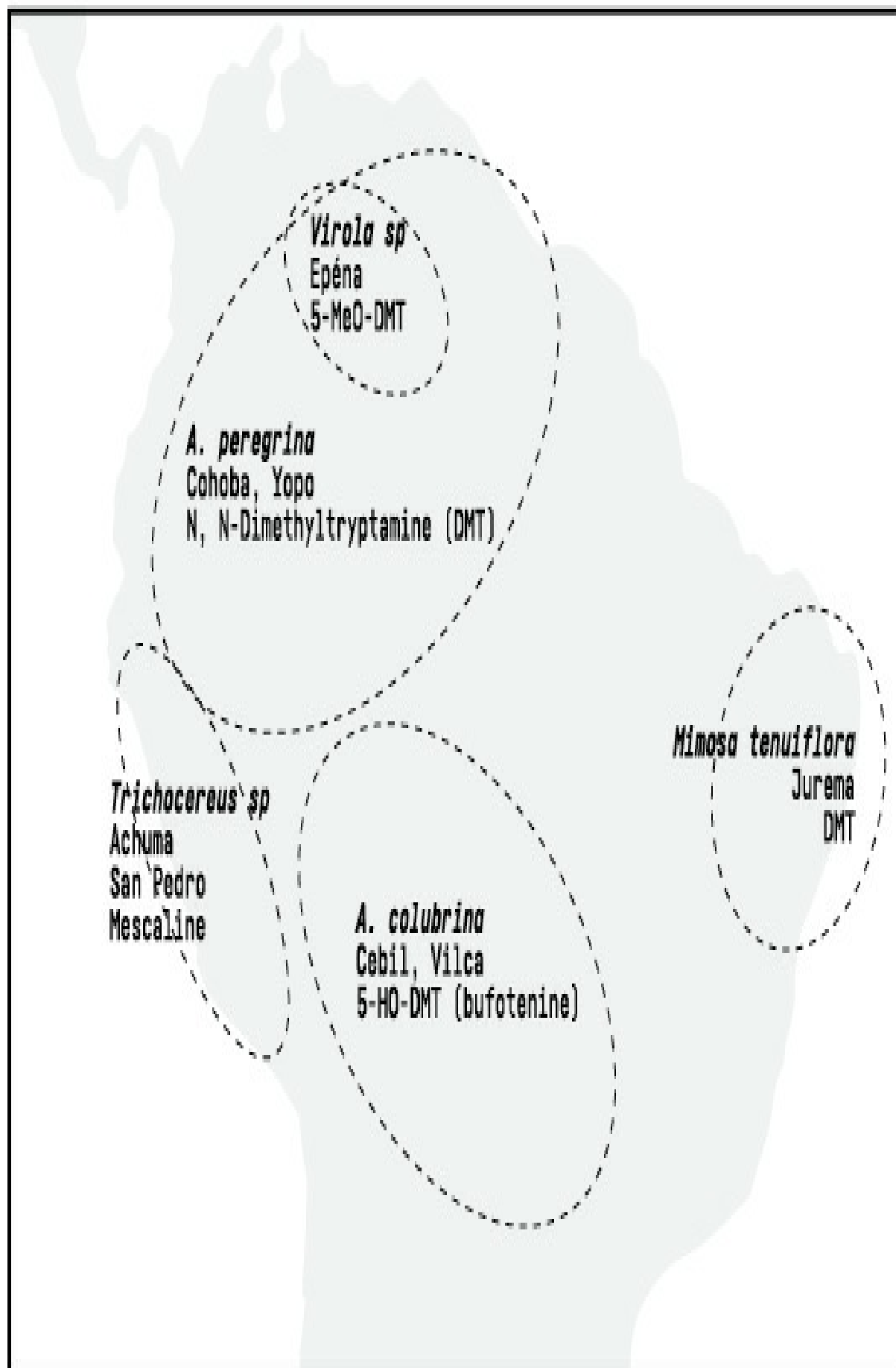
**Fig. 4** Solanaceous admixtures to *ayahuasca* and *yagé* include a. *Nicotiana*, b. *Brugmansia*, and c. *Brunfelsia* species.  
Photos by C. M. Torres.

**Table 1.** Selected *ayahuasca*-like potions.

|                        |                                                                                |                                 |
|------------------------|--------------------------------------------------------------------------------|---------------------------------|
| <i>ayahuasca</i>       | <i>Banisteriopsis caapi</i><br><i>Psychotria viridis</i>                       | Amazon Basin of Peru and Brazil |
| yagé                   | <i>Banisteriopsis caapi</i><br><i>Diplopterys cabrerana</i>                    | SE Colombia                     |
| jurema, ajuca          | <i>Mimosa hostilis</i>                                                         | NE Brazil                       |
| vino de cebil          | <i>Anadenanthera colubrina</i> seeds added to aloja (fermented algarrobo pods) | Wichi, Gran Chaco               |
| chicha con vilca       | <i>Anadenanthera colubrina</i> seeds added to germinated corn chihca           | Quechua, Central Andes          |
| yaraque                | <i>Anadenanthera peregrina</i> seeds added to fermented cassava                | Guahibo, Colombia               |
| Tetrapteryx methystica | No admixture plants                                                            | Makú, Vaupés, Colombia          |
| güeyo                  | Unknown admixture plants                                                       | Taino, Greater Antilles         |



**Map 1.** Map of South America indicating approximate area of potions mentioned in the text.



**Map 2.** Map of South America with approximate distribution of tryptamine use.

DMT is deaminated by the enzyme monoamine oxidase (MAO); the ingestion of  $\beta$ -carbolines may protect the DMT from deamination by MAO, and allow for oral activity. Unlike DMT, bufotenine (5-OH-DMT) and 5-MeO-DMT maintain some oral activity, but oral ingestion notably diminishes the effect (Ott, 2001, 103-104, 110). Fifty years ago, in the first *Ethnopharmacologic Search for Psychoactive Drugs* conference, Holmsted and Lindgren (1967, 365) proposed the notion of synergy between  $\beta$ -carbolines and tryptamines when they detected the presence of harmine and harmaline in Piaroa and Surará *Anadenanthera* snuffs of the Orinoco Basin. These researchers stated:

... some snuffs contain  $\beta$ -carbolines, either in combination with the simple tryptamines or solely. In South American botany,  $\beta$ -carbolines (harmine, harmaline, and tetrahydroharmine) are usually associated with the species of *Banisteriopsis*, wherefore it is very likely that this is their origin in the snuffs. Very likely this is an admixture to the snuff ...

The occurrence of both tryptamines and  $\beta$ -carbolines in the South American snuffs is pharmacologically interesting. The  $\beta$ -carbolines are monoamine oxidase inhibitors, and could potentiate the action of the simple indoles. The combination of  $\beta$ -carbolines and tryptamines would thus be advantageous.

My inquiry initially focused on the origins of *ayahuasca* and *yagé*. However, it soon became apparent that questions of origin were not restricted to sets of specific recipes, prescriptions, and localities. Instead, a construct related to plant interaction and modulation began to emerge. To investigate *ayahuasca* as a separate and distinct phenomenon is not an advantageous strategy. It should be considered in terms of the specific needs and circumstances that gave rise to these formulations and from the contemporary, perhaps privileged, point of view that makes it possible for us to contemplate a large sample of psychoactive preparations in South America. *Ayahuasca* and *yagé* should be seen within the wider South American visionary plant complex (smoking, snuffing, enemas and

unguents), and not as isolated classes of psychoactive drinks (Map 2).

An investigation into the origins of *ayahuasca* reveals numerous beverages distributed throughout South America, each being distinct and varying according to plant availability, cultural predilections for ingestion and ritual requirements. It should be stressed that there are no fixed recipes, but instead, there is constant variation even within the practice of an individual practitioner—it is a methodology marked by continuous change. Instead of pursuing the origins of a specific recipe, this inquiry attempts a search for the origins of a concept that understands issues of synergy between plant components, such that an effect can be modulated, enhanced and prolonged.

## ORIGIN STORIES OF AYAHUASCA AND YAGÉ

Tukano stories tell of a *yagé*-woman who gave birth to a luminous child born in a blinding flash of light:

The first men had gathered in the House of the Waters ... They were trying to find a beverage ... that would take them beyond the narrow confines of everyday experience, and so they were concocting different kinds of fermented beer ... There was a woman among them, the first woman in Creation ... When the Sun Father had created her ... he had impregnated her body through the eye; ... and now she was about to give birth and so she left the house and walked into the darkness of the forest. While the men continued to sing she gave birth to a male child, a child that was going to be *yagé* ... born in a blinding flash of light ... Slowly, the *Yagé* Woman walked toward the house and entered it ... The men were watching her and they almost fainted; the brilliant light and the sight of the blood-red child were causing them to lose their senses. They felt as though they were drowning in swirling waters ... The woman looked around and asked, “Who is the father of this child?”... Then all the men rose and cried: “We are all fathers of this child!” And they took hold of the infant’s body and tore it to bits. Each man tore off a part and kept it for himself. And ever since, each tribe ... had its own vine (Reichel-Dolmatoff, 1978,

3-4).

Archaeological evidence about the use of *ayahuasca* and *yagé* is lacking. Harmine has been detected in the hair of two mummies from archaeological sites (ca. AD 500-1000) in the Azapa Valley, northern Chile, although the results of the analyses are arguable (Ogalde et al., 2009, 471; see also Trout, 2008). Species of *Banisteriopsis*, *P. viridis*, and *D. cabrerana* have not been detected in archaeological sites. This is to be expected, since the habitat of these plants is not conducive to the preservation of organic remains. In addition, the great distance and climatic difference between the Atacama Desert and the Amazon makes the presence of *Banisteriopsis* in the Azapa Valley unlikely. DMT was not detected in the hair of these mummies (Ogalde et al., 2009, 471). The presence of  $\beta$ -carbolines in the hair of these mummies could be explained by the practice of smoking, and also of blowing tobacco smoke on patient's hair, frequent in South American healing practices (plus decades in museum storage rooms). Tobacco smoke contains harman and norharman, known MAO inhibitors (Herraiz and Chaparro, 2005).

The earliest printed reports of *ayahuasca* (Table 2) are those of Pablo Maroni (1737) and José Chantre y Herrera (1901). Chantre y Herrera compiled a history of Jesuit activity in the Marañón River area from 1637 to 1767. His compilation includes a detailed description of an *ayahuasca* ritual and a clear reference to the mixing of a liana with other plants. He did not provide a specific date for the following observation within the range of his history (1637 to 1767):

... an entire night is dedicated to divination. In order to achieve this, the most appropriate house in the community is chosen because many people will be attending the ceremony. Benches are placed on one side for the men and the rest of the space is left clear for the women. The diviner hangs his hammock in the middle and makes his raised platform or small stage and, beside it, places an infernal beverage that they call *ayahuasca*, which is singularly efficient in depriving one of one's senses. They make this concoction of lianas or bitter herbs, which, after a great deal of boiling, becomes very



thick. Since it is so strong as to derange a person even in small quantities, the dose is minimal, and fits in two small receptacles. The sorcerer, each time he drinks, consumes very small amounts, and knows very well how many times he can drink the potion without losing his sanity in order to carry out the ceremony with due solemnity and direct the chorus, since everyone responds to his invocation of the devil (Chantre y Herrera, 1901, 80).

Pablo Maroni (1737, 172), another Jesuit missionary to the Marañón River area ca. 1738-1740, attributed healing and divinatory qualities to *ayahuasca*:

For divination they drink the juice, some of white floripondio (*Brugmansia* spp.), that because of its shape they also call Campana, others use a liana that is called *ayahuasca* vulgarly, both very effective to deprive one of the senses, and even of life, in over-loading the hand. This they also sometimes use to cure themselves of habitual diseases, mainly of headaches. Drink, then, because he who wishes to divine conducts certain ceremonies, and being deprived of his senses lays face down, to avoid being suffocated by the power of the herb, he is thus many hours and sometimes even two and three days, until the inebriation takes its course. After this, he reflects on what the imagination represented, who alone and at times must remain in a delirious state, and this he takes as a fact and prophesies as an oracle.

The first botanist to identify the liana that forms the basis of *ayahuasca* and *yagé* as belonging to the genus *Banisteriopsis* was Richard Spruce (1873, 184). Spruce encountered the use of *Banisteriopsis* several times during his travels, ca. 1852-1853. He states:

In the accounts given by travelers of the festivities of the South American Indians, and of the incantations of their medicine-men, frequent mention is made of powerful drugs used to produce intoxication, or even temporary delirium. Some of these narcotics are absorbed in the form of smoke, others as snuff, and others as drink; ... Having had the good fortune to see the two most famous narcotics in use, and to obtain

specimens of the plants that afford them sufficiently perfect to be determined botanically, I propose to record my observations on them, made on the spot. The first of these narcotics is afforded by a climbing plant called *Caapi*. It belongs to the family of Malpighiaceae, and I drew up the following brief description of it from living specimens in November 1853 – *BANISTERIA CAAPI*, Spruce ... The lower part of the stem is the part used. A quantity of this is beaten in a mortar, with water, and sometimes with the addition of a small portion of the slender roots of the *Caapi-pinima* [*Tetrapteryx methystica*?]. When sufficiently triturated, it is passed through a sieve, which separates the woody fibre, and to the residue enough water is added to render it drinkable. Thus prepared, its colour is brownish-green, and its taste bitter and disagreeable.

**Table 2.** Earliest mention of *ayahuasca* potions.

|                                                                                                                       |                                                                                                                                 |                                                                            |
|-----------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------|
| Pablo Maroni - Noticias auténticas del famoso río Marañón y ... en los dilatados bosques de dicho río                 | Description of the use of ayahuasca and floripondio blanco ( <i>Brugmansia</i> spp.)                                            | Written ca. 1737                                                           |
| José Chantre y Herrera - Historia de las misiones de la Compañía de Jesús en el Marañón español.                      | Detailed description - no specific date given for this statement.                                                               | Information compiled from Jesuit documents covering the period 1637 - 1767 |
| Juan Magnin - Breve descripción de la Provincia de Quito,... y de sus misiones... a las orillas del gran Río Marañón. | Brief mention, no details given.                                                                                                | ca. 1734 - 1740                                                            |
| Manuel Villavicencio - Geografía de la República del Ecuador.                                                         | One of the first descriptions of self-experimentation.                                                                          | Written ca. 1850 - 1858                                                    |
| Alfred Wallace - Narrative of travels on the Amazon and Rio Negro.                                                    | One among a series of researchers almost simultaneously reporting the use of ayahuasca: Wallace, Villavicencio, Simson, Spruce. | Written 1851                                                               |
| Richard Spruce - On Some Remarkable Narcotics of the Amazon Valley and Orinoco                                        | First botanical description ( <i>B. caapi</i> ), mentions admixtures to the potion.                                             | Observations conducted 1852 - 1853                                         |

**Table 3.** Documentation of admixtures to *ayahuasca* potions.

|                                                                                                    |                                                                                                    |             |
|----------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------|-------------|
| Richard Spruce - On Some Remarkable Narcotics of the Amazon Valley and Orinoco                     | “.. with the addition of a small portion of slender roots of the <i>Caapi-pinima</i> .”            | 1852        |
| Alfred Simson - Travels in the wilds of Ecuador, and the exploration of the Putumayo River.        | Earliest mention of specific plants as admixtures. Differentiates between ayahuasca and yagé.      | 1874 - 1875 |
| Theodor Koch-Grünberg - Zwei Jahre unter den Indianern. Reisen in nordwest-Brasilien (1903 - 1905) | Distinguishes two species of caapi.                                                                | 1903 - 1905 |
| Joaquín Rocha - Memorándum de viaje.                                                               | Probable identification of <i>Diplopteryx cabrerana</i> as an admixture to yagé (“yerba que llaman | 1905        |

|                                                                                                                                        |                                                                                                 |                   |
|----------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|-------------------|
|                                                                                                                                        | chiripanga")                                                                                    |                   |
| P. Reinburg - Contribution à l'étude des boissons toxiques des indiens du Nord-ouest de l'Amazonie, l'ayahuasca, le yagé, le huantero. | Leaves of yagé ( <i>Diplopterys cabrerana</i> ) as admixture to a <i>Banisteriopsis</i> potion. | 1921              |
| William Burroughs - The yagé letters redux.                                                                                            | First mention of a Rubiaceae as an admixture plant.                                             | 1954<br>-<br>1956 |
| Homer V. Pinkley - Plant admixtures to ayahuasca, the South American hallucinogenic drink.                                             | First botanical identification of <i>Psychotria viridis</i> as an admixture to ayahuasca.       | 1965<br>-<br>1967 |

The history of admixtures to a basic *Banisteriopsis* potion is unclear (Table 3). Chantre y Herrera (1901) and Spruce (1873, 184) mention plant additives but are not specific about their purpose or identity. *Psychotria viridis* Ruiz & Pavon (Rubiaceae) was identified as an admixture plant in 1967. Pinkley collected specimens identified as *Psychotria viridis* among the Kofán. The Kofáns add leaves and fruits of this plant for the same reason that they add leaves of *Diplopterys cabrerana*, in order to "...increase their visions and to make them of longer duration" (Pinkley, 1969, 309).

William Burroughs, novelist and author of *The Yagé Letters* and *Naked Lunch*, during his search for yagé between 1952-1956, witnessed the addition of leaves to a *Banisteriopsis* potion while on a visit to Pucallpa (Burroughs et al., 2006, 95-97). He collected samples of the leaves and, with the help of an unnamed Peruvian botanist, identified the leaves as belonging to a species of *Rubiaceae*.

*Ayahuasca* and yagé could have points of origin in Northwest Amazonia, not earlier than the initial period of contact with Europeans (late 1500s?). The paucity of archaeological data and the lack of information about *ayahuasca* in early colonial documents, as well as imprecise descriptions of its use prior to AD 1850, suggest this approximate date. In contrast, snuffing and smoking are present in the archaeological record since at least 4,000 years ago (Table 4; Fernández Distel, 1980; Oyuela-Caycedo and Kawa, 2015, 32) and were documented by Spanish chroniclers from the earliest moments of the encounter (e.g., Aguado, 1956; Pané, 1999).

The question that results from this investigation is, If *ayahuasca* is indeed of recent invention, how and when did the knowledge of complex mechanisms of plant interaction develop? Essential to the answer are notions of: a) sequential use – chewing a *Banisteriopsis*

stem previous to snuff inhalation, ingesting a simple *Banisteriopsis* tea in preparation for snuffing sessions, and simultaneous use of coca and tobacco; b) addition of *Anadenanthera* seeds to fermented drinks; and c) location, time period, and plant availability.

## A CHEW OF CAAPI AND A PINCH OF YOPO

### (*ANADENANTHERA PEREGRINA* (L.) SPEG.)

Questions of origin should consider other methods of consumption that benefit from knowledge of plant interaction. Throughout the Orinoco River and its tributaries, there is ample documentation of chewing *caapi* stems in preparation for snuffing sessions in order to modify and prolong the effect of the DMT present in the snuffing powders (Gragson, 1997, 380; Reichel-Dolmatoff, 1944, 480; Rodd, 2002, 2008; Spruce 1970, 428). Sequential chewing of *Banisteriopsis* stems and nasal inhalation of *Anadenanthera* seeds were witnessed by Spruce (1970, 2, 428) in 1852. He described the chewing of *Banisteriopsis caapi* bark in conjunction with snuffing *yopo* (*A. peregrina*). This practice is also documented among the Guahibo, Pumé, and Piaroa.

Investigations among the Piaroa of southern Venezuela have shed light on the relationship between *Anadenanthera peregrina* (*yopo*) and *Banisteriopsis caapi*. Piaroa shamans consume *B. caapi* prior to snuffing and include *caapi* cuttings in the preparation of the snuff powder (Rodd, 2002, 2008).

The ethnographic evidence and pharmacologic research on the MAO-inhibiting effects of the harmala alkaloids clearly suggest that sustained chewing of *caapi* stems and/or drinking a *Banisteriopsis* tea could enhance the effects of the tryptamine-containing snuffs. This sequential consumption utilizes the human body to process the synergy between the harmala alkaloids present in *caapi* and the tryptamines in *yopo*.

**Table 4.** Antiquity of selected psychoactive plants in South America.

|                       |                                                                     |                                                 |
|-----------------------|---------------------------------------------------------------------|-------------------------------------------------|
| <i>Anadenanthera</i>  | Inca Cueva, Argentina (Fernández Distel, 1980).                     | ca. 2100 BC (smoking)<br>ca. 1200 BC (snuffing) |
| <i>Banisteriopsis</i> | Chantre y Herrera<br>Pablo Maroni                                   | ca. 1637 - 1787 AD<br>ca. 1737 AD               |
| <i>Brugmansia</i>     | <i>Brugmansia</i> representations, Chavin sculpture (Torres, 2008). | ca. 900 -700 BC<br>ca. 1400 AD                  |

|                            |                                                                                       |                                 |
|----------------------------|---------------------------------------------------------------------------------------|---------------------------------|
| <i>Nicotiana</i>           | Chiripa, Bolivia (Oyuela-Caicedo & Kawa, 2015)<br>Niño Korin, Bolivia (Wassén, 1972). | ca. 1200 BC<br>ca. 300 - 500 AD |
| <i>Erythroxylum</i> (coca) | Culebras, Ancash Perú (Engel 1957).<br>Asia, Cañete, Perú (Engel, 1963).              | ca. 2000 BC<br>ca. 1800 BC      |
| <i>Trichocereus</i>        | Las Aldas, Perú (Polia Meconi, 1996).<br>Garagay, Perú (Burger, 1995).                | ca. 2000 BC<br>ca. 1200 BC      |

## ANADENANTHERA POTIONS

Previous to the accounts of Maroni and Chantre y Herrera there is no mention of *ayahuasca* by the early chroniclers, and the archaeological record is silent about the subject. It should be stressed that the important issue is to acknowledge that native peoples had an understanding of plant interaction, and that plant exploration was guided by this knowledge. In South America, no plant is used as the sole ingredient of visionary preparations. Multiple ingredients are mixed in snuffs, fumatories, enemas and potions, or are of concurrent use, such as in the case of tobacco and coca.

Oral ingestion of *Anadenanthera* seeds has been recorded among diverse Amazonian cultures. The Guahibo prepare a drink called *yaraque*, which includes *yopo* powder. The Wichi of the Gran Chaco ingest *vino de cebil*, a fermented drink made from algarrobo (*Prosopis* spp.) and *Anadenanthera colubrina* (Vell.) Brenan seeds.

The addition of *vilca* (*A. colubrina*) to fermented drinks has been documented in the Central Andes during the early Colonial period (Cobo, 1964, 158, 272; Ondegardo, 1916, 29-30). Polo de Ondegardo (1916, Vol. 3, 29-30) made the first-known reference to *vilca* (*A. colubrina*) as a *chicha* additive in 1571:

... Those who wish to know an event of things past or of things that are to come ... invoke the demon and inebriate themselves and for this practice in particular make use of an herb called *vilca*, pouring its juice in *chicha* or drinking it by another way. Note that even though it is said that only old women practice the craft of divination and of telling what happens in remote places and to reveal loss and thievery, it is also used today by Indians not only by the old but also by the young.

Bernabé Cobo (1964, 272), writing ca. 1653, reported that *vilca* seeds were added to *chicha*. Garcilaso de La Vega (1970, 499; published 1609) documented a particularly strong *chicha*, known as

*uiñapu*, made from sprouted corn: “..some Indians, more passionate about inebriation than the rest of the community, steep the corn (*sara*) until it begins to sprout. They then grind it and boil it in the same water as other things. Once this is strained, it is kept until it ferments. A very strong drink, which intoxicates immediately, is thus produced ...” It should be noted that de la Vega references other ingredients to the brew but does not identify them.

## THE ARCHAEOLOGICAL EVIDENCE

Direct archaeological evidence for psychoactive potions is difficult to identify. I am unaware of published chemical analysis of archaeological *chicha* residues. Unlike smoking and snuffing, which require distinctive paraphernalia specific to their respective tasks, the sole presence of elaborate drinking vessels should not be seen as evidence of visionary potions (Figure 5). Supporting evidence for the antiquity of *ayahuasca* relies on an elaborately carved ceramic vessel attributed to the Milagros-Quevedo culture (500 BC - 500 AD), and other ceramic vessels of native cultures of Ecuador dating as early as 2400 BC (Naranjo, 1986, 121-122). There is no evidence to support the proposal that these receptacles were ever used to drink *ayahuasca* or *yagé*.

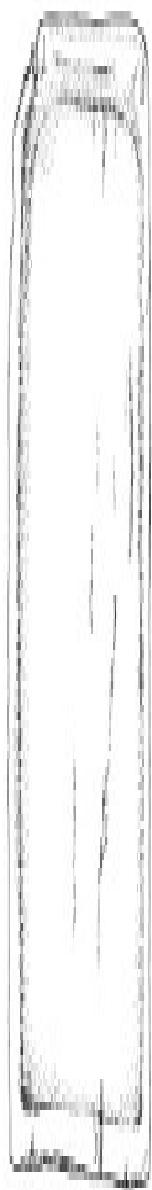
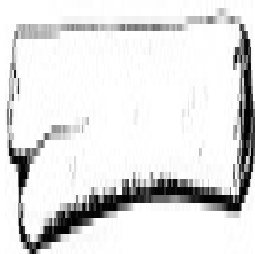
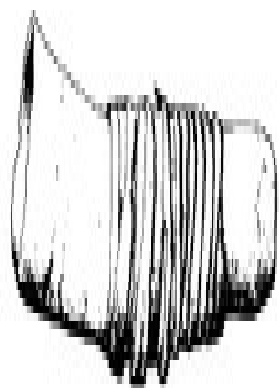


**Fig. 5** Comparison of instruments for smoking and snuffing with a cup with elaborate designs. **Left:** puma (*Felis concolor*) bone pipes, ca. 2100 BC, 13 cm (top), 11.2 cm (bottom), Inca Cueva, Puna de Jujuy, Argentina, Museo Etnográfico Juan B. Ambrosetti, Buenos Aires, Argentina. Center: whale bone snuff tray (11.7 cm), and bird and fox bone tube (17.5 cm). ca. 1200 BC. American Museum of Natural History, NY. Right: carved ceramic vessel, Milagros-Quevedo culture, 500 BC - 500 AD. Museo Arqueológico del Banco Central, Quito, Ecuador.

Previous to the descriptions provided by Maroni (1737) and Chantre y Herrera (1637-1767), evidence for *ayahuasca* or *yagé* is totally lacking. Documentation of the addition of *Anadenanthera* seeds to fermented drinks by Cobo, Ondegardo, and others raises the possibility of the existence of drinks analogous to *ayahuasca* in the Central Andes prior to Spanish contact. Since direct archaeological evidence is absent, the iconography of two ancient Andean cultures, the Moche and the Wari, could divulge the existence of visionary potions and brews.

The Moche territory encompassed the arid north coast of present-day Peru, near the city of Trujillo, between ca. AD 100 and 900. They were not a unified entity, but independent polities that shared an iconographic system. For the purposes of this study, Moche fine-line painting on ceramic vessels (Donnan and McClelland, 1999) offers a large iconographic sample that allows a glimpse into the probability of an *Anadenanthera*-based potion consumed in pre-Columbian times. Depiction of *Anadenanthera* trees in Moche ceramics was first proposed by Peter Furst (1974, 84), based on the design on a pottery dipper painted with a deer-hunting scene. Bipinnate leaves, pods contracted between seeds, a bifurcated trunk, and slightly arched branches are characteristic of *Anadenanthera* (Figure 6).





**Fig. 6** Moche Stirrup Vessel painted with male and female deer and *Anadenanthera* trees, 26 cm h., Fowler Museum at UCLA, collection number X73.237. Photograph by Don Cole.

Representations of deer in association with *Anadenanthera* trees are restricted to painted stirrup-spout vessels and ladles from Phase IV (ca. AD 500-650) of the Moche cultural sequence (Koons and Alex, 2014, 1050-1051). Male and female animals are depicted, although male representations are twice as common as female (Donnan, 1982, 238). *Anadenanthera* trees generally form part of deer-hunting scenes (Figure 7). Elaborately dressed individuals with supernatural attributes conduct the hunt. The ritualistic character of the event is further supported by the lack of evidence for eating deer meat in the Moche archaeological record (Donnan, 1982, 246). There is no evidence for smoking or snuffing.



**Fig. 7** Deer hunting scene, ladle (29.9 cm h), Moche, North Coast, Peru. Left: Art Institute of Chicago, Kate S. Buckingham Endowment, 1955.2277. Right: drawing by Donna McClelland, PH.PC.001-0166, Christopher B. Donnan and Donna McClelland Moche Archive, 1963-2011, Image Collections and Fieldwork Archives, Dumbarton Oaks, Trustees for Harvard University, Washington, D.C.

Deer-hunting scenes painted on four stirrup-spout vessels suggest the possibility that *Anadenanthera* preparations might have been administered orally (Figs. 8-11). The first I will discuss here represents a scene that takes place within a clearly delimited space (Figure 8). Above the painted scene, an elaborately dressed individual armed with a spear thrower sits next to a deer. Below, in the painted scene, a personage seats on a litter, and two elaborately dressed individuals hunt deer assisted by dogs in contorted poses. Spruce (1970, 2: 429) observed a Catauixí hunter administering *Anadenanthera* seed enemas to himself and his hunting dog “...to clear their vision and render them more alert!” The Piro of the upper Ucayali River also gave *Anadenanthera* to their dogs prior to hunting. To the right, next to a wall with stepped designs, two women walk carrying jars with domed lids and attached branches that correspond in shape to those trees identified as *Anadenanthera* on vessels with deer-hunting representations.



**Fig. 8** Top, Moche stirrup-spout vessel depicting a deer hunt (23 cm h.). Dallas Museum of Art, The Eugene and Margaret McDermott Art Fund, Inc., 1969.2.McD. Bottom, Drawing by Donna McClelland, PH.PC.001-0111, Christopher B. Donnan and Donna McClelland Moche Archive, 1963-2011, Image Collections and Fieldwork Archives, Dumbarton Oaks, Trustees for Harvard University, Washington, D.C.

In the second vessel (Figure 9), the two female figures are associated with seven jars with domed lids and attached *Anadenanthera* branches. The domed lids of two of the vessels are replaced by deer heads; the deer's nose attachment is similar to the one seen on the individual seated on the litter in the previous case. The deer heads substituting for the neck and lid of the jars suggest *Anadenanthera* as an ingredient of the liquid contained in these vessels. In the register above, an important personage and attendants are armed with spear throwers. A third vessel (Figure 10) represents a deer-headed human being holding a cup. Three vessels

with attached *Anadenanthera* branches, one with the lid removed, are located just below the deer-headed individual. This vessel demonstrates, once again, a connection between deer and *Anadenanthera* trees. Deer are also associated with visionary plants in other cultures. The *Wixárika* (*Huichol*) identify deer with peyote (Furst, 1976, 113); and in Siberia, reindeer are equated with *Amanita muscaria* (Wasson, 1972, 161).

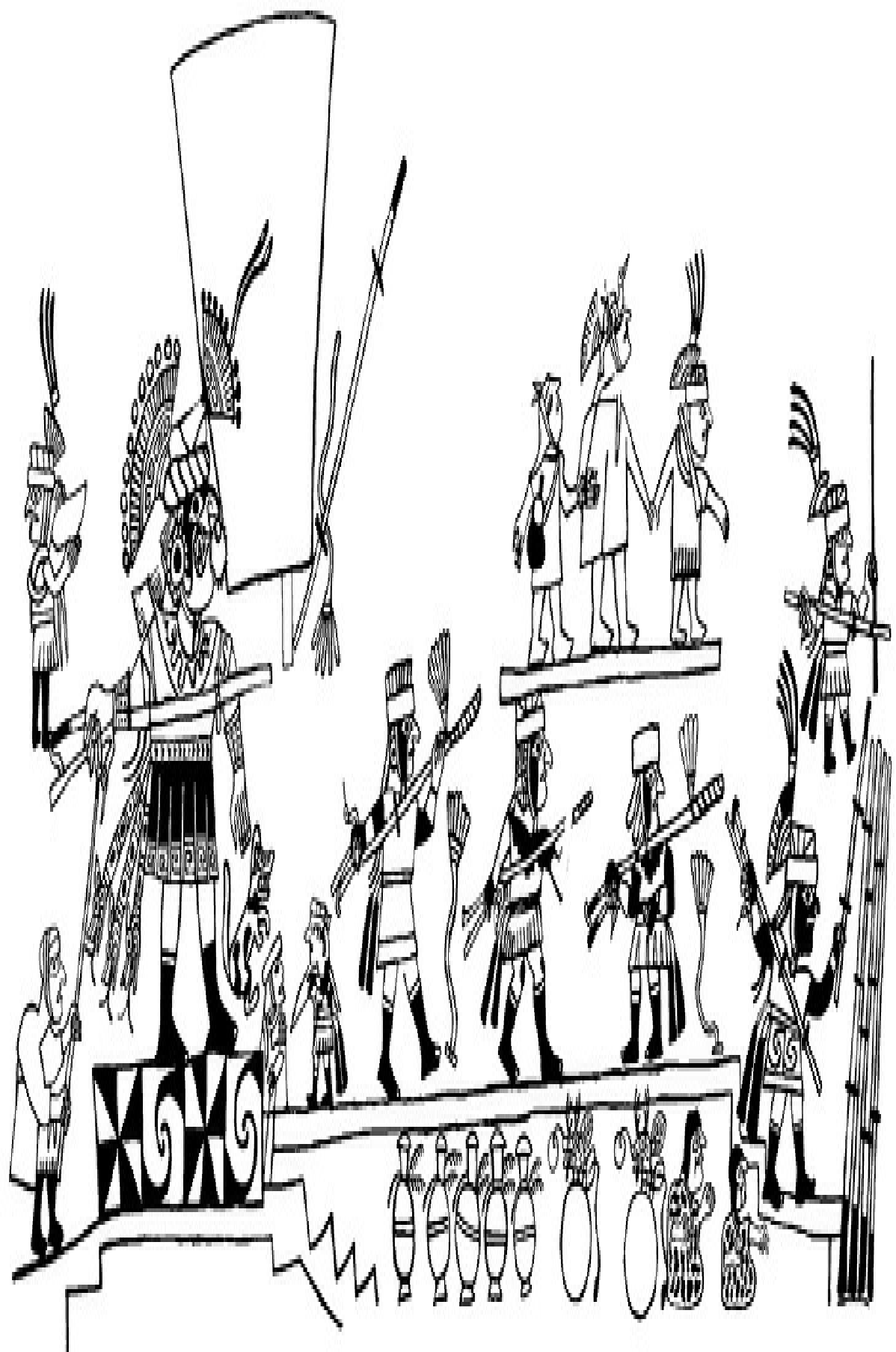


**Fig. 9** Moche stirrup-spout vessel painted with warriors armed with spear throwers and with jars and deer heads. Drawing by Donna McClelland, PH.PC.001-0074, Christopher B. Donnan and Donna McClelland Moche Archive, 1963-2011, Image Collections and Fieldwork Archives, Dumbarton Oaks, Trustees for Harvard University, Washington, D.C.

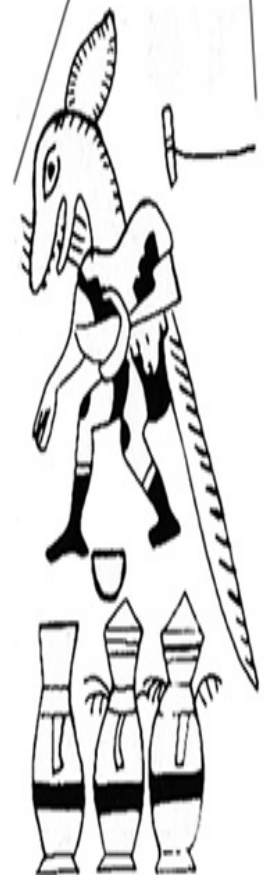
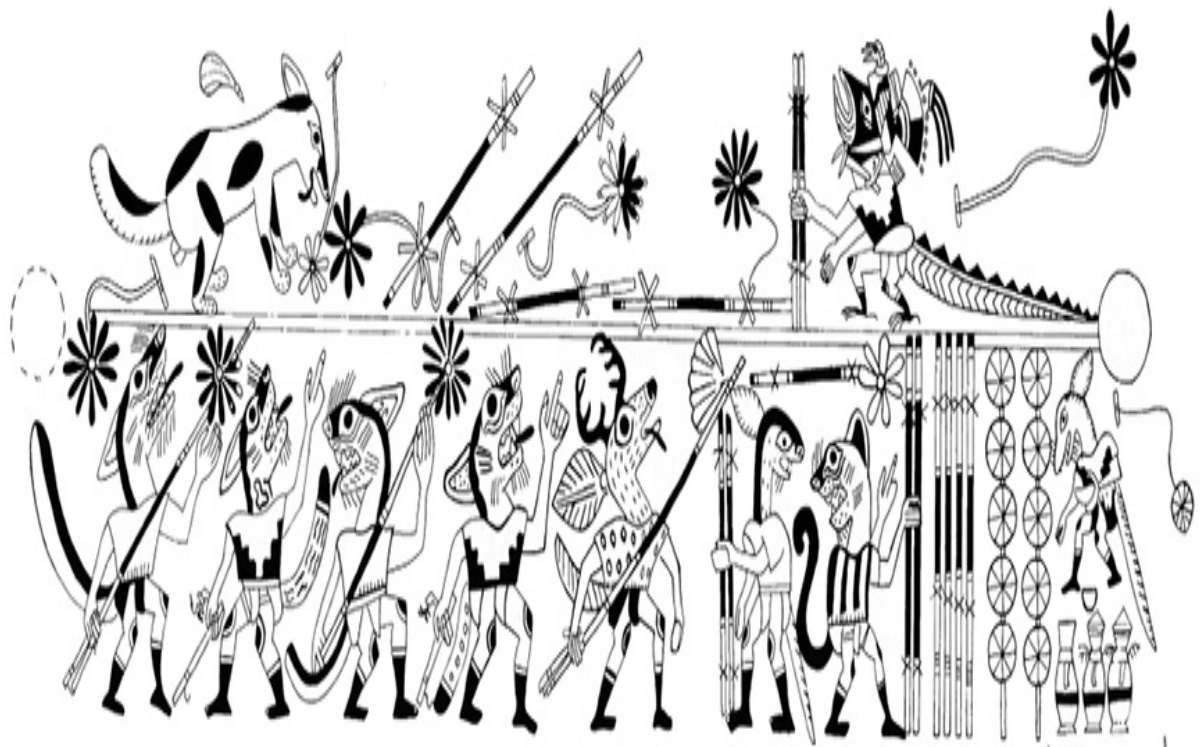


**Fig. 10** Moche ceramic vessel painted with deer-headed warriors armed with spear throwers. Drawing by Donna McClelland (after Donnan and McClelland, 1999: Figure 4.91).

A fourth stirrup-spout vessel (Figure 11) depicts, in modeled clay, a mutilated human being bound to a tree stump. The mutilated individual stands over a painted scene with similar elements to those on the second described vessel (Figure 9). On the lower register of the painted scene, a woman sits tending jars with *Anadenanthera* branches, while above her an individual standing on a platform and surrounded by armed attendants is offered a drinking cup.

Moche iconography related to the deer hunt provides rare evidence for the use of visionary potions by pre-Columbian inhabitants of South America. The constant association and identification of the deer with fruiting *Anadenanthera* trees, and the tree's association with these ceramic vessels and dippers, underscores the possibility of oral administration among the Moche. This is further supported by the scene where the drink contained in the jars is offered to an important personage (Figure 11).





**Fig. 11** Moche ceramic vessel depicting an important personage on a platform holding a cup. Drawing courtesy of Donna Torres.

Further evidence for visionary brews is seen in the iconography of the Wari (ca. AD 300-900). Wari territory encompassed the south central Andes and the adjacent coast. Patricia Knobloch (2000), in her study of Wari ceramics found at the site of Conchopata, near Ayacucho, Peru, presents suggestive evidence for potions containing *Anadenanthera* seeds (Figure 12). She has identified an icon as a probable representation of *Anadenanthera* flowers, leaves, and seedpods. Her identification is based on an image painted on a large ceramic vessel related to *chicha*-drinking ceremonies (Knobloch, 2000, 398). In addition to Wari ceramics, this icon is seen in monumental stone sculpture at Tiwanaku, Bolivia; additionally, the *Anadenanthera* icon is frequent in snuff trays from San Pedro de Atacama, Chile (Torres, 1987). A snuff tray from Tiwanaku is inscribed with an *Anadenanthera* tree emerging from a disembodied head (Figure 12). Given the absence of snuffing paraphernalia in the Wari area, Knobloch (2000, 397-398) suggests

that *Anadenanthera colubrina* could have been ingested as a drink. Citing Polo de Ondegardo (1916, Vol. 3, 29-30), she proposes that *A. colubrina* was added to *chicha* and was likely the beverage held by the large urns and jars found at Conchopata.

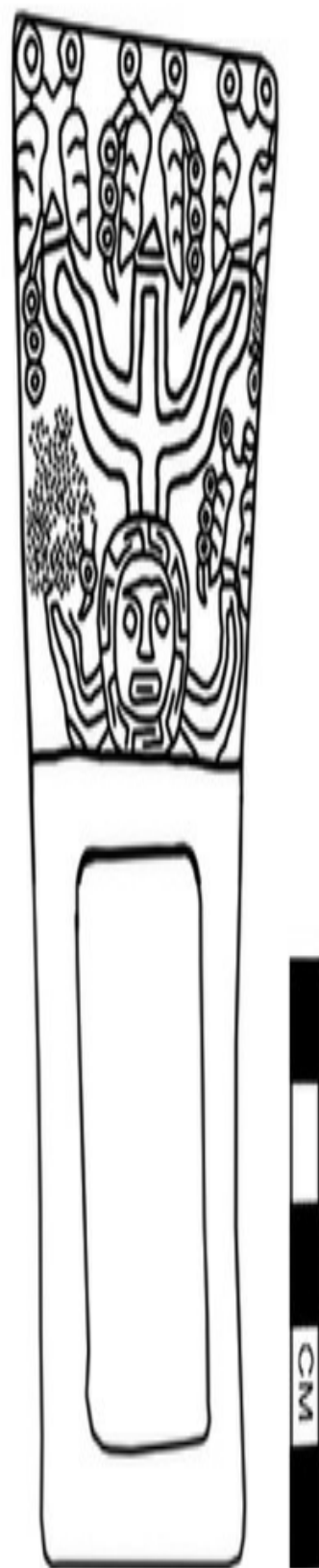
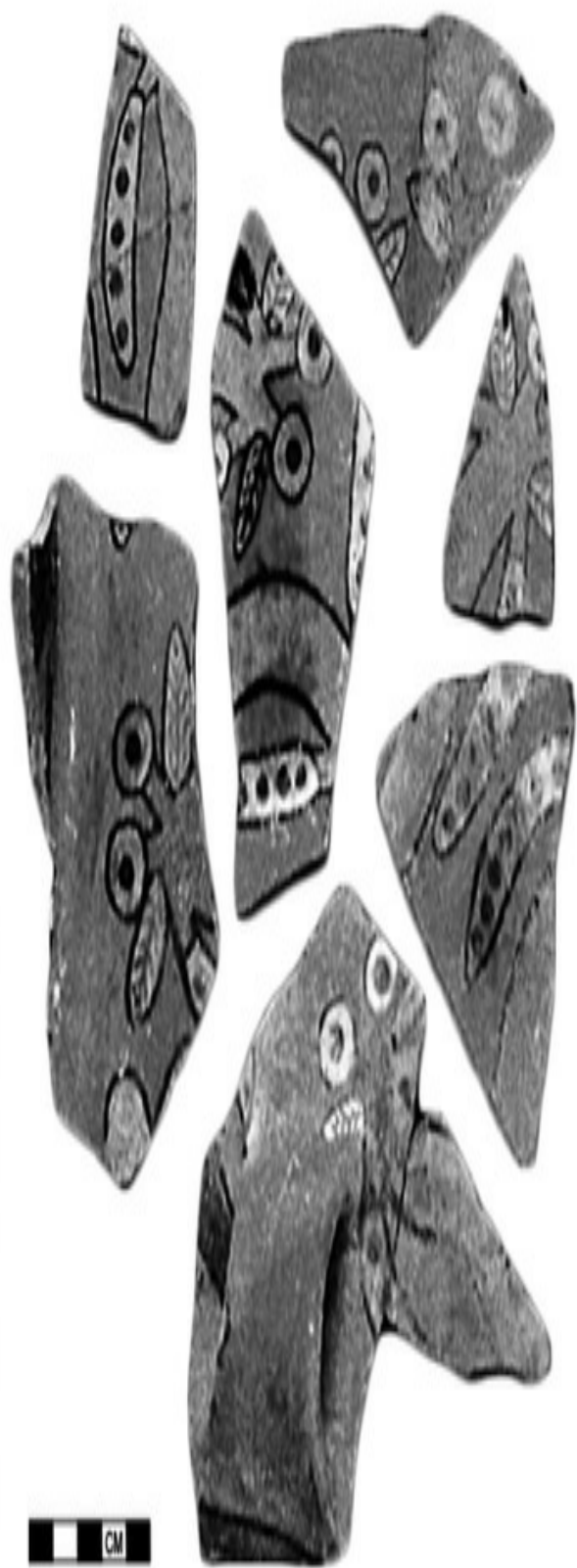


**Fig. 12** Two representations of *Anadenanthera* icon. Left, ceramic fragments from the Wari archaeological site of Conchopata, Peru. Photo courtesy of Patricia Knobloch. Right, snuff tray, wood, 12.8 cm, Tiwanaku, Bolivia. Peabody Museum of Archaeology and Ethnology, Harvard University, Alexander E. Agassiz collection number 75-20-30/8649.

Several authors (Goldstein, 2005, 208-210; Janusek, 2004, 224; Moseley et al., 2005, 17267, Figures 5-6) have reported clear evidence of extensive *chicha* production at the archaeological sites of Tiwanaku and Lukurmata in Bolivia, and Cerro Baúl in Peru. Apparently, these archaic *chichas*, as reported in early colonial documents, might have contained vegetable admixtures to the fermented corn *molle* (*Schinus molle* L.) or *Prosopis* base, the most frequent bases for fermented drinks in the Central Andes.

## CONCLUSIONS

Origin and invention are totally different categories of experience. Origin, as Walter Benjamin eloquently states, is the manner through which things or ideas come into life. Discovery and invention, however, are related to actual processes of creation. Selection of specific plants is guided by an intimate knowledge of environment and cultural needs of the community, and speaks directly about creativity and discovery. Any healer, any shaman, is keenly aware of all details of the landscape and of his/her life-space – not only plants, but also minerals, soil, weather patterns, etc. The exchange of knowledge with neighboring communities would most likely not be restricted to material goods. It would surely include transmission of ideas, pharmacological information, stories, and mytho/historical information, constructing a network that contributes to the creation of symbolic systems and complex approaches to the use of plants to modify states of consciousness.

The origin of *ayahuasca* and *yagé* must be seen within the large scale of interaction and ideological exchange that characterized native communities in the Amazon and the Andes. The evidence suggests multiple origin locations for *ayahuasca*, *yagé*, and analogous potions, and not a center from which a fixed recipe diffused. This incessant interaction is what gives origin to the potions and brews under consideration in this study. The origins of *ayahuasca* must be considered from two complementary points of view. The first should consider events that took place after

European contact, and the second should take into account developments that occurred in the Andes during pre-Columbian times, including consideration of fermented drinks.

Bufotenine retains about one third of its activity when orally ingested (Ott, 2001, 103-104, 110). Its potency as a smoke or snuff was well known, a factor that could suggest to a user to seek ways to enhance its oral activity. Issues of plant availability could also motivate a search for more efficient ways to prepare and consume psychoactive plants. The absence of *A. colubrina* in the western slopes of the Andes could have motivated a search for more effective ways of consumption and of enhancing and prolonging the oral activity of bufotenine.

The problem to be resolved in proposing *chicha* with an admixture of *Anadenanthera* seeds, as well as other plants, as one of the precedents for modern *ayahuasca* and *yagé*, is whether there are  $\beta$ -carboline alkaloids present in the brew that could potentiate the psychoactive tryptamines. The alcohol present in *chicha* is metabolized into  $\beta$ -carboline. Alcohol hydrogenase converts some of the alcohol into acetaldehyde; this compound reacts with tryptamines to produce  $\beta$ -carboline. Drinking *chicha* could thus potentiate the bufotenine present in *Anadenanthera* seeds added during the fermentation process. *Chicha* is most frequently made of sprouted corn, but in northern Chile, southern Bolivia, and northwest Argentina, seeds and pods of *Prosopis* species are the source of the beer known as *aloja*. Tryptamine and  $\beta$ -carboline have been detected in fresh leaves of *Prosopis nigra* Hieron, a tree present in northwest Argentina (Moro et al., 1975, 827). Also, *P. chilensis* (Molina) Stuntz and *P. alba* Griseb. contain tryptamine (Astudillo et al., 2000, 569, 571) that could easily convert into  $\beta$ -carboline in the presence of acetaldehyde. This information suggests that these pre-Columbian beers could be predecessors of *ayahuasca* and *yagé*, and imply knowledge of plant interaction. The widespread use of tobacco in healing and shamanic rituals should also be considered. Origins of knowledge of synergy between tryptamines and  $\beta$ -carboline emphasize the importance of tobacco, a constant presence in healing rituals (Bondeson, 1972; Oyuela-Caycedo and Kawa, 2015; Wassén, 1972). Tobacco smoke contains two  $\beta$ -carboline, harman and norharman, which are well-known

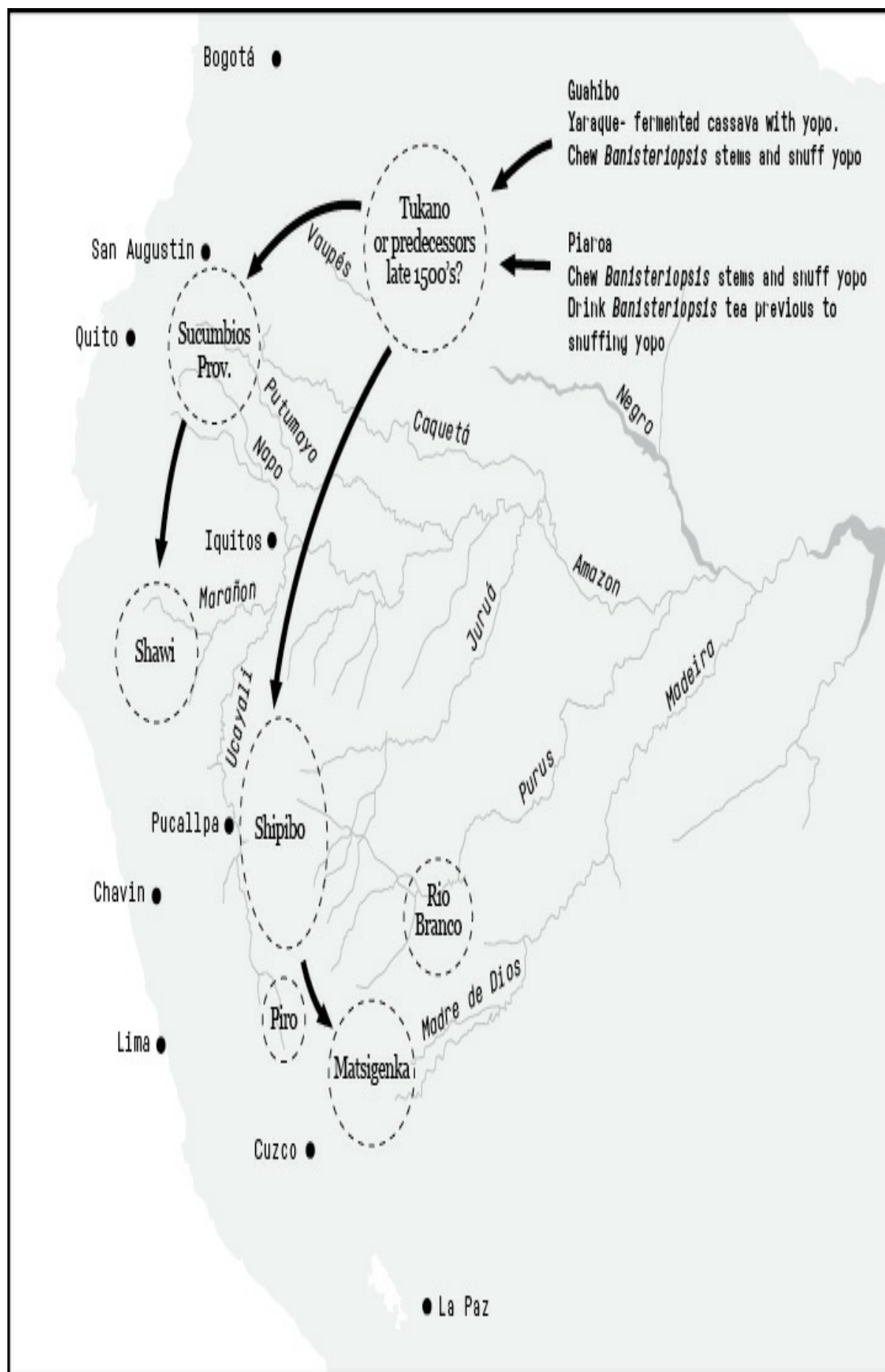
MAO inhibitors.

The key to understanding this origin phenomenon lies in the interaction and flow of ideas surrounding moments of population displacement. Cultural interaction patterns suggest that *ayahuasca* and *yagé* could have originated in the northwest Amazon, not earlier than the initial period of contact with Europeans ca. 1550-1650. I propose that *ayahuasca* and *yagé* resulted from the interaction of several visionary traditions coinciding in the northwest Amazon in the sixteenth century, stimulated by extensive population movements. Causes of population displacements during the early colonial period (1538-1767) include events that caused great disturbances in their respective areas. Among these, several are relevant to this discussion. The collapse of the Inca empire was motivated by many factors, including the execution of Atahualpa in 1533 and the capture of Cuzco by Francisco Pizarro (1533-1535). Subsequently, Spanish slave trading stimulated eastward movement of large percentages of populations from areas along the base of the Andes adjacent to centers of Spanish colonization. Portuguese slave trading along the lower Amazon provoked migration west upriver. Slavery produced a crisis in the area of the mouth of the Napo, which Spain and Portugal claimed. Indigenous people were forced to migrate upriver and seek refuge in Jesuit missions. After 1767, Jesuit missions disbanded, causing further population movement. This was followed a century later by the Rubber Boom (1880-1920). Healing and shamanic lore spread with these journeys. Population displacements carried knowledge of visionary preparations and familiarity with plants, environmental conditions, and historical information.

To the east of the proposed area of origin of *ayahuasca*, there is intensive use of sequential or simultaneous dosing, and of fermented drinks with an admixture of *Anadenanthera peregrina* seeds (Gragson, 1997, 380; Reichel-Dolmatoff, 1944, 480; Reis Altschul, 1972, 31). In the mid and upper tributaries of the Orinoco, the simultaneous consumption of *caapi* and *yopo* could be seen as *ayahuasca* analogues. The Piaroa chew *caapi* stems for 2 to 3 hours prior to snuff inhalation to enhance and prolong the visionary state. When the Piaroa desire a particularly strong snuff experience, a potion with *Banisteriopsis* as the sole ingredient is ingested prior to

the use of DMT- and bufotenine-containing snuff (Rodd, 2002, 2008). For the people of the tropical grasslands (llanos) of the Orinoco Basin in Colombia and Venezuela, the chewing and drinking of *caapi* prior to inhalation of powdered *Anadenanthera* seeds was a frequent modality for enhancement of the bufotenine present in the seeds. Sequential use, as seen among the Piaroa and the Guahibo, could likely be a precursor to the invention of complex potions such as *ayahuasca* or *yagé*, and clearly indicates a knowledge of issues of plant synergy.

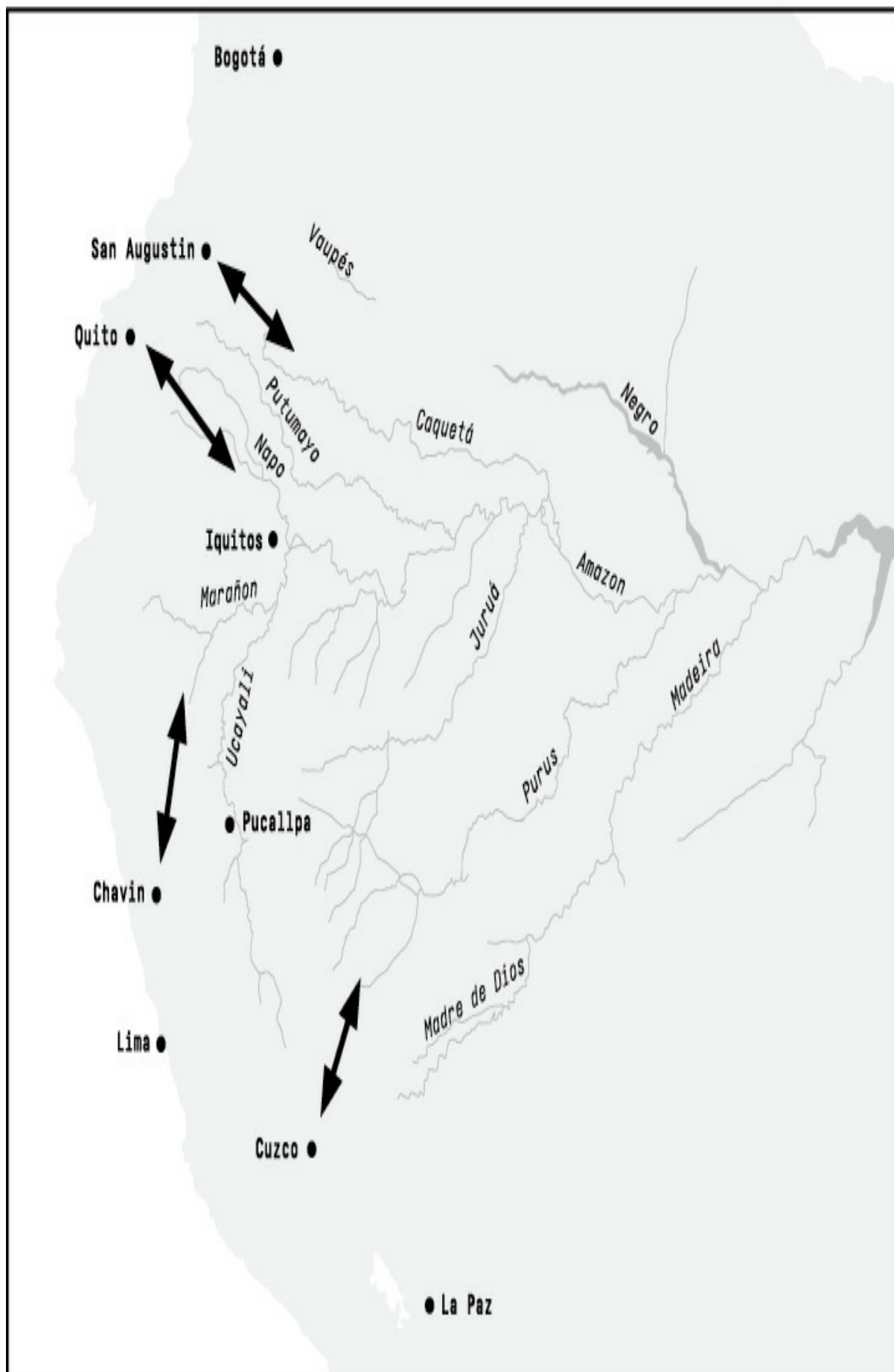
From northwestern Amazonia, the use of *ayahuasca* may have spread following routes of colonial/missionary expansion (Map 3; Shepard, 2014, 16). Brabec de Mori (2011) proposes, first, an expansion from the Tukano or their predecessors to Kichwa speakers related to Jesuit missions in Ecuador and Peru; and second, to the Quechua de Lamas (Lamas prov.) and Shawi people (Loreto prov.), and third, up the Ucayali and to the Brazilian state of Acre, probably associated with the movements of rubber workers (Brabec de Mori, 2011, 42). In its movement to the southwest, *ayahuasca* reached the Shipibo about two centuries ago (Brabec de Mori, 2014, 207). Gow, (2015, 57) demonstrates how the Piro of the Urubamba River in Peru may have known of the existence of *ayahuasca* ca. 1880, although they did not begin to use it until much later, probably ca. 1930. He proposes that *ayahuasca* is a recent introduction to the healing practices of indigenous populations of the southwest Amazon (Gow, 2015, 45). The recent distribution of *ayahuasca* in western Amazonia supports a date for the creation of *ayahuasca* sometime ca. 1550-1650.





**Map 3** Spread of the use of *ayahuasca* in western Amazonia.

Connections between the northern and northwestern Amazon and the Andes are evident in shared iconographic themes; this region has been a crossroad for exchange between the highlands and the tropical forest since early pre-Columbian times (Map 4). For example, connections between the highland Chavín culture (ca. BC 300-900) and the northwest Amazon are clear (Lathrap, 1971). The Tello Obelisk (Figure 13), a stone sculpture from Chavín de Huántar, depicts a caiman with supernatural attributes. The habitat of the caiman does not include the high Andes; instead, they thrive in the tropical forest. Sculpture in the Chavín style has been found in the upper drainage of the Marañón River, indicating accessibility and ideological exchange with the lowlands to the east of Chavín (Burger, 2008, 163; Morales Chocano, 2008, 148). Another example of Andean contact with the Amazon area is apparent in the culture of San Agustín, ca. BC 100-AD 500, located on the eastern slopes of the Colombian Andes. San Agustín is characterized by the presence of hundreds of stone carvings. There are details in the sculpture that clearly connect San Agustín with Amazonian cultures. Several sculptures depict an iconographic theme known as the “double” or “alter-ego,” commonly associated with shamanism in the Andes and in the Amazon (Figure 14). Stone sculptures in the San Agustín style have been found in the Upper Caquetá River (Friede, 1946, 196; Silva Celis, 1963, 397). The Caquetá and tributaries provide direct routes to the Amazon River.



**Map 4** Map showing zones of interaction between the Amazon and the Andes previous to contact with Europeans.

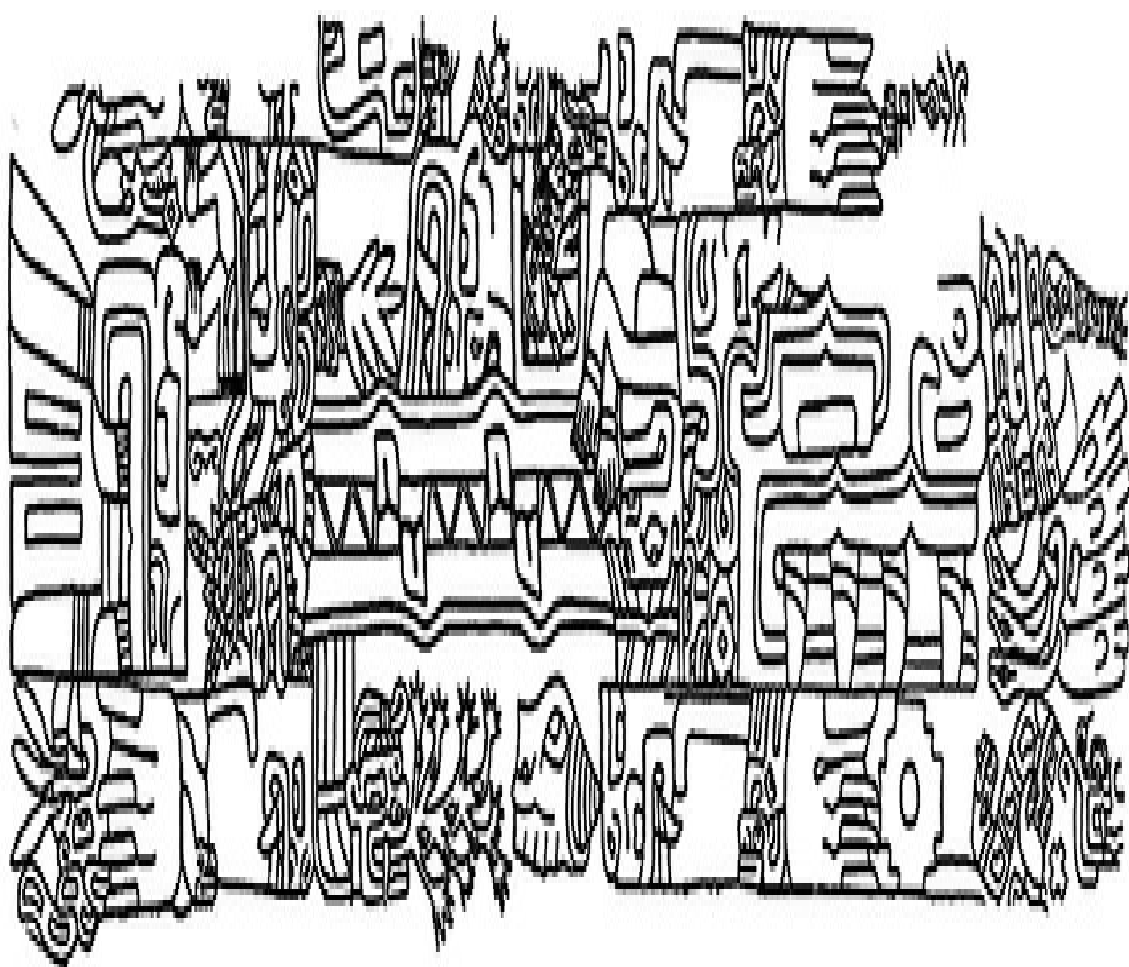
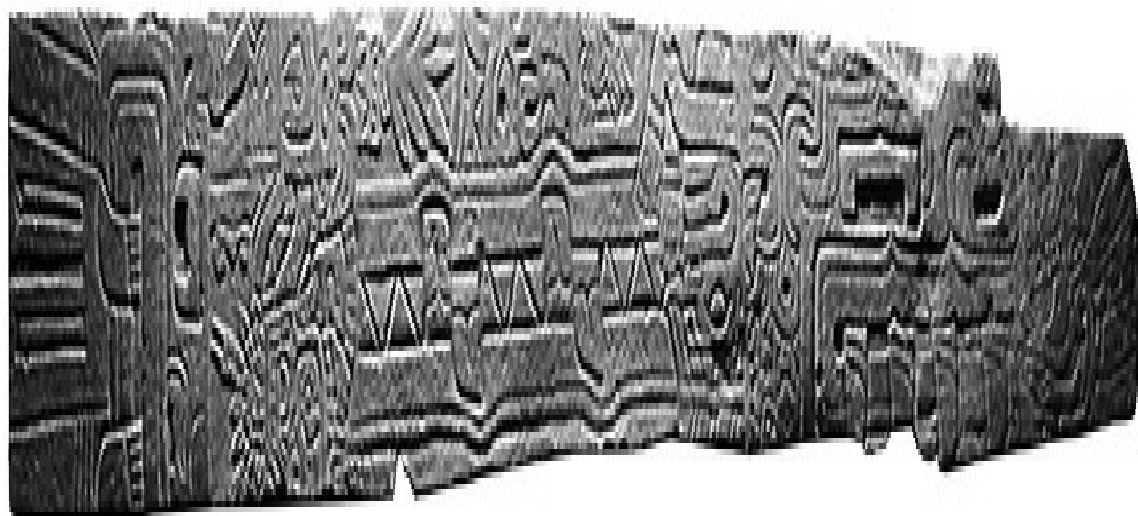


**Fig. 13** The Tello Obelisk, 2.52 m high, granite. Chavín de Huántar. Museo Nacional de Arqueología, Antropología e Historia, Lima (after Burger 1995: Fig. 141).

Information obtained from early colonial documents, and iconographic information from pre-Columbian cultures such as the Moche and the Wari, prove that potions and brews analogous to *ayahuasca* were in use in the Central Andes and adjacent coast since at least 500 AD. Sequential or simultaneous practices, such as those of the Piaroa and the Guahibo, including the chewing and drinking of *caapi* to potentiate snuffing sessions, combined with knowledge of fermented drinks (with the addition of *vilca* seeds, as well as other unknown plant ingredients) could have motivated a search of the local flora to create numerous potions and plant combinations. The numerous variations and lack of fixed recipes found in Andean and Amazonian visionary preparations attest to a dynamic pharmacopoeia, constantly inventing and reinventing itself in search of access to alternate states of consciousness. The importance of beer and tobacco should be stressed, as these two are shared by all of South American shamanism and provide a clear link through time and space.

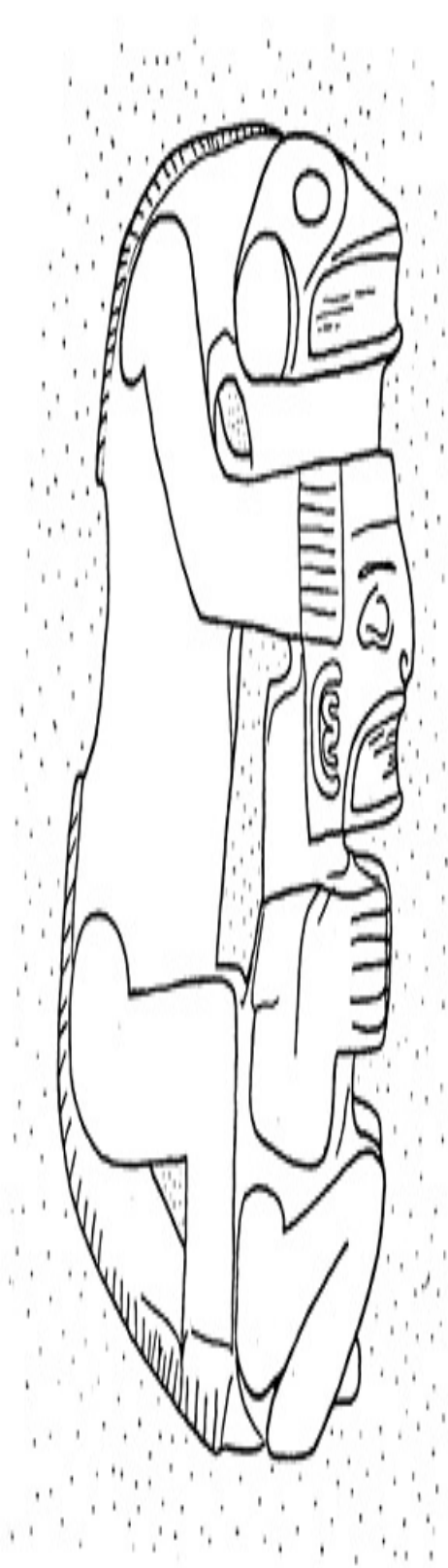


**Fig. 14** Alter-ego or double representations. Left, snuff powder container, stone, 17.5 cm, Trombetas River, Brazil. Museum of World Cultures, Gothenburg, Sweden, collection number 25.12.1. Right, stone sculpture, 3 meters, Alto de las Piedras, San Agustín, Colombia.

The most important factor gleaned by this investigation is knowledge of an understanding of the combined effect produced by varied admixture plants, and that plant selection is guided by an exacting familiarity with the immediate living space, and not by simple trial and error. This concept enabled and created multiple visionary preparations not limited by locality, or by the spread of a fixed recipe and related issues of plant availability. Multiple origin locations interacted with each other to create numerous plant combinations and delivery methods, such as drinking, smoking, snuffing, enemas, and unguents, each being appropriate to location, time period, and specific communities, and not to a center from which a fixed recipe diffused.

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# Plant Use and Shamanic *Dietas* in Contemporary *Ayahuasca* Shamanism in Peru

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*Eugenia Fotiou, PhD*

Assistant Professor of Anthropology, Kent State University

## ABSTRACT

*Ayahuasca* is a psychoactive plant mixture used in a ceremonial context throughout Western Amazonia, and its use has expanded globally in recent decades. As part of this expansion, *ayahuasca* has become popular among Westerners who travel to the Peruvian Amazon in increasing numbers to experience its reportedly healing and transformative effects. In and around Iquitos, Peru, shamanism is reinvented as local shamanic practices converge with Western ideas of spirituality and healing and create a hybrid and highly dynamic practice, which I call *shamanic tourism*. I use this term because the experience often involves the participation in a shamanic *dieta*, which involves fasting and the ingestion of non-psychoactive plants. In addition, it is a common practice in this context to use a variety of plants for bodily and energetic cleansing in the form of purges and ritual baths. Drawing from ethnographic fieldwork in and around the area of Iquitos, the epicenter of *shamanic tourism*, this paper will focus on some of the plants that *curanderos* and *ayahuasqueros* use in the area alongside *ayahuasca* and the ways these are perceived by healers and participants. I will show that the use of plants in this manner is intricately connected with Amazonian conceptions of the body.

## INTRODUCTION

*Ayahuasca* is a psychedelic plant mixture consumed in the form of a brew, which is prepared from the stems of the jungle liana,

*Banisteriopsis caapi* (Spruce ex Griseb.) Morton most often combined with the leaves of *Psychotria viridis* Ruiz & Pav. or *Diplopterys cabrerana* (Cuatrec.) B. Gates to produce visionary and purgative effects. The *Banisteriopsis caapi* vine is indigenous to the western and northwestern Amazon, but its use has expanded globally. For decades, *ayahuasca* was the stuff of legend, associated with scientists and literary writers, from the pioneer field ethnobotanist Richard Evans Schultes to the poet Allen Ginsberg and the writer William Burroughs. Today its use has expanded to a global level and has had an enormous impact on religious and neo-shamanic currents in the West. It has also attracted the attention of scientists internationally, who conduct research with *ayahuasca* in order to determine possible therapeutic uses.

In indigenous Amazonian shamanism, *ayahuasca* had a variety of uses. Depending on the ethnic group, it was used in communal rituals of men, singing and dancing, for locating game animals, divination, in warfare and conflict, to see faraway places, and for healing by communicating with spirits. It was also important in native art, cosmology, and ethnoastronomy, and in the Jaguar complex (Reichel-Dolmatoff, 1975). Among indigenous Amazonians, *ayahuasca* is very important in maintaining social order and in interpreting daily life events. Shamans, being mediators between the spirit and the human worlds, used *ayahuasca* to move freely between the two and negotiate and restore relations between them. Shamans also contact the “master spirits of the animals in order that the hunters may find game and influence the spirits of the seasons so that harvests will be abundant” (Langdon, 1979, 64). *Ayahuasca* is so fundamental for some groups like the Shuar (Jívaro) of the Ecuadorian Amazon that, as Michael Harner (1973) points out, the *ayahuasca* induced experience is seen as the true reality whereas normal waking life is considered simply an illusion. For the Shuar, the true forces behind daily life are in the supernatural realm and can only be accessed through the psychedelic experience. In addition, in many tribal cultures, *ayahuasca*, along with other mind-altering plants, is viewed as an intelligent being possessing a spirit (*ayahuasca* mama) who is able to communicate and transmit knowledge to humans through the visionary state (Whitten, 1976).

This paper is based on research that started with my dissertation fieldwork on *shamanic tourism* in Iquitos, Peru (Fotiou, 2010) and has evolved into an ongoing project focusing mainly on interculturality. The central anthropological issue I wanted to explore was how *ayahuasca* shamanism is constructed in different settings and contexts. More specifically, the question I set out to answer was: “Why do westerners pursue shamanic experiences and how are these experiences constructed in the context of shamanic tourism?” I argued that I do not see *shamanic tourism* as an anomaly but as consistent with the nature of shamanic knowledge, which has always been exchanged across and between cultures. Traditionally, in South American shamanism power and symbolism has been sought outside a particular cultural milieu. Moreover, in the West, esoteric knowledge has often been sought in faraway places (Helms, 1988); thus, this intercultural exchange is also consistent with Western tradition. I do not see tourism as an external force that imposes meaning on local shamanism; rather I showed that there is a two-way exchange and westerners adopt shamanic discourse as well, especially one that involves relationships with non-human persons. In addition, I argue that this phenomenon should be looked at in the context of a new paradigm, or rather, a shift in the discourse about plant hallucinogens, a discourse that tackles them as sacraments, medicines or teacher plants. Ritual, in this context, is instrumental and fosters self-transformation while at the same time challenging the participants’ very cultural constructs and basic assumptions about the world.

Recent scholarship (Winkelman, 2005) has shown that the western interest in *ayahuasca* is much more than a pretext for drug use but rather has a spiritual component and seeks to address an urgent need for self-transformation. In the Iquitos milieu, shamanism is reinvented as local shamanic practices converge with western ideas of spirituality and healing and create a hybrid and highly dynamic practice, which I call *shamanic tourism*. *Ayahuasca* is viewed by westerners as a healing force for bodily and mental disorders that stem from what is perceived as Western culture’s spiritual impoverishment. For participants in *ayahuasca* ceremonies, this healing is also part of a larger project for healing and transforming humanity.

I chose to use the term *shamanic tourism* as opposed to the more often used term *drug tourism* to refer to this phenomenon because I see a substantial difference between the two. The latter tends to be used when speaking of travel for the recreational consumption of drugs or, on rare occasions, travel to exotic places (popular destinations are Amsterdam, Southeast Asia, and South America) with the intention to smuggle illegal drugs. This is not the case with *ayahuasca* shamanism as others have pointed out (Winkelman, 2005). Even though there is a number of tourists that will try the experience out of curiosity – because it is so widely talked about in Iquitos – most people will begin their quest with a specific motive in mind. The physical and physiological unpleasantness of the experience alone disputes any claims for the recreational use of *ayahuasca*, as well. Finally, the experience often includes the participation in a shamanic *dieta*, which involves fasting and the ingestion of other “teacher plants.”

*Shamanic tourism* is a relatively new phenomenon that has escalated in the last decade. However, the western fascination with shamanism – including psychoactive plants and substances and the changes in consciousness that they produce – is deeply rooted in western intellectual tradition and the relationship of the West with the exotic and spiritual “other,” a history that has gone hand in hand with colonialism and exploitative relationships. The recent interest in *ayahuasca* is a continuation of this long history and belongs to its latest chapter that has been called the “psychedelic renaissance” (Joy, 1992; Cloud, 2007; Kotler, 2010; Sessa, 2012) – a renaissance dominated by the themes of healing, self-transformation, and the sacramental use of hallucinogens.

In this paper, I want to draw attention to our use of the word “drugs” in the context of the indigenous use of psychoactives and stimulants. These are usually used in specific contexts alien to the context where the discourse of drugs arose and carries certain political weight. These substances are often used alongside a multitude of other plants and substances that we often overlook because they have no apparent psychoactive effect. I argue that these dichotomies might be limiting the scope of our research efforts. I propose that we focus on these other plants, the contexts in which they are used and the ideologies surrounding that use. In

Amazonia, where plants are not used to change the user's consciousness but to imbue the body with certain properties, we need to work with local categories and not impose our own.

The idea for this paper came from my discussions with contemporary *ayahuasca* practitioners and my last couple of visits in the Peruvian Amazon. There is a large body of literature focusing on *ayahuasca* and its healing effects, but the large array of plants used around it are understudied. In this paper, I want to draw attention to these other plants and encourage future researchers to focus on them. I will first address Amazonian conceptions of the body that inform contemporary *ayahuasca* shamanism and will help illustrate how plants are used in this context. Then, I will discuss several examples of plants that are used in conjunction with *ayahuasca*, either before or after ceremonies. I will follow with a discussion of *dietas* as tools for transformation and knowledge acquisition including a recent ethnographic example.

## BODIES AND SUBSTANCES IN AMAZONIA

A review of the ethnographic literature on indigenous Amazonia reveals elaborate theories of the body and its creation through substances. There is an emphasis on fabricating the body relating to perspectivism, according to which all living beings have a soul, while bodies are markers of difference (Viveiros de Castro, 1998). Since the soul is the constant among living beings while bodies are unstable, there is a need for the management and fabrication of bodies through different substances and techniques. For groups such as the Muinane (Londoño Sulkin, 2012), social life is centered on the production of human bodies on the basis of substances. Substances have their own agency and are of divine origin. They were given to each Muinane lineage by divinities or mythical heroes and their misappropriation could turn them into poison (Londoño Sulkin, 2012). For the Cashinahua, the body is not a taken-for-granted biological fact nor does it “grow naturally”; rather, bodies are unstable and constantly constituted (McCallum, 2014) and “made” often with the ingestion of certain substances. According to Santos-Granero, persons “are not born as such, but must be intentionally manufactured or shaped through the input of a variety of substances and effects provided by parents and kin” (Santos-



Granero, 2009, 7).

A variety of substances of plant and non-plant origin are used to infuse the body with their properties at different stages of a person's life. Cashinahua boys are initiated into hunting via a prolonged diet that begins with using the frog skin to induce vomiting and then killing a boa to eat its tongue (McCallum, 2001). The idea is that the abilities of the boa are transmitted to the hunter and help them to kill large game animals. Among the Napo Runa, the location of the body's power is the flesh (Uzendoski, 2005); and one's body must change form and become strengthened, over the course of one's life. The Ashéninka use leaf baths to strengthen the body (Lenaerts, 2006). Among the Urarina, bodies are leaky and permeable; and there is a continuous process of sealing/ hardening/ ensouling the body through a variety of techniques involving objects and songs to develop and solidify the heart-soul (Walker, 2013). In addition, eating well is important for mental and emotional well-being (Walker, 2013). Similarly, the Barasana theory of the body "places extreme value on the regulation of exits and entrances" (Hugh-Jones, 1979, 119).

The role of altered states of consciousness and their relationship to acquiring knowledge should not be overlooked. For the Napo Runa, to be drunk is to open one's body to the spirit world so that one's "essence" is manifested; drunken states are seen positively, as a means of attaining knowledge (Uzendoski, 2005). For the Urarina, most knowledge has its source outside of human society and learning comes through ingesting herbal medicines or remedies, while keeping a strict regimen of fasting and other prohibitions (Walker, 2013). While acquiring a new skill there is an imprinting phase centered on disciplined practice (Walker, 2013). For example, to obtain spearfishing ability, one must tie strips of the inner bark of the *bijiurara* tree around the forearm, which leaves lasting scars (Walker, 2013); likewise, during the imprinting phase, the novice must throw the spear repeatedly, which incorporates the ability into the body. For the Cubeo, the brain and heart are connected, with the mind storing a replica of its knowledge within the heart; in addition, painting and ornamentation are meant to set the body in "a straight direction;" lastly, leaving the body in a disorganized state has the risk of illness or death (Goldman, 2004). McCallum has also

stressed the relationship between knowledge and health, showing on the one hand that among the Cashinahua the same substances and experiences that can be transformed into knowledge may also become illness-causing agents; and on the other hand, that “*illness can be understood as a disturbance in the body’s capacity to know*” (McCallum, 1996, 363).

Healing involves active manipulation of these principles and there is a variety of remedies for purposes beyond healing. For the Matsigenka, for whom illness is caused by harmful spirits that enter the body, toxic plants are used to “expel such intruders” (Shepard, 1998, 323). Illness is often considered to be the result of breaking food (Hugh-Jones, 1988) or behavioral taboos (Lenaerts, 2006), of which there are many. Among the Iquito, dieting is central during healing (Jernigan, 2011). Chevalier notes that healing prescriptions center around the same theme; for example, the patient must refrain from cultural exchanges with other persons (sexual, social and spatial isolation is required) (Chevalier, 1982 ); they must also not ingest cultural foods; basically, “anything that is cooked or highly valued by men but is quite superfluous to other living species” (Chevalier, 1982, 347). An Urarina remedy for strength involves drinking a decoction of the chuchuhuasi tree, crushed tapir bone and piri-piri (Walker, 2013). During the fast, all food must be cold and salt, gruel, sugar, manioc beer and banana drink are prohibited; in addition, the person must bathe continuously. If the fast is followed correctly, the novice will become brave but if not, they will emerge weak (Walker, 2013).

While these processes are utilized throughout a person’s life, they are instrumental in the shamanic apprenticeship during which knowledge and power are embedded in the shaman’s body. For the Achuar, shamanic apprenticeship involves “a change in the ecology of his physical system” (Descola, 1997, 338). This is achieved through “ascetic discipline” involving purging and a strict diet (Descola, 1997). At the end of the Desana “shaman’s” training, there is a closing ceremony which leaves the knowledge acquired dormant in the initiate’s body; therapeutic spells are put in his brain, while evil ones in his belly (Buchillet, 2004). For the Siona, a substance called *dau*, the root of the shaman’s power, forms and grows in the shaman’s body as he continues to ingest *yagé* (Langdon, 1992). Part

of this power might leave the shaman's body in the form of a dart or other object directed at someone else (Langdon, 1992). This accumulation of knowledge in his body makes a shaman vulnerable and in need for constant protection to avoid potential damage to his *dau* (Langdon, 1992). A similar process is present with the shamanic phlegm and *virotas* (darts) found among the Shuar as well as *mestizo* shamans in the area around Iquitos today, who still practice fasting and sexual abstinence during their apprenticeship.

## PLANTS USED IN CONJUNCTION WITH AYAHUASCA IN CONTEMPORARY AYAHUASCA RETREATS

During my fieldwork, I found that a multitude of plants are often used alongside with *ayahuasca*, often with similar objectives, as discussed above. First, there are a number of admixtures that *curanderos* add to the brew itself in order to influence its effects, depending on what a patient is trying to heal or what qualities they are trying to incorporate in the brew. Some have a list of admixture plants and barks that they always include in their *ayahuasca* brew. By adding these extra plants, they incorporate the spirits and the properties of these plants into the brew. These plants (and any plants used in this type of shamanism) are used for their energy and their spirit as much as they are for their pharmacological qualities. In fact, the difference between the two is not always clear. Plants are treated as living beings and their external characteristics reveal their spirit and qualities. Many tree barks that are used in the brew are used precisely for their strength and endurance, which is revealed by their vertical shape. This has a symbolic meaning as well; just like the physical trees support the *ayahuasca* vine, in the same way the bark from the trees in the brew supports the vine spiritually.

What follows is a list of plants and trees that might be included in the brew, and the properties they are meant to add to it: *Mapacho* – strength and protection; *Toé* – strength; *Ayahuma* – protection and healing *susto*; *Capirona* – cleansing and protection; *Chullachaquicaspi* – physical cleansing and healing; *Lupuna Blanca* – protection; *Punga Amarilla* – protection and drawing out of negative spirits and energies; *Remocaspi* – moving dense or dark

energies; Huayracaspi – create purging, help with gastro-intestinal ailments, bring mental calmness and tranquility; Uchu Sanango – protection, power and strength; Shiwawaku – healing and protection. It is obvious that protection from malevolent spirits and attacks from malevolent shamans is paramount, and several of the additive plants aim to this.

Some shamans have strong feelings about using additives in their brew and they are proud to report that they only use *ayahuasca* and *chacrana* or chacropanga. Most will add small amounts of *mapacho* and other plants such as toé (*Brugmansia suaveolens*) (Humb & Bompl. ex. Willd.; Bercht. & J. Presl.). Toé is a very controversial plant because it is considered to be used by *brujos* (sorcerers). Everybody agreed that it is a very powerful spirit; but I was told that it is a very defensive spirit as well. Some shamans will use a small amount of it, small enough to not cause any visionary effect, precisely for this protective quality. This is what one shaman had to say on the subject of additives:

We use a number of plants that a lot of other shamans consider to be plants that you don't use. And then they often use plants that we won't use. For instance, we use catahua, a lot of shamans say they won't use. They say it's venomous, they say it's a poison, they say it's dark, they say it turns you into the dark side and all these things. We don't believe it to be that way. We see it as a completely different spirit. Although they'll use piñon rojo, and the spirit of piñon rojo for us by the nature of it being a red plant is basically based in red magic, or red arts, which are all negative and have to do with black magic, or becoming basically a witch doctor to do witchcraft on people. (Anonymous, 2005; interview with shaman by author, n.d.)

Purification and cleansing are thought to be instrumental in *ayahuasca* healing; and not only is it a part of the *ayahuasca* experience itself, but it often precedes it by means of diet and purgatives. Certain dietary restrictions are meant to keep the body pure before the ceremony; these require refraining from spices, sugar, salt, oils, meat (especially pork, which is to be avoided for 30 days after the last ceremony), stimulants, and sex. Pork, especially its fat, is to be avoided because of its "dirty energy." Diet is very

important in other shamanic traditions as well; Siikala mentions that Siberian shamans fast, meditate and go into seclusion before ceremonies (1992).

The diet includes abstinence from sex for a few days before the *ayahuasca* ritual and for eight days afterwards. The idea behind this is that the plants remain in one's body for days after the ceremony and will continue to work and heal or teach the person, provided that they stay pure. Even though I could not get a consensus from my consultants on the reasons behind some of the rules, most shamans agreed on the prohibitions themselves. The only disagreement was on the topic of fruit. While some shamans would allow fruit to be consumed, other would not allow them because they contain sugar. On the day of the ceremony, one is not supposed to eat anything after noon; and it is advised to eat a light meal or just fruit and herbal teas throughout the day. On the day following the ceremony, one is not supposed to eat before noon nor use soap or toothpaste. Some shamans prefer to "break" the diet on the following day using salt and lemon taken directly under the tongue.

Regarding the sexual abstinence rule, shamans would have different theories as to why sex is prohibited—as well as different observational approaches. One shaman of European descent said that from what he had been taught, the spirit of *ayahuasca* is very jealous and does not want people to have sex when it resides in their body. In his opinion and from a western point of view, the rationale behind the prohibition is because sex is a very strong, very open, energetic exchange. The energies of the persons interfere with each other and it can "defocus" someone who is dieting and doing spiritual work. He added that it could also be because of taboos that were imposed by the Catholic Church, although there is no evidence to support that.

As mentioned, participants are encouraged to keep the diet for some time after the ceremony as the medicine continues to be in the body and bodily purity is desired for it to continue working. But if the diet is broken, the healing or spiritual work stops and there is the possibility of dire consequences; for example, Peruvian consultants have told me that they got skin rashes from breaking the diet early. Shamans and patients alike are known to be

“punished” by the spirits for not following the dietary restrictions. In one ceremony in which I was present, a young man who had eaten a full meal in the afternoon of the day of the ritual insisted on drinking with the rest of the group despite the warning of the shaman not to do so. After much persistence, he was allowed to drink and during the ceremony, he had a really hard time, vomiting and generally feeling sick, as well as having unpleasant and scary visions. The shaman pointed out to him several times during the ceremony that *ayahuasca* was punishing him for not having fasted.

On occasion, I have witnessed purgative plants being used to purify the body before an *ayahuasca* ceremony. This is usually done in the morning of the day of the ceremony. These plants will induce vomiting or diarrhea (or both). On one occasion, the latex of the *ojé* plant (*Ficus insipida* Willd.) was used. *Ojé* is quite toxic and a large quantity of water needs to be drunk to avoid poisoning, which induces powerful purging. On another occasion, the shaman gave *piñones blancos* (probably the nut of the *Jatropha curcas* L.), to a large group of tourists at an *ayahuasca* retreat. Most people retired in their individual rooms but throughout the day one could hear the purging sounds all over the camp. One of the guests said jokingly that the shaman was a “naughty witch” who had created a “vomit camp.” The shaman told me that she did this so that people would have less to purge during the ceremony and would suffer less. A similar practice is reported by Langdon among the Siona who use emetics to make the body lighter before *yagé* ceremonies (Langdon, 1992, 56).

## TOBACCO

I will finish this section with a discussion of the plant that accompanies *ayahuasca* most often and is considered most powerful by many groups in Western Amazonia. Tobacco, a plant vilified in Western cultures, is probably the most important plant in South American shamanism and one that contributes to its ambivalence. Fausto notes the absence of tobacco in “neoshamanic sites and rites” (Fausto, 2004, 158), while others have emphasized the importance of tobacco as food for the spirits in indigenous shamanism (Shepard, 1998; Freedman, 2015). The best-known study that focuses on indigenous use of tobacco and its importance

is the one by Johannes Wilbert (1972, 1975, 1987). In the cultures he discusses, tobacco was not used recreationally but always consumed in the context of a shamanic ceremony. In fact, nicotine, in appropriate dosages, is particularly well suited to produce in the shaman the chemical changes that activate the attack behavior of his jaguar-self (Wilbert, 1987). Today, tobacco is an important agent of the Jaguar shaman transformation complex of Amazonian shamanism, but nicotine is often considered of lesser significance than hallucinogenic compounds. For some ethnic groups, however, such as the Campa, it is the most important hallucinogen in high doses (Weiss, 1973). The Campa word for shaman is *sheripiári*, which contains the root *sheri*, which means tobacco. The Matsigenka word for shaman is *seripi'gari*, which can be translated as "the one intoxicated by tobacco" (Baer, 1987, 73).

Tobacco is used in shamanic initiations in order to experience symbolic death; it is believed that nicotine is exceptionally well suited to manifest the continuum of dying. Mentally, it is experienced as a journey of the soul outside the body; along the celestial road, the soul of the person in trance repeatedly encounters and escapes death (Wilbert, 1987). Among the Ayoreo of the north Chaco (Paraguay and Bolivia), it is said that the apprentice will drink nearly a liter of pulverized green tobacco and will fall into a coma; if he survives, he becomes a shaman (Califano, et al. 1987). Shipibo apprentices will also ingest great quantities of tobacco water in order to acquire their powers, but also use a variety of ingestion techniques such as chewing, drinking, smoking, snuffing and enema (Wilbert, 1987). Wilbert mentions six indigenous groups that use four or more ingestion techniques: Campa, Jívaro, Piro, Matsigenka, Shipibo, and Tucuna; these groups also consume *Ayahuasca* in a ceremonial context.

Additionally, tobacco is used to induce visions. The mention of visions following tobacco use is very frequent in the scholarly literature. As to the nature of the things seen, authors make occasional reference to the spirits, ancestors, demons, lightning, flashes, and a giant sun. Auditory hallucinations occurring simultaneously with visions include chanting and verbal messages. Unquestionably, however, tobacco ingestion is capable of provoking intense visionary experiences and of providing eschatological

scenarios on a grand scale. Tobacco is also experienced as a sight-and-vision-altering drug that permits the tobacco shaman to view the spiritual world (Wilbert, 1987).

Tobacco is not only used as a hallucinogen. Karsten (1964) reports that the Shuar ingest tobacco for three major reasons: as a universal remedy for all sorts of illnesses, as a prophylactic to strengthen the body; and as a narcotic to induce dreams. Tobacco is an important substance for the Muinane (Londoño Sulkin, 2012). Despite their initial fragility, men, using tobacco become capable of dealing effectively with anything that could cause them harm (Londoño Sulkin 2012); tobacco also provides people with “moral sociable discernment and predatory capabilities” (Londoño Sulkin, 2012, 100).

Tobacco, from the species *Nicotiana rustica* L. – called *mapacho* – was ever present in the ceremonies I observed; its spirit was considered extremely powerful, even though some healers might consider its spirit “heavy” and will not “diet” it. It is used throughout the region during the preparation of the *ayahuasca* brew when the smoke is blown on the pot where the *ayahuasca* is cooking. *Mapacho* is also blown on the plants that are going to be used before they are harvested and before they are placed in the pot. At the beginning of the ceremony, a shaman blows smoke in the four directions, both for protection and to establish the ceremonial space. Tobacco smoke is also blown on the ritual objects, including the *ayahuasca* bottle and each individual cup serving of the brew, as well as on the participants to cleanse and protect them. In every ceremony, there were large bundles of *mapacho* cigarettes close to the shaman. One of my consultants who was an apprentice, told me that if someone wants to be a shaman, they have to be willing to smoke several *mapacho* cigarettes during the ceremony, even if they do not normally smoke. The cigarettes can be purchased rolled at the Iquitos market. In the Iquitos area, there are ritual specialists called *tabaqueros* who specialize in tobacco use and consider tobacco a much more powerful spirit than *ayahuasca*.

## SHAMANIC DIETAS AS A TOOL FOR TRANSFORMATION AND KNOWLEDGE ACQUISITION



Shamanic initiation radically transforms the person who becomes initiated, but this transformation is not easy and is the result of years of training and isolation. In this context, the word apprenticeship is more appropriate than initiation, as there is a long training period before someone becomes a master shaman and it is a gradual process to get there. In the context of *mestizo* shamanism, shamanic knowledge is a combination of internal proclivity and apprenticeship and acquired knowledge. In this manner, a good shaman should have both the gift and a good teacher and they are expected to add their own creative touch to the teachings they receive. Some of the shamans I worked with started their apprenticeship after a life-threatening disease that was healed by a shaman – a theme very common in the literature from other regions, as well. In all cases, there was a radical transformation of those individuals who changed their life course and helped develop their confidence as healers.

Around the world, one is considered a shaman after they have received two kinds of teaching: ecstatic (in dreams and trances) and traditional, such as shamanic techniques (Eliade, 1959). The first one is given by the spirits and the second one by the master shaman. In Amazonia, often the training of the shaman requires fasting, vomiting, and sexual abstinence (Hugh-Jones, 1988); and the novice must obtain several spiritual weapons and tools of office. The novice also consumes strong hallucinogens and must master the trance state (Reichel-Dolmatoff, 1971) – all this while in isolation from the community and spending long periods of time in the jungle. During this time, the apprentice disconnects from society and comes closer to nature and the spirits from which he or she learns. Around Iquitos, the apprenticeship is a vital part of a shaman's credentials and the lineage of healers they belong to is very important, as there are significant differences between lineages. What is transmitted through the lineage is esoteric knowledge, ceremonial practices as well as other “property” or powers. *Icaros* (songs sang in *ayahuasca* ceremonies) and some of the shaman's powers are passed on by the teacher to the student, an example being the *yachay* (knowledge phlegm), which resides in the shaman's body and needs to be fed with tobacco (Freedman, 2015). A relationship with certain plant spirits is also expected; a

respected shaman is someone who has received powers from his master shaman as well as the spirits of the plants directly.

A central theme in the stories of the shamans I interviewed is that physical, psychological and spiritual cleansing preceded the beginning of the apprenticeship. The future shamans had to purge all dark and negative elements before they could become healers and accept the spirits of the plants and their teachings in their bodies. Not only is this an element of purification, but it is an important step for self-transformation as well. In addition, the future shaman has to suffer and sometimes even experience death and rebirth as is found in many cultures around the world (Dobkin de Rios 1984). Another important part of the process is sacrifice in the form of strict dietary and sexual prohibitions. According to my consultants, traditionally shamans would undergo extensive periods of fasting called *dietas*<sup>12</sup> (diets). The practice of *dietas* by individuals who do not have the intention of becoming *curanderos* is a more recent phenomenon. Today, this is something that is available to westerners and some people will choose to undergo a *dieta* while participating in *ayahuasca* retreats; more recently, I was told that because of the increasing association of *ayahuasca* with sorcery, groups of people will go to the jungle to diet other plants only and refrain from taking *ayahuasca* while in Peru. One of my consultants said:

**12.** Note that *dieta* is not the same as the *ayahuasca* diet that has to be observed by everyone who intends to drink *ayahuasca*.

In the jungle, I truly experienced the effects of witchcraft first hand and the power of those who use it. After talking with many healers in the area, I found out that all somehow experienced sorcery. Although Westerners may think it is something unreal, it is not. I know people from other parts of the world who also experienced it and decided not to drink *ayahuasca* in the jungle anymore. They only come here to diet and get more medicine, and go back to their countries as soon as they can, which I totally understand. (Anonymous, 2014, interview with shaman by author, June 18)

Plant *dietas* can be done for a variety of reasons, such as to be healed or to “learn medicine.” *Brujos* or sorcerers will diet certain

plants to learn sorcery. According to some lineages, it is good for healers to diet the same plants in order to learn how to protect themselves from sorcery. One of the shamans told me that:

There are many types of *dietas*. There are *dietas* for more protection, more guardians; *dietas* that serve to heal bones, muscles, organs; others that enhance you spiritually; others to strengthen you physically; others to strengthen you mentally. Each plant has its way. Ultimately, if we focus and welcome each plant letting it take us to what the medicine gives us, I believe that the same plant can give a person one thing from another. That's why I do not focus so much on what the plant is for. Because I have seen that the same plant, which is being ingested by the same people, doing the same things, eating the same food, doing the same *ayahuasca* ceremonies, to some it brings certain things, and to others something different. The purpose of diets is to heal. (Anonymous, 2014, interview with shaman by author, June 18)

The principle behind *dietas* is simple: the shaman, patient or anyone who wants to acquire knowledge from the plants ingests one or more plants followed by a strict dietary regimen for a period of time ranging from a few days to a few months. The *dieta* starts off rather strict and gradually decreases in strictness allowing the person to eat or drink more things; it is generally advised to ease back into a regular diet. Plant *dietas* are rather tedious and physically challenging since most of the plants ingested have noticeable effects on the body, especially when one is fasting, meaning eating most likely only rice and plantains or manioc. Ideally, during the *dieta*, the person is not to have vigorous physical activity and they are expected to spend most of their time lying in their hammock or bed—in other words, they are supposed to behave like a sick person. Some consultants have said that any kind of activity, even reading and writing, as well as contact with other people should be avoided. This is especially important for apprentices, but today is often not adhered to, given the practical challenges.

There are a number of principles, restrictions, and plants that are followed by most of the shamans in the area but different lineages of shamans will have their own rules or plants that they diet. This is

because each shaman works with different spirits, which may ask them to do things a certain way. Even within a lineage, there may be differences if the spirits impose different requirements on different shamans. Most diets last 8, 15 or 30 days, even though one often hears that a few decades ago shamans would diet for 6 months to a year at a time. One of my consultants said that his first diet was 30 days. Today this is rare and for most visitors, it is common to diet for an eight-day period; even if one diets for a longer period, they only drink the plants on the first four to five nights and some maestros will only give the plants on the first day. After that point, the *dieta* continues by following the dietary restrictions.

Things that are not allowed are sugar, alcohol, sex, pork, salt, spicy food, and drugs. Some consultants have said that the exclusion of these elements from the body allows the human spirit, body, and mind to be more open to the forest and the plants' teachings. Other things not allowed during the *dieta* are soap or toothpaste, and direct physical contact with others – except the shaman or other dieteros. After the *dieta*, no sexual contact – including masturbation – is allowed for 30 days, and pork is not allowed for at least six months. During the *dieta*, one should avoid the sun as well as any strenuous activity and should remain isolated as much as possible. For this reason, dieters will usually stay in a small hut in the jungle called a *tambo* for most of the duration of the *dieta*. In addition to rice, plantains, and *fariña* (manioc flour), some species of birds and fish are allowed. I was told that any fish with teeth are not allowed because they eat “basura” (garbage). Another shaman said that the reason they do not eat fish that have teeth is that they are aggressive. Fish with vivid colors or shapes on them are also not allowed to avoid the dieter's skin taking on these colors. The idea is that when one diets, they are ingesting not only the meat of the animal but also its spirit and properties. On the other hand, if one wants to be a brujo (sorcerer) they might want to eat fish with teeth to take on their aggressiveness. According to one of my consultants “to become a healing shaman, you will follow a very strict diet that will direct you into a place of pure medicine. In that place of medicine, you'll learn how to defend yourself, what they call *defensivas*. But that comes from medicine, it doesn't come from dark spirits” (Anonymous, 2005, interview with shaman by author,

n.d.).

During the period of the *dieta*, the spirits of the trees or plants will enter the dieter's body, where they will start the teaching literally from the inside out. They will also come to the person during their dream time and teach them. The person is not supposed to do any activity unless the plant they diet requires them to bathe a certain number of times in a day. In that case they are allowed to go to the river and bathe and then continue to lie down. If the diet is broken, the teaching will stop and sometimes consequences will ensue. Usually, the person faces the consequences the next time they drink *ayahuasca*, during their visions—meaning that they will suffer and they will in a sense be “punished” by the spirits.

Different plants are considered to teach different things and certain plants are more suitable for certain people. Some of the common plants that people will diet are ajo sachá, ayahuma, huayracaspi, lupuna blanca, capirona, huaca purana, huacapú, bobinsana, chullachaqui caspi, cumaceba, tamamuri, chuchuhuasi and remocaspi<sup>13</sup>. Each plant has certain properties and distinct teachings to offer. For example, ajo sachá is a plant that is said to treat problems of discomfort and general pain, generates heat in the body and reinforces overall physical strength, while chullachaqui caspi helps one to communicate with the spirit world. There is no standard way for choosing which plant to diet. If a person is dieting for healing, they diet the plant that the spirits will indicate to the shaman. Usually, at the beginning of the diet, an *ayahuasca* ceremony is done and the shaman determines which plant or plants the patient should diet. More experienced users might receive that information from *ayahuasca* themselves and they share that with the shaman.

**13.** For the botanical names of these plants, see Appendix.

Most people will participate in *ayahuasca* ceremonies during a *dieta*. This is considered dangerous by some because it puts the dieter in a very vulnerable position as *ayahuasca* opens the person up to the spiritual world – whereas the *dieta* in itself does not. I was told that if there is a rival shaman or negative energy in the area, they will not be able to “see” the dieter – he or she will not come into their awareness. But when one participates in *ayahuasca*

ceremonies rival shamans can hear the *icaros*; they can hear the ceremony vibrating and see the mesa (ceremonial altar) shining; therefore, it is safer not to drink *ayahuasca* during the time of the *dieta*. However, if one is working with master shamans, it is considered reasonably safe to drink *ayahuasca* during the *dieta*, because they are watching over the dieter and are able to protect them. I was told that during the *dieta*, one feels closer to the jungle and the plants and animals and it can be difficult to return to normal life, especially to an urban environment. After a *dieta*, a person is very open to anything and the negative energy of a city can affect them much more than it would have before they dieted.

There is a disagreement over the number of plants that is ideal to diet at any given time. Most shamans will diet one plant at a time and learn from its spirit. I have worked with one shaman that diets as many as 25 plants at a time, a fact that is frowned upon by other shamans and experienced users. They argued that it would be impossible to learn anything if you had so many teachers trying to teach you at the same time. For them, it is optimal to diet one plant at a time and concentrate on the energy and teaching of the particular plant.

According to some, to be a traditional *ayahuasquero*, *dietas* are not necessary. An *ayahuasca* shaman can only learn from *ayahuasca* and work with *ayahuasca*. *Ayahuasqueros* are considered by other specialists in the area, such as *paleros* or *tabaqueros*, to be weak and very easy to dominate. However, for *ayahuasqueros paleros*, experts in both *ayahuasca* and tree barks, *dietas* of trees barks are the most fundamental aspect of their practice. By ingesting them, they allow the spirits of the trees to enter their bodies and teach them directly. The greatest learning takes place within the period of the *dieta*, while during the ceremonies they learn how to utilize that medicine.

The frequency in which *dietas* are done varies. According to a European shaman I have come to know well over the years, it is good to diet at least once a year in order to cleanse and center oneself. He also saw dieting as an exercise in his own power. He believes that *dietas* are a good way for anyone to reflect on their lives, their patterns, and ways to change them. He said:

These plants have their genios (spirits), their fairies, their

goblins, whatever we want to call them. Their elementals. When you are dieting these eight days without salt, without sugar, as we are now, and you have taken the plant, and the plant is in you, you are allowing that plant to develop in you, but to your elemental as well. That month that you do not do certain things, let's say it's the valorization that you're going to give to that plant. If you are dieting well, then the spirit of that plant will be with you. If it is to cure a disease, it will help you cure the disease (if it is in your hands and in God's hands to heal it). If it is to learn, every time you need that plant in an icaro or something to heal someone, you will have the strength and power of that medicine in you. (Anonymous, 2014, interview with shaman by author, June 18)

Since 2013, I have been working on a collaborative book on sorcery together with a shaman, who I will call Juan, who is originally from Spain. According to Juan, sorcery has played an instrumental role in his life, often changing its course. Since we decided to work on the book together, he often experienced sorcery attacks during ceremonies and he was not able to complete any of his projects. During the attacks, he would often comment that "they don't want us to write the book." In 2014, I got severe diarrhea almost immediately after arriving in Iquitos and subsequently, probably due to dehydration, got a bladder infection, which went undetected until my body started shutting down. I had no desire to eat or energy to do anything at which point he took me to the hospital where I was diagnosed and took antibiotics.

Because of these events and because we were close and I had started perceiving certain things during ceremonies, Juan suggested that we both diet the ayahuma tree to fortify ourselves. His teacher had taught him that the spirit of ayahuma was very powerful and a very good guardian. It could teach one sorcery but at the same time how to protect oneself from it. Juan had an apprentice at the time who had just finished a long diet with ayahuma and felt extremely strong. The *dieta* consisted of drinking an infusion of the ayahuma bark on the first day and bathing with the pulp of its fruit on consequent days. In his lineage, the *dieta* also involved immersing oneself in water every morning, eating very little bland food, not talking or coming into contact with people and avoiding the sun.

Juan also had me diet camalonga, which I took on the second day of the *dieta* in order to heal. During one of our conversations, he said that it would help me accept the sickness and its larger significance. He said:

The gift (of the illness) is to contemplate the negative parts that it brings you. Meditate, feel, think about it. Why are you here? What is the gift that you are bringing me? Whether it is physical, mental or what the disease is. What does it create in you when you think about the disease? What patterns of behavior? [...] Because the root, if it is a gift sent to you from above, the root is not here. It is not in the physical. Even if it looks to me as if it's here. But the root ... you see the tree, but the root you do not see. (Anonymous, 2014, interview with shaman by author, June 18)

In 2015, I was once again in Iquitos, ready to head to the jungle to begin a series of *ayahuasca* ceremonies, when my purse containing my passport was stolen on the night before we were scheduled to leave for the jungle. Putting this in the context of the attacks Juan was experiencing as well as my illness in the previous year, he determined that shamanic intervention was needed. He was concerned that our work on the book was not welcome by local shamans and that they were trying to stop it. He decided that a powerful purging, followed by a protective bath was necessary to cleanse and fortify my body against future attacks. The protective bath contained tobacco, toé leaves and patiquina (Elephant's ear), which is generally known in the area to be a protective plant. Other friends in Iquitos have commented on its protective qualities and often people plant it near a house door for protection. This course of action had worked for him in the preceding year when he was experiencing a lot of attacks. I was told:

I learned about plants that sorcerers dieted, but could be used as protection as well. Dieting these plants for long periods of time could become a means to do evil. It is ideal to diet them for short periods of time so they become protectors. After my diet with tobacco and the baths with patiquina, tobacco and toé, I started feeling better and the ceremonies became more lucid. I felt much stronger, safer and protected. The attacks



did not end, but I dealt with them better.” (Anonymous, 2015, interview with shaman by author, June 7)

To induce the purge, he procured ojé, a plant mentioned in the literature as a powerful plant teacher (Luna, 1992). The plant is often ingested to get rid of parasites, but I have seen it used to cleanse the body before taking *ayahuasca*. A local shaman that was also present, told me repeatedly that after this cleanse I would feel stronger and that I would glow. I ingested the resin of the tree and spent the rest of the day by the riverside drinking gallons of water. This induced vomiting and diarrhea. By late afternoon I was exhausted and hungry, after which I rested and had a light meal. In the following days, we had several *ayahuasca* ceremonies. This last ethnographic example is not atypical of how people use plants alongside *ayahuasca* in contemporary *ayahuasca* retreats.



**Fig. 1** A pair of camalonga seeds, thought to be male and female.



**Fig. 2** Preparation of ritual bath with patiquina, toé leaves, and tobacco.

## CONCLUSION

I have shown that *ayahuasca* shamanism both from the perspective of the practitioners as well as the patients, involves much more than the ingestion of *ayahuasca*. In addition, as I was recently told, because of the increasing discussions of sorcery involved in *ayahuasca* shamanism, many travelers will travel to the jungle to diet other plants and will not partake of *ayahuasca* itself. Not only do shamans in Peru include a variety of other interventions, baths and cleanses among others, utilizing plants, but there is a great degree of specialized knowledge as evidenced in the different types of specialists in the area such as paleros and *tabaqueros*. There is a vast body of knowledge that needs to be more at the center of our research efforts and understanding local conceptions of the body will help elucidate the ways that these modalities work. According to Hugh-Jones “an anthropology of “peculiar substances” might usefully begin by thinking more about the consumption of stimulants or psychoactive substances in relation to the consumption of more ordinary fare” (Hugh-Jones, 1995, 48). He suggests focusing on ethnographic evidence of behavior and social interaction and a “more cultural approach focusing on categorization” (Hugh-Jones, 1995, 49). I would also urge us to reconsider terms such as “drugs” as foreign to the majority of the contexts that we are discussing here. In this case, even though many of the plants I have discussed are not psychoactive, the study of their use within the context of *ayahuasca* shamanism can only enhance our understanding.

Finally, considering several *ayahuasca* related deaths, some of which seem to be related to tobacco ingestion (Macdonald, 2017), more research is needed from a variety of academic disciplines to determine and minimize risks. The discourse has predominantly been that *ayahuasca* is safe unless someone suffers from certain conditions, but most of the recent deaths have been of young and healthy people, which should be cause for concern. Although researchers have pointed out that many of the deaths are probably due to incompatible drug use or prior pathology (dos Santos, 2013) further research on admixture plants and other purgatives used in

conjunction with *ayahuasca* can only enhance our understanding and prevent future fatalities. While research and exploration of the pharmacological properties of psychoactive plants is important, I argue that ethnography as well as ethnopharmacology are equally important when researching the plants used in conjunction with them. Venues such as this symposium and volume are important in forging these interdisciplinary collaborations and dialogue.

## APPENDIX

### LIST OF PLANTS

(As cited in McKenna, Luna, and Towers, 1995; Castner, Timme, and Duke, 1998; Duke and Vasquez, 1994; Duke, et al., 2009; Schultes and Raffauf, 1992; López Vinatea, 2000)

| Vernacular name             | Scientific name                                                                                                         |
|-----------------------------|-------------------------------------------------------------------------------------------------------------------------|
| Ajo Sacha                   | <i>Cordia alliodora</i> (Ruiz & Pav.) Oken                                                                              |
| Ayahuma                     | <i>Couroupita guianensis</i> Aubl.                                                                                      |
| <i>Ayahuasca</i>            | <i>Banisteriopsis caapi</i> (Spruce ex Griseb.) Morton                                                                  |
| Bobinsana                   | <i>Calliandra angustifolia</i> Benth.                                                                                   |
| Camalonga                   | <i>Strychnos</i> spp.                                                                                                   |
| Capirona                    | <i>Calycophyllum spruceanum</i> (Benth.) Hook.f. ex K.Schum. or <i>Capirona decorticans</i> Spruce (López Vinatea 2000) |
| Catahua                     | <i>Hura crepitans</i> L.                                                                                                |
| Chacruna                    | <i>Psychotria viridis</i> Ruiz & Pav.                                                                                   |
| Chagropanga, Chaliponga     | <i>Diplopterys cabrerana</i> (Cuatrec.) B.Gates                                                                         |
| Chiricaspi                  | <i>Brunfelsia chiricaspi</i> Plowman                                                                                    |
| Chiricsanango, Chuchuhuasha | <i>Brunfelsia grandiflora</i> D.Don                                                                                     |
| Chuchuhuasi                 | <i>Maytenus boaria</i> Molina or <i>Maytenus ebenifolia</i> Reiss. (Lopez Vinatea 2000)                                 |
| Chullachaquicaspi           | <i>Remijia peruviana</i> Standl. or <i>Tovomita</i> sp.                                                                 |
| Cumaceba                    | <i>Swartzia polyphylla</i> DC.                                                                                          |
| Huacapú                     | <i>Minquartia guianensis</i> Aubl. or <i>Vouacapoua americana</i> Aubl. (Lopez Vinatea 2000)                            |
| Huacapurana                 | <i>Campsiandra comosa</i> Benth.                                                                                        |
| Huayracaspi                 | <i>Sterculia apetala</i> (Jacq.) H. Karst.                                                                              |
|                             |                                                                                                                         |

|                                         |                                                                           |
|-----------------------------------------|---------------------------------------------------------------------------|
| Lupuna, Lupuna blanca                   | <i>Ceiba pentandra</i> (L.) Gaertn.                                       |
| Mapacho *                               | <i>Nicotiana tabacum</i> L. or <i>Nicotiana rustica</i> L.                |
| Ojé                                     | <i>Ficus insipida</i> Willd.                                              |
| Piñon blanco                            | <i>Jatropha curcas</i> L.                                                 |
| Piñon rojo, piñon negro, piñon colorado | <i>Jatropha gossypifolia</i> L.                                           |
| Patiquina                               | <i>Dieffenbachia</i> spp.                                                 |
| Punga amarilla                          | <i>Pseudobombax munguba</i> (Mart. & Zucc.) Dugand                        |
| Remocaspi                               | <i>Pithecellobium laetum</i> (Poepp.) Benth.                              |
| Shiwawaku                               | <i>Dipteryx odorata</i> (Aubl.) Willd.                                    |
| Tamamuri                                | <i>Brosimum acutifolium</i> Huber                                         |
| Toé, floripondio                        | <i>Brugmansia suaveolens</i> (Humb. & Bonpl. ex Willd.) Bercht. & J.Presl |
| Uchu sanango                            | <i>Tabernaemontana sananho</i> Ruiz & Pavon.                              |

\* Editor's Note: Mapacho is often claimed to be *Nicotiana rustica* L. in popular literature, however, there is no evidence to support this. The term "mapacho" is listed under the entry for *N. tabacum* L. in the *Amazonian Ethnobotanical Dictionary* (1994) and *N. rustica* is not listed in that publication. My colleague at UNAP, Curator of the Herbarium Amazonensis, Juan Ruiz, also confirms that "mapacho" is in fact *N. tabacum* L.

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# Spirit Bodies, Plant Teachers and Messenger Molecules in Amazonian Shamanism

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*Glenn H. Shepard, PhD*

Museu Paraense Emílio Goeldi, Belém, Brazil

## ABSTRACT

Western scientists and entheogen enthusiasts have used terms such as “psychoactive,” “hallucinogenic,” “psychedelic,” or more recently, “entheogenic,” to refer to shamanic plants and substances. Yet in all their permutations, such terms reinforce the foundational Cartesian dichotomy between body and mind, substance and spirit, the finite and the infinite. Indigenous peoples of the Amazon, by contrast, do not distinguish the mental or spiritual effects of shamanic plants and substances from their physiological or sensory properties. Among the Matsigenka people of Peru, for example, the term *kepigari* (which could be translated as “toxic,” or “intoxicating”) encompasses the physiological, sensory and cognitive dimensions of shamanic experience under a single, unified concept. The Matsigenka and other Amazonian peoples make no distinction between a shamanic plant’s active pharmacological ingredients and what we might refer to as the anthropomorphized “soul” that animates and infuses it with agency. Indeed, for the Matsigenka and other Amazonian peoples, the body can sometimes be used as a synonym for what we would refer to as the soul, and vice versa. And yet just as ethnobotanists might overlook the philosophical ramifications of indigenous ways of knowing, anthropologists in Amazonia, increasingly concerned with ontological questions, often overlook the material and phenomenological basis of indigenous knowledge. Indigenous concepts surrounding the sensory properties, body/mind

manifestations and spiritual properties of shamanic plants transcend Cartesian dualism. Specific plants and plant-based substances are sometimes personified by Amazonian shamans as “plant teachers.” Scientific findings about the role of messenger molecules in plant communication and an emerging appreciation of “plant intelligence” provide new windows of understanding into the deep truth behind shamanic concepts.

## STARS HAVE BODIES

Sitting out on a tropical night under a clear, shimmering sky, still reeling from the latest round of strong tobacco snuff, I ask Machipango why stars are alive. For over twenty years, Machipango has patiently endured these question-and-answer sessions about the most obvious things in the universe. Tonight, I am back on a subject that has intrigued me since my very first lesson in Matsigenka grammar: the animate/inanimate distinction. The Matsigenka language treats “animate” subjects and objects as grammatically masculine, taking the prefix *i-* at the head of possessed nouns and verbs and the suffix *-ri* for the direct or indirect object of verbs, while “inanimate” objects are grammatically feminine, taking the prefix *o-* at the head of possessed nouns and verbs and the suffix *-ro* for direct and indirect objects. Most animals for the Matsigenka are animate (masculine), with some exceptions like frogs and deer (because they are mythological female seducers), while water, soil and rocks are inanimate (feminine). Curiously, most plants are *not* treated as animate things by the Matsigenka: they “grow,” (*oshivokake*), but cannot move of their own volition (*tenga anutake*). On the other hand, money is animate, as are rubber, stars and other celestial objects such as the sun and moon. The basic distinction seems to be between things that exhibit locomotion or apparently volitional movement (doesn’t money flee from the hands as inexorably as a bouncy rubber ball?), and those that mostly stand still.

I know all this, yet nonetheless, I ask probably for the twentieth time, “What about plants? What about stars?”

And Merino answers, predictably, “Plants don’t move, they just stand there. The stars move across the sky.” But then he says something I wasn’t expecting:

“Stars have bodies.”

But I’m translating. What he really says is, *Aiño ivatsa*.

Now *ivatsa* is a curious word, because it may be used to refer to the body in a very physical sense, as in meat, flesh, the whole body or physical presence, but can also be used in reference to the invisible human essence or “spirit body” of certain personified beings. So on the one hand, animal meat is *ivatsa*, as is raw flesh exposed in a wound. The human body is also *ivatsa* (*novatsa*, “my body”). One can use the same phrase as a question to ask whether so-and-so is actually home: *aiño ivatsa*? “Is his body there?” i.e., “Is he physically present? Is he home?” (compare with English, “Is anybody home?”). Of course, we, too, refer to stars and planets as “celestial bodies,” but what we mean by this is something very different, indeed almost the opposite of what Machipango was saying. To refer to a star as a ‘celestial body’ is to emphasize its corporeal physicality while denying it any form of consciousness, animate nature or ‘soul’. But when Machipango says ‘stars have bodies’, what he means is that they have *human* bodies, which necessarily implies that they, like humans, have spirits or souls.

The soul for the Matsigenka is not an invisible force relegated to the pineal gland, as it were. Rather, the soul is what activates all bodily functions and gives it appetite, manifesting itself as the muscle and fat on a healthy body. Without ‘life essence’ (*yani*), the body is merely skin and bones. ‘Skin’ (*itaki*, also ‘tree bark’) and ‘bones’ (*itonki*), rather than flesh, are considered to be the inert aspects of the body. Flesh, muscle, blood and fat are all signs of the life force (*yani*) present in a healthy body. The life essence of animals is passed on to those who consume their flesh. Without meat (*ivatsa*) in their diets, people grow hungry (*itasegaka*), skinny (*imatsataka*), and ill (*imantsigataka*). A sick person or an old person who is thin and frail is as good as dead: The soul has already left the body, the flesh has been eaten away, and all that remains are the inanimate skin and bones. A person stricken by sadness likewise loses their appetite, wastes away, and eventually dies due to the flight of their soul.

According to Matsigenka myths and origin stories, in ancient times all species of animals, as well as the sun, moon, stars, and other beings, were human, which is to say, they had human bodies,

lived in human societies and possessed the trappings of human culture. Through a series of episodes related in Matsigenka myths and tales, these different beings were transformed into their current form, assuming the diverse bodies and habits of different animal species, celestial beings, spirits, certain plants, and so on. Primordial beings, the *Tasorintsi* or “blowing spirits” first used the transformative powers of tobacco and other psychoactive plants to breathe diversity into the animal and plant kingdoms. Thus, a transformative, shamanistic act is thought to underlie the observable taxonomic disjunctions between related species of organisms.<sup>14</sup> And yet, despite these transformations in their outward form and appearance in the current world of day-to-day existence, such spirit-beings still possess a human form that is invisible under ordinary circumstances, but which becomes visible in dreams and special states of consciousness. This underlying “body human” possessed by diverse cosmological beings is something we Cartesian Westerners wouldn’t call a body at all; if we were to call it anything, we’d likely call it a “spirit” or “soul.”

**14.** In this sense, the process we call evolution is driven, for the Matsigenka, by past and present shamans. The transformative cognitive effects of psychoactive plants are invoked by the Matsigenka to explain the same conundrum of evolution that Linnaeus once pondered: How did the world come to be filled with such a great diversity of plants and animals, all different and yet apparently more or less related to one another? For Linnaeus, the answer was the Mind of God. For the Matsigenka, the answer is God’s Mind on Drugs (Shepard 1999).

To distinguish between the mundane, visible form of such cosmological beings and their manifest, transcendent human body, I have heard a number of expressions that seem to defy our Cartesian, Western instincts. For example, the screaming piha (*Lipaugus vociferans*) or *vuimpuio* in Matsigenka, is a drab forest bird with an unmistakable song that begins like a low cat-call and then builds as a rising, whistled crescendo and finally bursts out in a ringing, explosive finale: *vui-vui-vui... VUIM-PUI-OH!*, hence the Matsigenka name for the animal. The *vuimpuio* bird is considered to be a helper to the Matsigenka shaman. The true *vuimpuio*, the one that appears to the shaman in trance – what we might call its “spirit” – is called *ivatsa*, “his body,” which is to say, *human* body. Its mundane form, visible to anyone walking in the forest, is merely *ivanki*, “his wings.” By the same token, the snake we see in the

forest is merely *ichakore*, “his arrow,” the poison dart the snake uses to kill its human prey, just as humans use arrows to hunt wild boar. The true snake is an invisible human hunter, called *ivatsa*, “his body,” possessing a human body and form, but who looks upon human beings as wild boar or tapirs to be hunted, killed and eaten (Shepard, 2002a). Jaguars and other predators likewise look upon human beings as game animals. By the same token, game animals like peccaries and tapir see themselves as human, while human hunters appear to them as jaguar-like predators.

Such concepts are widespread among Amazonian indigenous peoples, who conceive of the relationships among different beings of the cosmos in ecological terms (Reichel-Dolmatoff, 1976; Århem 1996). The notion of predation is especially important in Amazonian cosmologies (Fausto, 2007); and the status of different species, beings and bodies within the cosmic food chain depends upon their point of view. Hence, this theoretical paradigm has been dubbed “perspectivism” (Lima, 1996; Viveiros de Castro, 1996). What unites the various beings of the cosmos is not, as Western science would have it, their universal biological nature, but rather their universal *human nature* (Viveiros de Castro, 2002). Amazonian ethnography is replete with examples of perspectival relations with the animal world, and yet curiously, given the prominence of plants in the tropical rainforest ecosystem, contemporary anthropologists have showed far less interest in indigenous peoples’ conceptions of and relationships with plants (but see Daly 2015; Oliveira 2016).

## PLANTS HAVE SOULS

Continuing our conversation on the grammatical status of different “animate” vs. “inanimate” beings, I pressed Machipango on the subject of plants. Generally, the Matsigenka do not consider plants to be “animate” in the sense of possessing locomotion and volition: Plants “grow,” and hence do possess a “life force” (*ainyo ani*). However, they don’t “walk,” and for that reason, they are generally not treated as animate (for grammatical as well as philosophical purposes). There are exceptions, however. For example, the rubber tree, and certain other plants containing latex, are treated as grammatically animate (“masculine”), due to the flowing latex and elastic nature of the dried resin. Most

psychoactive plants are also considered to be animate beings with spirit “masters,” (*itinkami*), owners (*shintarorira*) or “mothers” (*iriniro*) who can appear in human form during dreams or altered states of consciousness to pass along healing powers and other forms of knowledge to those who use them properly.

The Matsigenka word for soul or spirit, *suretsi*, can also be used to refer to the heartwood of a tree or the pith of an herbaceous plant. When the core of a tree dies and its leaves stop growing, the term to express this is *okamasuretake*, “its core – its soul – has died.” Moreover, *suretsi* also refers to the pharmacological principles of medicinal, toxic or psychoactive plants. The activity of medicinal plants is described as *okitsitingake osure novatsaku*, “its soul infuses my body” (Shepard, 1999a, 2004): Note the use of the inanimate, “feminine” prefix *o-* on both the verb *okitsitingake* (“it infuses”) and the noun *osure* (“its soul”). When one cooks a medicinal plant, its “soul” infuses the herbal brew, often made visible by a change in the coloration of the liquid. Then, when one drinks the tea, the “soul” of the plant, manifest in its taste or odor as well as coloration of the liquid, then “infuses” the blood, nerves and muscles, spreading its medicinal, toxic, or other effects throughout the body. Thus, again contradicting our Cartesian instincts, not only can “inanimate” things have a soul, but also the “soul” can have observable, physical manifestations that are passed from one being to another.

### MATSIGENKA: ‘THE PEOPLE’

The Matsigenka are people of the *montaña*, the rugged rainforests of the upper Amazon fringing the eastern slope of the Andes. They currently number about twelve thousand people inhabiting the Urubamba, upper Madre de Dios, and Manu River basins in southeast Peru. The Matsigenka language belongs to the pre-Andine group of Arawakan languages, most closely related to Nanti, Ashaninka (Campa), Nomatsiguenka and Caquinte. The term *matsigenka* means simply, ‘people;’ and when referring to the human status of animals, certain plants and other beings, either in the mythical past or in the shamanic present, the noun is turned into a verb; *i-matsigenkatake* or *o-matsigenkatake*, “he/she takes on human form.”



The Matsigenka have traditionally practiced long-fallow swidden agriculture, growing manioc, plantains and bananas, maize, sweet potatoes, cotton, annato, beans, peanuts, chili peppers and a variety of other crops in small gardens cleared out of the forest (Johnson, 1983). Fish, game, fruits and other wild foods gathered from the forests and rivers of their environment are also essential in their diet. The Matsigenka traditionally lived in small settlements of extended families clustered according to a matrilocal (or uxorilocal) pattern of residence: a man marries out of his home village and goes to live with his wife's family (Johnson, 2003). In the past, such matrilocal settlements were widely dispersed and highly autonomous. As the Catholic Church, Evangelical missionaries and the Peruvian state have increasingly penetrated into the hinterlands, Matsigenka families have settled near mission outposts or government school houses, forming more densely populated, formally recognized "Native Communities" that can total hundreds of families. Since the 1980s, oil and gas prospecting activities have increasingly affected Matsigenka communities in the lower Urubamba region (Izquierdo & Shepard, 2003). The recent construction of the Camisea gas pipeline has caused lasting social, economic and political transformations in the communities of that region (Shepard, 2012). Though I have worked in many communities throughout the broader Matsigenka territory, most of my work has been among communities within Manu National Park somewhat buffered from the rapid rate of cultural changes going on currently outside this protected zone (Shepard et al., 2010).

### KEPIGARI: THE CONCEPT OF MEDICINES AS POISONS

Toxic, caustic, purgative, hallucinogenic, and other noxious plants figure prominently in the medical system of the Matsigenka. Like many indigenous peoples of the tropical rainforest, the Matsigenka are connoisseurs in manipulating plant compounds through domestication, preparation, and dosage to enhance desired effects while avoiding fatal toxicity. In describing toxic plants and their physiological activity, the Matsigenka use the term *kepigari*. The term invokes a chain of interrelated meanings: bitterness, toxicity, lethal poison, purgative and emetic properties, nausea and dizziness, psychoactivity, and shamanistic ecstasy. The relationship

between plant toxicity and curative power is fundamental to the Matsigenka's understanding of illness and healing: Medicines are also poisons, used to purge the body and soul of illness and illness-causing spirits (Shepard, 2005).

The term *kepigari* is derived from the root *-piga-*, 'to turn around, spin around, feel dizzy,' and hence by extension 'nausea, intoxication.' *Kepigari* refers to all toxic, poisonous, narcotic and psychoactive substances: alcohol, tobacco and other psychoactive plants; purgatives, emetics and poisonous plants; venomous snakes, frogs, insects and toxic mushrooms; any substance – from vanilla orchids to gasoline – with an overpowering "intoxicating" odor; and menstrual blood, known as *ogepigariaate*, "the poison that flows" (Rosengren, 1987). Many plants and other substances that are *kepigari* are also *kepishiri* ("bitter") or else have an "intoxicating odor," *kepigarienga*. Bitter, pungent and other noxious plants are sought out by Matsigenka healers because their toxic properties are said to hurt, kill and expel intrusive illness-causing agents, whether spiritual or material in form (Shepard, 2004).

*Kepigari* refers to the physiological state of intoxication, including bouts of dizziness, fainting, nausea and vomiting, as well as drunkenness, shamanic ecstasy and even insanity. In chants that accompany shamanistic ceremonies, singers evoke the physical and cognitive sensations of these experiences, and *kepigari* is intoned frequently to denote the whirling, giddy sensation of ecstasy. Plants used to induce altered states of consciousness like tobacco, *ayahuasca* and *Brugmansia* (fundamental to the Matsigenka shaman's transformative powers) are all *kepigari*. I hesitate to use Western terms like "psychoactive," "narcotic," "hallucinogenic" or "psychedelic" to refer to these shamanic substances, since such terms reinforce the foundational distinction René Descartes drew between *res extensa* ("extended [i.e. in space] things"), or material substance, versus *res cogitans* ("thinking things"), or mental substance. Cartesian dualism between mind and body remains a fundamental problem in Western science and philosophy; in working with peoples who have different notions about the world and its various substances and beings, we find ourselves tripping over it all the time. For example, when we say a plant is "psychoactive" or "psychedelic," we focus on mental, emotional and

psychic states, as if these were somehow separate from physiological effects in the body. By calling such substances “hallucinogens” we further denigrate them by assuming that the visions they produce are mere hallucinations, fantasies, fallacies.

The term *entheogen*, “revealing God (or the divine) within” (Ruck et al., 1979), was coined to overcome the bias and derogatory nature implicit in terms like “hallucinogen.” And yet, the Greek term *theos* at the root of the expression ironically reinforces the tenets of Cartesian philosophy by emphasizing the third substance posited by Descartes, namely God, *res infinita*, a special kind of “thinking substance” that, unlike mortal human thought, is infinite in scope. Indeed, many entheogen users focus their enthusiasm on the spiritual and religious aspects of their experiences, while minimizing, or even consciously attempting to eliminate, unpleasant physiological side-effects like nausea. For the Matsigenka, there is no such thing as “side effects,” since the physical, mental and spiritual dimensions of shamanic plants are all integrated with their overt chemosensory properties (bitter taste, toxicity) into the single concept of *kepigari*, “intoxicating.” Transcendental effects in consciousness go hand-in-hand with unpleasant effects in the body such as nausea, vomiting, sweating, shaking and dizziness, which are in turn signaled, encapsulated, and transmitted through specific empirical, sensory properties (bitter, astringent, caustic) associated with toxicity. The more intense the toxic effects endured by the body, the more profound are the visions experienced by the soul: The stronger the poison, the better the medicine.

## SUBSTANCE, SOUL, AND SENSATION: A SENSORY ECOLOGY OF MEDICINAL AND SHAMANIC PLANTS

Sensory properties like taste, odor, color, texture and so on serve for more than just identifying plants and transmitting this knowledge to others. Rather, sensory cues and perceptions are crucial to understanding how medicines interact with illness agents in the body, how illness enters and affects people, and how people relate to one another and to other beings in the cosmos. This approach, which I have called “sensory ecology” (Shepard, 2004),

builds on the work of other anthropologists who have explored cultural variations in sensory experience (Stoller, 1989; Classen, 1990; Howes, 1991). Sensory ecology seeks to appreciate and analyze indigenous understandings of sensory experience, attending to the interwoven biological, cultural, experiential and cosmological dimensions of sensory experience. Here, I apply the approach of sensory ecology to a number of important toxic, medicinal, and psychoactive plants in the Matsigenka pharmacopoeia.

Tobacco and shamanism are synonymous for the Matsigenka: The shaman is *seripigari*, “the one intoxicated by tobacco” (Baer, 1992). Tobacco (*Nicotiana tabacum* L.) is consumed by the Matsigenka in many forms: smoked (*nopenatakeri*) in pipes, drunk in liquid form (*oani*), chewed in a concentrated, bitter quid (*opatsa*) and blasted up the nostrils as powdered green snuff (*opane*). Tobacco is judged by how painful (*katsi*) it is to the taste or in the nostrils. The intensity of the tobacco’s pain (*katsi*) is proportional to its intoxicating strength (*kepigari*), which is also a measure of the shamanic strength of the person who prepared it. The more painful the tobacco, the more powerful the shaman. Tobacco is like food for shamans and their spirit allies: As their powers grow, shamans come to relish the pungent nourishment of tobacco over ordinary food. By sharing tobacco snuff or quid in daily life, and especially during an *ayahuasca* session, Matsigenka men reinforce social bonds while performing a mystical exchange of powers through the physical medium of the tobacco substance (Shepard, 2015a). Tobacco snuff is prepared by drying and grinding fresh, green tobacco leaves to a fine powder, mixed with the ash of specific kinds of tree bark. In addition to its social and shamanic functions, tobacco can also be used to fight off the nasal congestion caused by colds, or to dispel bad dreams by physically “hurting” (*okatsitakeri*) the illness vector or harmful spirits causing discomfort. Likewise, tobacco quid tossed near the watery lair of an anaconda acts to ‘burn’ (*otegakeri*) the snake and frighten it away.

Tobacco quid or paste, *opatsa seri*, is prepared by boiling cured tobacco leaves with pounded *Banisteriopsis* liana until it is reduced to a thick, dark, bitter paste which is absorbed using native cotton (*ampeí*) to form a quid that is stored in bamboo tubes. *Opatsa seri* is taken during *ayahuasca* sessions to augment the visionary

experience, or can be taken alone to induce dreams. The master shaman swallows *opatsa seri* and then regurgitates it, giving it to his apprentice mouth-to-mouth in a mystical kiss, thereby passing on his shaman's soul and his supernatural powers.

One Matsigenka shaman explained *opatsa seri* in this way (Shepard, 1998: 325):

*Opatsa seri* is a seed. When you swallow it, it is like planting a seed in your heart. Your tobacco (*pisere*) is your soul (*pisure*). Each time you take *opatsa seri*, your soul grows like a tree. Not the ordinary soul, but the shaman's soul, the soul of the *Saankariite*. Your brother. Not everyone has a tobacco soul, only the *seripigari*. My teacher long ago gave me his tobacco (*isere*), thus giving me his soul (*isure*). Just like I have now given you my tobacco (*nosere*), which is my soul (*nosure*).

He emphasized the similarity in the sound of the words *nosere*, "my tobacco," and *nosure*, "my soul," suggesting they were virtually synonymous: a clear example of how shamanic powers can be gained and transmitted through the transfer of specific, usually toxic, substances.

Like many other Amazonian peoples, the Matsigenka currently prepare the *ayahuasca* brew by boiling the liana *Banisteriopsis caapi* (Spruce ex Griseb.) C.V.Morton with leaves from one or more species of the *Psychotria* shrub. The Matsigenka name for *Banisteriopsis* is *kamarampi*, literally, "vomiting medicine," emphasizing the plant's purgative properties. Though *ayahuasca* is mostly known in Amazonia for its religious and medical uses, a main goal of *ayahuasca* use among the Matsigenka of the Manu River is to help men improve their hunting skills. Consumption of *kamarampi* is thought to cleanse a man's body of contamination from improperly cooked meat, menstrual blood and other sexual and dietary impurities (Shepard, 2002b; see below). While the emetic properties of *kamarampi* cleanse the hunter's body, the psychoactive properties allow the hunter's soul to visit the *Saankariite* ("invisible ones," benevolent forest beings) and convince them "not to be stingy" (*gani itsaneakaro*) with their pets, the game animals of the forest. Matsigenka men of the Manu take *Banisteriopsis* frequently throughout the rainy season, when many forest fruits are ripe and the game animals, especially large primates

like woolly and spider monkeys, are fat. When you ask Matsigenka men why they take *ayahuasca*, they typically answer, “I take *ayahuasca*, the next day I go out and kill two monkeys.” The Matsigenka avoid taking *ayahuasca* during the dry season, because they say the spirit world is full of dangerous fires caused by the *Saankariite* who, like the Matsigenka, burn their gardens during that time of year.

Prior to the 1960s, the Matsigenka of the Manu region did not use DMT-containing *Psychotria* species as an admixture to *Banisteriopsis*. Instead, they prepared *Banisteriopsis* by boiling it for long periods of time until it was reduced to a honey-like consistency, sometimes mixing it with tobacco in the preparation known as *opatsa seri*, noted above. Various other plants were used as admixtures, and their use appears at least partly related to the presence of brightly colored venation or markings on some species’ leaves, said to produce colorful patterns during trance (see Shepard, 1998). The Matsigenka of the Manu region learned to use the *Psychotria* admixture from Matsigenka fellows from the neighboring Urubamba river who had come to the region, ironically enough, in the company of Protestant missionaries (Shepard, 2015b). The plant was already present in their environment, but since the knowledge came from the Urubamba region, they refer to it now as “Urubamba-leaf,” *orovampashi*. Although *Psychotria viridis* Ruiz & Pav. is the most frequently mentioned *ayahuasca* admixture in the literature, the Matsigenka consider this to be a dangerous plant, used by sorcerers of rival tribes such as the Shipibo and Piro. The Matsigenka name for *P. viridis* is *irorovampashi pijiri* (“*Psychotria* of the bat”) or *yakomamashi* (“anaconda leaf”) since it is said to be “owned” by these animal spirits, who bring on terrifying visions of bats or snakes. The Matsigenka consistently use another as yet unidentified *Psychotria* species which they refer to as *orovampashi-sano* (“true *Psychotria*”). This plant, they say, causes no unpleasant visions of bats or snakes, but only “good” visions of birds and happy, dancing *Saankariite* spirits (Shepard, 1998). Their observations appear to hint at different concentrations of different DMT-related compounds in closely related species. These examples also attest to the wide variety of traditional uses and preparations which

preceded the more homogenous current *ayahuasca* tradition that apparently spread in the aftermath of the rubber boom (Shepard, 2015b).

The cultivated *Datura* relative, *Brugmansia suaveolens* (Willd.) Bercht. & C.Presl, is known to the Matsigenka as *jayapa*, *saaro*, or simply, *kepigari* (“intoxicant, poison”). Containing potent tropane alkaloids such as atropine and scopolamine, it is considered to be the most intoxicating (*kepigari*) and strongest of all medicines. Frequent use is considered to be dangerous, and I have documented several cases of deaths owing to overdose or excessive use (Shepard, in press). Great care is taken in the preparation and dosage of *Brugmansia* due to its high potency and toxicity. The fresh leaf can be heated and applied as an external plaster for broken bones, stomach aches, arthritic pains, swelling and other conditions, consistent with biomedical uses of atropine. A small dose may be given orally to a woman suffering from difficult childbirth, a practice that recalls the use of scopolamine to induce “twilight sleep” during childbirth in American hospitals in recent times. A larger, vision-inducing dose of *Brugmansia* infusion may be given orally as a last resort to treat people suffering from severe trauma, chronic illnesses, or suspected sorcery. During these sessions, the patient can spend days, even weeks in a trance where spirit beings, white-robed doctors or the spirit “mother” of the plant herself appear to them to reveal the true source of their suffering, remove any intrusive sorcery objects and repair the physical or spiritual damage. Apprentice shamans may take a large dose to open a channel of communication with the *Saankariite* forest spirits. During the intense, dream-like state of *Brugmansia* trance, shamans may also receive new agricultural varieties from the *Saankariite*, especially manioc cuttings and medicinal sedges (Shepard, 1998; Shepard, 1999b). *Brugmansia* plants that have gone to seed in old gardens or along river courses are referred to as “*Brugmansia* of the caiman” (*iayapate saniri*), and considered to be extremely dangerous when ingested, leading to soul loss or death.

Amazonian ethnobotanists in the tradition of Richard Evans Schultes have shown a special interest in psychoactive plants. Yet among the Matsigenka, the concept of *kepigari* is not restricted to

vision-inducing shamanic plants, but embraces a wide range of other toxic, caustic, emetic and purgative plants used for a variety of purposes. For treating recently cut umbilical cords and the tropical skin disease leishmaniasis, the Matsigenka use a number of toxic plants including curare species<sup>15</sup> (*Curarea*) and the highly toxic cultigen *Solanum mammosum* L. The bitterness (*kepishiri*) and painful causticity (*katsi*) of these plants is said to “embitter” (*okepishitakeri*), “hurt” (*okatsitakeri*), and “kill” (*ogamagakeri*) the illness-causing vectors.

**15.** I have collected and identified most of the plant species mentioned in this and other published works. However, in order to protect Matsigenka intellectual property rights, I refrain from publishing full species information for all but the most commonly known, widespread species.

The Matsigenka attribute many gastrointestinal and skin conditions as well as ear, eye, and tooth infections to the activity of tiny worms (*tsomiri*) that enter the body and gnaw at the affected part. Although they are aware of parasitic intestinal helminths, the conception of *tsomiri* is broader, embracing microscopic illness-causing agents much like our own folk concept of “germs” or “microbes.” Many illnesses are treated by ingesting or applying plants with strong, noxious sensory properties – bitter, astringent, pungent, caustic, sour (Shepard, 2004). Such properties are manifestations of the plant’s soul (*osure*), a holistic healing force that infuses (*okitsitingakero*) the herbal decoction and the body of the patient. Pathogenic agents react to noxious properties much like humans, suffering pain and discomfort, retreating, and at high enough doses, perishing. In other cases, the Matsigenka take specific steps to detoxify overly poisonous plants to render their usage safe, especially for children. One species of *Anthurium* known as *matsontsorishi*, “jaguar leaf,” is known to cause severe skin irritation when handled raw. However, when boiled long enough in water, the noxious properties are attenuated and the concoction is used to bathe newborns in order to protect them from illness.

## EAGLE EYES: THE ETHNOPHARMACOLOGY OF HUNTING MEDICINES

A significant portion of the Matsigenka pharmacopeia is dedicated



to what is often referred to in the literature as “hunting magic” (Daly et al., 1992). According to my observations, there seems to be more pharmacology than magic at work. Some 25% of the Matsigenka pharmacopoeia belong to a category that should be more properly called “hunting *medicines*,” referred to in Matsigenka as *kovintsari*, “to have or achieve good aim.” Being a good hunter is not only about having keen eyesight, good aim and a strong, sturdy grip on the bow. The hunter must, in the first place, be able to see the animals in the forest. A hunter who has “lost his aim” is not only unable to fire his arrow straight, he is, in a deeper sense, unable to locate and visualize game animals. This happens because he has violated behavioral, dietary and sexual taboos that offend the “masters” (*itinkami*) or “owners” (*shintarorira*) of game animal species (see also Fausto, 2008). (Note that the same terms are used to refer to the owners or spirit-masters of psychoactive and other powerful plants). Purity, both spiritual and bodily, are fundamental to a hunter’s tracking skills, physical stamina and “aim.”

A man can lose his aim by eating spoiled or improperly cooked meat. For example, if his wife allows a pot of meat to boil over and spill into the flames, the sizzling broth vaporizes and its odor wafts into the forest, where the “owner” of that particular species smells the telltale sign of improperly prepared meat and becomes angry, saying, “Who is wasting my pets?” The spirit owners of game animal species raise wild animals much like humans raise chickens or dogs, and they can reveal or hide their “pets” to specific hunters as they see fit. If possible, a man should avoid carrying the animal he has killed, lest his body become infused with the odor of the animal’s blood, thereby warding off the animals and their master the next time he goes to the forest. A companion, typically a brother-in-law or teenage boy, carries it for him. A man should never eat the head of the animal he has killed. To eat the head is to take on, quite literally, the point of view of the dead animal, breaking down the balance in the predator-prey relationship. Sexual intercourse the night before a hunt, or any contact with menstrual blood or menstruating women, said to smell like carrion or raw meat (*janigarienka*), also takes away a man’s aim: the strong odors of sexual fluids and menstrual blood likewise offend and frighten game animals and their spirit-masters.

When a man violates these norms, he thus loses not only his aim, but his ability to encounter animals in the first place. Such a man's body is said to reek with the carrion smell of spoiled meat or raw blood, and his soul becomes possessed with the spirit of the vulture. A number of species of purgative and emetic plants are taken by hunters to clean themselves of sexual, dietary, and ritual impurities. Fathers prepare their adolescent sons for manhood and hunting through a rigorous regimen of purgative, emetic or psychoactive hunting medicines belonging to a wide range of botanical families. Frequent use of *ayahuasca* during the rainy season is part of this broader practice associated with hunting medicine. Many hunting medicines are bitter or induce fits of vomiting or diarrhea of various degrees of severity. The more bitter and the more extreme the purgative effect, the better the medicine. The idea behind purgative remedies is to clean out the body of the spoiled meat and carrion-eating vulture spirit and replace it with the harpy eagle's hunting spirit. *Pakitsa*, the harpy eagle, is the epitome of hunting prowess for the Matsigenka.

Matsigenka men also apply the leaf-juice of numerous plant species (mostly Rubiaceae) to their eyes in order to clarify vision and instill the hunter with the soul of the harpy eagle, *Pakitsa* (Shepard, 2002b). The acidic or mildly caustic eye-drops cause the eyes to sting and water intensely for a few minutes, like getting lemon juice or chili peppers in the eyes. The stinging sensation is the sensory cue indicating that the "soul" (*osure*) of the plant is "infusing" (*okitsitingakeri*) the man's body, starting with the eyes, spreading through the head and descending into the torso, arms and hands through the muscles and veins. When hunting, the plant's soul also infuses the bow and the arrow with its power.

Cultivated sedges (*Cyperus* spp.), referred to as *ivenkiki*, are an especially important part of Matsigenka hunting lore, and of medicinal practices more generally. Individual Matsigenka men and women can cultivate dozens of sedge varieties in a single garden. There are sedge varieties for treating fevers and headaches, for dispelling nightmares, for healing arrow wounds and snake bites. Women cultivate sedge varieties for protecting babies from animal spirits, facilitating childbirth, for reducing or increasing fertility, for improving their skill in spinning and weaving cotton and resolving

domestic disputes. Men cultivate a plethora of sedge varieties as hunting medicines, each sedge variety corresponding to a specific game animal. Many of the sedge varieties appear to be botanically identical, and only their owners are able to distinguish them. Given the tremendous diversity of uses for what appear to be nearly identical plants, ethnobotanists had long overlooked sedges in the Amazon, until it was discovered that cultivated sedge varieties in the Amazon harbor a systemic, mutualistic infection of the fungus *Balansia cyperi* (Plowman, *et al.*, 1990), which belongs to the Clavicipitaceae, the same family as rye ergot (*Claviceps purpurea*) from which medically important ergot alkaloids, including psychoactive lysergic acid derivatives closely related to LSD, are extracted. Like rye ergot, the *Balansia* fungus (and not the sedge plant itself) produces a number of ergot-like compounds. Ergot alkaloids are known to constrict blood vessels, alter uterine contractions, and at high enough doses cause convulsions and hallucinations. The Matsigenka's use of different sedge varieties to treat wounds and snakebites, to staunch birth-related hemorrhaging and to alter fertility are consistent with the physiological properties of ergot alkaloids. Hunters carry specific sedges along on the hunt and consume them just before shooting an arrow. The hunter chews the root bulb, which has a bitter, aromatic taste, and then spits the masticated bulb onto his hands, on the bow, on the arrow, and towards the game animal. The sedge is said to infuse the hunter's body and weapon with its power, while mesmerizing the animal. The vasoconstrictive and psychoactive properties of ergot alkaloids may contribute to the hunter's heightened state of awareness, calm and perception.

*Brunfelsia* spp., belonging, like *Brugmansia* to the Solanaceae, are used widely throughout the Amazon for treating a variety of conditions, especially arthritic pains (Plowman 1981). The Matsigenka recognize several folk species: *sankenke* ("purifying shrub"), *oshetopari* ("spider monkey root"), *shimakoa* ("fish plant") and *pakitsapari* ("eagle root"). *Pakitsa*, the harpy eagle, is the epitome of hunting prowess for the Matsigenka. In ancient times, *Pakitsa* walked the earth in human form and taught these and other hunting medicines to the Matsigenka (Shepard 1998). *Kaviniri*, apparently a distinctive species of *Brunfelsia*, is said to instill such

formidable hunting powers that the user turns into a jaguar and becomes a threat to his own family (Shepard 2014). *Brunfelsia* is prepared as a tea or cold infusion, and produces dizziness, nausea and a unique, needle-like prickling sensation in the hands and feet for several hours to several days. Depending on the dosage, *Brunfelsia* consumption can produce visions, convulsions or even coma. The Matsigenka describe the tingling, prickling sensation with the phrase, *tseki-tseki-tseki-tsek!*, the sensation of needles pricking the skin. This sensation is the physiological manifestation of the infusion of the plant's soul (*osure*) into the hunter's body, giving him the same clear eyesight and ferocious hunting ability as the plant's owner, the harpy eagle.

#### DISCUSSION: PLANT TEACHERS, PLANT INTELLIGENCE AND MESSENGER MOLECULES

The Matsigenka ingest a wide range of bioactive plants, following careful modes of preparation and administration, in order to infuse their bodies with chemical compounds that are selected and recognized according to specific sensory manifestations. The physical absorption of plant substances is understood to establish an intimate relationship with the personified "owners" or "masters" that infuse these plants with spiritual power: in short, transubstantiation. The concept of direct apprenticeship from plants is widespread among indigenous as well as non-indigenous peoples of the Amazon. As Luis Eduardo Luna (1984: 140, 142) writes in his study of *mestizo ayahuasca* healers or *curanderos* in Amazonian Peru,

Crucial to shamanic practices is the belief that many plants, if not all plants, each have their own "mother" or spirit. It is with the help of the spirits of some of these plants, which I have called "plant teachers", that the shaman is able to acquire his powers... Informants insist that the spirits of the plants taught them what they know.

According to Eduardo Viveiros de Castro (2004: 468), such ways of knowing stand in direct opposition to the Western philosophical tradition, where knowledge is achieved through objectification, which is to say, de-subjectification:

Amerindian shamanism is guided by the opposite ideal. To know is to personify, to take on the point of view of that which must be known. Shamanic knowledge aims at something that is a someone – another subject. The form of the other is *the person*.

For Viveiros de Castro (ibid.), Amerindian peoples view social relationships, as defined by cosmological perspective, to form the primary substrate of the universe, while physical substances are secondary:

Our traditional problem in the West is how to connect and universalize: individual substances are given, while relations have to be made. The Amerindian problem is how to separate and particularize: relations are given, while substances must be defined.

Viveiros de Castro implies not only divergence between Western and Amerindian ways of knowing, but a nearly perfect, dichotomous inversion. Presenting indigenous ways of knowing as a mirror-image of our own risks simplifying the internal complexity of indigenous knowledge while at the same time reproducing the problematic Cartesian dichotomy (nature/culture, mind/body, matter/spirit) from the other side of the looking glass. In this review of Matsigenka pharmacology and pharmacognosy, I have sought to show how their understandings of illness agents, spirit beings, and shamanic powers are revealed through the direct experience of specific plant substances. In this sense, the Cartesian divide simply falls away. Plant-based chemical compounds are not so much material vehicles that open neural networks or pathways of communication with spirit beings, they *are* those spirit beings in and of themselves, manifested through specific sensory cues and transubstantiated in the physical process of infusion and absorption into the holistic spirit-body.

Ingold (2000) resists the anthropological tendency to dichotomize indigenous and scientific ways of knowing, emphasizing the holistic quality of environmental perception whether among indigenous peoples, field biologists or ethnobotanists. His description of how environmental knowledge is learned and transmitted captures the texture of my long apprenticeship with Matsigenka shamans,

hunters and herbalists: “When the novice is brought into the presence of some component of the environment and called upon to attend to it in a certain way, his task, then, is not to decode, but rather to discover for himself the meaning that lies within it” (ibid: 20). Ingold draws a distinction between the symbolic *cipher*, that must be decoded, and the holistic *clue* that is revelatory in itself, that “opens up the world to perception of greater depth and clarity” (ibid). Odor, taste and other chemosensory properties used by the Matsigenka to ascertain and understand the powers of medicinal and shamanic plants are “clues” in this holistic sense.

In the case of psychoactive plants, their revelatory nature emerges directly from the material properties of specific chemical substances. In this sense, and contrary to Viveiros de Castro’s (ibid) formulation, substance and relation are not only both equally “given,” but indeed intimately entwined. Psychoactive compounds mimic the structure of specific brain hormones known as neurotransmitters, responsible for chemical communication across the junctions (synapses) between neurons. Due to their specific three-dimensional chemical structure, neurotransmitters bond with specialized receptor sites on the surface of the post-synaptic neuron, causing it to relay electrical impulses along its own axon. Due to their similar, but not identical, chemical structures, psychoactive compounds bond with specific neurotransmitter receptor sites, magnifying, suppressing, or otherwise altering their activity. For example, psilocin, found in hallucinogenic “magic mushrooms,” is a tryptamine derivative that mimics the structure of 5-hydroxytryptamine (5-HT), the chemical name for the neurotransmitter serotonin. Psilocin, ibogaine, dimethyltryptamine (DMT – found in the *ayahuasca* brew), LSD, and other compounds found in traditionally used psychoactive plants and fungi belong to a class of compounds known as indole alkaloids, all derived from the same basic tryptamine structure.

Though a fair amount is now known about *how* psychoactive plants and compounds produce their peculiar effects on the human mind, it is still largely a mystery as to *why* certain plants produce such compounds. Alkaloids and other physiologically active compounds do not appear to be directly involved in the primary metabolic activities of plants. For this reason, they have been

referred to as “secondary” plant compounds. And yet alkaloids contain nitrogen, a limiting element in plant growth, which means they are produced at a significant metabolic cost. Some have theorized that toxic compounds in plants evolved as chemical defenses to deter animals from eating their leaves, stems, roots, fruits, or seeds during particular life cycle phases.

Gottlieb and Borin (2005: 34) have pointed out that the most important secondary compounds driving animal-plant interactions, namely alkaloids and polyphenols, may not, in their evolutionary origins, have anything to do with attracting or deterring predators. Instead, these compounds likely evolved to communicate information across cell membranes:

The primordial function of micromolecules in organisms, and probably the reason for their original appearance, does not concern attraction, defense or any other ecological function, but membrane construction... Considering the principal properties of micromolecules, e.g. small molecular mass, polarity, chirality, chemical reactivity (structural variation), different and variable half-lives, sporadic occurrence and antioxidant potential; it is possible to suggest that these molecules are messengers of information.

Up to 100,000 different compounds belonging to at least twenty different classes of molecules with communicatory roles have been identified for plants, and insights are now emerging as to their specific functions in transmitting information within cells, between cells of the same plant, among individuals of the same or different plant species, and with other organisms, notably animals and fungi. The analysis of such communication within, between and beyond different organisms is known as biosemiotics (Witzany 2008). Biosemiotics includes the analysis of combinations (syntax), context (pragmatics) and content-specific meanings (semantics) of chemical and other forms of signaling between organisms.

Traditional students of plant physiology have concluded that the growth patterns and developmental adaptations of plants in response to various stimuli such as light, water, nutrients, gravity and herbivory to be rote, genetically programmed adaptive responses. Trewavas (2003) reviews a wide range of research findings that suggest that plants show a capability for learning and

problem-solving that goes beyond mere passive vegetative response, constituting a form of “plant intelligence.” Trewavas (2003: 2) further points out that “the suite of molecules used in signal transduction are entirely similar between [animal] nerve cells ... and plant cells.”

Such scientific findings give new levels of meaning to indigenous understandings of “plants as teachers.” Compounds that may have originally emerged to facilitate communication of information within and between plant cells, now continue to serve as messenger molecules, transmitting information across multiple levels: the intra and inter-cellular, the inter-organismal and biospheric, as well as among multiple beings across different layers of the cosmos. By bringing indigenous understandings into dialog with biochemical insights, native and scientific concepts can illuminate one another, without privileging one perspective over the other. The empirical, sensory properties of plants can be seen, both by scientists and shamans, as concrete chemical signs that emerge within a complex web of information, transmission, communication and ultimately, relation between diverse beings, each with its own syntax, semantics, pragmatics and goals. The concept of plants as teachers is more than metaphor: it is a profound and accurate description of shamanic biosemiotics.

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# Broad Spectrum Roles of Harmine in *Ayahuasca*

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Dale Millard

Wasiwaska, Research Center for the Study of Psychointegrator Plants, Visionary Art and Consciousness, Florianópolis, Brazil

## ABSTRACT

*Ayahuasca* is an Amazonian psychoactive plant beverage used ceremonially, normally containing *Banisteriopsis caapi* (Spruce ex Griseb.) Morton as a base ingredient and an admixture plant, either *Psychotria viridis* (Ruiz & Pav.) Schult. in Brazil and Peru, or *Diplopterys cabrerana* (Cuatrec.) B. Gates in Colombia and Ecuador. In the latter case it is normally referred to as *yagé*. In the Amazon, *ayahuasca* is commonly prescribed to combat psychospiritual as well as physical ailments (Dobkin de Rios, 1972).

This paper seeks to provide an overview from both past and current literature on harmine, demonstrating its wide variety of therapeutic activity inducing antimicrobial, anti-diabetic, anticancer, antidepressant, antiparasitic, DNA-binding, osteogenic, chondrogenic, neuroprotective and other effects. Harmine is by far the most abundant constituent of the medicine *ayahuasca*. Its presence in pharmacologically active amounts may therefore provide a rationale for its contribution in *ayahuasca*'s wide application in traditional medicine and its general reputation for treating a broad range of diseases and ailments.

Some of the psychoactive and physiological roles of harmine have been known since Lewin published his paper on banisterine in 1928. Harmine has now received the attention of the international scientific community, looking at a broad range of activities that allude to the possible applications of harmine in several different areas of medicine. In more recent years studies have begun looking at both the endogenous and physiological roles of

dimethyltryptamine. Similarly,  $\beta$ -carbolines are found in various body tissues and fluids.

A major role of harmine in the synergistic effect of *ayahuasca* chemistry is to function as a monoamine oxidase inhibitor (MAOI) that allows dimethyltryptamine to become orally active, though as a molecule on its own, harmine also shows some potent and broad-spectrum activities. The findings discussed in this paper may suggest future opportunities in areas where conventional medicine is facing challenges.

## AIMS AND OBJECTIVES

This article explores the  $\beta$ -carboline constituents of *ayahuasca*, with special attention paid to the dominant alkaloid harmine, its potential role in primary healthcare and as a natural-product medicine. However, not all of the physiological properties of harmine have been discussed. Focus has been placed on those areas deemed of most value, as well as some of the interesting lesser-known effects. As *ayahuasca* is a complex brew of chemicals, it is not the author's intention to undermine the roles that any of the other chemical constituents may play in producing healing effects. Some of this chemistry is likely to be synergistic in its effect, as is already known to be the case with harmala alkaloids and tryptamines.

It is hoped that this review may help readers, researchers, policy makers and consumers of *ayahuasca* explore some of the hidden potentials of harmine and raise general awareness as to its possible therapeutic role in this medicine.

## METHODOLOGY

The material cited in this paper was derived from a variety of sources. In-depth online searches using the search engines Google, Science Direct and PubMed were conducted. Private libraries as well as the author's personal archives were consulted. Personal comments and ideas shared in general conversation have also been included. In the introduction, aims and objectives and conclusion sections, the personal beliefs and viewpoints of the author have been included.

## INTRODUCTION

*Ayahuasca* is a Quechua term used to describe the sacred Amazonian medicine used ceremonially and for a host of other purposes. Aya + huasca, translated as death/spirit + vine, traditionally refers to the vine *Banisteriopsis caapi*. Other plants such as *chacrana* (*Psychotria viridis*) in Brazil and Peru, and *yagé* (*Diplopterys cabrerana*) in Colombia and Ecuador) (Shultes, 1957) are considered admixture plants incorporated for a desired effect. In several Amazonian tribes such as the Tukano (Shultes, 1976), *Banisteriopsis* preparations are consumed without the addition of admixture plants.

*Ayahuasca* has become a well-documented global phenomenon (Tupper, 2006) and in this global community *ayahuasca* generally refers to a preparation of *Banisteriopsis caapi* in combination with a dimethyltryptamine source plant.

Since the 1970's when anthropologists first started focusing on the uses of *ayahuasca*, much has been documented in terms of cultural use for many different purposes such as hunting, war, healing of psychosomatic illness, magical or ritual purposes, etc. (Dobkin de Rios 1972). Sadly, there are no systematic studies, and no major attention seems to have been paid to the use of *ayahuasca* in the treatment of various physiological diseases found in the Amazon. The author found only scant references (Rodrigues et al., 1982; Karsten, 1964; Karsten, 1935; Spruce, 1908) mentioning its use amongst *mestizos* for treating physical ailments. This was perhaps due to the astonishing visionary psychoactive effects of the medicine, which captivated the attention of early explorers and researchers. It can be supposed that since then, much of this type of medicinal knowledge may have disappeared, though this area should still remain open as an important avenue of research.

*Ayahuasca* certainly contains bioactive chemicals with a broad range of physiological properties, many of which can be exploited as medicine. More recently there has been much interest shown in the physiological properties of compounds contained in *ayahuasca*. The endogenous compound dimethyltryptamine (DMT) is believed to have important physiological properties. A sigma-1 ligand, DMT is known to play a pivotal role in many pathologies (Fontanilla et al, 2009; Frecska et al, 2013).

## POSSIBLE ROLES OF HARMINE AND $\beta$ -CARBOLINES IN NATURE

$\beta$ -carbolines are widely and commonly distributed in nature. These compounds have been detected as component substances in many different tissues of living organisms and continue to be discovered across many plants from different families, as well as fungi, mammals, reptiles, birds, and in humans. Although the exact evolutionary role these substances play in organisms and natural systems is at present poorly understood, some preliminary studies discussed here may disclose possible functional roles.

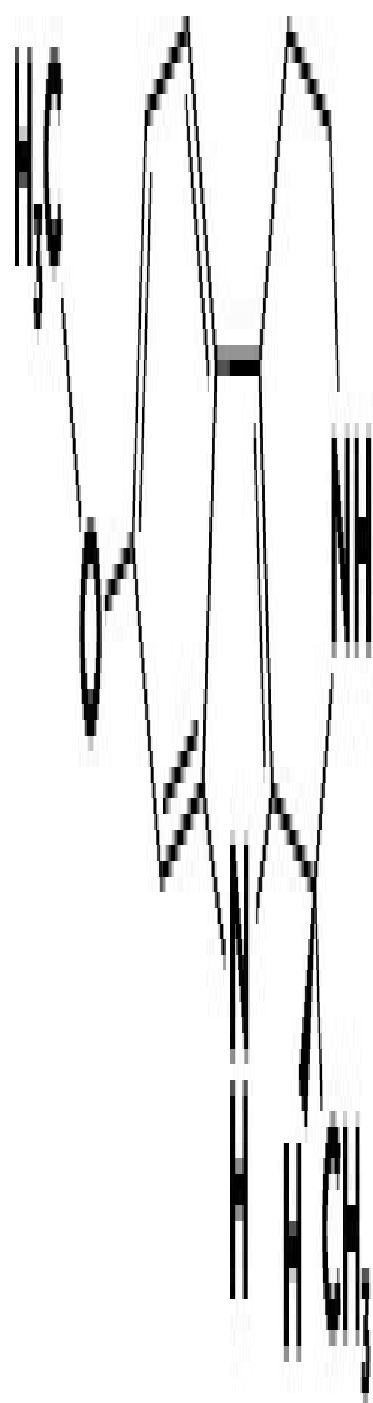
As  $\beta$ -carbolines are increasingly being discovered in nature and as endogenous substances in humans, the discovery of their many functions is important, regarding both the role they play in our intrinsic health/biological systems and when introduced through medicine or diet.

When *ayahuasca* vines are harvested with machetes in tropical conditions, they tend to recover rapidly. Many other plants would not tolerate such harvesting practices in such microbe-rich environments. This tendency to strongly resist rot and disease may point to the possible antifungal and antibacterial role of  $\beta$ -carbolines in plants such as *Banisteriopsis caapi* which contain high levels of these substances.

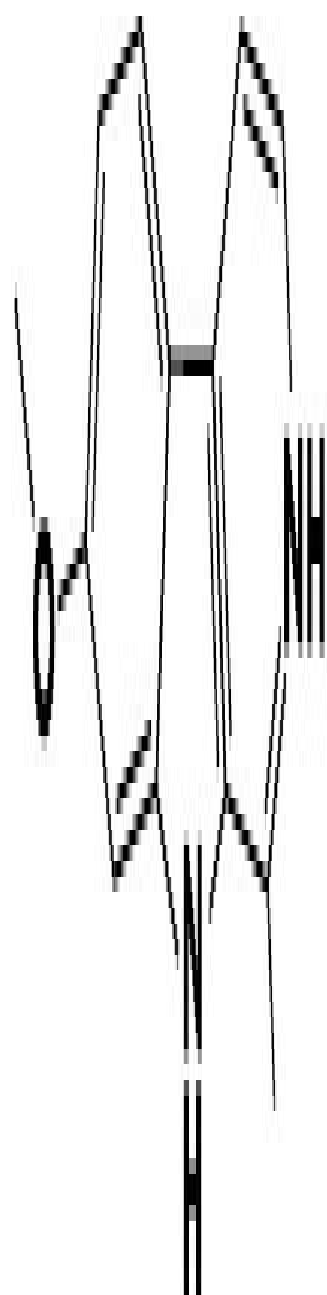
One study claimed that root hairs of the Peruvian root vegetable *oca* (*Oxalis tuberosa* Molina), propagated in sterile media, were found to produce  $\beta$ -carbolines/harmine only when challenged by the introduction of microbes. This article was subsequently retracted on the basis that the authors failed to prove that the fluorescent exudates from the roots were in fact harmine (Bais et al., 2002). A study screening for antimicrobial properties of harmine postulates that the results suggest that harmala alkaloids have a defense role in plants (Reza and Abbas, 2007).

$\beta$ -carboline, also known as norharmane, is the prototype substance in the class of compounds known as  $\beta$ -carbolines. It is one of two known ultraviolet-fluorescing substances found in the cuticles of scorpions (Wankhede, 2004). The other is a methylated coumarin-type compound. Reasons why scorpions display this fluorescence remain unclear. As nocturnal creatures, they likely see

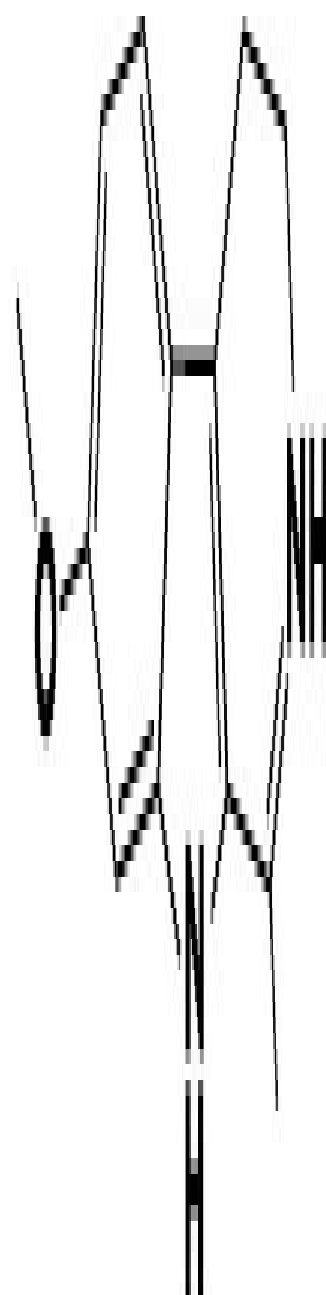
in this spectrum of light, and this attribute would help them naturally select partners for reproduction. All species of scorpions display unique mating “dances.” This suggests  $\beta$ -carboline may be involved in signalling.



tetrahydroharmine



Harmine



Harmaline



At least three  $\beta$ -carboline derivatives are endogenous chemicals found in the corneas (eye lenses) of human beings. Corneas are subject to continual oxidative and photic stresses. A study suggests these derivatives play a role in protecting tissues from oxidative stress (Pari et al., 2000). It is intriguing to find these compounds present in the lens, the area where photons enter the body and reach the brain. As  $\beta$ -carbolines are known to become activated or charged under ultraviolet light, it suggests a possible relationship to the photodynamic properties of these substances. Further research may well uncover the dynamics of such a relationship.

Harmin increases spatial learning in mice (Dandan et al., 2015). Spatial learning is an aspect that is important to the growth and survival of plants, especially jungle lianas like *Banisteriopsis* that hope to eventually reach the canopy, finding their place amongst fellow plant species. Although concepts such as plant intelligence, memory and learning have long been held to be the realm of quasi-science, new experiments are showing that in fact plants do possess such behaviors (Gagliano et al., 2014).

It seems that  $\beta$ -carbolines are polyfunctional in nature. In the human body they are certainly capable of performing several different functions, and this flexibility of function makes them good candidates for medicines targeting broad-spectrum activity.

## NOTES ON THE CHEMISTRY AND PHARMACOLOGY OF BANISTERIOPSIS

To date, there has been much published on this subject. Refer to (Mckenna et al, 1984; Rivier and Lindgren, 1972) for comparisons of chemical profiles of *ayahuasca* brews. In summary, *ayahuasca* essentially consists of *Banisteriopsis* plus a DMT-admixture plant (usually *Psychotria viridis* or, in the case of *yagé*, *Diplopterys cabrerana*). *Banisteriopsis* is the main source of the three  $\beta$ -carbolines that typically occur in the brew—harmin, tetrahydroharmin and harmalin. Although much variation exists, a general estimate of the proportions in a “typical” *ayahuasca* brew could be in the order of harmin constituting around 45%, tetrahydroharmin 25% and harmalin 5%, with dimethyltryptamine making up the remaining 25% of the total

alkaloid volume.

Although the scope of this article focuses mainly on harmine, both harmaline and tetrahydroharmine (THH) also play important roles in MAOI inhibition amongst other things. Tetrahydroharmine has shown to bind to serotonin transporters in blood platelets (Callaway et al., 1994), and given *in vitro*, it induces neurogenesis in the brain (Riba et al, 2017). THH also has approximately double the half-life (around 660 minutes) of harmine and harmaline, and has been anecdotally suggested to be partly responsible for the “afterglow” effect reported by many *ayahuasca* drinkers.

Harmine has some of the same properties as harmaline, though in some areas great differences are seen. For example, harmine has been shown to bind over 100 times more efficiently to DNA. Harmaline on the other hand is used in animal models to induce tremors and amnesia (Louis and Zheng, 2010). Although this is probably a dose-related phenomenon, it does raise some concern with respect to ingesting this compound in large doses, as essential tremor (ET) is a serious condition. Although this is unlikely to be a problem with *Banisteriopsis* species, the practice of preparation of “*ayahuasca* analogues” using Syrian rue (*Peganum harmala* L.), which has much higher levels of harmaline, should in the author’s opinion be exercised with caution.

It is known that variation exists in the levels of these chemicals between individual plants and between different brews analyzed. The *Banisteriopsis caapi* varietal *tucunacá* appears to be the most common variety used in the preparation of *ayahuasca* these days. Compared to another variety of this species, *caupuri*, which is possibly what Spruce collected in 1853 (Luna, pers, comm.), and described as “Swollen at the joints”, there is a vast difference in their chemical profiles. Considering the emerging evidence for  $\beta$ -carbolines’ therapeutic role in so many pathologies, varieties like *caupuri* are in need of further study for their potential application in medicine. Varieties with higher levels of  $\beta$ -carbolines may find special application in conditions such as depression and neurodegenerative diseases.

| Variety | Harmine   | Harmaline | Tetrahydroharmine |
|---------|-----------|-----------|-------------------|
| Caupuri | 8.68 mg/g | 0.69mg/g  | 5.06mg/g          |
|         |           |           |                   |

|Tucunacá|5.50mg/g |0.11mg/g |0.19mg/g

**Source:** Rosana Lucas Serpico, 2006. *Ayahuasca*: Revisao Teorica e Consideracoes Botanica sobre as species *Banisteriopsis caapi* e *Psychotria viridis*. Universidade Garulhos.



*Banisteriopsis caapi* var. *tucunacá*



*Banisteriopsis caapi* var. *caupuri*

Some results reported by (Callaway, 2005a) found more equal, proportional amounts of harmine and tetrahydroharmine in brew samples. It was speculated that due to fermentation the beverage had become acidic with time, and that in an acidic substrate both harmine and harmaline degrade into tetrahydroharmine (Callaway, 2005b). It is significant to point out that the dominant alkaloid in all fresh *ayahuasca* brews analyzed thus far is always harmine and that the importance of this compound in producing the broad-spectrum effects of *ayahuasca* should not be underestimated.

## NEUROLOGICAL EFFECTS

$\beta$ -carbolines display broad psychopharmacological effects through binding to benzodiazepine, imidalozone, serotonin and opiate receptors and through inhibiting monoamine oxidase (MAO) and DYRK1.

Perhaps, due to the early discovery of the psychoactive properties of harmine in medicines such as *ayahuasca*, its effects on the nervous system have generated much research interest to date. Much of this research has been published elsewhere, but for the scope of this article only the highlights of this research are discussed. Some of these results have proven to be astonishing, and several studies suggest that both *Banisteriopsis* and harmine hold strong promise for the treatment of several neurodegenerative diseases, including Alzheimer's, Parkinson's, and Huntington's (Muhammad et al., 2010). It has been shown in animals and humans that harmine produces a marked degree of neurogenesis, which holds the possibility of reversing some of the neural damage caused in neurodegenerative conditions. In 2016, a Brazilian team showed that harmine stimulates proliferation of human neural progenitors (Dakic et al., 2016 ). In addition, harmine has shown an ability to stimulate the release of dopamine, validating its usefulness in certain diseases related to dopamine deficits.

Preliminary harmine studies with both harmine on its own and also in the *ayahuasca* brew are beginning to show great promise with regards to depression. Current global estimates report that around 350 million people have a major depressive disorder. The antidepressant effects of *ayahuasca* have shown to be immediate and long lasting. In 2015, a collaboration between a group of

Brazilian and Spanish scientists reported on the rapid, acute antidepressant and anxiolytic effects observed after only a single dose of *ayahuasca* when compared to slower-acting traditional antidepressants (Sanches et al., 2016). At the time of writing, there are no further studies strongly supporting these findings.

*Ayahuasca* has been reported in several studies to be of great value in treating addictions. It is difficult to know for certain whether it is the experience itself or the pharmacological effects that are responsible for this efficacy. It is probable that both aspects are of value in treating addiction. *Ayahuasca* and specifically harmine have been the subjects of several studies focusing on substance dependence. In an increasing number of trials, harmine and  $\beta$ -carbolines have shown to be useful in treating cocaine, amphetamine, opiate and alcohol dependence (Owaisat et al., 2012). Harmine activity at a receptor level correlates with several receptors known to be important in treating addiction.

## CANCER

Traditionally, *ayahuasca* has been used in the Amazon region for treating cancer. There is anecdotal evidence, especially from the Brazilian syncretic churches and the global *ayahuasca* community, of cases where *ayahuasca* has cured or been beneficial in cancer treatment (Schenberg, 2013). It is difficult to separate whether or not these reports are attributed to the *ayahuasca* experience itself or to the actual chemistry contained in the brew. It is true that both harmine and DMT have reported properties that can fight cancer, with harmine especially showing promise in the treatment of certain cancers.

The 2017 annual report for The American Cancer Society estimates that nearly 1,700,000 new cancer cases will be diagnosed in the United States alone per year, of which nearly 600,000 are expected to result in death. Out of the total data spectrum of cancers affecting all sites, 13% are considered to be rare cancers. Thus we can expect the emergence of new and rare types of cancer.

Modern society and lifestyles often dictate that individuals are exposed to abnormal levels of stress, whether psychological, dietary or environmental, as is often the case with industrial toxins and agrochemicals found in our food. The epidemic and emergence of

viral disease, as well as smoking and other substance-related behaviours, are all capable of affecting us at a genetic level and causing mutations at a cellular level that potentially could develop into cancerous tumors. In addition, these unnatural stresses can lead to immune disorders, which further inhibit resistance to cancers.

Current conventional therapies in the treatment of cancer include surgery, radiotherapy, chemotherapy and molecular-targeted therapy. Existing chemotherapy drugs are not ideal and have numerous side effects, including myelosuppression, hepatotoxicity and immunosuppression (Leite et al, 2012). Therefore, there is an urgent and growing need to seek out safer alternative therapies and chemotherapy compounds. Harmine displays interesting, multiple anticancer properties in its ability to induce programmed cell death (apoptosis) in tumors, prevent proliferation and metastasis as discussed in the research results below.

The ability of harmine to effectively bind to DNA—100x more effectively than harmaline (Nafisi et al., 2010)—lends to interesting possibilities with regard to cancer therapies. Harmine is a small molecule, and biological responses caused by mutagenic, carcinogenic and anti-tumor agents are often associated with the binding of small molecules to DNA. Harmine interacts with DNA via intercalative modes and causes major DNA structural changes (Nafisi et al., 2010).

In several studies, harmine has demonstrated genotoxic abilities to damage the DNA of malignant cells, thus preventing proliferation and growth of tumors (Nafisi et al., 2010; Cao et al., 2005). In the reviewed literature, the terms ‘genotoxic’ (Boeira et al., 2002) and ‘antigenotoxic’ are used to describe properties of harmine. It should be understood that whilst genotoxicity is often confused with mutagenicity, all mutagens are genotoxic, whereas not all genotoxic substances are mutagenic. Based on evidence thus far, harmine falls into the latter category.

Harmine is named after the medicinal plant *Peganum harmala*. It has a long-standing reputation in the Middle East for treating cancers of the stomach. Recent research from China has shown that harmine induces pro-death autophagy and apoptosis in human gastric cancer cells (Zhang et al., 2013). The enzyme cyclooxygenase

has been shown to be important in the development of cancers, specifically gastric cancers. The Chinese investigators showed that harmine was able to induce apoptosis and inhibited tumor cell proliferation, migration and invasion through downregulation of cyclooxygenase-2 expression in gastric cancer (Zhang, et al., 2013).

Harmine interferes and restricts blood supply to tumors (anti-angiogenesis). In mice infected with B16F-10 melanoma cells, , harmine significantly decreased tumor-directed capillary formation, at a dose of 10mg/kg, whilst it increased immune anti-tumor factors such as interleukin-2 (Hamsa and Kuttan, 2010).

A recent study proved *in vitro* that a harmine derivative called CM16 inhibited the growth of oligodendroglioma and melanoma cancer cell lines through targeting protein synthesis (Carvalho et al, 2017).

Melanomas are notorious for metastasis and for chemo resistance. As some forms do not respond well to current chemo or radiotherapy, often the only option is resection. Therefore, it is desirable to look for phytochemicals that show efficacy in melanomas. In a 2011 study in India, it was shown that harmine caused cell death in melanomas and regulated some transcription factors and proinflammatory cytokines (Hamsa and Kuttan, 2011).

An *in vitro* study demonstrated in several different types of cancer lines that harmine displayed a dose-dependent inhibitory effect on cell proliferation against all human carcinoma cells tested, and that harmine was identified as a useful inhibitor of tumor development (Jimenez et al, 2008).

Other  $\beta$ -carbolines and harmine derivatives are being investigated as potential anticancer drugs. A newly synthesized  $\beta$ -carboline called DH332 exerts effective anti-tumor activity *in vitro* and *in vivo*, and has the potential as a promising drug candidate for lymphoma therapy (Gao et al., 2014).

The harmine-containing medicinal plant *Peganum harmala* has also shown to have anti- growth properties in a cell line of breast cancer (Shabani et al., 2015).

## CIRCADIAN RHYTHMS

A curious genetic effect of harmine has been observed in a study whereby harmine was shown to modulate circadian period. All



living creatures are subject to biological rhythms. The master clock that generates these circadian rhythms in mammals is found in the suprachiasmatic nucleus of the hypothalamus. These rhythms control many processes in the body such as sleeping and waking, blood pressure, heartbeat and hormone secretion. Even cells have their own clock, known as the “cell autonomous clock.” Genes are also controlled by these rhythms, which determine timely processes such as the order of protein folding. Harmine has been shown to affect these core clock gene networks and has been suggested as a new candidate to control period length in mammals. The results of this study suggest harmine affects clock genes in peripheral tissues such as the liver, and not at the master clock level in the hypothalamus (Onishi et al., 2012). What makes this important is that it is known that disruption of circadian period is linked to several different pathologies such as insomnia, cancer, depression and metabolic syndrome (Bechtold et al., 2010).

## PARASITES

*Ayahuasca* has a strong reputation in the Amazon for its ability to treat parasitic infections. Parasitic infections are diverse and vary geographically, as well as the sites in the human body that they infect and colonize. In the developing world, as well as in rural areas of the developed world, parasitic infections often go unnoticed and are not diagnosed in time, resulting in potentially dangerous infections that are difficult to treat and often require the use of potentially toxic drugs. Treatments for parasitic infections through conventional medicines often have limitations, mostly due to toxicity issues and the development of drug resistance in parasites.

Several constituents of the *ayahuasca* brew are likely responsible for certain antiparasitic effects. For example, in gut-borne parasites, the various tannins in *ayahuasca* brews would likely bind with the proteins of foreign organisms as well as to gastric mucosa, thus inhibiting these organisms’ ability to infect the body systemically and rendering them ineffectual. It could thus be expected that *ayahuasca* would be of some value in potentially treating common gastric infections such as giardia, flagellates and possibly even amoebic infections.

Harmin, being a small molecule, has the ability to cross

membranes in the body. Of special interest is harmine's ability to enter cells and effectively kill blood-borne parasites for which many of the conventional medicines are not ideal and in some instances show serious side effects and toxicity. Harmine has been investigated in the treatment of some of these parasites.

Toxoplasmosis is a peculiar disease that has been around since humans started domesticating cats. It can be active for a lifetime in all mammals, though the tachyzoite parasite *Toxoplasma gondii* Nicolle & Manceaux needs to return to a feline to complete its reproductive cycle. Although this parasite may not cause obvious symptoms in humans, in certain instances, for example immunocompromised individuals such as HIV patients, infections can become acute and even potentially fatal. Up to half the world's population is believed to be infected with latent toxoplasmosis (Flegr et al, 2014). This disease has been listed as one of the "neglected parasitic infections" by the World Health Organization.

A number of studies have shown that this often asymptomatic infection may lead to other pathologies (Alomar et al., 2013). Of particular interest is this parasite's ability to affect the nervous system and cause changes in behavior. Experimentally infected rodents lose all fear of feline scents and urine, thus insuring the host will be captured by a feline and thus the parasite will complete its life cycle. Neurological pathologies including schizophrenia have been observed in humans, with the artwork of Louis Wain being partly responsible for bringing this disease to public attention. It has even been linked to the cause of a unique syndrome known as "crazy cat lady syndrome" popularized by the media (Flegr et al., 2014). Serological estimates suggest that between 30 and 50% of the global population is infected, while in some regions it is estimated that up to 95% of the population is infected (Flegr et al., 2014). *Toxoplasma gondii* is capable of invading many different tissues and forming cysts, and if acquired during pregnancy, it has been linked to a condition known as congenital toxoplasmosis. In newborn babies it is associated with chorioretinitis (which can cause blindness), hydrocephaly, microcephaly and abortion (Tamomh et al., 2016 ).

An *in vitro* study showed that low doses of less than 40  $\mu$ M of harmine were shown to have a strong inhibitory effect on

*Toxoplasma* parasite invasion and replication, and showed no toxicity to the host cells. The study recommended that harmine be explored in potential drug development as a treatment for this disease (Alomar et al., 2013).

## MALARIA

Malaria remains a very serious disease with high incidence of both morbidity and mortality. The disease is associated with infection caused by parasites in the genus *Plasmodium*, of which about 200 species are known. Globally, five species are known to infect humans. Transmission takes place through female mosquitoes of the genus *Anopheles*. In 2015, the World Health Organization reported 212 million cases and an estimated 429,000 malaria deaths worldwide, with 90% of these occurring in Africa. In the last decade, substantial progress was made in its treatment and prevention. This was largely due to various global efforts to control the disease, and the development of artemisinin-type drugs based on the medicinal plant *Artemisia annua* L. At present, treatment globally consists largely of artemisinin-based drugs, together with a partner drug to limit development of resistance. Of great concern is the emergence of artemisinin-resistant strains from Southeast Asia and elsewhere.

Harmine has been identified as a potential drug in the treatment of malaria. Of relevant interest is the widespread traditional use of known  $\beta$ -carboline-containing plants such as *Guiera senegalensis* J.F.Gmel.in West Africa, and *Eurycoma longifolia* Jack in Southeast Asia for the treatment of malaria. Both species are highly regarded for efficacy in many ailments in the regions they come from. In 2012, a Canadian study showed that harmine is a potent antimalarial, and proved its mechanism in combating malaria by targeting heat shock protein 90 (Hsp90) (Shahinas et al., 2012). This is a very interesting target for drug development as heat shock proteins are among the most highly expressed cellular proteins across all species and are a known target in various forms of cancer (Csermely et al., 1998). This target has been identified as having potential application in many diseases. In *Malaria Journal*, exciting new research was published showing both *in vitro* and *in vivo* anti-malarial activity of novel harmine-analogue heat shock protein-

inhibitors. The article recommends harmine analogues as a possible partner for artemesinin in the fight against malaria. In addition, this study showed that harmine analogues inhibited *Plasmodium falciparum* Welch, the most common and dangerous form of malaria, and reduced parasitaemia in micromolar concentrations, as well as having an additive synergistic effect when combined with dihydroartemesinin (Bayih et al., 2016).

## LEISHMANIA

Leishmaniasis is a vector-borne parasitic disease spread by the bite of certain types of sandflies. These insects harbor parasites of the genus *Leishmania*, of which at least 20 species are known to infect humans. The World Health Organization estimates that between 4 to 12 million people are currently infected, with 2 million new cases and between 20,000 to 50,000 deaths occurring annually in some 88 countries, and has classified leishmaniasis as a neglected tropical disease. Leishmaniasis has a mortality rate that approaches 90% for untreated patients (Herwalt, 1999). A 2014 French study showed harmine had weak anti-leishmanial activity, while on the contrary harmaline, also a component of the *ayahuasca* brew, showed strong activity (Di Giorgio et al, 2004). Antimony-type compounds have been the first line of defense, though these need to be given intravenously or intramuscularly, and are not entirely satisfactory (Murray, 2000). Therefore, it is recommended that a search for new anti-leishmanial compounds be undertaken.

## CHAGAS DISEASE

Chagas disease is one of the most serious protozoan diseases in Latin America and is categorized as a neglected tropical disease by the Centre for Disease Control and Prevention. It is caused by a parasitic infection normally involving *Trypanosoma cruzi* Chagas. The vector for this disease are the Triatomid bugs, also known as “kissing bugs.” Harmine has been shown to inhibit the protozoan *Trypanosoma cruzi*. When this disease reaches a chronic stage, current medicines only slow the progression, but do not effectively cure the disease. The World Health Organization estimates 6.6

million people were infected in 2015, with mortality estimated at around 8000. An *in vitro* study showed harmine induced programmed cell death in cells infected with *Trypanosoma brucei* Plimmer & Bradford at a concentration of less than 100  $\mu$ M (Rosenkranz and Wink, 2008).

## ANTI-DIABETIC

Diabetes type 1 and 2 are serious disease burdens affecting an estimated 380 million people globally. Diabetes is caused by an insufficiency of the pancreatic  $\beta$  cells in producing insulin, which metabolizes sugar in the body. The growth of these cells declines dramatically after birth. A potential cure or treatment would be to facilitate the growth of more insulin-producing pancreatic  $\beta$  cells. An urgent need has been established to discover a compound capable of doing this.

At present, diabetes type 1 is normally controlled through insulin injections. This is not ideal, as often insulin resistance is encountered, necessitating an increase in insulin dosage. There is also the inconvenience of regularly having to test blood glucose levels to ascertain how much insulin is needed, as too much or too little can dangerously alter blood sugar levels.

In 2015, one group screened over 100,000 compounds, with only harmine showing ability to cause pancreatic  $\beta$  cell division in rats, demonstrating the uniqueness of this molecule. The proposed mechanism is due to the nuclear factors of activated T-cells (NFAT) family of transcription factors as likely mediators of human  $\beta$  cell proliferation as well as  $\beta$  cell differentiation (Wang et al, 2015) Harmine also induced an increased sensitivity to insulin. The partial regrowth of these cells is truly encouraging, as this is the first time it has been demonstrated. This approach also holds hope for a host of other sugar-metabolic conditions.

## ANTI-INFLAMMATORY

Inflammation is currently understood as a major underlying factor associated with many chronic pathologies. An exciting new 2017 study showed evidence that harmine is an inflammatory inhibitor through the suppression of NF- $\kappa$ B signalling. In addition, it

uncovered a new potential of harmine for treating infectious disease: “Our data suggest that harmine may be responsible for the anti-inflammatory effect of *P. harmala* and *ayahuasca*, and may have a potential role for inflammatory and infective diseases.” (Liu, 2017)

## BONES AND JOINTS

Diseases of bone and joint tissue are numerous. They include common pathologies such as osteoarthritis and immune-related rheumatoid arthritis, osteoporosis, fracture and less frequently, genetic disorders and cancers. In these diseases, bone or cartilage tissue damage is normally observed. Treatment at this stage is often symptomatic and requires the use of steroidal drugs such as cortisone. Though these steroidal drugs may provide symptomatic relief, they work by blocking certain immune processes and do not offer any real hope of curing the diseases. Furthermore, anabolic drugs that aggressively promote osteoblastogenesis and bone formation are insufficient for effective treatment of these diseases (Yonezawa et al., 2011a). The “Holy Grail” for preventing and treating these diseases would be to discover compounds that prevented degeneration of these tissues or could stimulate their outgrowth once the pathology has expressed. Harmine has shown some very interesting and encouraging results in this regard in several ongoing studies that were conducted in China and Japan recently. A study by Hu and Xie (2016) reports that harmine can exert regenerative and protective effects on bone and cartilage tissues by regulating the proliferation, differentiation and metabolism of osteoclasts, osteoblasts and chondrocytes. A Japanese study (Yonezawa et al., 2011a) report that harmine inhibits osteoclast differentiation and bone resorption *in vitro* and *in vivo*. In the same year, the same group proposed the mechanism, releasing a paper under the title “Harmine promotes osteoblast differentiation through bone morphogenetic protein signalling” (Yonezawa et al., 2011b). Their findings suggest that harmine has bone anabolic effects and may be useful for the treatment of bone-decreasing diseases and bone regeneration. Bone morphogenetic proteins (BMPs) deserve some further explanation, as they are considered important in many processes in the body. They are

multifunctional growth factors that interact with specific receptors on a cell surface. In the embryonic stage, they are considered important for the development of the heart, central nervous system and cartilage, as well as postnatal growth and skeletal development and formation. More recent research is showing importance in practically all tissues of the body, including the brain (Bragdon et al, 2010). In one author's eloquent phrasing, "BMPs are now considered to constitute a group of pivotal morphogenetic signals, orchestrating tissue architecture throughout the body" (Milano et al, 2007 ). Over 20 BMPs have been discovered so far in the human body and the delicate balance of their signalling mechanisms is considered fundamental in many pathologies. Cancers are often associated with misregulation of BMP signalling systems. For example, the absence of BMP signalling is an important factor in the progression of colon cancer (Kodach et al, 2008), and conversely, overactivation of BMP signalling is believed to be important in development of adenocarcinoma of the gastrointestinal tract (Milano et al, 2007). The role harmine can play in modulating BMPs is an area of important research.

## ANTIMICROBIAL PROPERTIES

There have only been a few studies reporting on the antimicrobial properties of harmine. Antimicrobial activity has been ascribed to both harmine and harmaline. The author has heard of Amazonians applying *ayahuasca* externally to treat skin infections, and  $\beta$ -carbolines may well be involved in killing microorganisms. Antifungal activity was also shown in one study (Ahmad et al., 1992) where harmine was effective against all eight dermatophytes (skin fungi) tested. In another study, antibacterial activity was shown against *Staphylococcus aureus* Rosenbach, *Escherichia coli* (ex. Migula) Castellani & Chalmers and *Proteus vulgaris* Hauser. Antifungal activity was also shown against *Candida albicans* (C.P. Robin) Berkhout (Nenaah, 2010). Harmine has also demonstrated activity against both gram-negative and gram-positive bacteria (Ahmed et al., 1991).

A fascinating effect first looked at in 1981 is the discovery that certain  $\beta$ -carbolines, including harmine, can be charged with ultraviolet light to display even greater antibacterial properties

(McKenna and Towers, 1981). These are referred to as the “photodynamic” properties of a compound and is an area worthy of further research for its potential in drug development and therapeutic strategizing.

## ANTIVIRAL PROPERTIES

Viral diseases are a great threat to many populations of the world. The risk of emergence of new viral disease and resistance is always present. Transmission in a population may be rapid, as is seen in the Ebola virus. Furthermore, climate change is expected to play a large role in the spread of these diseases. The numerous viral diseases that exist are beyond the scope of this paper, though it includes several epidemic diseases, for some of which there is currently no known cure—for example, Human Immunodeficiency Virus (HIV). Due to rapid resistance, monodrug therapies have limitations and it is always advisable to seek out new and safer antiviral compounds to keep up with emerging resistance. In line with this,  $\beta$ -carboline compounds structurally lend themselves to new drug design, and a number of these harmine derivatives have been investigated for antiviral properties.

Some of these compounds have shown important and intriguing antiviral effects.  $\beta$ -carbolines have received research in Dengue virus serotype 2, Herpes simplex virus (HSV 1 and HSV 2)(Deyan et al, 2015) and even Human Immunodeficiency Virus (HIV). Harmine, being such a small molecule, can cross nuclear membranes and potentially confer activity where viral particles encode within the DNA. As harmine is capable of affecting multiple targets challenged by viruses, it is likely that further research will reveal new antiviral properties.

The research in  $\beta$ -carbolines in Dengue virus is worth mentioning, as Dengue fever is the most prevalent and fastest-spreading viral disease worldwide. In an Argentinean study (Quintana et al, 2016), research was conducted not on harmine itself, but on two close derivatives: a natural  $\beta$ -carboline harmol, and a synthetic 9N-methylharmine. Interestingly, these two compounds showed inhibitory effects against all Dengue serotypes tested, with greatest inhibition for DENV2. In this study, it was discovered that the effects were due not to direct antiviral activity but rather to these  $\beta$ -



carboline impairing the maturation and release of viral particles out of the cell, thus impeding cell-to-cell transmissions. The authors of this paper recommend that “further investigation of  $\beta$ -carbolines by performing a structure-activity analysis of new derivatives obtained from the active compounds and additional study of their mechanism of action would represent a promising approach for the development of novel antiviral agents to deal with DENV infections” (Quintana et al, 2016).

A particular challenge is treating viral diseases where the virus is able to go into latency, as is the case with retroviruses. Herpes simplex viruses (HSV1 and HSV2) are retroviruses that are highly prevalent in many populations, and sadly, therapeutic options to treat them are limited. HSV1 infection may result in corneal blindness and encephalitis, and HSV2 infection leads to *herpes genitalis* (Deyan et al, 2015). Current treatment revolves around antiviral medications like acyclovir, to which resistance has already emerged. Harmine was found to potently inhibit HSV2 infection through several different mechanisms and has been suggested as a valuable candidate for further study as a potential agent for blocking the HSV infection (Chen et al, 2015).

With regards to HIV infection, a recent study (Brahmbhatt et al, 2010) screened a number of  $\beta$ -carboline derivatives as potential inhibitors of HIV, and identified 1-formyl- $\beta$ -carboline-3-carboxylic acid methyl ester derivative as an active agent against HIV. Further investigation and modification of this lead compound is in progress.

## CONCLUSION

It seems, at least to the author, that there has indeed been a bias in the Western understanding of *ayahuasca* towards visionary aspects and experiential phenomena. Although these are considered paramount to the experience and research into the potential for *ayahuasca* in treating psychiatric and psychological problems is gaining momentum. Little is known to date about the application of this medicine in treating diseases of the body. It is only through anecdotal information that we know that Amazonian practitioners use *ayahuasca* for a wide variety of physiological diseases and complaints.

Harmine already demonstrated a remarkably broad spectrum of

activity, which supports the hypothesis that, if taken at regular intervals in nontoxic dosages, as is the case in the vast majority of *ayahuasca* drinkers, it may well have wide-reaching and positive health-enhancing properties. The evidence presented thus far, in particular concerning diseases for which conventional medicine is currently challenged, demonstrates the usefulness of this compound, and specifically of *ayahuasca*, as a potential medicine not only in the treatment of psychiatric and psychosomatic problems but in a wide variety of human physiological pathologies. The seemingly remarkable ability of harmine to interfere with crucial metabolic processes in such a wide range of pathological organisms and cancerous cells, but still promote the healthy outgrowth of neural networks, bone and joint tissues and pancreatic  $\beta$  cells, is of great interest and importance, especially as these tissues normally degenerate in all of us with age.

The role of harmine and *ayahuasca* in the treatment of depression is of considerable value and importance, considering the rising incidence of this disorder in global populations and the controversial, limited success of modern antidepressant medications.

The newly demonstrated effects that harmine is showing in many notoriously stubborn parasitic infections is an exciting area of research and can potentially help a great deal in preventing and treating these types of infections.

Finally, the ability of harmine to bind so strongly with DNA, resulting in predominantly positive effects and so far no demonstrated real toxic effects in a global population of *ayahuasca* consumers, is intriguing.

This leads to interesting speculation in a world where, in the last 200 years since the industrial revolution, we have undeniably reached a situation whereby we regularly place undue chemical stresses on our environment and our bodies, evidenced by mutations at a genetic level potentially causing modern-day cancers. It can be speculated that harmine and similar compounds common in nature may even provide organisms with an evolutionary advantage at a genomic level through this intercalation with DNA.

As both the  $\beta$ -carbolines and dimethyltryptamine are endogenous compounds and constitute the main areas of pharmacological

activity in *ayahuasca*, perhaps these discovered effects point to possible functions that these compounds serve in the body. In addition, discovery of the function(s) these molecules serve in nature may help us in our targeting and development of new medicines.

Harmine and  $\beta$ -carbolines, being natural compounds that are available in a wide range of botanical sources and with such broad-spectrum activity, certainly have a potential role to play both in primary healthcare in the undeveloped world and in the discovery of new medicinal properties. The recent international research interest in harmine has evoked its exciting therapeutic potential. It is hoped that further research will help uncover and explain more of these mysteries.

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# Viva Schultes - A Retrospective

## [Keynote]

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Mark J. Plotkin, PhD, I Brian Hettler II  
& Wade Davis, PhD III

I. President, Co-founder;

II. GIS & New Technologies Manager: Amazon  
Conservation Team Arlington, Virginia

III. Dept. of Anthropology, Univ. of British Columbia

*This paper is a companion piece to the Amazon Conservation Team interactive map journal plotting thirteen years of work in the Amazon by legendary ethnobotanist, Richard Evans Schultes. This online resource follows Schultes' explorations through geo-referenced herbarium specimens, photographs and field notebooks, accompanied by historical digital maps. Wade Davis' biography of Schultes, One River, was an invaluable source of information in reconstructing his life and travels. The Schultes Map is available at [amazonteam.org/maps/schultes](http://amazonteam.org/maps/schultes).*

### INTRODUCTION

Richard Evans Schultes was often called the Father of Ethnobotany. He was quick to point out, however, that ethnobotany began when Pharaoh Hatshepsut sent an expedition to the Land of Punt 3500 years earlier, and that he was not quite that old. Such self-deprecating humor was one of his hallmarks and played a large role in the trust and friendship that friends, students, and his many informant colleagues, from Oklahoma to the Amazon, placed in him.





*Richard Evans Schultes, a freshman at Harvard, 1933*

Schultes – ethnobotanist, taxonomist, writer and photographer – is widely regarded as one of the most important plant explorers of the 20th century. In December 1941, he entered the Amazon rainforest on a mission to study and document how indigenous peoples employed local plants for medicinal, ritual and practical purposes. He would follow in the tradition of great Victorian era explorers, spending over a decade immersed in near-continuous fieldwork. In total, Schultes would collect more than 24,000 species of plants, including some 300 species new to science.

Schultes' geographic area of focus was the northwest Amazon, an area that had remained largely unknown to the outside world, isolated by the Andes to the west and dense jungles and impassable rapids on all other sides. Schultes lived amongst little-studied groups, mapped uncharted rivers, and was the first scientist to explore some areas that have been little researched since. His notes and photographs are some of the only existing documentation of indigenous cultures in a region of the Amazon on the cusp of change.

Throughout his travels, Schultes' love of plants and respect for indigenous knowledge of the forest helped him earn the trust of the communities he encountered. He found that the shamans he met were often willing, if not eager, to discuss their plants and their

practices with outsiders who had a common appreciation for plants.

Schultes was not only an accomplished scientist: his teachings at Harvard University had a profound impact on countless students. His vivid descriptions of Amazonian peoples and creative classroom demonstrations, such as the use of a blowgun, inspired hundreds of students into careers in biology, anthropology, medicine and conservation, and his many writings on the importance of shamanic wisdom and the therapeutic potential of psychotropic plants remain as important today as the day they were first published.

The special significance of Schultes' research derives in part from ideal timing: he arrived in the Amazon at a time of massive change for the peoples he encountered and ultimately for the great forest itself. In our map journal that accompanies this paper, available at [www.amazonteam.org/maps/schultes](http://www.amazonteam.org/maps/schultes), we retrace Schultes' journeys, exemplify his vast botanical collection – a great legacy to science – and explore the natural and cultural context of the environments he traversed, then and now, impressing upon us the immense importance of their conservation.

## EARLY LIFE AND EXPLORATION

### BEGINNINGS

Born in Boston, Massachusetts on January 12, 1915, Richard Evans Schultes was the grandson of immigrants; German on his father's side and English on his mother's. He was raised in East Boston in a house that still stands at 276 Lexington Street. At the time, East Boston was predominantly Irish – in fact, according to biographer Wade Davis, Schultes' mother attended school with Joseph Kennedy, Sr., father of JFK. That Schultes grew up in an Irish-American enclave as descendant of both Germans and English must have set him apart from most of the people of his age in his neighborhood. This ability to survive and thrive as an outsider in a challenging setting was to prove excellent training for life as an ethnobotanist.

At the age of eight, Schultes contracted a severe stomach ailment which kept him home and bedridden for many weeks. Looking for a book to read to the child, his father Otto visited the public library and checked out *Notes of a Botanist on the Amazon and the Andes*

by 19th-century English botanist Richard Spruce, who had spent 15 years exploring the Amazon in the mid-19th century, meaning that Schultes heard about *ayahuasca* before he turned ten. Richard E. Spruce – who had the same initials as Richard Evans Schultes – became the personal hero of the young American who was to follow in Spruce's footsteps many years later.

As a young man, Schultes excelled in school and received a full scholarship to Harvard, in which he enrolled in the fall of 1933 to study pre-medicine. There, he took a job filing papers at Harvard's Botanical Museum on Oxford Street just north of Harvard Yard, earning thirty-five cents an hour. The museum's vast collections of plants and accounts of the people who used them intrigued young Schultes, and inspired him to enroll in a class entitled "Plants and Human Affairs," taught by Oakes Ames, a renowned orchidologist and Director of the Harvard Botanical Museum.

One day in class, Ames announced that each student would be expected to submit a term paper at the end of the semester, and they had to choose a subject based on one of the books at the back of the classroom. Determined to choose the shortest book possible, at the end of the class Schultes hurried to the bookshelf and selected *Mescal: The Divine Plant and Its Psychological Effects*, a 1928 publication by German psychiatrist Heinrich Klüver, one of the early studies of peyote. The author described the small, blue-green cactus native to the Texas – Mexico border that was said to induce powerful visions. Intrigued by what he had read, Schultes asked Ames if he could write his undergraduate thesis on the magical cactus. Ames agreed, but with one proviso - Schultes must study peyote in situ among the Kiowa of Oklahoma.

### SCHULTES AMONG THE KIOWA

In 1936, Richard Evans Schultes headed west from Boston to Kiowa lands in Oklahoma on what undoubtedly represented the greatest adventure of his young life; he had never previously been west of the Hudson River. Schultes and anthropology graduate student Weston La Barre shared driving duties, making their way west in a broken-down 1928 Studebaker that La Barre had received in exchange for his train ticket. The pair arrived in Anadarko on June 24, 1936.

Their main local contacts were Charlie Apekaum (aka Charlie Charcoal), a local Kiowa leader, and his aunt Mary Buffalo, a Kiowa elder with extensive knowledge of plants. Mary Buffalo appreciated Schultes' and La Barre's willingness to listen and learn, and gave them deep insights into the Kiowa use of medicinal and ritual plants. Mary demonstrated how soaps were made from yucca roots and dyes from fruits, how willow bark was chewed to relieve toothaches, and how smoked sumac was employed for spiritual and physical purification before peyote ceremonies. She even revealed the contents of the "Ten Medicine Bundles", a sacred item that had been in her family for generations and was adorned with twelve scalps. Many evenings, Mary would build a sweat lodge out of hides and saplings over a hole in the earth filled with red-hot stones, where Schultes and La Barre would endure the heat for hours while listening to the Kiowa elders pray.

Over the course of the summer, they visited numerous villages, taking peyote two to three times a week. The ceremonies were led by a Roadman - the local term for traditional healer - which usually began with the participants smoking tobacco around a fire in contemplative silence. The Roadman would then pass around a leather bag full of peyote buttons and throw juniper on the fire, filling the tipi with aromatic smoke. He would chant songs accompanied by the fast-paced beating of a buckskin drum, which continued intermittently throughout the night as the participants fell into a world of rhythmic, colorful visions. Schultes typically took ten to twelve buttons of peyote, while some of the Kiowa men would consume as many as forty.

Schultes formed three lifelong bonds on that Oklahoma adventure. The first was with the plants themselves. Emerging from the Kiowa tipi, he reported that the cacti had brought him experiences beyond the description of contemporary science. The second inextricable link was with the nations and bands themselves: his mind-altering experiences under the guidance of the Kiowa Roadmen had opened his eyes to different ways of knowing and healing.

The third firm bond formed was that with his colleague, anthropologist Weston La Barre. Two years after their trip west, La Barre published *The Peyote Cult* as his first book. It was immediately considered a landmark psychological anthropology

text. Schultes, in turn, observed how well-trained anthropologists could acquire a penetrating ability to perceive many otherwise invisible aspects of culture. Though today Schultes is widely regarded as the father of ethnobotany, some of his greatest work was done in collaboration with experts from other disciplines, such as the chemist Robert Raffauf or the mycologist Gordon Wasson – not to mention the shamans themselves.

Schultes recalled that Oklahoma experience fondly to the end of his life, and stated after that trip that he considered everything west of the Hudson River to be “Indian Country.”

### TEONANACATL: FLESH OF THE GODS

While researching peyote, Schultes encountered numerous references to intoxicating mushrooms employed by the Aztecs for divinatory purposes, known as teonanácatl or “flesh of the gods” in Nahuatl, the Aztec language. Accounts of teonanácatl being served at the crowning of the Aztec emperors Ahuitzotl in 1486 and Montezuma in 1502 intrigued Schultes.

Surviving pre-Columbian documents offer ample evidence of the cultural importance of teonanácatl. The 14th century Mixtec document *Codex Vindobonensis Mexicanus* includes repeated references to mysterious mushrooms: on the top left of the 14th page, seven gods each grip pairs of mushrooms. A prince holding two mushrooms is seated in front of Quetzalcoatl, who chants while beating a drum made from a human skull. Quetzalcoatl is also shown in a bird mask, carrying a woman on his back who is wearing a mask adorned with four mushrooms. The scene is believed to show the first encounter between the gods and teonanácatl.

The Spanish associated these rituals with devil worship and tried to identify the psychoactive mushroom so that they could eliminate these pagan ceremonies. Despite their best efforts, they never determined the source of the teonanácatl.

Despite the historical evidence of psychoactive mushrooms being used in Mexico, William Safford – a leading botanist with the U.S. Department of Agriculture - insisted that teonanácatl referred to peyote. He claimed that the Indians were trying to mislead the Catholic Church so they could consume their sacramental peyote in secret. Safford also cast doubt on the botanical knowledge of both

the Aztecs and the early Spanish chroniclers.

Schultes was skeptical of Safford's theory. There was little resemblance between the peyote cactus and the fungi; furthermore, the Harvard ethnobotanist knew that peyote was a plant of the northern deserts rather than the tropical regions of southern Mexico. In an adroit bit of ethnobotanical detective work, Schultes located a letter addressed to the herbarium director J.N. Rose from an Austrian national in Mexico named Blas Pablo Reko.<sup>16</sup> Writing from Guadalajara, Reko stated that Safford was mistaken and that teonanácatl was a magic mushroom celebrated and consumed by the Mazatec in the state of Oaxaca. In 1936, Schultes headed to Oaxaca to investigate.

**16.** Reko, BP (1923) Letter to J.N. Rose, Herbarium Sheet No. 1745713. U.S. National Herbarium, Washington, D.C.

If the plains of Oklahoma and the Kiowas and their magic cacti seemed like a different country to the young scientist from East Boston, Oaxaca and the Mazatec must have appeared a different continent. Oaxaca in southernmost Mexico is somewhat remote even today, but in the 1930s it was all but off the map. Home to 16 different indigenous nations, often separated by soaring mountain ranges that can reach 12,000 feet, Oaxaca remains the most ethnically diverse state in all of Mexico, home to the Mazatec, Zapotec, Mazateco, and Mixe cultures, among others.

Schultes met Blas Pablo Reko in Mexico City and traveled by rail to Huautla, the capital of Mazatec country, in search of a local shopkeeper who was said to have firsthand knowledge of the mushroom cults. They explored around Huautla and the nearby city of San Antonio Eloxochitlán with little success. There were rumors of mushroom cults, but Schultes and Reko were unable to find definitive proof.

One day, as Schultes was drying plants in town, he was approached by a middle-aged Mazatec man with a dozen fresh mushrooms. A local merchant identified these as 'los niños santos' (the "sacred children"). Schultes received an assortment of mushrooms, and within the handful Schultes identified a species of *Panaeolus* (later named *Panaeolus campanulatus* var. *sphinctrinus*) and *Psilocybe cubensis*. This was the first identifiable

botanical collection of teonanácatl.

A later analysis by Schultes' colleague chemist Albert Hofmann of Sandoz Labs – who later became famous as the creator of LSD - eventually extracted compounds from these mushrooms that helped lead to the creation of some of the first beta blocker cardiac drugs.

## OLOLIUQUI: VINE OF THE SERPENT — THE MAGIC MORNING GLORY

Schultes had also heard of another plant sacred to the Aztec: coaxihuitl, “the vine of the serpent”, more commonly known as ololiuqui. The seed was said to be taken orally and employed for divination. A native person's 1632 ‘confession,’ recorded by a Spanish priest, confirms the cultural importance of the plant: “I have believed in dreams, in magic herbs, in peyote, and in ololiuqui, in the owl....”

The Spanish Chronicles described ololiuqui as having a twining habit, with heart-shaped leaves, long white flowers, and seeds similar to lentils. Based on this description, 19th century botanists suggested that ololiuqui was a plant in the morning glory family, the Convolvulaceae. In 1897, a Mexican botanist, Manuel Urbina, defined the plant as *Ipomoea sidaefolia*, and it is now known as *Turbina corymbosa*.

The ethnobotanically-challenged Safford once again disagreed, saying that no member of the morning glory family had shown narcotic or toxic properties and that ololiuqui could therefore not possibly be *Ipomoea sidaefolia*. Safford believed that the Native nations were again trying to hide the true identity of ololiuqui, which he believed was *Datura meteloides*, a well-known and highly toxic hallucinogen from the Solanaceae family.<sup>17</sup>

<sup>17</sup>. Safford W.E., 1915. An Aztec narcotic. *Journal of Heredity* 6:291-311 July

Safford W.E., 1923. Peyotl. *Journal of the American Medical Association* 77:1278-1279

Schultes returned to Oaxaca in April of 1939, planning to investigate further. He began in the town of Chiltepec, on the eastern side of the Sierra Madre de Oaxaca, where he bought provisions and hired a young Chinantec named Guadalupe Martínez-Calderón to serve as a field assistant and guide. Over a

series of expeditions from May to July 1939, they crisscrossed the Chinantla rainforest, climbing Cerro Zempoaltepetl, Cerro Cuasimulco, Cerro Zacate, and crossing the difficult Cerro de los Frailes. They passed through the territories of many different ethnic groups, visiting and collecting plants with Maztec and Zapotec colleagues.

One night in San Juan Lalana – the same town where Schultes was bitten by vampire bats several weeks before – he and Guadalupe struck paydirt when they found the house of an elderly *curandero* (traditional healer) covered by a giant morning glory vine, full of fruit. The *curandero*'s only source of revenue was selling the seeds from this massive climber. Guadalupe called the vine a-muk-ia, medicine for divination. Schultes knew that it must be *ololiuqui*. He identified the plant as *Rivea corymbosa*, finally determining the mysterious botanical identity of the Aztec's "vine of the serpent."

### SCHULTES AND THE PSYCHEDELIC ERA

In 1952, the English poet (and author of *I, Claudius*) Robert Graves sent Schultes' paper on *teonanácatl* to Gordon Wasson, an American banker and Vice President of J.P. Morgan & Co. in New York, who had a deep and abiding interest in the role of mushrooms in European and Asian cultures. Intrigued by the paper, Wasson and his wife, a Russian physician, launched a series of expeditions in search of *teonanácatl*, ultimately locating and consuming the sacred mushrooms in 1955.

Two years later, Wasson published *Seeking the Magic Mushroom*, a photo essay about his experiences with the fungi, in the May 13th, 1957 issue of *Life* magazine. The essay would become a cult hit, leading many spiritual seekers to Mexico in the 1960s. John Lennon, Bob Dylan, Mick Jagger and Keith Richards are said to have followed in Schultes' footsteps in search of "los niños santos." Schultes' research would eventually influence many other popular counterculture figures, like William S. Burroughs, Allen Ginsberg, Aldous Huxley, Carlos Castaneda, and Terence McKenna.

Ever sober-minded, Schultes had little patience for those who raved about their experiences with mind-altering plants. After William Burroughs described a *yagé* (*ayahuasca*) trip as a mind-opening metaphysical experience, Schultes' response was, "That's



funny, Bill, all I saw was colors!”

Schultes’ mission was to document sacred plants and investigate their potential to create new medicines. His trailblazing research into the hemisphere’s most powerful mind-altering plants – peyote, magic mushrooms, *ayahuasca*, and *Datura* – unintentionally helped to spark the psychedelic era.

## SCHULTES IN THE AMAZON THROUGH THE EMERALD DOOR

“My own acquaintance with the promise of ethnobotanical conservation began in 1941, when I first went to the Amazon Basin. I had just earned my PhD at Harvard, and I had been offered two jobs. One was as a biology master at a private school in New England; the other was a ten-month grant from the National Research Council to go to the Amazon region to identify the plants employed in the many kinds of curare the Indians use for hunting. I decided on the Amazon – which is fortunate, because otherwise I would probably still be a biology [teacher]!”

In September 1941, twenty-six-year-old Richard Evans Schultes arrived in Colombia for the first time. The adventure commenced on his very first day when – on a lark – he took the Bogotá trolley to the southern end of the line. There, he followed a stone staircase up to foot of the lush, green mountains that bordered the eastern part of the city, where he noticed a small orchid nestled among some ferns at the base of a small tree. Gently, he plucked the specimen out of a soft bed of moss. Lacking plant-collecting equipment, he pressed the little specimen inside his passport for safekeeping. The orchid would prove to be new to science, later named *Pachyphyllum schultesii* in his honor, one of more than 120 species that would eventually bear his name.

## THE SIBUNDOY VALLEY

In late 1941, Schultes headed south to the headwaters of the Putumayo River with the main goal of researching arrow poisons, which were then showing promise as muscle relaxants used alongside anesthetics, especially with abdominal surgeries. The young ethnobotanist also hoped to determine the botanical identity of yoco, a strong stimulant employed by local tribes that was

mentioned in several historical accounts.

Schultes' entry point to the Putumayo was the Sibundoy Valley, a bowl-shaped depression at 2,200 meters above sea level on the edge of the southern Colombian Andes. The flat, roughly circular valley is surrounded on all sides by steep mountains, and is usually engulfed by clouds and inundated by heavy rains that are funneled into the valley, forming the headwaters of the Putumayo River.

Schultes had been in the field for hardly a week when he learned of the Japanese attack on Pearl Harbor. Disappointed to have to cut his trip short, he made plans to return to Bogotá to report to the American Embassy. On February 12, 1942, as travel preparations were being made, Schultes wandered up the mountains northeast of Sibundoy into the páramo of Tambillo where he found a new species of *Espeletia*, the bizarre genus of treelike daisies that give the páramo an otherworldly appearance. The species would later bear his name: *Espeletia schultesiana*.

*Espeletia*, commonly known as frailejón, is a genus in the sunflower family that lives in the páramo, a wet and windswept grassland ecosystem found above the tree line in the high Andes, typically around 3,000 meters. Páramo ecosystems have distinct levels based on elevation: higher areas are typically open fields of tussock grasses with scattered frailejones and other low shrubs, while lower elevations contain fragmented forests with a high diversity of orchids, ferns and epiphytic bromeliads. Páramos are considered to be "evolutionary hot spots" for plant diversity.

Páramo vegetation is uniquely adapted to the cold temperatures, excessive moisture, overcast skies and strong winds found at high elevations. *Espeletia* has a thick trunk with a spiraling pattern of dense, hair-covered leaves that hang down after dying, acting as insulation. The succulent, hair-covered leaves help capture water vapor from the near-constant cloud cover, transferring it through their roots into the soil. The highly organic soils of the páramo support water retention, creating a layer of thick, waterlogged soil similar to peatlands.



These highland wetlands are important water regulators in the health of the river systems, providing clean, naturally filtered water. Today, the páramos in Colombia cover just 1.7 percent of the national territory yet produce 85 percent of its drinking water.

After a brief stay in Bogota awaiting orders from the American Embassy, Schultes was told he had a few months before the Embassy required him for an undisclosed mission. He returned to Sibundoy in February 1942, stopping along the road from Pasto to collect plants on the páramo of San Antonio.

### THE INGA AND KAMENTSÁ PEOPLE

The Sibundoy Valley is home to two indigenous ethnic groups: the Inga and the Kamentsá. The two groups speak distinct languages and have different mythologies and origin stories, but are nearly identical in their social organization, lifestyle, modes of subsistence, and worldview.

The Kamentsá say their ancestors are the original inhabitants of Sibundoy. They speak a language isolate, believed to be the sole surviving dialect of a lost language spoken by pre-historical and early historical Quillasingas, a political federation centered in the Pasto region of modern day Colombia (Sañudo, 1938). Kamentsá shamans are masters of both lowland and highland plants, including those of the páramo.

The Inga are more recent arrivals to the valley and speak a dialect of Quechua, the official language of the Inca Empire that is still widely spoken throughout the Andean regions of Peru, Ecuador and Bolivia. There are several theories as to how the Inga arrived in

Sibundoy: some claim the Inga are the descendants of Inca nobility, or of a group of Peruvians relocated by the Inca. Other scholars argue the Inga could have arrived as yanaconas, an indigenous bureaucratic order brought by the Spanish from Quito to serve as interpreters and intermediaries. The Inga are also thought to have arrived in several waves, with the first group settling in Santiago some centuries ago, and a second group settling in San Andres in the 18th century, arriving from the Amazonian lowlands in the south (Levinsohn, 1976).

Led by the charismatic cacique (chieftain) Carlos Tamoabioy, the Inga and Kamentsá in the late 17th century created a political unification that endures to this day (Bonilla, 1972). Under this unification, the Inga-Kamentsá territory was defined by the high peaks around the valley: Patascoy, Bordoncillo, Aponte, Juanoy and Portochuelo. In March 1700, Tamoabioy fell ill. Already in his seventies and knowing he was dying, the great cacique decided to dictate his will with two Spanish noblemen as witnesses. In the will, Tamoabioy listed the locations of the major land holdings that constituted the roughly 12,000-hectare indigenous resguardo (reserve). Three copies of the will were made and entrusted to the cabildos (administrative councils) of Sibundoy Grande, Santiago and Aponte for safekeeping.

### SCHULTES ENCOUNTERS AYAHUASCA

Schultes' main teacher in Sibundoy was Salvador Chindoy, a renowned Kamentsá shaman who could often be seen in public markets in Bogotá and Quito, talking about his medicinal plants and selling herbs. Chindoy believed that the plants themselves had taught him how to use them for medicinal purposes. He



would consume *yagé* or *borrachero*, another hallucinogenic plant concoction, and have a young apprentice record his vision-induced



*Schultes with shaman Salvador Chindoy,  
Sibundoy Valley, 1985.*

insights throughout the night so that he could read them in the morning. One of Chindoy's most gifted students was his nephew, Pedro Juajibioy, who also became one of Schultes' closest friends, colleagues and guides.

Schultes often told journalists (including William Burroughs) that *ayahuasca* had little effect on him and that he only saw a few flashes of color. However, Pedro Juajibioy was there the first night Schultes took the potion, and many years later vividly recalled that Schultes sang and told stories the entire time. When asked what Schultes had said, Juajibioy shrugged his shoulders and replied: "We don't know – it was all in English!"

Schultes also wrote about taking another species of *ayahuasca* (*Tetrapterys methystica*) with the Bara Maku peoples of the Rio Tikié in Brazil and noting how powerful the effects were. In retrospect, Schultes was a very private man in some ways, and presumably chose not to share his personal visions with the many people who continually badgered him for details.

### BORRACHERO: THE TREE OF THE EVIL EAGLE

Schultes was particularly fascinated by the great diversity of *borrachero*, also referred to by South American cultures as "the tree of the evil eagle." Most *borrachero* medicines were derived from variations of the genus *Brugmansia*, rich in tropane alkaloids and highly psychoactive. These plants were grown and used by indigenous cultures from Colombia south to Chile, but no place holds more species diversity than Sibundoy.

No fewer than eleven variants of *borrachero* were employed in Sibundoy. The rarest versions were typically found in gardens near the houses of the most powerful and accomplished medicine men. Some of the species were dramatically different, highly atrophied forms with thin or deformed leaves, likely the result of centuries of cultivation by the shamans of the Sibundoy.

One of the strongest of the atrophied *Brugmansias* induced strong visions for hours, with effects lasting for several days. This was a stunted plant with deformed leaves that looked as though they had been eaten by caterpillars, and was fittingly called munchiro borrachero (“drunken caterpillar”). Varieties also were named after water (buyé), the hummingbird, the deer, and the boa constrictor.

The strongest of the local medicines and the most favored hallucinogen of Kamentsa payés (shamans) for prayer and divination was *Borrachero culebra* (“drunken snake”). According to local shamans, the effects were so deeply transformative that a dose could put a person to sleep for four days. The plant had a variety of other uses as well: the leaves were used to make an infusion, and, when heated in water, the leaves and flowers were used to relieve tumor, swollen joints, and persistent chills and fevers. *Borrachero culebra* was extremely rare, found only in the gardens of Salvador Chindoy and a handful of other shamans. Schultes planted it in the garden of the church and around the seminary, in keeping with of his droll sense of humor.

The plant appeared so dramatically different from other *Brugmansia* or *Datura* varieties that Schultes described it as a new genus: *Methysticodendron amesianum*, named in honor of his botanical mentor Oakes Ames. This classification has been debated, with some suggesting that the atrophied appearance was the result of a viral infection or the mutation of a single gene. Today the plant is most commonly referred to as *Brugmansia aurea* (Hybrid) *culebra*, a classification that Schultes agreed with later in life as genetic research helped elucidate the relationships between different varieties and species of plants.

## INTO THE LAND OF THE KOFÁN

Schultes traveled down the road to Puerto Asís, stopping to collect plants with Inga communities along the Uchupayaco River and in Puerto Limon. He remained at Puerto Asís for two weeks before heading downriver to Puerto Ospina, a military base at the mouth of the Sucumbíos River. There, he met Colonel Gómez-Pereira, a Colombian officer who offered to mount an expedition up the Sucumbios when he heard of Schultes’ desire to explore the headwaters. Along the way, the Colonel would also help teach him

the basics of the notoriously difficult Kofán language.

The Sucumbíos, or San Miguel as it is more often called in Colombia, forms part of the international border between Colombia and Ecuador. Colonel Gómez-Pereira and his gunboat, the *Mercedes*, had been assigned to patrol the country's borders to prevent entry by the Brazilians, Ecuadoreans and Peruvians into a region that was still disputed in the early 20th century. On March 27, 1942, the *Mercedes* set off up the Sucumbíos.

The Sucumbíos drained the territory of the Kofán, a nation that had remained largely isolated from the outside world in the 1940s with the exception of a few missionaries and rubber traders. At the time of the Spanish Conquest, the Kofán were numerous and had successfully resisted Huayna Capac and the Inca Empire. By the 17th century, disease and enslavement had reduced their population to some twenty thousand individuals. Several waves of epidemics that the missionaries introduced in the 20th century further reduced Kofán numbers to fewer than a thousand at the time of Schultes' visit.

Their isolation from the outside world was reinforced by their warlike reputation and the variety and toxicity of their arrow poisons, but what repelled others often attracted Schultes. "I do not believe in hostile Indians," he remarked on many occasions. Schultes believed that "native people, if properly approached and treated, are friendly and sometimes willing to share their knowledge with the interested scientist."

The *Mercedes* arrived at the Kofán village of El Conejo on March 29, 1942. Schultes and Gómez-Pereira were greeted by an elder Kofán shaman, dressed in a blue cotton cusma (a type of long shirt), with layers of necklaces made from peccary tusks, seeds, and shells; his face was adorned with intricately painted red lines from achiote berries and a macaw feather jauntily inserted in his pierced nasal septum.

Schultes found that the Kofán had more shamans relative to population size than any other band or nation in the northwest Amazonia. He described them as "deeply knowledgeable men with unusual intelligence and imposing personality." By reputation, they were experts in manipulating spiritual forces to prescribe cures for illnesses and even solve socio-political problems. Some Kofán

shamans believed that, when in a plant-induced trance, they could turn themselves into jaguars and roam the rainforest at night.

Other Amazonians considered the Kofán shamans exceptionally powerful. These medicine men regarded the ritual hallucinogenic brew *yagé* as their sacrament and consumed the beverage at least once a week. Entire villages would sometimes participate in the ceremonies.

At the time of Schultes' visit, ten Kofán villages were recorded: four on both the Aguarico and Sucumbíos rivers, and two more on the Guamués River to the north in Colombia. Schultes stayed at El Conejo for several days, collecting plants, observing the routines of daily life, taking photographs and spending the evenings learning from the shamans. With Conejo as a base, he paddled up the Sucumbíos to Santa Rosa, followed a traditional Kofán path south to the Aguarico River in Ecuador, and poled up the Quebrada Hormiga, crossing over the Guamués River.

### CURARE: FLYING DEATH

Schultes had come to Kofán territory to document their renowned mastery of arrow poisons. Curare – a blanket term for all arrow poisons prepared from tropical plants, particularly those that cause respiratory paralysis – is one of the few words in the English language derived from Amazonian dialects. The use of curare was first brought to the attention of western science by the eccentric British explorer Charles Waterton in the early 19th century. Schultes began his fieldwork in the northwest Amazon just as curare medicines were becoming important muscle relaxants in abdominal surgery. He and others believed that the study of curare varieties and their admixtures could lead to both new medicines and a better understanding of the human nervous system.

The Kofán had an intricate cultural system built around the preparation of curare. Certain shamans specialized in curare production. They had to know the correct times to collect bark, what part of the liana to use, and how the plants should be prepared. (“Liana” are any slow-growing, woody vines.) This knowledge was passed from one generation of payés (shamans) to the next, following a long and difficult training period and starting with an apprenticeship at an early age.



Stipulated practices had to be followed for the creation of curare for special purposes, and the shaman had to observe strict fasting from certain foods when preparing curare. The intricate mixing of plants was accompanied by chanting, believed to maximize the toxicity of the plants; poison intended for use on large animals or humans required the chanting of two shamans.

Schultes would eventually identify and document more than 70 species of plants employed to make curare in the Amazon. The most common varieties consisted of highly poisonous plants, such as those of the *Chondrodendron* or *Strychnos* genera, combined with admixtures, typically non-toxic plants that the locals believed served as amplifiers. He also observed the Kofán employing the sap of the *Virola* tree, a hallucinogen, when producing certain curare poisons. Many years later, his student Homer Pinkley documented the Kofán along the Colombia-Ecuador border making curare from a relative of the cinnamon family.

### FISH POISON: BARBASCO

The most commonly-employed Amazonian fish poison is derived from lianas of the genus *Lonchocarpus*, often readily identifiable by both a cucumber-like odor and a relatively bright yellow wood. The fish poison is generally known as barbasco in Spanish-speaking America, timbo in the Brazilian Amazon and neku in the Guianas. The phrase “fish poison” is a bit of a misnomer, because the active compound, rotenone, stuns the fish rather than killing them. The chemical enters the fishes’ gills and interferes with their ability to intake oxygen, causing them to rise to the surface where hunters wait with bows and arrows drawn. (Today, in the western world, rotenone is employed as a biodegradable pesticide.) Such fishing expeditions are often followed by major celebrations and feasting.

Schultes remained on the Sucumbíos for several weeks before heading east to Puerto Ospina, where he briefly paused before traveling upstream on the *Mercedes* to explore the lower Guamués. When he returned to Puerto Ospina in early May 1942, he caught a military flight to Tres Esquinas on the Caquetá River, eager to find another flight to Bogotá so that he could deposit his Kofán plant collections at the city’s herbarium and then return to his beloved rainforest. He spent several days waiting for his plane in a

Koreguaje village on the Caquetá, where he observed their preparation and use of coca.

### DOWN THE MIGHTY PUTUMAYO

In mid-May, Schultes flew to Puerto Leguísimo, a military base on the Putumayo River south of Puerto Ospina. There, Schultes met up with Nazzareno Postarino, a young Italian from Mocoa whom he hired as an expedition assistant. Schultes spent several days collecting on the Rio Caucaya before heading down the Putumayo on May 19, 1942 aboard the *Ciudad de Neiva*, a three-story, wood-burning paddle wheeler.

Schultes' plan was to explore two of the major tributaries of the Putumayo. First, he would ascend the Cara Paraná, meaning "river with canoes," and then cut overland to the Igara Paraná, the "river without canoes," a reference to its many rapids. From there, he hoped to purchase a dugout canoe from the natives and continue downriver all the way to Tarapacá near the Brazilian border.

Schultes and Postarino were entering the territory of the Witoto and related Bora, Andoke, and Ocaína peoples. The Witoto were exceptionally numerous: whereas most Amazonian bands numbered in the hundreds or low thousands, the Witoto population was estimated to be about 50,000 at the beginning of the 20th century, inhabiting a lowland territory ranging from modern day Colombia to Peru. Early Witotos were described as a peaceful people known for large ceremonies of singing and dancing.

### AMBIL, THE TOBACCO PASTE

While he was on the Putumayo, Schultes observed Witotos preparing a tobacco paste known as ambil in Colombia and chimu in neighboring Venezuela. The Witoto would mix tobacco leaves and salt-like minerals extracted from other plants, cooking them down into a thick black paste periodically placed between the cheek and gums as a stimulant. Ambil was an important part of many ceremonies, and almost always taken when chewing mambe, a dried and powdered form of the sacred coca leaf.

Ambil is an unusual form of tobacco preparation most commonly found among the peoples of the northwest Amazon, although similar concoctions have been found in northern Colombia and in

the Guianas. Ambil is also consumed in *ayahuasca* ceremonies by some bands, and often partaken as a stimulant and appetite suppressant on long boat rides or hikes through the forest.

Few people in the industrialized world realize that tobacco has long been considered a sacred plant in Native American cultures. Archeological sites associated with tobacco cultivation in use have been dated to well over a thousand years. Tobacco was and is a stimulant, digestive, emetic, fumitory, and trade item. Even today, it is commonly found in gardens throughout the Amazon.

## MANGUARÉS: THE JUNGLE GRAPEVINE

At dawn in Witoto territory, Schultes often heard the sounds of manguarés, large drums fashioned from tree trunks that had been hollowed out with burning stones. Each drum had a narrow opening running lengthwise, with larger openings at the top and bottom. The drums were struck with drumsticks tipped with wild rubber; blows to either side of the opening produced distinct tones. Manguarés were suspended from the rafters of malocas (longhouses) and used as musical instruments for ceremonial occasions and for communicating over long distances to announce festivals or summon council meetings. Manguarés have been reported to have an audible range of six to ten miles, depending on the size of the drum and the surrounding topography. Amazonian historian John Hemming described manguarés in his book *Tree of Rivers*: “A code is arranged, based upon the difference of tones and the length and number of blows struck, so that all kinds of messages can be exchanged.” As Schultes would later say: there really was a jungle grapevine.

In the 1970s, Schultes returned to the Amazon aboard the Alpha Helix research vessel, accompanied by several other eminent scientists. Schultes and his colleagues walked into a Witoto village, where they were met by two local women. The women welcomed the visitors in Spanish and asked them what they wanted. Schultes replied that what he really wanted was some coca powder – in fluent Witoto. Taken aback, the women squealed and laughed – and then brought the coca!

## THE SEARCH FOR YOCO

Schultes arrived in Puerto Ospina in early July 1942. Thin and exhausted after nearly six months of nearly continuous fieldwork, he was eager to rest and recover. Schultes was relieved to receive a comfortable cabin on a Colombian military gunboat, thanks to his friend Colonel Gómez-Pereira.

One morning, Schultes was surprised to hear a knock on the door to his cabin. The visitor was a Colombian marine who told him that someone wished to speak with him. Schultes looked over the railing of the gunship to see a Kofán he had met on the Sucumbíos River. The Kofán was holding a section of the *yoco* liana, the plant Schultes had been fruitlessly searching for throughout his journey down the Putumayo. The Kofán told him the plant was in full bloom not far from Puerto Ospina.

*Yoco* had been in use for hundreds if not thousands of years, and was mentioned repeatedly in early Spanish chronicles. Schultes had first read about the plant in the book *Northwest Amazons*, written by the British Captain Thomas Whiffen, who spent a year in the lower Putumayo in 1908. Florent Claes, a Belgian botanist who traveled with the Capuchin priest Gaspar de Pinell in 1925, identified *yoco* as a forest liana in the genus *Paullinia* (related to the well-known guarana – *Paullinia guarana*), but was able neither to find a specimen in fruit or flower nor to determine it to species. The Spanish botanist José Cuatrecasas later found *yoco* growing on the forested banks of the Putumayo River at Puerto Piñuña Negra, but once more the plant lacked fruits and flowers and could neither be adequately described nor identified. The precise botanical identity of the plant remained a mystery that Schultes was eager to solve.

Locals said that *yoco* was almost impossible to cultivate, and was therefore collected in the rainforest. Indigenous communities consumed *yoco* in a beverage made by scraping off the bark and pressing the milky sap into cold water. Ingestion alleviates hunger and fatigue, often allowing one to go for up to two days without food while also providing a sense of focus and overall well-being. (A chemical analysis reveals that, in addition to other active ingredients, *yoco* bark yields about 3% caffeine, stronger than coffee.) Several Kofán communities insist that *yoco* consumption also helps prevent malaria.

The plant was a dietary staple of the bands living in western

Caquetá and Putumayo in Colombia and adjacent parts of Ecuador and Peru. Most indigenous households of these areas kept a supply of yoco stems, and preferred never to leave for the forest without carrying the plant. Yoco was so important to them that they would simply pick up and move their village to another location when local supplies had been depleted. It also was an integral part of many of these cultures' morning rituals: they would rise at dawn, rinse their mouths in the river, and drink a gourdful of *yoco* before eating any food. The first gourd was followed by another about a half an hour later, with even more ingested for hunting or fishing trips. Regional bands were able to distinguish fifteen varieties of yoco, including *yoco blanco* and *yoco colorado*, all of which fell within a well-defined indigenous system of classification.

Schultes had seen *yoco* in use throughout his explorations of the Putumayo watershed. The first was with the German rancher Jorge Fuerbringer and some local natives, who had led him to *yoco* outside of Mocoa in 1941, but the plant was not in fruit or flower. He found other sterile specimens in an Inga community in the headwaters of the Uchupayaco River in February 1942, between the Putumayo River and Teteyé River in March 1942, and at the Kofán community of El Conejo on the Sucumbíos in April 1942.

On July 6, 1942, after twenty hours of travel, Schultes and the Kofán came to a spot in the forest about 15 km along the trail from Puerto Ospina to Puerto Asís where the ground was covered in small flowers. After the group felled a few small trees, a large woody vine came crashing to the ground. Schultes had identified another species new to science, and named it in honor of the indigenous appellation: *Paullinia yoco*.

Many a liana had I cut down, only to find it flowerless and, in this condition, without value for taxonomic study. All the Indians of the upper Putumayo River knew of my quest. In June, when the rivers rose, flooding all the forests, I decided to end my trip and return to Bogotá. My legs were covered with ulcers from walking through the swamps and ... when I arrived at the Colombian naval base on that river, the clean bunk which the commander of one of the river gunboats offered me pending the arrival of an aeroplane felt regal. Three days before the arrival of the plane, an Indian came

paddling down with the news that he had located a flowering yoco. He assured me it was only four hours' walk through the forest. I hesitate. The pains in my legs, I confess, nearly won out. By, finally, I agreed to go, half expecting to find just one more flowerless liana. It was a terrible pilgrimage of six or seven hours on foot, most of the time knee-deep in water and mud. On arrival, I saw an enormous liana, the tiny flowers of which were strewn far and wide on the forest floor. We had to fell seven trees before the treasure would fall into our laps... that collection not only enabled us to identify an interesting drug but provided me with a species new to science. (From Schultes' Field Notes, 1946)

## THE APAPORIS: WORKSHOP OF THE GODS

### WORLD WAR II & SCHULTES' RUBBER MISSION

As Schultes made his way down the Putumayo River in 1942, Nazi Germany was consolidating control of continental Europe after conquering Poland in 1939 and France in 1940. German U-boats were devastating British shipping in the Atlantic while the German army turned its hungry gaze east towards the eastern European countries and the Soviet Union.

In early 1942, Schultes left the rainforest and presented himself at the American Embassy in Bogotá in order to enlist in the Allied cause. He expected to be sent back to the States to undergo basic training and then be shipped to the European battlefield. Much to his surprise, he was told he could do far more to help his country by returning to the Amazon on a special mission to find high-yielding and disease-resistant strains of rubber trees.

A steady supply of rubber was vital to the war effort. Each Sherman tank required a half ton of rubber; a heavy bomber required a full ton. Some warships contained 20,000 rubber parts. Rubber was not only a component on every single wheel of every single vehicle, it coated every wire. At the outbreak of World War II, 90% of the global supply of rubber was being produced in plantations in the European colonies of Southeast Asia, mostly the Dutch East Indies and British Malaya.

The day after the attack on Pearl Harbor, the Japanese invaded

British and Dutch colonies in Southeast Asia to secure access to rubber, a vital resource that had been cut off from Japan by economic sanctions. The Japanese nearly-simultaneously invaded the Philippines, British Borneo, Hong Kong and, later, British-controlled Singapore and Java and Sumatra in the Dutch East Indies. By May 1942, Japan had conquered a wide arc of territory, from Burma in the west to New Guinea to the south and north to Iwo Jima, thereby controlling a substantial portion of the world's rubber supply.

## HEVEA: THE ODYSSEY OF THE TREE THAT CHANGED THE WORLD

Schultes later referred to rubber as “the tree that changed the world in one century.” In fact, it was a remarkable set of circumstances that led to the global dependence on Asia for a product originally derived from an Amazonian tree.

Rubber was initially collected exclusively in the wild, often by corrupt enterprises led by ruthless rubber barons who enslaved local peoples through both insurmountable debt and extreme cruelty. All attempts to establish rubber plantations in South America ended in disaster, due to incessant depredations by leaf blight and *Dothidella* fungi. Attempts to transport rubber seeds out of South America also failed, as the oily seeds quickly spoiled and perished.

Henry Wickham, a British adventurer, spent many years living in the Amazon and Orinoco in the mid-19th century, and published a book on his travels. Wickham had a keen interest in economically useful plants. He collected the cinchona seeds in Peru and Ecuador that later became the source of quinine plantations in India and Ceylon, producing valuable anti-malarial drugs for the British Empire.

In 1876, Wickham was in Santarem when a steamship of recent vintage – appropriately named the S.S. Amazonas – forged up the Amazon River on an inaugural voyage from Liverpool to Manaus. While the ship was making its way downriver, Wickham learned that a corrupt businessman had left the S.S. Amazonas without cargo for the return trip. Seizing this opportunity, Wickham instructed his indigenous associates to collect rubber seeds that

happened to be ripening at that moment. Previous seed shipments had been sent by sailing ships, and the few days saved by the faster steamboat helped ensure that some seeds survived the voyage to England. More than 70,000 seeds were collected and transported to the Royal Botanic Gardens at Kew outside London, of which 2,800 survived. The resulting seedlings were packaged in glass-domed cases and shipped through the Suez Canal to Ceylon, Singapore and other tropical European colonies.

After initial difficulties cultivating and efficiently harvesting the latex in Asia, rubber plantations grew in popularity as methods improved. In 1907, there were over 10 million rubber trees in Ceylon and Malaya. Just two years later, Malaya had planted more than 40 million specimens. New techniques for tapping trees were developed: by making only a light incision in the bark, the rubber trees could be harvested more frequently and at a younger age without impeding growth or killing the tree. Selective breeding of genetic lines doubled production within a generation. As the Asian plantations expanded and grew more productive, the Amazon rubber industry collapsed, and Southeast Asia became the dominant provider.

With the Japanese threatening the European colonies in Southeast Asia, the United States government realized that its reliance on rubber from these regions was a vulnerability. In response, the U.S. established the Rubber Reserve Company to determine how best to establish flourishing rubber plantations in the Americas.

Early accounts indicated that blight-resistant species of *Hevea* might exist in other less-explored regions of Amazonia, especially the northwest Amazon, which reports – including those by Richard Spruce in the mid-1800s – suggested might be the origin of the genus. Schultes' mission was to explore these remote areas and estimate how many such species, and members thereof, existed in a given region. His first assignment was to investigate three sites in the upper Caquetá watershed said to be rich in wild rubber.

I joined this organization and immediately plunged into the rubber forests of Colombia as an explorer, searching out the densest [stands] and best type of rubber, mapping rivers, and reporting on their navigability and other tasks preparatory to the rebirth of the wild rubber industry. I became intensely



interested in the rubber plant, the more so since I saw, from studies in the field, that botanically there was so much to do before we lay claim to even a preliminary understanding of the numerous wild species of the commercial rubber: *Hevea*. (Schultes' field notebook, 1952)

On December 26, 1942, Schultes left Bogotá by train, bound for Neiva to the southwest, from where he continued south to Pitalito to meet the expedition team. Over the next two weeks, the team made their way slowly across the mountainous terrain, crossing from the headwaters of the Magdalena River to the upper Villalobos River. As the expedition moved slowly over the rugged terrain, Schultes found several varieties of cacho blanco ("white rubber"), a high-quality rubber, and discovered a new species of *Hevea* known as *Hevea Colorado* or "red rubber." He and his colleagues also found many scarred trunks and disfigured stumps that indicated this area had been overharvested and ravaged by caucheros (rubber tappers) in earlier decades, leaving few healthy and productive mature rubber trees.

Schultes had hoped to reach the Inga community of Yunguillo in the headwaters of the Caquetá, but the terrain proved too difficult and the expedition had to turn back. The difficult conditions and low density of remaining rubber trees meant the area was of little use for their purposes.

### CHIRIBIQUETE: THE LOST WORLD

Schultes' next mission was to investigate the remote rainforests of the Apaporis River, which, though one of the least-known rivers in Colombia, was yet believed to contain a huge supply of rubber. This assignment brought him to one of the most inaccessible and spectacular landscapes in the Amazon, inhabited by a mysterious people reputed to be fierce cannibals.

On March 3, 1943, Schultes arrived in Miraflores, a newly created rubber station on the upper Vaupés River in southeast Colombia. The expedition began with an ominous start: many supplies failed to arrive or were severely delayed. Schultes was also unable to find anyone familiar with the upper Apaporis to help guide the expedition, though a local chief in Puerto Nare did warn of its treacherous rapids.

Schultes assembled a small scouting team and ascended the Vaupés River to the confluence of the Unilla and Itilla rivers, a location known as Puerto Trinidad to local caucheros. From Puerto Trinidad, the team spent fourteen hours hacking their way through dense forests overland before finally reaching the Macaya River at a series of rapids.

That same evening, a young member of the expedition team attempted to swim across the river, but was caught in the current and pulled into and under the twisting rapids. His body was never recovered. The next day, Schultes returned to Miraflores to report the death. To commemorate this tragedy, the rapids were named “Cachivera del Diablo” – the “Devil’s Cataract.”

After a quick trip to Bogotá in early April, Schultes returned to Miraflores on April 18, 1943. There, he and Everett Vinton, a fellow explorer also working for the RRC, assembled an expedition team of 28 men and set to work establishing a twenty-mile supply trail from Miraflores to Puerto Trinidad and then on to the Macaya. After slowly accumulating the necessary supplies, they cleared a high piece of land and built a camp at the confluence of the Macaya and Ajajú rivers. The rustic camp included a kitchen, dining hall, store rooms, sleeping quarters for thirty men, and a rough landing strip on the opposite bank of the Macaya. They named the camp “Puerto *Hevea*” because of the high concentration of rubber trees in the area. This locale can still be seen as a clearing in satellite imagery.

On May 14, while the expedition crew was clearing the forest and setting up camp, Schultes set off across the Macaya to explore the immense sandstone mountain that had loomed in the distance for many weeks. As he climbed, the dense forests gave way to a rocky savannah. Arriving at the broad summit, a magical landscape was revealed: thousand-foot-high granitic domes and tabletop sandstone mountains emerged from the pristine rainforests all around him. Waterfalls roared over the edges of cliffs, through giant caverns, and into unspoiled rivers.

The sober-minded Schultes – never a man given to poetic flights of fancy – was deeply impacted by this enchanted landscape. He would later say that these eerie rock formations seemed like giant sculptures left over from God’s workshop: “It was from these first tentative experiments,” Schultes mused, “that He had gone out and

built a world.”

Schultes climbed to the summit of Cerro Chiribiquete, part of the larger Chiribiquete mountain range that runs for more than 240km from north to south. The Chiribiquete range can be divided into five distinct parts: the Chiribiquete, Cuñaré, Yarí and Araracuara ranges, and the Mesa de Iguaje. Chiribiquete is bordered to the east by the Apaporis River, whose two major tributaries, the Ajajú and Macaya, originate in the Yarí River to the west. To the south, the Yarí – also originating in the savannas – crosses through the southern portion of Chiribiquete, where it joins with its major tributary, the Mesay, originating in the least-explored central region of the range. The Caquetá River cuts through the Araracuara highlands, forming the spectacular thousand-foot-high canyons of Araracuara, memorably captured in one of Schultes’ most famous photographs.

### THE GUIANA SHIELD

Chiribiquete forms the westernmost extent of the Guiana Shield, an ancient geological formation stretching along the northern edge of South America from central Colombia to the northern Atlantic coast. It contains some of the oldest rocks on earth, dating back to the Precambrian era almost two billion years ago, long before the Andes were formed. This ancient mountain range has been grotesquely eroded over time, leaving unusual granitic rock formations and flat, table-topped sandstone mountains with sheer cliffs known as tepuis.

The Guiana Highlands harbor some of the world’s most spectacular waterfalls, like Angel Falls in Venezuela and Kaieteur Falls in Guyana. Pico da Neblina, at over 9,800 feet, is the highest point in lowland Amazonia. Due primarily to its remoteness, the Guiana Shield contains some of the most pristine rainforests in the world, features high levels of biodiversity, and is home to many endemic species, particularly in and on the isolated massifs.

On these mountaintops, Schultes gathered the first-ever botanical collections from this awe-inspiring region. In his book *One River* (1996), Wade Davis describes Schultes’ experience on Cerro Chiribiquete:

What Schultes found on the summit was a grassland

interspersed with dense brush of low gnarled shrubs, an island of savannah perched a thousand feet above a tropical rain forest. Adapted to the dry conditions, the plants were reduced in size, and many bore glossy leathery leaves, often coated with heavy waxes or dense pubescence. Their bark was either thick and corky, or thin and coated with wax. Epiphytes had exaggerated pseudobulbs for water storage, and many plants grew low to the ground and had dense rosettes of leaves. The roots were especially well developed, penetrating the cracks and fissures in the rock, reaching like veins across the face of cliffs. The growth forms were exceedingly strange, the overall aspect of the flora elfin and bizarre. (*One River*, p.319)

Schultes found several new species that day, including *Vellozia phantasmagoria*, a ghostly herb from the small genus of monocots found in northern South America and adjacent Panama. As he cut through the forest, his clothes became covered with a sticky latex, leading to the discovery of two new rubber plants: *Senefelderopsis chiribiquetensis*, a relative of balata, and *Hevea nitidia* var. *toxicondendroides*.

The expedition completed construction of their first canoe in early June of 1943. Unfortunately, a motor that had been promised never arrived, so Schultes and a small crew paddled their way up the sweeping curves of the Ajajú River, surrounded on both banks by majestic and mysterious tabletop mountains. After several days on the water, the expedition passed a set of rapids near the mouth of the Macuje River, and continued upstream to the Yaya-Ayaya River. The ecosystem began to transition as they paddled west up the Ajajú: The rocky, sandy terrain gave way to flooded forests less likely to harbor rubber trees. Finding the Yaya-Ayaya riddled with rapids, the expedition turned back and descended the Ajajú.

#### THE BELL MOUNTAIN — CERRO CAMPANA

On June 6, Schultes and his crew turned north up the Caño Negro, a small tributary of the Ajajú on the northernmost side of the Chiribiquete highlands. In front of them loomed an imposing series of steeply sloped domes with soaring peaks, one of which was known as the Cerro Campana — the “Bell Mountain.” Schultes described Cerro Campana in his book *Where the Gods Reign*:

...the isolated quartzitic mountains of [Chiribiquete] are sentinels of a mysterious past. The Cerro de la Campana is one of the westernmost vestiges of these hills and is so strikingly awesome that it is wrapped in legend in the Indian mind. All Indians believe that fierce thunderstorms and torrents can be caused by beating upon a thinly eroded slab near the summit. When struck with another stone, it sends forth a bell-like tone.”

In his ascent of the isolated massifs, Schultes noted that those who once lived there had created strange and wonderful cave paintings on the walls and in rock shelters. These ancient designs, painted with dark red dyes, depict chaotic mosaics of people, animals, shamans, hunters, and dancers.

Jaguars with intricate spot patterns leap through the air. Shamans hold long staffs and palm fronds above their heads while hunters stand alert with barbed spears, ready to be launched. Abstract spiral designs emerge from the torso of animal-human hybrids as the creature undergoes a mysterious spiritual transformation. The paintings portray fish, frogs, birds, and unrecognizable animals. Hundreds of red handprints are the only remaining signature of a mysterious people that created this ancient artwork before disappearing into the jungle.

Schultes was one of the first explorers to observe these paintings, in what would turn out to be one of the largest concentrations of pre-Columbian cave paintings in all of Amazonia. Later research found as many as 8,000 paintings on a single wall. To this day, the region remains largely unexplored, with experts having little idea of the total number of cave paintings, their date of creation, or their precise origin.

### CARIJONAS OF CHIRIBIQUETE

As he explored the Chiribiquete highlands, Schultes’ guide was Barrera, a young Carijona he had met along the Vaupés River. Barrera accompanied Schultes along the visits to the Macaya and Ajajú Rivers, and had taught the ethnobotanist about the mythological importance of Cerro Campana as well as the local uses of various plants.

Near the Apaporis River, they found *Markea coccinea*, an

epiphytic vine with red flowers valued by the Carijona for mystical ceremonies and to expel intestinal parasites. Carijona medicine men would treat dementia by traveling to the top of Cerro Chiribiquete to gather the leaves and stems of a species that was eventually named by Western science in Schultes' honor: *Piper schultesii*. They would soak these plants parts in water or a ferment them before giving them to elderly patients "who sit without talking all day." Schultes noted that these plants could be kept dry for several months without losing their strong pungency and were also used in a tea to relieve coughs and chest infections. The Carijona also knew and used herbal remedies for fevers, fungal skin infections, and ringworm, and to relieve the symptoms of malaria.

The Carijona had dominated the Chiribiquete region for more than four hundred years, at one point totaling more than 25,000 people. Within a hundred years of contact with the outside world, the Carijona were reduced to less than a thousand members. As Schultes journeyed through Chiribiquete, the former heart of Carijona territory, he knew he was recording important ethnobotanical information from a dying people who would soon cease to exist as an intact cultural entity. He was in a race against time as he traveled, recorded and collected plants with some its last members.

#### DOWN THE LITTLE-KNOWN APAPORIS RIVER

The expedition's next goal was to descend the 1,350-mile Apaporis, one of the most isolated and least-known of rivers in the Amazon basin. Schultes knew this task would not be easy: on a previous overflight, he had counted more than a dozen daunting rapids, including an enormous waterfall followed by a mile-long canyon that nearly obscured the river running through it.

Setting off down the Apaporis, they passed the first set of rapids, the Cachivera de Chiribiquete, some twenty miles from Puerto Hevea. After proceeding smoothly through 20 miles of open river, they encountered a set of fierce rapids that nearly capsized the canoe. Barely reaching the shore, they were forced to haul the boat ashore and hike back to Puerto Hevea overland through the trackless rainforest, all the while carrying an injured man. They needed additional workers to portage the upcoming rapids.

Nearly a week later, they once again continued down the Apaporis. Although slowed by a rainstorm that damaged many of their supplies, they were eventually able to advance nearly fifty miles through many treacherous rapids. Deciding they would not safely reach the mouth of the river, they once again decided to return to Puerto Hevea by land, leaving the canoe behind.

In his book *One River* (1996), Wade Davis describes Schultes' revelation on the trek back to Puerto Hevea:

As he moved along the shore he realized that the counts he had been making from the water had been consistently low. When he factored this error into his survey results, he discovered that the upper Apaporis...supported more than a quarter million rubber trees. Properly exploited, they would yield almost a million pounds of rubber a year. (*One River*, page 321)

After a brief stint in Villavicencio and Bogotá to recover from a blood infection that nearly killed him (the “doctor” turned out to be a veterinarian), the undaunted Schultes returned to Miraflores on August 25, 1943. His next expedition would cross overland on a trail from Puerto Nare to the Apaporis, below the rapids that halted their progress down the river two months before.

It was a difficult journey, and the team struggled to carry an extraordinarily heavy, sixteen-meter boat overland across the thirty-six mile trail they had hacked through the forest. It was thankless, backbreaking work: the journey took fourteen days and left them exhausted and demoralized.

Beginning below the final rapids of Chiribiquete, Schultes was finally able to continue his descent of the Apaporis, which from that point remained unbroken by rapids for nearly three hundred miles. The work proceeded smoothly, and Schultes counted many mature and harvestable *Hevea guianensis* trees along the bank of the river. This was ideal rubber territory.

As they proceeded, Schultes also mapped the course of the Apaporis using a tedious but surprisingly accurate technique: As they progressed, Schultes would actually pace a kilometer on the shore of the river, marking each end with a white flag. This also allowed him to measure the speed of the river as the boat drifted from one marker to the next. As they drifted down the Apaporis,

Schultes used his compass to keep track of the boat's orientation. Together with his kilometer pacings, this permitted him to plot river's course and produce the first map of the Apaporis; it was an ingenious, low-tech approach more akin to those employed by early Victorian explorers like Alfred Russel Wallace (who had been trained as a surveyor) than the cartographers of today.

At one point, Schultes and his team observed a ridge rising in the distance, and the mouth of a blackwater river emptying into the Apaporis, known as the Kananarí. There they encountered a Taiwano, busy fishing for his dinner. So remote was the territory they had crossed that this fellow was the first person they had encountered for six months.

Later, with the Taiwano guiding them up the Kananarí, a massive sandstone plateau known as Cerro Isikburi rose abruptly out of the forest to their right, adorned with numerous ribbon-like waterfalls cascading from the summit.

As they ascended the Kananarí, they passed giant boulders engraved with highly stylized figures of unknown ancient origins. They spent the night in a Kubuyarí maloca on the Caño Paco with similar designs painted on the walls in yellow, red and black. Their hosts explained that the designs represented *yagé* visions.





## ETHNOGRAPHIC NOTE: ETHNIC GROUPS OF THE LOWER APAPORIS & VAUPÉS REGION

The lower Apaporis and Vaupés region represent one of the most complex linguistic areas in the Amazon, if not the world. It harbors some fifteen Tucano languages and a few other less commonly spoken and unrelated dialects, such as Makú. Tucano-speaking bands of the region include the Makuna, Barasana, Tanimuka, Cubeo, Taiwano, and Letuama.

Interestingly, many cultural groups in this region have a socially obligatory multilingualism wherein indigenous community members are expected to marry someone of a different language group and learn their language; to marry someone belonging to the same language group is considered akin to incest. Due to these social norms, the indigenous peoples of the region are able to speak a remarkable number of languages and maintain a diverse array of cultures and cultural traditions.

This linguistically and culturally diverse territory made for an exceedingly interesting research area for Schultes, as each ethnic group had different oral histories and different medicinal uses for local plants. However, the complex linguistic traditions often made it difficult for him to communicate, especially with elders who spoke little or no Spanish. Never easily discouraged, Schultes responded by learning the basics of some the local languages.

### THE PALM OF THE SPIDER WEB

At dawn, Schultes emerged from the maloca and went to bathe in the river. Through the early morning mists, he noticed the graceful silhouette of a stand of palm trees growing on the nearby rapids. Known locally as caranaí, the palm would be a species new to science: *Mauritiella cataractarum*, found only on rocky riverbanks near rapids.

The Makuna call this tree bö-pö-ma – the tree of the spider web – due to the resemblance of the crown to gigantic spider webs as one looks upwards through the canopy from a canoe. They say the palm was planted before man came to earth from the Milky Way. In this

primordial era, the “Spirit of the Sun” threw fishing nets (the spider web) from the sky onto the lands below, indicating where the Makuna should settle and build their malocas. Schultes would later observe that most Makuna settlements are found near rapids, giving their location a dually cosmological and ethnobotanical origin.

As they descended the Kananarí, the Kubuyarí chief warned Schultes of the perilous rapids that lay ahead. He claimed these were dangerous places inhabited by the spirits of the dead whose presence was manifested by strange spirit faces on the cliff walls.

Schultes had been ordered not to pass the falls of Jirijirimo, but now, with a barely functioning outboard motor, dwindling supplies, and little chance of successful hunting, this would be virtually impossible. He would have to face the rapids.

Schultes was an aficionado of the classics, often travelling with *The Illiad* or *The Odyssey*, which he would translate from the ancient Greek when he spent endless days in longhouses waiting for the rains to cease during the wet season. After such a risky and hazardous journey down the Apaporis, he likely recalled the famous lines from Virgil’s *Aeneid*: “The descent to Hell is easy; the return, impossible!”

At the beginning of October 1943, Schultes and his small crew set off at dawn. As the river narrowed and increased in speed, Schultes heard a distant rumble and saw a plume of mist in the distance. Huge sandstone slabs emerged from the churning river. The crew navigated over to the right bank against the river’s strengthening force. Tired as they were from the long journey, they slowly carried the boat along an overland trail.

### ANCIENT RAMPARTS: JIRIJIRIMO & YAYACOPÍ

Schultes had arrived at one of the great natural wonders of Colombia: the falls at Jirijirimo. For much of its lower course, the Apaporis is broad and meandering, measuring 1,500 meters across before arriving at an ancient mass of hard, metamorphosed rock that forces the powerful river through a chasm just 40 meters wide.

Preceded by nearly a kilometer of rapids, the fall itself begins with several giant rock steps before the water tumbles over a vertical drop some 30 meters high. During the rainy season, the high water almost completely covers the rocks with churning whitewater; in the

dry season, the water is barely visible as it falls between the rocks. Schultes mused that – when viewed from a plane during the dry season – it appeared that the falls could be forded by jumping from one rock to the next, “but such is not the case” (Field Notebook).

As his crew rested, Schultes carefully picked his way along the side of the gorge against the perpetual mists and deafening roar of the falls. There, Schultes noticed a strange plant with alga-like leaves clinging to the rocks. Unfortunately, he was travelling without his plant collecting equipment for the first time of his career, due to the journey’s difficulty and many overland portages. He vowed to return to study this plant, which he did eight years later, in 1951.

He would learn that local Makuna called the plant moo-á, and they used it as a form of table salt by reducing its leaves to ashes. Sodium chloride, the basis of salt common to most of the world, does not exist in the Amazon, and for centuries indigenous communities throughout the Amazon have used the potassium-rich ashes of river herbs to flavor their food.

A species of *Rhyncholacis*, the plant is a member of the Podostemaceae family of aquatic plants. These herbs have developed remarkable adaptations to the difficult riverine habitat: “The podostemonaceous plants have tough, alga-like leaves that come out at the height of the rainy season and clothe the rocks where the flood will reach its fullest. The tiny white flowers have blossomed in time to set ripe fruit for the fullest sweep of the waters” (*Where the Gods Reign*, 98).

After hauling the canoe overland around the falls, they resumed their journey down the Apaporis, shortly thereafter to find a mysterious chasm.

The mighty Apaporis, after it tumbles over the Falls of Jirijirimo, enters a long and narrow chasm walled in by high vertical cliffs. At one point the whole river disappears into a tunnel, flowing tranquilly and deep through the curious fault. This is a place of awful mystery to the Indians of the area who, except for the medicine-men, never travel through the chasm, and the tunnel is known to them only through hearsay.

(*Where the Gods Reign*, 56)

After emerging from the Jirijirimo canyon, the Apaporis resumed its tranquil path for another 5 miles, until arriving at a massive,

horseshoe-shaped falls known as Yayacopi. Schultes later wrote “the thundering falls of Yayacopi strike awe into the hearts of the Indians of the region, accustomed as they are to the titanic forces of angry waters everywhere in the Apaporis basin” (*Where the Gods Reign*, 62).

The rapids of the Apaporis – of which Yayacopi and Jirijirimo are the largest – have strong spiritual significance to the Makunas and other nations of the lower Apaporis. It is said that in ancient times a fierce group inhabited the headwaters of the Apaporis River. This warlike band would attack the Makunas, at one point nearly annihilating them. A primordial shaman determined to protect his people took *yagé* for seven days, allowing him to commune with friendly spirits. Together, they raised a series of mountains across the Apaporis, forming impassable rapids imbued with magical spells that have protected the people of the lower Apaporis ever since.

Schultes noted that Makuna shaman would make pilgrimages to perform elaborate incantations at the foot of Yayacopi. The Makuna would also paddle for several days to fish in the richly stocked whirlpools at the base of the falls. However, they never willingly traveled above the rapids, leaving the upper Apaporis uninhabited for many decades.

In view of the natural beauty and complexity of this waterfall there can be little wonder why the Indians ascribe a supernatural origin to it. (*Where the Gods Reign*, 86)

At night, in the malocas of the indigenous groups living below the waterfalls, Schultes would sit with the shamans and other elders, imbibing coca powder and tobacco syrup. There, he listened to mythical stories about the ancient past and about the thunderous waterfalls of Jirijirimo and Yayacopi. The Tucano language family spans Colombia, Ecuador, Brazil and Peru. Members of an eastern group – the Coreguaje, Siona, and Secoya – are completely isolated from the western group. It is believed that the Carijona invasion of the 1500s led to the division of the Tucano-speaking groups, lending credence to the oral history that the great waterfalls were protection against fierce cannibal invaders.

## THE ROCK OF NYI

Although low on supplies, Schultes turned north off the Apaporis to paddle up the Pira Piraná River, arriving at one of the most elaborate rock carvings in the entire northwest Amazon: the Rock of Nyi. Located on the banks of the Pira Paraná almost exactly on the equator, the Rock of Nyi is a remarkable feat of artistry: five and a half feet tall, the stylized anthropomorphic design is carved into an extremely hard granite boulder, at times cut half an inch deep.

The Rock of Nyi is revered by local indigenous groups. For them, this petroglyph honors four mythical cultural heroes who used the sacred trumpets of the Yurupari to create the rivers, mountains, ritual artifacts and cosmos, while confronting evil spirits and turning them into stone.

Schultes noted that the Pira Paraná featured more rock carvings than neighboring rivers. Most were located in inaccessible locations near swiftly flowing narrows in the river or at rapids or waterfalls. Sacred petroglyphs such as Nyi account for just a few of the many holy sites known to the peoples of the lower Apaporis and Vaupés, nearly all of which are connected to their view of the mythological origins of the world.

The Tucano-speaking nations of the lower Apaporis believe that humanity originates in the Amazon, known to them as the “River of Milk”, and in the Pira Paraná, which they call the “River of Water of the Yurupari.” The mouth of the Amazon is said to be the original maloca of the Yurupari and the “Door of the Waters” from which life emanated. It is here that ancestral anacondas lived, receiving great knowledge from the jaguar spirits of the Yurupari.

Per this mythology, in primordial times, a great noise sent the anacondas fleeing the maloca, and scattering out into the ocean. Supernatural “creators” gathered them, giving each a name such as the Celestial Anaconda, the Anaconda of Remedy, the Fish Anaconda, and the Water Anaconda. From the Door of the Waters, the Ancestral Anacondas emerged to migrate up the Amazon River, dividing into separate paths. As they ascended, the anacondas designated the territories of the lower Apaporis.

As the ancestral anaconda swam up the Amazon, they periodically halted to provide their gifts of knowledge and sacred plants, in the process creating a variety sacred sites imbued with spirits. The

indigenous peoples of the lower Apaporis and Vaupés believe that these sacred sites are interconnected, spanning not only their territory but the entire Amazon basin as well.

These sites are divided into categories with distinct rules for how they must be maintained. Mountains and stones are believed to be sacred places of ancestral importance, and held in high reverence. Savannas, especially in swampy headwaters, are areas that cannot be utilized for any purpose. Rivers and lakes can be used, but with restrictions. Sometimes it is necessary to be accompanied by a shaman, or to first receive permission from them to visit sacred sites.

The sites are said to be inhabited by ancient spirits who local people believe are the true owners of the world. It is these spirits that ensure the health and prosperity of the surrounding peoples and forests, making sacred locales important areas of pilgrimage and concentration to help mankind maintain a connection to and equilibrium with nature.

The Tucano-speaking groups of the Apaporis and Vaupés region practice elaborate ceremonies in accordance with annual harvest calendars, which they believe maintain spiritual balance and prosperity within their territories. These ceremonies are led by traditional healers known as the “Jaguar Shamans of the Yuruparí,” who, after ingesting *yagé*, coca, and chicha (a fermented beverage), undertake vast spiritual journeys between sacred sites, cleansing their territory as they travel, thereby preventing sickness and hunger while promoting spiritual well-being within their communities.

These ceremonies are accompanied by chanting, and punctuated by haunting music played on bamboo pan pipes, thumping sticks and leg rattles, all of which are made from locally available plants and designed to bring on a trance state as the shamans and their people connect with the Cosmos.

## OVERLAND TO THE MIRITI PARANÁ

Immediately after arriving in Jinogojé in February 1952, Schultes made plans to travel overland south to the remote Mirití Paraná River, home to the little-known Yukuna, Tanimuka and Matapi. Born in the lightly forested lowlands between the Apaporis and

Caquetá, the blackwater Mirití Paraná flows for more than three hundred miles over seven major rapids before emptying into the whitewater Caquetá River.

In early March of that year, Schultes and Jacome Cabrera descended the Apaporis from the mouth of the Pira Paraná and turned to paddle up the Popeyacá River for two days, passing several malocas along the way. Cabrera was the perfect guide: the son of a Colombian father and a Tukano mother, he had spent most of his life in the region and fluently spoke several of the local languages.

Approaching the narrow headwaters of the Popeyaca, they abandoned their canoe and proceeded on foot, undertaking the difficult overland hike through the forest to the headwaters of the Guacayá – the largest tributary of the Mirití Paraná.

After a day of walking, they came upon an isolated massif emerging from the forest. It seemed as if a titanic boulder had split in half, creating two small mountains. The Tanimuka know this odd peak as the “Mountain of the Little People” and believe that tiny people emerge in swarms from caves and crevices to attack intruders with powerful magic. Thunder and sickness are said to originate in these mountains when the chief of the little people is preparing magic and poisons.

Schultes and Cabrera continued on to the Guacayá, spending a week there with the Tanimuka, Yukunas and the Matapies, whose language had been lost a generation before. Cabrera knew that these communities would soon be hosting a great festival, one of five throughout the year corresponding to annual harvest cycles. The upcoming festival would be the spectacular *Kai-ya-ree* - the Dance of the Spirits - in celebration of the pupunha, or peach palm harvest.

### BACTRIS GASIPAES: THE PEACH PALM

Known as chontaduro and peijibaye in Spanish, pupunha in Portuguese, and peach palm in English, *Bactris gasipaes* was domesticated in the western Amazon in Pre-Columbian times and spread as far north as Central America. The large, orange or reddish peach palm fruits are typically boiled or roasted. Some are instead used for dry meal, suitable for storage throughout the year, an important quality in the rainforest environment where food items



usually spoil quickly. Peach palm fruits are also used to prepare a *chicha*, a delicious and mildly alcoholic drink prepared by kneading the flesh of the fruit in water to create a kind of mash, which is then tightly packed into baskets and buried for several weeks, allowing it to ferment into a nutritious beer. It is an essential component of multi-day indigenous ceremonies: entire canoes are filled with the beverage, and the festivities continue until the *chicha* is no more.

## *KAI-YA-REE — THE DANCE OF THE SPIRITS*

Schultes returned to the Guacayá at the end of April 1952, as the final preparations for the festival were underway. Schultes referred to the ceremony as the *Kai-ya-ree*, but it is also known as the Baile de Muñeco - the Dance of the Dolls - a name believed to have been ascribed by outsiders in the 20th century but commonly used by indigenous inhabitants of the Mirití-Paraná river even today. The celebrants had begun to gather from as far as five days away, congregating about a day's walk away from the maloca where the ceremony would be held.

When ready for the festival to begin, the maloquero – the so-called “owner” of the maloca, typically a chief or a shaman – sends a signal using the enormous manguare drums made from hollowed tree trunks that are audible up to a six-hour walk away from the maloca, even further when the sound travels along the river rather than through the rainforest. As each participant arrives, the chief of the dance performs an unusual chant, recounting the events of the previous year. The Yukuna chief opens the ceremony by circling around the maloca three times while carrying a six-foot rattling wand.

The ceremony begins at midnight, and participants wear elaborate costumes of brown barkcloth shirts and long, free-flowing grass skirts, dyed pitch black along the bottom edge. Intricate, sometimes grotesque masks of black and yellow are worn to represent devils, spirits and many forest animals, including tapirs, bees, squirrels, monkeys, and jaguars. The ceremony consists of a long series of individual dances, each dedicated to a different animal or spirit and each with its own intricate step and chant. The dances dedicated to the animal spirits mimic their movements and sometimes their vocalizations.

As far as we know, Schultes was the first western scientist to participate in this unique ritual, and described the various dances in his seminal paper "Palms and Religion":

The young boys, those from eight to twelve years of age, dressed in the typical shirt but with the head covered with a hammered bark hood upon which the facial features of a monkey have been delineated, begin with the Monkey Dance. It is a quick, lithe dance mimicking the nervous jumping of monkeys from branch to branch; and the boys carry leafy branches which they wave rhythmically while chanting in high-pitched voices, very suggestive of the chattering of monkeys in the tree tops.

The Jaguar Dance, with characteristics stealthy half steps interrupted on occasion with pounces and a whining, snarling catlike chant, is performed by only the nimblest and most experienced of dancers. The mask is a superb creation: a replica in black pitch of a jaguar head, replete with eyes flashing with tiny pieces of mirror. Whiskers, and snarling mouth set with wooden teeth.

The Tapir Dance, slow and lumbering, has a fanciful tapir-head mask, and the Anteater Dance mask stands out among all the others because of its realistic, long, curved snout. In the Deer Dance, the movements are graceful and rapid in the extreme, consisting mostly of intricately interweaving in a running, darting step performed with and unbelievable mimicry of the deer's nervous and frightened manner. A low, sustained buzzing chant accompanies the Wild Bee Dance, and a similar song honors another insect in the Wasp Dance; the masks for both are most ingeniously fashioned with the tufts of tree cotton or kapok to simulate the hairiness of the insect. The most unexpected beauty attends the Dance of the Bats, the masks for which are strikingly representative of the bat and the chants for which are squeaky and shrill to mimic the bat's voice. (Schultes, 1972)

The ceremony continues for 56 hours, the dancers stopping only to fortify themselves with enormous quids of mambe (coca powder), peach palm beer, smoked game, and titanic snorts of tobacco snuff.

So important was this ritual to Schultes' thinking and worldview that he prominently displayed the photos of the Yukunas taking snuff and Yukunas wrestling in his office in the Harvard Botanical Museum.

Tobacco is not smoked during the *Kai-ya-ree*, but great gourdfuls of snuff are made. The older men dry and pulverize finely the tenderest leaves of tobacco (*Nicotiana tabacum*) and mix with the powder equal amounts of the leaf ashes of the yam (*Dioscorea* spp.); the resulting snuff is a greyish-white powder which is administered in teaspoonful doses through hollow bird-bone snuffing tubes. The Yukunas are excessive snuffers, just as they are extraordinary consumers of coca. ... It is an honor to be offered a snuffing by a friend who fills the tube with snuff, inserts one end in his mouth, the other end in the recipient's nostril, and gives a strong but quick puff. (Schultes, 1972)

In addition to celebrating the harvest of the peach palm, the ceremony is meant to commemorate the evolution of the nation and its place within the universe. The Dance is said to have originally been taught to the neighboring Letuama by a mythic ancestor so that the reverent could express their gratitude to the surrounding spirits, plants (particularly the peijibaye), and animals (particularly fish) for support and sustenance. Through this celebration, the animals are said to be both placated and domesticated, replacing the wildness of nature.

### COSTUME PREPARATION

Schultes was intrigued by the ingenious use of plants to create the elaborate costumes used during the festival. The coarse brown shirts are created by hammering the inner bark of the llanchama (*Olmedia aspera*), a common 20-meter tree of the fig family. The ankle-length skirt is made from the peeled bark of a large tree of the Brazil nut family. The lower section of these skirts are submerged in a dark grey water-clay mixture, causing a chemical reaction between the clay and the bark that permanently dyes the skirt a striking shade of glossy black. The dancers wore rattling anklets to help punctuate the rhythmic steps of the dance. They were made from the cultivated fruits of a vine of the cucumber family, the

Cucurbitaceae. Schultes immediately recognized that this was a species previously unknown to science, and named it *Cayaponia kathermatophora* when he returned to Harvard.

The intricate masks were made by spreading the pitch from the brea tree (*Symphonia spp.* and *Moronobea spp.* – tall, yellow-sap-bearing trees of the Clusiaceae family) across a bark cloth hood prepared from the same llanchama tree. The black dyes of the mask are created by extracting a yellow pitch from the tree and boiling it for several hours to darken the color, remove sticky properties, and cause it to harden faster. The end result is a shiny pitch black, adding an element of the macabre to some of the demon masks.

### YUKUNA MALOCA DESIGN

The Yukuna malocas where these dances are performed represent the largest works of art in the Amazon rainforest, serving as a remarkably efficient architectural design with deep symbolic meaning. These longhouses can stand over three stories tall and over 15 meters in diameter.

They feature a unique and instantly recognizable shape: a round base topped by a semiconical roof with two gabled openings oriented to the east and west that permit air and sunlight to enter and cooking smoke to escape. The windows, sometimes called “ears” in local languages, are effectively designed and constructed to keep the maloca inhabitants dry despite the pervasive tropical downpours.

In the past, a Yukuna longhouse could serve as a home to 200 people and would last for about fifteen years. The Yukuna still build these magnificent structures entirely from wild plants: the great roofs were usually woven from “puy” (*Lepidocaryum tenue*) or “carana” (*Mauritia carana*) palm leaves, the latter when the malocas are built on or near white-sand savannas. The palisade walls are constructed of the wood of the *Aspidosperma excelsum* – a tall and strong forest tree, often used to make canoe paddles elsewhere in Amazonia – and the great structural support beams seem to be trunks of “acapu” trees (*Vouacapoua americana*). Most astonishing of all is that even today, these structures are built without nails: all materials are woven together or tied with rainforest vines and lianas.

According to Dr. Martin von Hildebrand, the leading authority on the people of this region, the Yukuna maloca serves as a place of residence, a ceremonial center, a cemetery, a sundial and a model of the cosmos. The central region between the four central posts is a sacred space that serves as the ceremonial center of maloca life. The surrounding area between the four inner posts and the second ring of posts is a public space. The periphery of the maloca near the outer palisade is where the families eat, sleep, rest and bury their dead.

The malocas are also divided along north-south and east-west axes, with certain sections reserved for traditionally male activities such as preparing and chewing coca, and others for traditionally female activities such as preparation of cassava. The triangular windows in the peak serve as an astronomical instrument, used by the Yukuna to track the equinox based on the movement of the sun across the floor. In sum, in the globe's hottest and wettest ecosystem, the maloca keeps her inhabitants cool and dry as well as spiritually nourished.

### BETRAYAL BY THE USDA

In December 1943, after descending 600 miles down the Apaporis River, Schultes and his crew arrived at La Pedrera with less than a gallon of gas, as the outboard motor sputtered and died. Schultes had been declared missing months earlier after an overflight ordered by the Rubber Reserve Company failed to reveal the missing expedition crew. When he strolled into the herbarium in Bogotá several months later with a load of plant specimens under his arm, several colleagues were said to have nearly fainted.

Schultes felt a special connection to the Apaporis. From his groundbreaking explorations of its headwaters in Chiribiquete, to his long, perilous descent of the river, he knew it like no other foreigner.

On his initial descent of the Apaporis, he had meticulously charted the course of the river and made detailed counts of *Hevea* on its banks, finding and identifying unique and potentially valuable varieties. His mission would soon change from mere inventory to coordinating the collection of *Hevea* specimens, including seeds that might enable the creation of disease-resistant plantations in the

Americas.

In the course of this work, Schultes often returned to the Apaporis, establishing rubber stations at Soratama and Jinogoje and coordinating rubber latex collection efforts in those regions. He and his indigenous colleagues had scoured some of the least-known and most inaccessible rainforests in the world to bring back a trove of rubber specimens of all shapes and sizes, some high-yielding, others pest-resistant.

The U.S. government decided that the only means to prevent future scenarios in which the U.S. might be deprived a supply of natural rubber was to create plantations in the New World. Schultes' new mission was to collect seeds from a variety of rubber species to establish a repository of *Hevea* genetic diversity for future research. With this germplasm bank, experts would be able to experiment with interbreeding to increase productivity and resistance to pests and diseases.

As denizens of equatorial regions, these trees could not be grown in North America, so another secure and ecologically suitable site was sought. The people in charge settled on a famous botanical station in Turrialba, Costa Rica due to its favorable microclimate and distance from areas already affected by the rubber blight. It was believed that Schultes' botanical treasures could be safely planted and nurtured by fellow scientists in the most stable of the Central American republics.

However, due to the end of the war and advances in synthetic rubber manufacture, the need to create a sustainable supply of natural rubber became less urgent. Even though many products still required natural rubber – automobile tires, surgical instruments, etc. – the World War was long over, eliminating the most pressing threat. In an act of great shortsightedness, the U.S. government eliminated the rubber program on October 12, 1953.

Schultes wanted to compile all of his rubber notes and knowledge into a comprehensive report, but his request for support was denied. Needing a source of income upon his return to the United States, Schultes took the only position available as curator at the Harvard Orchid Herbarium. This job had formal legal stipulations that demanded complete focus on orchids, making it impossible for Schultes to continue his rubber work for several years. He would

never finish his comprehensive rubber report, an enormous loss to science.

## THE AMAZON: THEN AND NOW

### SCHULTES AS A CONSERVATIONIST

Once he began his work in South America in 1941, Schultes became a strong conservation advocate, championing partnerships with indigenous communities to protect the Amazon rainforest.

Schultes knew well that the rainforests of South America contained an extraordinary wealth of chemical compounds that could benefit humanity if properly researched and utilized. Felling the forest not only diminished biodiversity (and fueled climate change, as we now know), it also destroyed the hidden chemical wealth of plants that might provide the basis for lifesaving medicines or economically valuable products.

Throughout twelve years of immersive fieldwork, Schultes was continually impressed by the botanical and medical knowledge of his indigenous colleagues. He saw that in the rainforest, many indigenous people were able to distinguish plants far beyond even what a Harvard-trained botanist would be able to recognize. He observed indigenous people as they combined unrelated plants to create novel and powerful effects, and remarked that such understanding could be of great benefit to the world at large.

However, as Schultes often said: “The Indians’ botanical knowledge is disappearing even faster than the plants themselves.”

Schultes advocated for working with indigenous communities to record and transmit traditional knowledge. He believed this strategy would benefit the well-being of the communities and yield immense conservation benefits that could in turn, benefit humanity.

Seventy-five years after Schultes first explored the Amazon, reflecting on what has changed in these regions provides a valuable lesson on what has been lost, and what is left to protect.

### SIBUNDOY VALLEY

In the early 1940s, Schultes was enchanted by Colombia’s picturesque Sibundoy valley and its fascinating inhabitants. He explored the otherworldly highland páramo ecosystem, discovering

many plant species new to science. He learned about these plants from Inga and Kamentsá, who possessed an extensive botanical knowledge and utilized the greatest diversity of the psychoactive plant remedies that Schultes encountered during his travels.

Today, there are some 13,000 Inga and Kamentsá people in the Sibundoy Valley, about one-third of the valley's total population. There are still many Inga and Kamentsá taitas (shamans) and elders working to protect their knowledge of medicinal plants, including members of the Union of Indigenous *Yagé* Healers of the Colombian Amazon (UMIYAC) and the Union of Women Healers (ASOMI). Many Kamentsá people still speak their unusual and unique language.

The Sibundoy Valley changed rapidly during the second half of the twentieth century. Improved road access led to rapid colonization and the displacement of Inga and Kamentsá communities from much of their ancestral lands. In recent years, the region has been embroiled in controversy due to extensive mining activity and the construction of a new highway leading from Pasto to Mocoa. Indigenous communities have led the protests against mining activity and the road, which they see as a threat to their way of life.

Since 2015, the Colombian government, local indigenous associations, and the Amazon Conservation Team have partnered to carry out the formal expansion of more than 80,000 hectares of indigenous reserves in the upper Putumayo River region. These expanded reserves provide Inga and Kamentsá communities with improved legal land rights over their ancestral territories, while also establishing a protective ring around the Sibundoy Valley, helping to protect water-rich páramo ecosystems in the headwaters of the mighty Putumayo River, the most important waterway in the Colombian Amazon.

## KOFÁN TERRITORY

When Schultes visited in 1940s, the Kofáns were renowned for their powerful shamans, who possessed perhaps the most extensive plant pharmacopoeias of all the Colombian Amazon. They were masters of the plant-based poisons whose chemical compounds revolutionized surgical anesthetics. Schultes noted they knew numerous unstudied herbal remedies, including a potential



anticoagulant that he felt had important commercial potential.

In the 1940s, Kofán territory reached from the Guamuéz River in southern Colombia to the Aguarico river in northern Ecuador. Schultes noted that this equatorial region had perhaps the highest amount of plant diversity he encountered throughout his travels.

Oil was discovered in Kofán territory in the 1950s, leading to extensive extraction and contamination from ruptured wells and pipelines. Oil extraction and the related development of roads and infrastructure sparked a flood of colonization, displacing the Kofán from their ancestral territories. Since the 1980s, the Kofán suffered terribly during Colombia's internal conflict.

The Kofán now live on several indigenous reserves on both sides of the Ecuador / Colombia border. Several protected areas have been established for the protection of Kofán lands. In 2008, Kofán communities partnered with the Colombian National Parks Service and the Amazon Conservation Team to establish the 10,204-hectare Orito-Ingi Ande Sanctuary for Medicinal Plants and Flora, marking the creation of a unique new land designation recognizing the botanical knowledge of indigenous communities and the cultural value of medicinal plants.

## WITOTO

In 1942, Schultes traveled through the lower Putumayo river basin, finding Witoto communities still recovering from the terrors and abuses of the rubber boom less than a generation before. Even though their culture had been severely abused by rubber barons and later missionaries, the Witotos still maintained their language and much of their culture, employed many medicinal plants, and still danced to the sound of their *manguare* drums made from hollowed trees. Seventy years after Schultes began his work in their territory, the Witoto communities maintain many aspects of their culture.

To protect tribal lands, the Predio Putumayo Indigenous Reserve was created in 1988, encompassing a huge tract of land between the Caquetá and Putumayo rivers, a territory home to Witoto, Bora, Miraña, Andoque, Ocaina, Muinane, and Nonuya nations. The reserve now measures 5,819,505 hectares, making it one of the largest legally demarcated indigenous territories in the entire Amazon, nearly equal in size to the state of West Virginia. The

Puerto Zábalo Los Monos and Monochoa Witoto reserves were also created in 1988, covering a combined 474,573 hectares north of the Caquetá River, later expanded by a combined 567,890 ha.

The creation of these vast indigenous reserves was part of a larger effort in the late 1980's to secure land rights for all indigenous peoples of the Colombian Amazon. During the Presidency of Virgilio Barco Vargas and following the leadership of Martín von Hildebrand as Head of Indigenous Affairs, the Colombian state legally demarcated an area of more than 100,000 square miles of communal indigenous lands through the creation of 162 Resguardos Indígenas, later encoded into law in the 1991 Colombian Constitution.

### CHIRIBIQUETE

After his 1943 expedition to Chiribiquete, Schultes was deeply impressed with its spectacular lost world mountains, keeping a photo of the Cerro Campana prominently displayed on the wall of his Harvard office for over five decades. He was one of the first to report the prehistoric cave paintings in Chiribiquete, and was a constant advocate for the creation of a natural park to protect the cultural and botanical treasures of Chiribiquete.

Largely due to his initiative and his urging, in 1989, the 1,300,000-hectare Chiribiquete National Park was created by the Colombian government, thus protecting one of the most unique and pristine ecosystems and cultural sites in the entire Amazon.

In 2013, the Chiribiquete National Park was nearly doubled to more than 2,750,000 hectares, making it the largest national park in Colombia and the second largest national park in Amazonia. The park was expanded in part to protect as many as three uncontacted or isolated indigenous communities living in the region. The Chiribiquete park expansion represents just a part of Colombia's cutting-edge strategy to safeguard vulnerable isolated indigenous communities, through an innovative collaboration between local indigenous communities, the Colombian government, and the Amazon Conservation Team.

### YAIGOJÉ-APAPORIS

Schultes spent years based in the lower Apaporis River region in

the 1950s, learning about the complex culture and ethnomedical knowledge of the many Tucano-speaking groups in the region. These groups were remarkably multilingual and possessed perhaps the most complex and sophisticated worldview in the Amazon.

The lower Apaporis River region has seen persistent threat from mining activity seeking to exploit the minerals of the rivers, hills and forests sacred to the Tukano peoples. There are several existing mining titles with many more applications pending. The 2013 announcement of a “Strategic Mining Reserve” covering much of the Vaupés region was widely denounced and is on hold for now, thanks to efforts the local communities and the Gaia Amazonas Foundation.

These nations received legal title to their lands with the creation of the approximately 3,500,000-hectare Gran Vaupés Indigenous Reserve and the approximately 1,000,000-hectare Yaigojé Apaporis Indigenous Reserve. The Yaigojé Apaporis National Park was created in 2012 to provide increased protection and protect subsoil resources from potential mining activity. In 2011, UNESCO recognized the Jaguar Shamans of the Yuruparí as part of the intangible heritage of humanity in need of protection, marking the first time an entire culture complex has received this designation.

### MIRITÍ-PARANÁ

In 1952, Schultes participated in the three-day-long *Kai-ya-ree* ritual dance with the Yukuna and Tanimuka of the Mirití-Paraná. This was just one of the Yukuna and Tanimuka’s five annual dances, which had maintained the practice of many of their traditional ceremonies. Schultes adored the Yukuna, always saying that they ranked among the strongest, kindest, friendliest and most reliable peoples that he knew.

Today, the proud Yukuna and Tanimuka communities of the Mirití-Paraná still maintain their traditional dances and ceremonies, including the *Kai-ya-ree*, long ago danced by Schultes as he truly entered the rainforest realm. Thanks to the Colombian government, local colleagues and the Yukuna and Tanimuka themselves, the Mirití-Paraná Indigenous Reserve, encompassing the entire Mirití River watershed, was created in 1981 and now has an area of more than 1,500,000 hectares, larger than the state of

Connecticut.

## SCHULTES AND THE ETHNOPHARMACOLOGIC SEARCH FOR PSYCHOACTIVE DRUGS IN RETROSPECT

Schultes never failed to point out that he did not “discover” new hallucinogens – the indigenous peoples had been using them all along. From his first encounter with peyote in the Kiowas’ Oklahoma tipis to his field research on teonanácatl / magic mushrooms, ololiuqui, *ayahuasca* and Virola snuff, he never wavered in his belief that these species and the wisdom of the shamans who employed them offered great potential for western patients and medicine. Schultes strongly believed that these shamanic approaches to treatment offered novel approaches to understanding, diagnosing and treating the human mind in ways beyond the reach of western physicians. Moreover, he believed that these plants harbored novel chemicals which could serve as the bases for new medicines. Given that the compounds extracted from the Mexican mushrooms played a role in the development of the first beta blockers and that western doctors are seeing promising results in the treatment of intractable ailments like PTSD and depression using compounds like mescaline and *ayahuasca* alkaloids, Schultes’ wisdom and field results maintain their relevance and their promise – both today and in the foreseeable future.

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AFRICA, AUSTRALIA & SE ASIA

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# *Kabbo's !Kwaiń: The Past, Present and Possible Future of Kanna*

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*Nigel Gericke, MD*



## ABSTRACT

### PART I

The history of the use of *kanna*, the traditionally used plant material derived from a number of *Sceletium* species, is given from 1610-1971. This overview includes fragments of history documenting European ships docking in the Cape to search for *kanna* roots as a “ginseng” to trade in the Far East, and an ethnographic record from the 1700s transcribed directly from //Kabbo, a /Xam San “Bushman” from the Breakwater Convict Station in Cape Town, who gave us the name *!k”wai* for *kaauwgoed*, the Dutch name for *kanna*, and his own account of the uses of the plant.

### PART II

The recent ethnobotany, ethnopharmacology and pre-clinical research on a commercialized standardized extract of *Sceletium* (trademarked Zembrin®) is given for the period 1995 to 2017. *In vitro* studies have demonstrated that the major alkaloids of *kanna*, including mesembrine, mesembrenone and mesembrenol, are responsible for the psychoactivity of *Sceletium*, and have dual serotonin reuptake inhibitory (SRI) activity and phosphodiesterase-4 (PDE4) inhibitory activity. The effect of the extract of *Sceletium tortuosum*, Zembrin®, on brain electrical activity has been studied *in vivo*, demonstrating by discriminant analyses that the quantitative EEG electropharmacogram of the extract plots in close proximity to the plots for *Ginkgo biloba*, *Rhodiola rosea*, and also to the first-generation pharmaceutical PDE4 inhibitor Rolipram, indicating the potential of this extract for managing anxiety and depression and enhancing cognitive function.

### PART III

Clinical experience with *Sceletium* is summarized and the results of pilot randomized, double-blind, placebo-controlled clinical



studies on the extract of *Sceletium tortuosum*, Zembrin®, are presented, including:

- A safety and tolerability study.
- A pharmaco-Magnetic Resonance Imaging study.
- A study on cognitive function domains using CNS Vital Signs, a computerized neurocognitive test battery.
- A study looking at changes in brain electrical activity in response to cognitive and emotional challenges; changes in psychometric tests; and changes in the Hamilton Anxiety Scale (HAM-A).

## PART IV

Scenarios on the future of *kanna* and alkaloids derived from *kanna* are considered.

### **Folk names for traditionally used *Sceletium* species**

|                |                                                                                                                                                       |
|----------------|-------------------------------------------------------------------------------------------------------------------------------------------------------|
| <i>kanna</i>   | Nama-speaking Khoikhoi people. Sometimes also written <i>canna</i> and <i>channa</i> .                                                                |
| <i>kougoed</i> | Afrikaans-speaking people of European or mixed descent, derived from the earlier Dutch <i>kaauwgoed</i> or <i>kauwgoed</i> , meaning “chewing stuff.” |
| !k”wai         | Also !k”wai:n. /Xam-speaking San people. This language is now extinct.                                                                                |

## BOTANY

The genus *Sceletium* of the Family Aizoaceae, Mesembryanthemoideae, is characterized by the distinctly skeletonized leaf venation visible in dried older leaves. *Sceletium* is a genus with a climbing, or decumbent, habit and succulent leaves that sometimes have prominent idioblasts, or bladder-like cells. The flowers range from white or yellow to pale pink. The fruit capsules contain numerous very small kidney-shaped seeds, brown to black in color.

The genus is distributed in the arid southwestern parts of South Africa, including parts of three provinces: Northern Cape Province, Western Cape Province, and Eastern Cape Province. The plant populations and individual plants are typically widely scattered, but in the *Kougoedvlakte* (literally translated as “Chewing Stuff Plains”) of Namaqualand in the Northern Cape Province, and in the *Kannaland* district (literally, “The Land of Kanna”) in the Western

Cape Province, the plants were once locally abundant and traded widely.

Klak et al. (2007) proposed a single genus, *Mesembryanthemum*, that includes members of the genus *Sceletium*. However, for the purpose of this paper, the use of the genus *Sceletium* is retained, and the genus *Mesembryanthemum* (sometimes spelled *Mesembrianthemum* in former times) is used when quoting historical texts.

The taxonomy of *Sceletium* is complex, and will hopefully become clearer when species based on standard plant morphological features can be interpreted in the light of DNA-bar coding and plant chemistry. Eight *Sceletium* species are recognized in the revision by Gerbaulet (1996):

*Sceletium tortuosum* (L.) N.E. Br.  
*Sceletium crassicaule* (Haw.) L. Bolus  
*Sceletium emarcidum* (Thunb.) L. Bolus ex H.J. Jacobson  
*Sceletium exalatum* Gerbaulet  
*Sceletium expansum* (L.) L. Bolus  
*Sceletium rigidum*, L. Bolus  
*Sceletium strictum* L. Bolus  
*Sceletium varians* (Haw.) Gerbaulet.

To illustrate the taxonomic complexity at the species level, the following synonyms have been used for *Sceletium tortuosum* (L.) N.E.: (Nortje, 2011).

*Mesembryanthemum aridum* Moench  
*Mesembryanthemum concavum* Haw.  
*Mesembryanthemum tortuosum* L.  
*Pentacoilanthus tortuosus* (L.) Rappa and Camorrone  
*Phyllobolus tortuosus* (L.) Bittrich  
*Sceletium boreale* L. Bolus  
*Sceletium compactum* L. Bolus  
*Sceletium concavum* (Haw.) Schwantes  
*Sceletium framesii* L. Bolus  
*Sceletium gracile* L. Bolus  
*Sceletium joubertii* L. Bolus  
*Sceletium namaquense* L. Bolus var. *namaquense*  
*Sceletium namaquense* L. Bolus var. *subglobosum* L. Bolus  
*Sceletium ovatum* L. Bolus

## PART I

### HISTORICAL REPORTS, 1610 - 1971

Early visitors to the Cape of Good Hope in the 17th century frequently emphasized the value attached to *kanna*. The captains of trading ships en route to the East Indies thought of the roots of *kanna* as a Cape ginseng, and also called it *ningin* root or *ningimm* root, a corruption of vernacular names used for the ginseng root they had seen in Japan and China. Ships of the East India Company, stopping off at the Cape en route to Japan to stock up on fresh water, fruit and vegetables, were instructed to search for the roots as a valued item for trade.

#### 1610

The English East Indiaman *The Globe*, under the command of Captain Hippon, stopped to replenish water supplies at the Cape of Good Hope en route to the East Indies. Captain Hippon's lieutenant, Peter Floris, reported:

Being by Gods grace here arrived, wee presently fell to the ordering of the shippe, and hooping of our caske to fill freshe water, for much refreshing was not here to bee had att this tyme of the yeare, by the greate quantitie of rayne, being now in the chieffeste of winter so that the mountains laye covered with snowe : during which tyme wee used great diligence in seeking of the roote Ningimm according to our instruction, the aforesaid 2 Holland shipps being expressly come thether for the same purpose, being one of Japan that first discovered the secret; butt, being winter tyme, there was for this tyme no more to bee done but to go awaye as wyse as wee came, for the olde roote being decayed and rotten, the new leaf began onely to come foorth, so that had it not bene by reason of some information that was gotten of one who here shalbee nameles for dyvers considerations sake, wee shoulde have bene fayne to have departed without notice thereof, the right time of gathering the same being in December, January, and February, being called by the inhabitants Canna. (Moreland,

1934)

## 1615

Purchas 1625: Saldanha Bay, approximately 130 kilometers north of the Cape of Good Hope: “The Countrey people brought vs downe of the Root Ningin, whereof wee bought one handful for a piece of Copper an inch and halfe broad, and two inches and halfe in length. Our men got [some], but not [so] full, nor ripe, this being not the [season], which in the full perfection is as tender and [sweet] as [anise seeds]. On the twentieth wee [set sail].” “Ningin, a medicinable root much prized in Japan” .

## 1660

“It was the control over fields of canna that made the Inqua king Hijkon “chief lord of all kings and potentates”, for he was one of the patrons whose power flowed from the precious canna that grew in the desert” (Gordon, 1996, quoting from Jan van Riebeeck’s journal, 21-22 Sep. 1660, from the Archives of the Nederlandsche Oost-Indische Compagnie).

## 1662

In 1652, the Vereenigde Oost-Indische Compagnie or VOC (the Dutch East India Company), founded a refreshment and recuperation station at the Cape of Good Hope for the benefit of the crews of its fleets trading between Europe and Asia. The station was to supply fresh fruit and vegetables, meat and clean water to the VOC ships whose crews were decimated by scurvy during the long ocean voyages. In 1662, the first commander of this station, Jan van Riebeeck, received *kanna* and sheep from the indigenous people in exchange for gifts, and pronounced that *kanna* is similar to Chinese ginseng (Smith, 1966).

## 1685

### DUTCH EXPEDITION TO NAMAQUALAND (GERICKE, 2014)

In 1657, the first commander of the VOC’s refreshment station at the Cape, Jan van Riebeeck, heard from an indigenous interpreter that the copper in indigenous tribal earrings and beads came from

the Namaqua, a tribe of pastoralists who lived to the north of the Cape. Between 1659 and 1663, seven expeditions were dispatched north to the land of the Namaquas to look for copper and any other riches, but they all failed, unable to penetrate through the mountainous and difficult terrain. In 1679, Simon van der Stel was appointed commander of the settlement at the Cape of Good Hope by the VOC, and concerned himself with the development of agriculture and viticulture and the improvement of the company's botanical and herbal garden. In April 1682, some Namaqua people visited the VOC fort at Table Bay with pieces of good quality copper ore. Expeditions sent north to find the source of the copper ore failed, unable to cross the mountainous terrain.

In 1685, Hendrik van Rhee de tot Drakenstein, a VOC commissioner, arrived at the Cape and gave Commander van der Stel permission to personally lead an expedition to find the Copper Mountains. In addition to the search for copper, the expedition was charged with cultivating friendly relations with the Namaquas, describing the country, and documenting useful plants. The expedition, which left the Cape of Good Hope on 25 August 1685, was a major undertaking. The party included van der Stel as commander, his three slaves, fifty-six people of mainly European extraction, a prince from Makassar (now within Indonesia), forty-six local people of mixed ancestry as drivers and leaders for the wagon train and accompanying stock animals, and a number of Khoikhoi translators. The expedition included a carriage, seven wagons, eight carts, a boat for river crossings, and two small cannon. Technical specialists accompanying the expedition included a navigator, a mineralogist, and the apothecary and artist Heinrich Claudius, who also served as the expedition's cartographer. Claudius had been sent to the Cape from Batavia in the East Indies to collect botanical specimens for a private collector, and was then retained at the Cape by the VOC on account of his exceptional abilities as naturalist and artist.

It is not known what became of the original journal of the 1685 expedition, or of Claudius' original drawings, but copies of excerpts from the expedition journal and accompanying drawings were made shortly after the expedition. One of the copies of the journal is in the collection of Trinity College Library, Trinity College MS. 984

(TCMS), and is thought to have been removed from the Archives of the Dutch East India Company in 1691 or 1692. TCMS includes seventy-one pages of coloured drawings believed to be the work of Heinrich Claudius, with descriptive text on alternate folios. The drawings include two landscapes within the Copper Mountains, a Namaqua man and woman, forty-three plants, eleven birds, nine reptiles, one fish and eight insects. Watercolor copies of Claudius' drawings are in the collection of the Iziko South African Museum in Cape Town, known as the Codex Witsenii (CW). These copies were made in 1692 for Nicolaas Witsen, a prominent citizen of Amsterdam and a director of the Amsterdam Chamber of the VOC. A third manuscript on the expedition, written by Jan Commelin (JCMS) about 1687, is held by the Staatsbibliothek Kunturbesitz, Berlin, as ms. germ. qu. 238.

The journal entry in TCMS, which accompanies a fine painting easily recognized as *Sceletium* and including the flower and skeletonized lower leaves, states:

This plant is found with the Namaquaas and then only on some of their mountains. It is gathered in October and is called *Canna*. It is held by them and the surrounding tribes in as great esteem as the betel or areca with the Indians. They chew the stem as well as the roots, mostly all day, and become intoxicated by it, so that on account of this effect and its fragrance and hearty taste one can expect some profit from its cultivation. Found on the 20th October. (Waterhouse et al., 1979)

The journal entry in Codex Witsenii, accompanying a copy of the painting of *Sceletium*, states:

This is from the Namaquas and also other nations the famous *kanna*, which they carry in the mouth daily and chew, as the Indians do with Areca, and who do it often can easily get drunk from it, it is held in great esteem by them, like all things that corrupt the mind, and make drunk. And that there is something particular in these plants is seen not only from the activity, but also the pleasant and cordial taste, are found nowhere but on certain mountains in the country of the Namaqua and collected in October; found 20 October 1685.

## 1686

Guy Tachard (1651–1712), also known as Père Tachard, was a French Jesuit missionary and mathematician of the 17th century who was sent on two occasions to the Kingdom of Siam by Louis XIV, and en route spent time at the Cape of Good Hope. Translated from the original French,

This captain, pleased with his gifts, sent us in gratitude two fat tail sheep, each tail weighing more than twenty pounds, with a large vessel full of milk, and a certain herb which they call Kanna, it is apparently this famous plant that the Chinese call Ginseng; for Monsieur Claudius, who has seen it in China, asserts that he had found two plants at the Cape, and shows us the whole figure which he had painted in nature.” (Tachard, 1686)

## 1726

François Valentijn was a Dutch minister, naturalist and author. In his *Beschryvinge van de Kaap der Goede* (Descriptions of the Cape of Good Hope), he noted that the “Canna of the Hottentots closely resembles the Chinese root Nisi or Ginseng” (Serton, 1971).

## 1731

Peter Kolben was sent to the Cape of Good Hope with letters of introduction from the mayor of Amsterdam, with a mandate to compile a comprehensive description of South Africa for geographical research and surveying. He wrote detailed accounts of the geography, climate, flora and fauna, followed by a study of the indigenous Khoi people (called Hottentots at that time), covering their language, religion, lifestyle and customs:

There is a Root, gather'd in the *Hottentot* Countries, called Kanna; which is in [such Esteem] among the *Hottentots* for its great vertues that they almost adore it. What greatly enflames the Value of this Root, is its Scarcity; for 'tis very rarely found. They look upon it as the [greatest] Chearer of the Spirits, and the [noblest] Restorative in the world. They will give [almost] any Thing in Exchange for it; and will, any of 'em, run Twenty Miles upon an Errand, or perform a hard Day's Work, for a

very small Bit of it. With a piece of Kanna you may manage ‘em [almost] in any Manner you [please]. You win their hearts Forever by [presenting] them with the smallest Chip of it; and they will run, fetch and carry for you like your Slaves, under [so] charming an Obligation...I have often [seen] the Effects of *Kanna* upon *Hottentots*. They chew and retain it a [considerable] Time in their Mouths. But taking generally too much of it at a Time, it drowns ‘em in Intoxications. They chew it not long, before their Spirits [visibly] [rise], their Eyes brighten, their Faces take a jovial Air, and they [Sport] and wanton under a [thousand] Gaieties of Imagination. But in the End it [Strips] ‘em of their [Senses], and throws ‘em into the [wildest] *Deliria* (Kolben, 1731).

## 1763

De la Caille (1763): “The Canna of the Hottentots is entirely different from [Ginseng]. I have seen both, they are entirely different. They harvest the root in the months of November and December, add water and put some honey in it, and leave it in the rocks to ferment. They drink it while it lasts, abruptly unable to do anything. When the supply is exhausted, they are long sick; eating orca restores them.”

## 1772-1775

Carl Peter Thunberg was a Swedish botanist and physician who had been a student of Linnaeus. He made two journeys to the Eastern Cape region of South Africa between 1772 and 1774, and reported that valuable narcotic plants were found in the vicinity of the present-day town of Oudtshoorn in the Little Karoo, in an area formerly occupied by the Attaqua Khoikhoi. This area of South Africa is still known as Kannaland. According to Thunberg (Forbes, 1986),

Kon, was a name given by the Hottentots to a shrub that grew here (*Mesembryanthemum emarcidum*) and was famous all over the country. The Hottentots came far and near to fetch this shrub with the root, stalk and leaves which they stamp together, and afterwards twist them up like pig-tail tobacco; after which they let the mass ferment, and keep it by them for



chewing, especially when they are thirsty. If it be chewed immediately after fermentation, it intoxicates. The word kon is said to signify a quid; the colonists call it canna root. It is found in the driest fields only, and is gathered chiefly by the Hottentots, who live near this spot. These afterwards hawk it about, frequently to a great distance, and exchange it for cattle and other commodities.”

## 1851

The Great London Exhibition of 1851 may have been a pivotal moment in the history of *Sceletium*, where the plant was exposed to international visitors that would have included physicians, chemists and pharmacists. A collection of the most important Cape botanical medicines was sent to the exhibition from Cape Town by Messrs S.H. Scheuble & Co. (Gunn and Codd, 1981). Karl Wilhelm Ludwig Pappe, a German-born physician and botanist who moved to Cape Town to practice as a physician, wrote a small book as a commentary to accompany the exhibited medicinal plants. In the entry for *Sceletium tortuosum* (as *Mesembryanthemum tortuosum*. Lin.), Pappe wrote, “This species, a native of the Karroo, appears to possess narcotic properties. The Hottentots, who know it by the name *Kauw-goed*, are in the habit of chewing it, and become intoxicated, while the farmers use it in the form of decoction or tincture, as a good sedative” (Pappe, 1868).

## 1856

Confusion between *kanna* and ginseng seems to have persisted well into the 19th century, with a French-English Dictionary of the time describing *kanna* as a species of ginseng (Collot, 1856).

## 1858

The distinction between processed and unprocessed plant material, and differences in the activity of different *Sceletium* species, is made by Tully: “*Mesembryanthemum emarcidum*, like *Nicotiana tobacum*, is not narcotic until it has undergone a certain change in consequence of it being treated in a peculiar manner. *Mesembryanthemum tortuosum* is considered narcotic without any such change” (Tully, 1858).

## 1873

The Bleek and Lloyd Archive of the University of Cape Town is a remarkable collection of /Xam San oral literature, language and ethnography documented in Cape Town by W. H. I. Bleek and Lucy C. Lloyd between 1870 and the early 1880s. They became aware of a group of /Xam San prisoners at the Breakwater Convict Station in Cape Town and received permission for //Kabbo to stay in their Mowbray home as a research participant. Later, other San prisoners were also allowed to stay in the house, including ≠Kasiŋ. //Kabbo, meaning “Dream”, stayed with Bleek and Lloyd between February 1871 and October 1873. He was sent from the Breakwater Convict Station, where he had been imprisoned for two years for stock theft or sharing in the spoils of theft, as prisoner Number 4628. ≠Kasiŋ arrived at Bleek and Lloyd for the first time from November 1873 until March 1874, after //Kabbo had left. He had been imprisoned at the Breakwater Convict Station for culpable homicide and served four years of a five-year sentence as prisoner Number 4435 (Digital Bleek & Lloyd, 2017).

//Kabbo and ≠Kasiŋ were shown a number of “Bushman medicines” that had been found in the hut of a “Bushman sorcerer”, and their comments on these medicinal plants were transcribed into English by Wilhelm Bleek and Lucy Lloyd (MSS BC151 006; Prader-Samper, 2007). I was surprised to find that none of the botanical names of these plant medicines was known. Two informants, //Kabo and ≠Kasiŋ independently identified the same plant sample as *kaauwgoed*, and on this basis the botanical identity was established as *Sceletium* sp. since no other South African plant has before or since been given this Dutch vernacular name. Indeed, the Afrikaans name for *Sceletium* to this day is *kougoed*, derived from the older Dutch *kaauwgoed*, meaning “chewing stuff.” We finally have the first reports on the uses of *Sceletium* from indigenous people, in their own words, as well as the original /Xam San name for the plant as !k”wa:ĩ or !k”wai:n.

Bleek’s notes documented from //Kabbo !k”wa:ĩ singular and plural. *Kaauwgoed*

A small plant found on the great mountains growing out of crevices in the rocks. It is chewed by Bushmen, and gives

strength to their limbs; and takes away pain and makes their memory strong. The two Bushmen from Stuurmansfontein had some with them to enable them to walk till they met the wagon. Is found around the Berg Bushmen.

Lloyd's notes documented from ≠Kasiŋ !k"wai:n Kaauwgoed

If a little child that is still being suckled is ill inside, they take a little piece of it, & put it into a spoon of cold water, & rub it about in it, the water becomes yellow (like tobacco water), and they give it to the child to drink. Men and women chew it; and swallow their saliva. The plant is in some cases short, but in others long, like a pumpkin in growth. It grows on the ground. It grows in ≠Kasiŋ's place.

## 1874

The botanical identity of a sample of *kougoed* was confirmed to be *Mesembryanthemum tortuosum* and the uses of it were described: "The Koegoed [sic], besides being used as stated by Mr. Keyworth as a sedative for cattle, is chewed by the Hottentots as an intoxicating agent, and appears to possess narcotic properties which deserve further attention" (Holmes, 1874).

## 1876

Twenty-five years after the Great London Exhibition, *Sceletium* may have become available as a botanical medicine in the United States, evidenced by the inclusion of *Mesembryanthemum tortuosum* in C.E. Hobbs' *Botanical Hand-Book* (Hobbs, 1876) and in J.M. Nicholl's *Botanical Ready Reference* (Nicholl, 1895). These books were lists of botanicals apparently in common use in the United States, and written for apothecaries and pharmacists. In both books, the plant was classified as a narcotic.

## 1896

The first pharmacological research on *Sceletium* was reported by Isaac Meiring in the Transactions of the South African Philosophical Society. In this paper, Meiring gives the locality the plant material came from, the vernacular name as "*Hottentot's Kauwgoed*" and had the plant material used in his experiments botanically identified as *Mesembrianthemum tortuosum* L.:

Like so many Cape plants, it has great medicinal virtues ascribed to it, chief of which are its soporific influence on young children and its curative and quieting effect on them when suffering from acidity. It is alleged that for these purposes the plant is very widely used, the method of procedure being one or two drops of the juice of the green plant is given to the child, who then enjoys a deep, quiet rest for several hours.

Meiring made a crude alkaloid extract from the plant, and noted that when injected into a frog it had a marked hypnotic effect. He then went on to do some “clinical experiments” with a tincture of dry plant material, and found it had marked pain-relieving activity “without concomitant bad effects.” Meiring then gave his remaining plant material to a Dr. Rubenstein to take to Germany, where a Dr. Fromm in Freiburg found it contained a compound capable of being crystallised, and which resembled morphine in its action (Meiring, 1896).

## 1898

In his book *Die Heilpflanzen Der Verschiedenen Völker Und Zeiten*<sup>18</sup>, Dragendorff lists two species of *Sceletium*: “*Mesembryanthemum anatomicum* Hav. (*Mesembryanthemum emarcidum* Thbg). Herb is used as a light narcotic (and smoked). Also *Mesembryanthemum tortuosum* L.” (Dragendorff, 1898).

<sup>18</sup> Rough translation: The Medicinal Plants of Different Peoples and Times.

## 1905

Juritz stated that *Mesembryanthemum tortuosum* is soporific, causes dilatation of the pupil, and decreases sensation (Juritz, 1905).

## 1913

Zwicky isolated a crude alkaloid extract from *Mesembryanthemum tortuosum*, which he called mesembrine, and on testing with various chemical reagents concluded that there was no similarity between cocaine and mesembrine; he further concluded that this active principle, mesembrine, was also found in

*Mesembryanthemum expansum*. In the first detailed documentation on self-ingestion of Sceletium plant material and alkaloid extract, Zwicky reported the following observations (Zwicky, 1913):

I. After chewing 5g of Sceletium:

The taste was bitter, astringent, unpleasant, irritating to the mouth. During the chewing, tingling was noticed on his tongue, later weak anaesthesia in the mouth, which lasted for some time. The pulse remained normal, while the temperature was weakly increased from 36.9 ° to 37.1 °. I noticed nausea, headache, loss of appetite.

II. After taking a decoction of 15g of Sceletium at 14:00:

Half an hour after taking the decoction I felt blood pressure in the head and slight headache, but it did not last long. I had the feeling that the food was not digested and only at 10:30 in the evening appetite returned. In general, the effects were not very different from the 1st experiment. ; in any case, they were not 3 times as strong as the first.

III. After taking 0.15g of an alkaloid concentrate extracted from Sceletium at 15:00:

Congestion of the head, noises in the ears, tiredness accompanied by slight tremors in the arms and legs, headache, general depression; loss of appetite until 10 in the evening.

## 1928

The Khoikhoi chew the leaf for the relief of toothache and pain in the abdomen, “the effect apparently being narcotic” (Laidler, 1928).

## 1937

Crystalline pure alkaloid was isolated from Sceletium plant material obtained from Namaqualand (Rimington and Roets, 1937), identified as mesembrine, and assigned the formula  $C_{17}H_{23}O_3N$ . It was concluded that this formula is identical to hyocyamine and atropine, suggesting that mesembrine is a tropane alkaloid.

## 1960

All *Sceletium* species “contain the poisonous principle “mesembrine” a relative of cocaine and other principles” (Jacobsen, 1960). Jacobsen noted that *kougoed* was still being made traditionally and sold, and concluded “perhaps it may give a valuable medicine.”

## 1962

*Sceletium tortuosum* “is used as a narcotic by the African in the Queenstown district” (Watt & Breyer-Brandwijk, 1962). A geologist and mining engineer observed that “the Nama have a universal addiction to *kougoed*”, and it “is also used by the Nama for the relief of all types of pain, and to relieve hunger...A Nama mother chews the root and ejects her saliva into the mouth of her child from an early age” (Watt & Breyer-Brandwijk, 1962).

## 1971

Herre (1971) stated that while other members of the Aizoaceae also contain mesembrine, it is present in lower concentrations than in *Sceletium*, which produces mesembrine when grown in North Carolina, but not in Europe and northern countries. He noted that the German pharmaceutical company C.F. Boehringer & Söhne of Mannheim was investigating *Sceletium*, and also the company S.B. Penick in New York.

**Table 1.** Summary of historical reports on preparation and uses of *Sceletium* species

| SUBJECT    | NOTES                                                     | REFERENCES                                                                                                      |
|------------|-----------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------|
| Species    | <i>Mesembryanthemum tortuosum</i>                         | Tully, 1858; Pappe, 1868 ; Hobbs, 1876; Nicholl, 1895 ; Meiring, 1896; Juritz, 1905; Zwicky, 1913; Tully, 1858; |
|            | <i>Mesembryanthemum emarcidum</i>                         | Forbes, 1986; Holmes, 1874                                                                                      |
|            | <i>Mesembryanthemum anatomicum</i>                        | Dragendorff, 1898                                                                                               |
|            | <i>Mesembryanthemum expansum</i>                          | Zwicky, 1913                                                                                                    |
| Folk names | Ningin, Ningimm                                           | Purchas 1625; Moreland, 1934                                                                                    |
|            | Kanna, Canna                                              | Tachard, 1686; Kolben, 1731; Moreland, 1934; Serton, 1971; Smith, 1966; Wilson, 2002; Forbes, 1986              |
|            | Kauw-goed;<br>Kaauwgoed;<br>Kauwgoed; Koegoed,<br>kougoed | Holmes, 1874; Meiring, 1896; Marloth, 1917; Smith, 1966; Forbes, 1986                                           |

|             | !k"wa:ĩ ; !k"wai:n                                                                                                                                                                                                 | Prader-Samper, 2007                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|-------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Preparation | Roots fermented with honey<br>Whole plant fermented<br>Tincture<br>Cold water infusion<br>Drops of freshly squeezed plant<br>Smoked<br>Roots chewed, saliva given to infant                                        | De La Caille, 1763<br>Forbes, 1986<br>Pappe, 1868<br>Prader-Samper, 2007<br>Meiring, 1896<br>Forbes, 1986; Dragendorff, 1898<br>Watt & Breyer-Brandwijk, 1962                                                                                                                                                                                                                                                                                                                                                                                  |
| Activities  | Intoxicant<br>Narcotic, Sedative,<br>Hypnotic<br>Decrease sensation,<br>local anaesthesia<br>Nausea, loss of appetite,<br>decrease hunger<br>Toothache<br>Elevate mood<br>Analgesic<br>Pain<br>Endurance<br>Memory | Waterhouse et al, 1979; Kolben, 1731; Tully, 1858; Pappe, 1868; Holmes, 1874<br>Kolben, 1731; Tully, 1858; Pappe, 1868; Holmes, 1874; Hobbs, 1876; Nicholl, 1895; Meiring, 1896; Dragendorff, 1898; Juritz, 1905; Laidler, 1928; Watt & Breyer-Brandwijk, 1962<br>Juritz, 1905; Zwicky, 1913; Watt & Breyer-Brandwijk, 1962<br>Zwicky, 1913; Laidler, 1928<br>Laidler, 1928<br>Kolben, 1731<br>Meiring, 1896; Laidler, 1928; Watt & Breyer-Brandwijk, 1962<br>Prader-Samper, 2007; Laidler, 1928<br>Prader-Samper, 2007<br>Prader-Samper, 2007 |

## PART II

### ETHNOBOTANY, ETHNOPHARMACOLOGY & PRE- CLINICAL RESEARCH 1995-2017

#### ETHNOBOTANY

In late 1991, I was given a sample of *kanna* by the ethnobotanist Fiona Archer, who had been documenting local plant uses in Namaqualand for an MSc degree in anthropology at University of Cape Town. At the time, I was searching for South African plants with psychedelic activity. On inquiring if she had encountered possible psychoactive plants from Namaqualand, Fiona told me about a plant called *kougoed*, traditionally used by locals, and that when she had tried some it felt as if her perceptions of time and space had been altered. Fiona gave me a brown paper bag containing about 500g of stringy, brown, traditionally fermented and dried *Sceletium*. I chewed a few grams of the plant material, and after about fifteen minutes, the plant caused a rather sudden rush of euphoria. Over the following hour, this gradually changed to a feeling of deep calm that persisted for some four or five hours. Following from this intriguing initial experience, my wife Olga, myself and Fiona began a period of self-experimentation and gave samples of *kanna* to friends, fellow doctors and psychiatrists,

anthropologists, botanists and an African traditional healer. I wrote up some of this early experimentation in Smith et al., 1996:

Additional information on the effect of *kougoed* has been documented from a dozen individuals who self-experimented with the traditionally prepared plant material, and provided oral anecdotes of these experiences. Most users found that *kougoed* induced a marked anxiolytic effect. One informant used about 5ml of powdered *kougoed* orally before giving a lecture he was anxious about. He reported feeling relaxed throughout the lecture with no cognitive impairment. Many users felt that *kougoed*, on its own or with alcohol, enhanced social intercourse at parties and functions. Users felt considerably less inhibited and self-conscious, and more open than usual in conversation with strangers. One user claimed she felt that *kougoed* was a “truth drug”. Of *kougoed*, some claimed there was a synergistic effect with alcohol, and with smoked *dagga* (*Cannabis sativa*). One experimenter, a polysubstance abuser, used *kougoed* in addition to alcohol (whiskey) and smoked *dagga*. He experienced a traumatic flashback to a violent event he had participated in during a regional armed conflict.

A polysubstance abuser, addicted to nicotine and a frequent abuser of alcohol and *dagga*, reported that after a single dose of *kougoed* he felt no craving for alcohol, *dagga* or nicotine for 4 days. Some reported euphoria as well as a feeling of meditative tranquility. Several users felt that the relaxation induced by *kougoed* enabled one to focus on inner thoughts and feelings, if one wished, or to concentrate on the beauty of Nature. Some informants reported heightened sensation of skin to fine touch, as well as sexual arousal. A senior traditional healer, not previously exposed to *kougoed*, tried it and announced that it “relaxes the mind” and makes one’s body feel “light” the following day.

From 1995 to 1999, I undertook detailed ethnobotanical studies on *Sceletium* in the field to document the local uses of the plant, and to determine whether the plant had addictive potential. The focus of this field work was in the rural hamlets of Paulshoek and Nourivier in the Kamiesberg mountains of Namaqualand, not far from the



1685 trail of the Dutch expedition led by Simon van der Stel. Fieldwork was also undertaken in the vicinity of *Kougoedvlakte* (the area named after the once-abundant wild *Sceletium tortuosum* resource of this arid plain), and interviews and discussions were held with shepherds and goatherds in the western area of what is now the Riemvasmaak Community Conservancy. In rural hamlets, elderly male and female members of the local community, who had themselves used *Sceletium* for many decades, were interviewed. Three key informants, recognized by the communities for their specialist knowledge on medicinal plants, were selected for more detailed interviews: the renowned traditional healer Gert Dirkse or “Oom Gert” (meaning Uncle Gert) living near Paulshoek; a younger healer, Jap-Jap Klaase, living in Nourivier; and the shepherd Lodewyk Mories, living near the farm Ratelkraal situated between the towns Springbok and Pofadder.

Some of this ethnobotanical research has been published in Smith et al., 1996, Gericke & van Wyk, 2000, and in Gericke & Viljoen, 2008. *Sceletium tortuosum* is typically harvested by local people during the dry-season months from October through to January, when the plants have partly died back and become yellowish in colour. The plants are often found growing under woody shrubs, partially shaded and sheltered from the wind and from foraging by animals. The died-back yellowing plants are regarded as having more “power” than the vigorously growing green plants of the June to August winter rainy season. The plant is cut above the ground, leaving the roots and a small portion of stem behind to resprout. While some collectors gather the entire uprooted plant, older healers claim this is not following tradition and will prevent the plants from regenerating. The collected succulent plant material is crushed with a large stone on a flat rock and the resulting dripping wet fibrous pulp is put into a plastic bag. According to local people, traditional sheepskin bags were used in former times. The plastic bag is tied to exclude air, and the material is allowed to macerate in the hot sun for eight days with intermittent mixing. On the eighth or ninth day, the plant material is spread on a flat rock to dry in the sun, resulting in dry clumps of amorphous, light brown plant material with a characteristic musty “old socks” smell. This is the traditional *kougoed* or *kanna* of the Namaqualanders.



The late Gert Dirkse, right, the last great healer of the Kamiesberg Mountains, with *Sceletium tortuosum*, and Jap-Jap Klaase, left.



## ADDICTION POTENTIAL

The following excerpt is taken verbatim from a field report (Gericke, 1995). In order to assess the potential for addiction, I had asked my friend Dr. Greg McCarthy, an academic addictionologist, to accompany me on a field trip to Namaqualand and give me an independent opinion on this. Sadly, Greg passed away in 2016, still working as an academic psychiatrist and addictionologist.

“In order to assess whether *Sceletium* use leads to addiction or dependence, a consultant psychiatrist from the Cape Town Drug Rehabilitation Centre, Dr. Greg McCarthy, accompanied Dr. Gericke on a field trip to Namaqualand to investigate the use of *kougoed* by traditional healers and members of rural communities. Dr. McCarthy is a consultant psychiatrist at Valkenberg Hospital Community Service, and was recently a consultant at Avalon, an alcohol treatment centre. He serves on the Western Cape Alcohol and Drug Forum.

“The DSM-IV criteria for dependence were translated into a questionnaire appropriate to the rural population. Three well-respected traditional healers, and eight long-term regular users of *kougoed* were interviewed. All were cooperative and open. There was clear convergence of the anecdotes and all denied any hallucinogenic or psychotomimetic effects of *kougoed*.

“While *kougoed* is used as a euphoriant or intoxicant, almost solely by elderly men, its medicinal qualities are highly regarded by the entire community. The recognized medicinal uses include use as an hypnotic or sedative, as a mild laxative, as a gripe-water, for abdominal cramps, and for alcohol rehabilitation. All research participants were adamant that *kougoed* was less habit-forming than alcohol, tobacco or *dagga* [*Cannabis sativa*].

“Tolerance was denied by all users except one, who reported “*jy raak gewoond daaraan*” [“you get used to it”]. It was not clear whether he was referring to true tolerance, where increasing doses are required to bring about the same effect, or whether he was referring to the fact that one gets accustomed to the use of *kougoed*, as the naïve user can experience nausea.

“Withdrawal signs or symptoms were not reported by anyone. This significant finding is reliable, because even regular users run out of

supplies of *kougoed* due to decreased availability of the material. Mr. Mories (pers. comm.) reported there were no signs or symptoms of withdrawal even if a person ran out of *kougoed* after six months of habitual use. Some regular users would perhaps have a slight feeling as if something was missing, and some would make an effort to contact friends who may have some *kougoed*, but would not run into any difficulties if no more was obtained. All confirmed it would be far easier to give up *kougoed* than alcohol, tobacco or *dagga* [*Cannabis sativa*].

“An idea of the social and occupational functioning of the informants was easy to gauge although formal employment is scarce. The local environment is harsh, and daily living requires hard work, including walking long distances to collect brushwood for firewood, shepherding sheep and goats, and ploughing wheat-fields using donkey-drawn ploughs. There were no reports of “social dropouts” from habitual *kougoed* use, and use in this rural context can be viewed as a socially sanctioned activity. It is not possible to extrapolate what effect habitual use of *kougoed* as an euphoriant would have outside of this context.

“The medicinal use of *kougoed*, administered for specific indications, in lower doses, taken less frequently and for a finite duration must be seen as entirely separate from use as an euphoriant.” (Gericke, 1995).

## WELL-BEING

*Kanna* was commonly used by elderly men and women for a sense of calm and well-being. Elderly research participants, some in their eighth and ninth decade of life, were interviewed who had chewed quids of *kanna* daily throughout their adult lives. A small quid of fermented *Sceletium* is kept in the cheek and sucked, and the resulting saliva is swallowed. For a sense of calm and well-being, the quid is removed about fifteen minutes later. Men in the community then place the wet quid in their hatband to dry out so it can be sucked on or chewed later, a sequence repeated a number of times during the day. The author was cautioned “*Doktor, jy moet leer hoe om dit te gebruik*” – “Doctor, you must learn how to use it” – because once one begins feeling intoxicated by it, one has already chewed far too much. The intention of these users is to enjoy a

pleasant sense of well-being, not to get intoxicated.

### INTOXICATION

There were convergent reports that some people, invariably older males rather than females, did indeed use *kanna* on occasion as an intoxicant or euphoriant. No visual or auditory hallucinations were associated with the intoxication, and the state was described as being similar to being intoxicated with alcohol: “*dis onse droë drank*” – “it is our dry liquor” (Lodwewyk Mories, pers. comm., 1995). Plants from particular areas are regarded as being more potent intoxicants, and through the traditional “fermenting” process, the *kanna* would give a better “trek” – euphoria or a high. Younger men in the community were not using *kanna* at this time, and it seemed the use of tobacco, alcohol and possibly also *dagga* (marijuana) had displaced the former use of *kanna* by younger people in these rural communities.

### INSOMNIA

*Kanna* is used as a hypnotic, with a small quid kept in the cheek by some users when going to bed. Paradoxically, some participants reported that if too much *kanna* was used, it would in fact cause insomnia.

### ALCOHOLISM

Both of the healers, Gert Dirkse and Jap-Jap Klaase, maintained that *kanna* was used to wean alcoholics off of alcohol, but only if the alcoholic was committed to stop drinking. Alcohol was replaced by the chewing of *kanna*, and it was not considered to be a problem for the person to subsequently stop using the *kanna*. In some cases, a strong decoction of *kanna* would be added to a bottle of wine, so that if the alcoholic drank this wine it would cause vomiting and an aversion to wine.

### CONSCIOUSNESS

The healer Gert Dirkse maintained that using *kanna* “opened the mind”, and he used both hands expanding out from his temples to demonstrate this (pers. comm., 1999). He denied that the plant could cause any visions.

## PREGNANCY

A quid of *kanna* is commonly chewed by women during pregnancy for treating nausea, indigestion, or for treating constipation in pregnancy. It was noted that if one took too much it had a sedating effect. The plant was not known to cause abortion or congenital defects.

## PARTURITION

Infusions of *kanna* are taken to help expel any remaining afterbirth, to help contract the uterus, for abdominal pain after giving birth and for indigestion.

## INFANTS

*Kanna* is commonly administered to infants to treat colic, excessive crying and stomach cramps. A small amount of dried herb (the samples demonstrated were estimated to be ~200-500 mg) or fermented dried herb is wrapped in cloth and dipped in breast milk in a teaspoon until the liquid has turned slightly brown. A few drops of this liquid are given orally to make the infant sleep restfully. Dried fermented herb is also lightly fried in sheep fat taken from the tail of a fat-tail sheep; this is strained through a cloth and kept in a small bottle. One to two drops of this medicated liquid fat are given to an infant with colic. The baby usually falls asleep soon after the administration of the drops. None of the mothers had ever heard of an infant needing to be taken to a doctor after too much *kanna* had been administered; they acknowledged that sometimes too high a dose is inadvertently given, but all that happens is that the baby will sleep for some hours.

## CHILDREN

Hot-water infusions or decoctions of *kanna* are given to children for constipation, abdominal pain, winds and also as a “*kalmeermiddel*” or calming medicine. A child suffering from abdominal pain will fall asleep soon after the *kanna* is administered.

## OTHER

*Kanna* is also used in Namaqualand to treat asthma, abdominal



cramps, constipation and headache.

## RAW MATERIAL SUPPLY

Elderly Namaqualanders confirmed that *kanna* had once been plentiful, but was now very scarce as it had been overharvested for sale to local trading stores and shops in the local towns, including the town of Springbok. Lodewyk Mories (pers. comm., 1995) recalled a time when as a young boy in the 1940s, he had seen wagonloads of *kanna* being transported from Namaqualand, presumably destined for Cape Town. Some local farmers maintained that wild stocks of *Sceletium* had been eaten by overgrazing sheep; however, indigenous shepherds with more intimate knowledge of the eating habits of stock maintained that sheep would only nibble on *Sceletium* and then move on, and that it was not the sheep that had depleted wild stocks of *Sceletium*, but people who had overharvested the plant, who had “run after the money.”

It was clear that for the development of a product (at that time, for the South African pharmaceutical company Pharmacare Limited, as I was the Phytomedicines Development Manager), wild-harvesting of plants would not be ecologically sustainable, and that selections of *Sceletium* would need to be cultivated from scratch as a new crop. For this purpose, plant chemotype studies were started by Professor Ben-Erik van Wyk, and plant propagation and production studies were started by the late Professor Earle Graven and Myke Scott of Grassroots Natural Products. This work was on contract to Pharmacare Ltd., and directed by myself. From 1999 onward, the propagation and production of *Sceletium* work was continued by Du Roi Nurseries, and in 2004 by Niche Botanicals (Pty) Ltd., in cooperation with Hannes de Lange, PhD. The first successful large-scale commercial production of a select chemotype of *Sceletium tortuosum*, both under shade-house conditions and open-field conditions, was achieved in 2008 by Du Roi Nurseries and H.L. Hall and Sons Ltd., growing the plants on contract to the South African company HG&H Pharmaceuticals (Pty) Ltd. It had taken more than a decade of investment in research into plant selection, propagation and production studies to demonstrate that *Sceletium* could be grown successfully on a large scale as a new commercial South

African crop. The reliable supply of raw material with a defined alkaloid content and composition finally allowed the development of a standardized and characterized spray-dried extract of the plant, suitable for all subsequent pre-clinical and clinical research.



Cultivated *Sceletium* for the production of the standardized extract Zembrin®.

## CHEMISTRY

The literature on the *Sceletium* alkaloids has recently been thoroughly reviewed (Krstenansky, 2017), and validated analytical methods have been described for quantifying the major mesembrine-type alkaloids including mesembrine, mesembrenol, mesembrenone, mesembranol,  $\Delta^7$ mesembrenone, and epimesembranol (Patnala & Kanfer, 2010; Shikanga et al., 2012).

Based on the alkaloid skeleton, Jeffs et al. (1982) separate *Sceletium* alkaloids into four structural groups:

- I. the 3aaryl-*cis*-octahydroindole class (e.g., mesembrine)
- II. the C-seco mesembrine alkaloids (e.g., joubertiamine)
- III. alkaloids containing a 2,3-disubstituted pyridine moiety and two nitrogen atoms (e.g., *Sceletium* alkaloid A4)
- IV. a ring C-seco *Sceletium* alkaloid A4 group (e.g., tortuosamine).

The revision of Gerbaulet (1996) recognizes eight species of *Sceletium*, of which the alkaloids in *Sceletium strictum*, *Sceletium subvelutum* (= *Sceletium varians*), *Sceletium tortuosum*, *Sceletium joubertii* and *Sceletium namaquense* have been studied in great detail. The latter two species are now considered synonyms of *Sceletium tortuosum*. The local utilization of *Sceletium* as *kanna*, *kaauwgoed* or *kougoed* has included a number of *Sceletium* species and a wide range of *Sceletium* alkaloids. Compounds that have been isolated from the genus *Sceletium* are presented in Fig 5.

## EXTRACT SCELETIUM TORTUOSUM, ZEMBRIN®

The first standardized extract of *Sceletium tortuosum* was made by the German company Gehrlicher GmbH in 1999 on contract to my consulting company, African Natural Health Close Corporation. The first fully standardized and characterized extract of *Sceletium tortuosum*, Zembrin®, was produced to EU-GMP standards by the Spanish company Polifenoles Naturales SL. The company is now renamed Nektium Pharma SL, and continues to manufacture the extract Zembrin® on contract to the company I co-founded, HG&H

Pharmaceuticals (Pty) Ltd. This extract was developed and commercialized from a cultivated special selection of plants that are relatively rich in mesembrenol and mesembrenone as the major compounds, and relatively low in mesembrine and mesembranol. Zembrin® is standardized to contain 0.4% total alkaloids by weight, with the relative alkaloid composition of mesembrenone + mesembrenol  $\geq 60\%$ , mesembrine  $< 20\%$ , and mesembranol must be present in the UPLC profile. The structures of these four compounds are given in Figure 6.

#### PRIOR INFORMED CONSENT BENEFIT-SHARING AGREEMENT

The development of a product from a medicinal plant used by indigenous people has to take into consideration the contribution that indigenous knowledge – past and present – makes to the foundational ethnobotanical research that gives a preliminary indication of safety, therapeutic indications, and in the case of *Sceletium*, the apparent lack of potential for dependence. Local participants were able to point out plants that they considered mild in effect in terms of euphoria or intoxication (called *mak* or “tame” plants), and plants which they considered a *trek* variety, which were considered to be far more potent plants than the *mak* variety and which could cause euphoria or intoxication, especially after fermentation.

Two years before the launch on the South African market of the standardized *Sceletium* extract Zembrin®, a prior informed consent benefit-sharing agreement was negotiated and signed between the South African San Council (SASC) and HG&H Pharmaceuticals (Pty) Ltd. (HG&H). The agreement was signed on 21 February 2008, and must be one of the first such agreements entered into with indigenous knowledge holders. This agreement was the result of many months of meetings and discussions with the South African San Council, who were supported in their negotiations by the internationally recognized human rights attorney Roger Chennels, ensuring that the SASC were well informed and that the agreement reached by the two parties was aligned with international best practices.

This benefit-sharing agreement recognized that the San were the primary indigenous knowledge holders of the South African

endemic plant *Sceletium tortuosum*. The SASC in turn recognized that the original ethnobotanical research conducted by myself in the Namaqualand communities of Nourivier and Paulshoek contributed important information on the uses of *Sceletium*. In recognition of this contribution to the project, the SASC agreed to share 50% of royalty payments made to SASC with these two communities in an agreement signed on 30 June 2008 (Gericke, 2011). Royalty payments have been made to the SASC by HG&H from 2008 to the present time, at a rate of 5% of royalties on all sales of the extract *Sceletium tortuosum*, Zembrin®, and an additional 1% royalty on the use of the SASC logo on products containing Zembrin®. The payments are based on total invoiced sales, not on “profit” (revenues after costs). The SASC in turn have paid 50% of the royalties to the two communities of Paulshoek and Nourivier, represented by local community organizations established for this purpose. All payments are made into a South African Government trust fund established for this purpose, and are then paid out in full to the SASC, who in turn pay the two Namaqualand community groups. This prior informed consent benefit-sharing agreement has been cited as a positive case study in the commercialization of a product derived from indigenous knowledge (Iatridis and Schroeder, 2016).

## PHARMACOLOGY

### SEROTONIN REUPTAKE INHIBITION (SRI)

On 25 July 1989, President George Bush, in response to reports by the National Advisory Council of the National Institute of Neurological Disorders and Stroke and the National Institute for Mental Health (NIMH), and the urging of Congress, signed a presidential declaration designating the 1990s as the Decade of the Brain, a national research endeavor to better understand how the brain and nervous system is organized, how it functions, why it fails to function and what can be done to prevent and treat dysfunction. As part of this research, NIMH screened large numbers of compounds through a research agreement with the company Novascreen. In November 1995, I was working as a Visiting Scholar at the US Pharmacopoeia (USP), and not far from USP was the

NIMH. I was introduced to Dr. Linda Brady, who was then the chief of the Neuropharmacology and Drug Discovery Program. Dr. Brady kindly agreed to screen an extract of *Sceletium* as well as isolated pure mesembrine. Both the extract and mesembrine turned out to be exceedingly potent 5-HT uptake inhibitors in the radioligand binding screening and in a subsequent functional assay. This work formed the basis for US Patent 6,288,104 (Gericke and Van Wyk, 1999), which disclosed the use of mesembrine and related compounds, and extracts of *Sceletium* standardized to these compounds, as serotonin-uptake inhibitors (SRIs), and the use of these compounds in pharmaceutical formulations for the management of depression, anxiety, drug dependence, bulimia and obsessive-compulsive disorder.

Subsequently, the standardized *Sceletium* extract Zembrin® was confirmed to be an SRI with an IC<sub>50</sub> of 4.3µg/ml, and mesembrine was found to be the most active alkaloid against the 5-HT transporter (SERT), with a K<sub>i</sub> of 1.4nM (Harvey et al , 2011). See Table 2 below. In fact, mesembrine is a more potent inhibitor on SERT than fluoxetine (Prozac).

**Table 2.** The inhibitory constants (K<sub>i</sub> in nM) for three mesembrine alkaloids on the serotonin transporter.

| Compound     | Inhibition of SERT<br>K <sub>i</sub> nM |
|--------------|-----------------------------------------|
| mesembrenone | 27                                      |
| mesembrine   | 1.4                                     |
| mesembrenol  | 63                                      |

## PHOSPHODIESTERASE-4 INHIBITION (PDE4 INHIBITION)

I self-experimented with isolated pure mesembrine on a number of occasions from 1996 to 1999, on some occasions with a friend and fellow natural products enthusiast, Dr. George Davidson. Isolated pure mesembrine, taken sublingually in tincture form or on a blotter, resulted in a tangible entactogenic effect with an onset of action some ten to fifteen minutes after taking 100µg. Higher doses at about 500µg gave an experience not dissimilar to MDMA but far more tranquil. It was clear that there had to be additional CNS

mechanism/s of action in addition to the SRI activity.

The results of the broad *in vitro* screening of the Scelletium extract Zembrin® and some isolated alkaloids is reported in Harvey et al., 2011. Zembrin® was found to be an inhibitor of the phosphodiesterase-4 (PDE4) enzyme in addition to being an SRI (Harvey et al., 2011). The three isolated mesembrine alkaloids tested were all found to be PDE4B inhibitors, with the most potent of the three being mesembrenone, which is about one third as potent as the prototypical research PDE4 inhibitor Rolipram (Harvey et al., 2011; MacKenzie and Houslay, 2000). See Table 3 below. US Patent 8,552, 051 (Harvey et al., 2013) discloses the use of mesembrenone as a dual SRI and PDE4 inhibitor.

**Table 3.** PDE4 inhibition of the prototypical PDE4 inhibitor Rolipram and the Scelletium alkaloids mesembrenone, mesembrine and mesembrenol.

| Compound     | PDE4B Inhibition<br>IC <sub>50</sub> μM |
|--------------|-----------------------------------------|
| Rolipram     | 0.13                                    |
| mesembrenone | 0.47                                    |
| mesembrine   | 7.8                                     |
| mesembrenol  | 16                                      |

While SRIs and selective SRIs (SSRIs) are widely used for the treatment of anxiety disorders and depression, the combination of an SSRI with a PDE4 inhibitor has been argued to have synergistic therapeutic potential. Repeated treatment with SSRIs can upregulate PDE4 (Ye et al., 2000), which in turn reduces sensitivity to SSRIs in response to long-term treatment. The treatment with a dual SSRI and PDE4 inhibitors may thus have a therapeutic advantage (Cashman et al., 2009). Enzymes in the PDE4 family catalyze the hydrolysis of cyclic AMP (cAMP) and have a critical role in controlling the intracellular concentration of cAMP and increasing phosphorylation of cAMP-response element-binding protein. PDE4s are found throughout the brain but their levels are decreased in depressed individuals not on medication, reflecting a downregulation of the cAMP cascade that can potentially be restored using PDE4 inhibitors. The prototypical PDE4 inhibitor Rolipram has been shown in both animal and clinical studies to have antidepressant activity (Terburg et al., 2013).



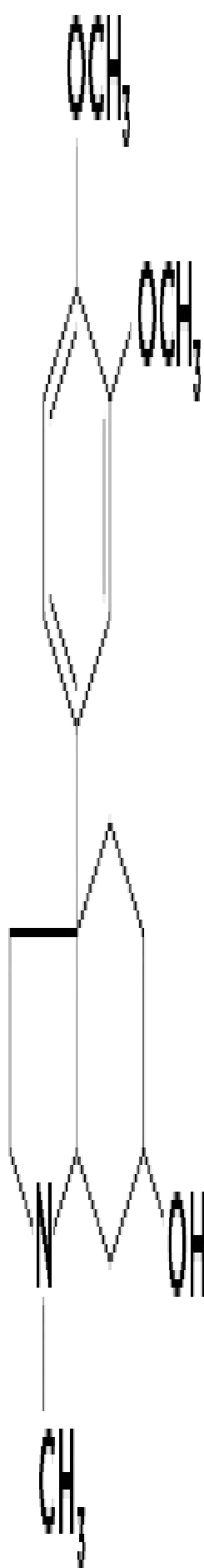
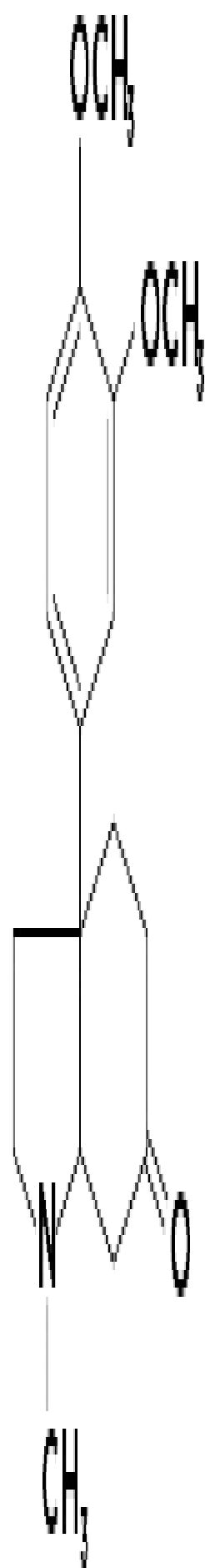
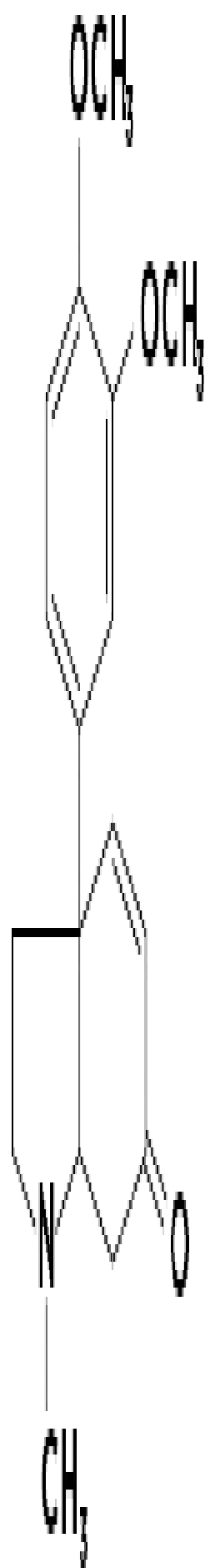
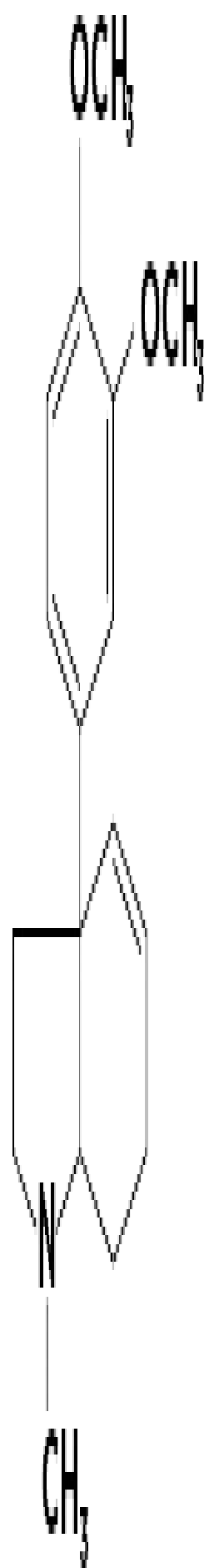


**Fig. 1** The four alkaloids quantified in the standardized *Sceletium* extract Zembrin.

## PRE-CLINICAL RESEARCH

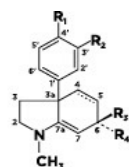
Prior to the development of a standardized extract, I sent samples of milled *Sceletium tortuosum* plant material to colleagues in Japan who were interested in studying the effect of *Sceletium* in a veterinary clinic setting. The veterinarians reported that the *Sceletium* reduced cage stress and travel stress in cats, and decreased the excessive nocturnal crying and barking of aged cats and dogs with a clinical diagnosis of dementia. These results have been published in Japanese (Hirabayashi et al., 2002; Hirabayashi et al., 2004; Hirabayashi et al., 2005).

*Sceletium* extract Zembrin® was studied in a 14-day repeated oral toxicity study conducted at 0, 250, 750, 2500, and 5000 mg/kg body weight/day (equivalent to total mesembrine alkaloids of 0, 1, 3, 10, and 20 mg/kg bw/day). A 90-day subchronic repeated oral toxicity study was conducted on *Sceletium* extract Zembrin® at 0, 100, 300, 450, and 600 mg/kg bw/day (equivalent to total mesembrine alkaloids of 0, 0.4, 1.2, 1.8, and 2.4 mg/kg bw/day). Since *Sceletium* species were known to be psychoactive, a functional observation battery, including spontaneous locomotor activity measured using the LabMaster ActiMot light-beam frames system, was employed. Parameters such as locomotion, rearing behavior, spatial parameters and turning behavior were investigated. No mortality or treatment-related adverse effects were observed in the rats in the 14- or 90-day studies. In the 14- and 90-day studies, the No Observed Adverse Effect Levels (NOAEL) for Zembrin® were 5000 and 600 mg/kg bw/d, respectively, the highest dose groups tested (Murbach et al., 2014), equivalent to the NOAEL for total mesembrine alkaloids of 20 and 2.4mg/kg bw/day.

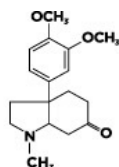
In a model of restraint-induced psychological stress it was found that a dose of only 5mg/kg of *Sceletium* extract (although not stated in the paper, this was Lot #8587 of Zembrin®) given by gavage reduced restraint stress-induced self-soothing behavior, as well as decreased stress-induced corticosterone levels (Smith, 2011). This dose is equivalent to a total alkaloid dose of only 20 µg/kg bw/day.

The effect of single doses of *Sceletium* extract Zembrin® on rat

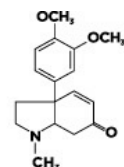
brain electrical activity was studied using wireless EEG recordings in free-living rats. 3 doses of the Scellium extract Zembrin® and vehicle (0, 2.5, 5.0 and 10.0 mg/kg, equivalent to total mesembrine alkaloids of 0, 10, 20 and 40 µg/kg) were given by gavage. The resulting electropharmacograms (plotted from Fast Fourier Transformation of the analogue EEG recording for each frequency range) of Zembrin® were compared to the databased electropharmacograms of reference herbal extracts, dietary ingredients and the pharmaceutical PDE4-inhibitor Rolipram. Zembrin® had a similar electropharmacogram to the electropharmacograms for extracts of *Ginkgo biloba* and *Rhodiola*. A discriminant analysis confirmed these similarities and also demonstrated that Zembrin® had a similar electropharmacogram to citicoline, a compound originally developed for cognitive enhancement, and to the PDE4-inhibitor Rolipram. These results provide support for future translational clinical studies on Zembrin® to investigate the activity of the extract on cognitive function in Mild Cognitive Impairment, for treating depression and as an analgesic (Dimpfel et al., 2016).



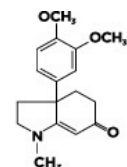
The 3a-aryl-cis-octahydroindole skeleton



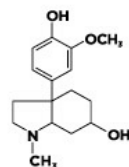
mesembrine



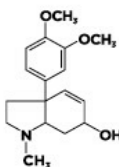
mesembrenone



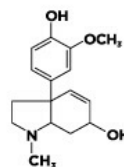
Δ<sup>7</sup>mesembrenone



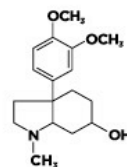
4'-O-demethylmesembranol



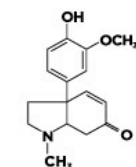
mesembrenol



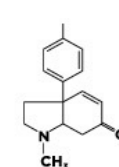
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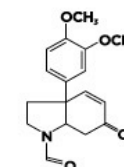
mesembranol



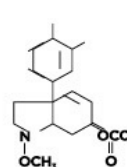
4'-O-demethylmesembrenone



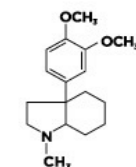
scoletenone



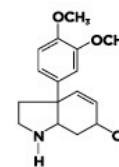
N-demethyl-N-formylmesembrenone



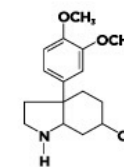
O-acetylmesebrenol



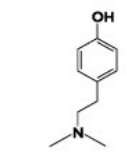
mesembrane



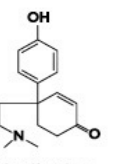
N-demethylmesembrenol



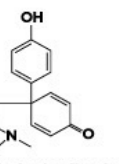
N-demethylmesembranol



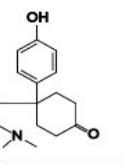
hordenine



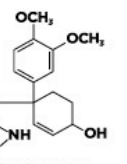
joubertiamine



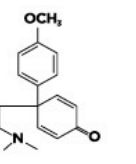
dehydrojoubertiamine



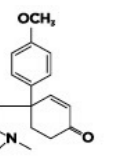
dihydrojoubertiamine



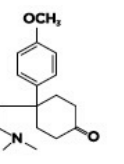
joubertinamine



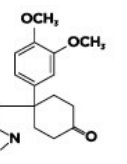
O-methyldehydrojoubertiamine



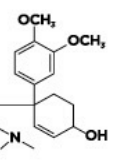
O-methyljoubertiamine



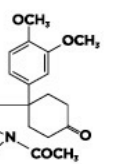
O-methyldihydrojoubertiamine



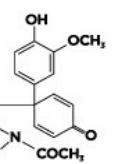
3'-methoxy-4'-O-methyljoubertiamine



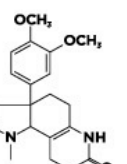
3'-methoxy-4'-O-methyl



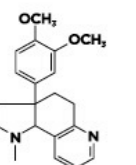
4-(3,4-dimethoxyphenyl)-4-(2-acetyl(methylamino)ethyl)cyclohexanone



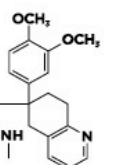
4-(3-methoxy-4-hydroxyphenyl)-4-(2-acetyl(methylamino)ethyl)cyclohexadienone



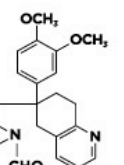
"unnamed alkaloid"



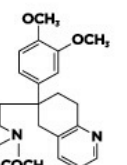
scoletium alkaloid A4



tortuosamine



N-formyltortuosamine



N-acetyl tortuosamine

**Fig. 2** Structures of alkaloids isolated from the genus *Sceletium* (Gericke & Viljoen, 2008).

## PART III

### CLINICAL STUDIES ON SCELETIUM EXTRACT

### ZEMBRIN®

#### INTRODUCTION

The following three case reports on the clinical use of *Sceletium*, presented at the 4th International Conference on Phytotherapeutics on 23-25 February 2001, Kurrajong, NSW Australia, are the first clinical case reports for this plant and demonstrate that the plant has therapeutic potential for anxiety and depression. These historical case reports are given in full from Gericke (2001).

#### 1. PATIENT WITH A FIRST EPISODE OF SEVERE DEPRESSION WITH MARKED ANXIETY REPORTED BY THE AUTHOR

H.M., a 29-year-old female doctor, presented at my practice asking for a natural treatment for severe depression. She had had no previous psychiatric history, no history of epilepsy, head injury or substance abuse, and had a past medical history of atopic eczema and occasional asthma, not presently on any medication.

#### MAIN COMPLAINT

A four-month period of depressed mood with diurnal variation: the depression was far worse in mornings, improving somewhat as the day progressed. There was an obvious physiological shift with decrease in appetite, weight loss and insomnia with difficulty initiating sleep and early morning waking. Markedly decreased energy and drive were a significant problem for the patient. The symptoms were accompanied by feelings of anxiety and somatic symptoms of anxiety including palpitations and epigastric discomfort. Other symptoms of note included suicidal ideation, feelings of worthlessness, lack of concentration and motivation, tearfulness, emotional lability and general loss of interest in life.

#### TREATMENT

The patient requested to be put on *Sceletium*, having heard about

it from a colleague who is a psychiatrist, and was started on a low dose of 50mg [milled plant material] as a tablet taken in the mornings.

The patient initially reported a transient increase in anxiety after taking medication, which would last up to three hours. This effect was no longer apparent after a week of continual use. No changes in libido were noted, and libido had not been affected by the depression either. A sustained improvement in mood was reported from somewhere between 1-2 weeks of continual use of 50mg *Sceletium* taken daily, with a marked decrease in the generalized anxiety. The patient's insomnia improved at the onset of treatment. There was a marked improvement in drive and energy, accompanied with a return of interest in the mundane activities that constitute much of everyday living.

The only side effects elicited were the initial transient increase in anxiety and some initial appetite suppression, neither of which was severe enough to warrant discontinuation of treatment, and both of which were no longer apparent after the first two weeks of treatment.

## CONCLUSION

A low dose of *Sceletium* (50mg daily) taken orally as a tablet proved to be a very effective anxiolytic and mood elevator in a first episode of a major depression. The *Sceletium* was discontinued after 4 months of continual use with no signs or symptoms of withdrawal, and there has so far (about 6 months) been no return of symptoms of anxiety or depression.

## 2. PATIENT WITH POSTNATAL MAJOR DEPRESSIVE DISORDER.

REPORTED BY DR OLGA GERICKE MUDR (VIENNA) FC  
PSYCH. (SA)

A 28-year-old married housewife with two children, aged three and a half and two months old respectively, presented with depressive symptoms that she had had since the seventh month of her second pregnancy. Complaining of depressed mood, increased sleep, overeating, low energy, increased anxiety to the point of

perceptual illusions and depersonalization, feelings of worthlessness, psychomotor agitation, thoughts of death, decreased ability to concentrate and forgetfulness. She also complained of inability to bond with her newborn and felt very irritable and aggressive towards her three-year-old. The patient had self-medicated with St John's Wort (*Hypericum perforatum*) over the last two weeks, with minimal effect.

### PAST PSYCHIATRIC HISTORY

Severe postnatal depression after her first child, needed hospitalization, was on Aurorix (Moclobemide) for two years with limited success and discontinued it due to side effects. Her first onset of depression was at age 16, which was treated with Amitriptyline and therapy.

### PAST MEDICAL HISTORY

Pre-eclampsia with first pregnancy and currently hypertension, obesity.

HABITS: nil.

PRESENT MEDICATION: ACE inhibitor for hypertension.

FAMILY AND SOCIAL: Disruptive upbringing, mother suffered from severe depression and was hospitalized frequently, both sisters suffer from panic disorder.

### DIAGNOSIS

- Major depressive disorder, recurrent, severe, postnatal onset
- Borderline personality traits
- Hypertension

### TREATMENT

The patient was started on *Sceletium* 50 mg [milled plant material] in the morning and at lunchtime. The immediate effect (the first day of treatment) was mood elevation, significantly decreased sleep (from 14 hours a day to eight hours a day) and increased energy. The patient voluntarily started doing housework again. After four weeks of treatment, symptoms of mild depression and anxiety were present again. After six weeks of treatment with

*Sceletium*, and supportive therapy and group sessions with a postnatal depression support group, the patient appeared to be fully recovered and is presently well on a maintenance dose of 50 mg *Sceletium* twice a day.

### COMMENT

To date, I have successfully used *Sceletium* in 10 patients with a diagnosis of Major Depressive Disorder according to DSM-IV criteria. My patients are usually more severely depressed or anxious than the clients of psychologists and patients of general practitioners, and most of them have been on various pharmaceutical antidepressants before. Most of the patients had a strong anxiety component to the depression. *Sceletium* alleviates anxiety very quickly, though in sensitive individuals the first dose can actually increase the anxiety for about half an hour, after which it is relaxing. My starting dose is usually 50mg in the morning and most patients increase it to an additional 50mg at lunchtime or early afternoon. If taken later, it can cause insomnia in some patients. In some patients I have had to increase the dose to 100mg/12 hours.

### 3. CASE REPORT BY CHERYL INGGS

B.A. HONOURS, MA(CLIN. PSYCH.) RHODES

The client is a 19-year-old university student who started therapy (once a week) towards the end of her second year (1999). She completed her bachelor's degree at the end of 2000 and has just entered her Honours degree.

#### THE CLIENT PRESENTED WITH THE FOLLOWING:

Axis I : Dysthymia. She felt despondent and "trapped inside", she isolated herself and "couldn't see a way out", was sometimes tearful, alternating with an emptiness inside and a pervasive sense of sadness; she had low self-esteem, a loss of interest in activities with social withdrawal, loss of motivation, some distractability and short-term memory loss, tiredness, lethargy, hypersomnia and loss of appetite with occasional "comfort eating" mostly of junk food. There was no suicidal ideation.

Axis II : Borderline Personality. Described feeling "out of touch"



and depersonalized, with some self-mutilation (scratching her upper arm and wrist). Some impulse binge-drinking when socializing. She had tried “ecstasy” (MDMA) and indulges in marijuana very occasionally. A baseline mood of depression alternating with anxiety and a feeling of tension particularly around her studies and exam performance (sweaty palms, constipation and hair loss). Feelings of emptiness and fear of abandonment. Inappropriate and intense anger. Battling with a sense of self and identity, feeling unsure of who she is, feeling distant, isolated and lonely.

### THERAPEUTIC ISSUES

The client clearly presented with long-standing dysthymia and some anxiety. She had also been sexually abused from age 12-15. She is the middle child and only daughter of an emotionally absent father and a career-oriented mother on whom the client is emotionally dependent. She vacillates between idealizing her mother when she is available and feeling abandoned by her when she is unavailable. The client carries a great deal of anger, and has body-image problems coupled with a fear of sexual intimacy.

### TREATMENT

The therapeutic approach was from a self-psychology model providing a containing environment with careful intervention and gentle interpretation. The client was able to be very insightful but lacked the capacity to process the insight in any meaningful way. She presented with an ongoing sense of emptiness and depersonalization, with a deep despondency and hopelessness. *Sceletium* was administered as a 50mg tablet daily from October 2000. Within ten days, the patient said that her mood had lifted and that she felt slightly less depersonalized. She was able to feel more focused, more engaged and not so socially “distant.” She doubled her dose to two 50-mg tablets daily just prior to her examination (November 2000) and described feeling less anxious and more able to cope with her usual examination anxiety. An interesting development on *Sceletium* was that she described feeling less inclined to overindulge in alcohol (she said that it didn’t taste as good).

## CONCLUSION

The client clearly has personality problems that require ongoing therapy. However, what is significant is that the *Sceletium* certainly helped her feel more contained, lifted her mood and also helped with anxiety. There is a sense in which the *Sceletium* has stabilized her to the point where we were able to actively engage in some of the more pressing therapeutic issues.

The rapid improvements in mood and anxiety in these initial three patients provided the impetus for the development of the proprietary standardized and characterized *Sceletium* extract Zembrin® for formal clinical research.

### SAFETY & TOLERABILITY (NELL ET AL., 2013)

The safety and tolerability of *Sceletium* extract Zembrin® was studied in the first formal clinical study of a *Sceletium* extract. In this randomized, double-blind, placebo-controlled clinical study, two doses of Zembrin® (8mg and 25mg, equivalent to total mesembrine alkaloids of 32µg and 100µg respectively) were taken orally once daily for three months by healthy adult volunteers. No efficacy variables were assessed. The extract was found to be safe and well tolerated. An interesting aspect of the study was unsolicited positive effects on well-being noted in patients' side-effect diaries by some participants taking the extract, including improved coping with stress and improved sleep at night.

### PHARMACO-FMRI STUDY (TERBURG ET AL., 2013)

The acute effects of extract Zembrin® were investigated in a pharmacofMRI study focused on anxiety-related activity in the amygdala and the connected neuro-circuitry. In a double-blind, placebo-controlled cross-over design, 16 healthy university student participants were scanned during performance of an emotion-matching task under low and high perceptual loads. Amygdala reactivity to fearful faces under low perceptual load conditions was attenuated, with a decreased blood oxygenation level-dependent (BOLD) signal for Zembrin® compared to placebo on low-load exposure to fearful faces compared with neutral challenges in the bilateral amygdala ( $P < 0.01$ ) after a single 25mg (equivalent to 100µg total mesembrine alkaloids) dose of Zembrin®. Follow-up

connectivity analysis on the emotion-matching task demonstrated that amygdala–hypothalamus coupling was also reduced. These results demonstrated, for the first time, the attenuating effects of an extract of *Sceletium* on the threat circuitry of the human brain and provided supporting evidence that this extract may have anxiolytic potential by attenuating subcortical threat responsivity. These results are consistent with the *in vitro* dual serotonin reuptake inhibition and PDE4 inhibition reported by Harvey et al., 2011.

#### COGNITION-ENHANCING ACTIVITY (CHIU ET AL., 2014).

In a randomized double-blind placebo-controlled cross-over clinical study normal healthy older subjects (total n=21) (mean age: 54.6 years  $\pm$  6.0 yrs; male/female ratio: 9/12) received either a 25 mg capsule of *Sceletium* extract Zembrin® (equivalent to 100mg total mesembrine-alkaloids) or placebo capsule once daily for 3 weeks. The primary endpoint was to examine the neurocognitive effects of the extract using the CNS Vital Signs battery of tests. Zembrin® at 25 mg daily dosage significantly improved executive function (p0.022) and cognitive set flexibility (p0.032) compared with the placebo group. Positive changes in mood and sleep were also found, and the extract was well tolerated. It was concluded that PDE-4 inhibition with the resulting cAMP-CREB cascade may play a role in these cognitive enhancing effects of Zembrin®.

#### ACTIVITY ON EEG, PSYCHOMETRY, AND ANXIETY (DIMPFL ET AL., 2017).

In a randomized, double-blind, placebo-controlled clinical study, the effect of 25mg or 50mg of Zembrin® (equivalent to 100µg and 200µg of total mesembrine alkaloids, respectively) was studied in comparison to placebo after daily repetitive intake for 6 weeks. Sixty healthy male (n = 32) and female (n = 28) subjects between 50 and 80 years old (59.7  $\pm$  5.43 and 56.7  $\pm$  5.88 years, respectively) were recruited. The EEG was recorded bipolarly from 17 surface electrodes. Six cognitive tests were performed: d2-test, memory test, calculation performance test, reaction time test, number identifying test and number connection test. Three questionnaires were included: Profile of Mood States, Hamilton Anxiety Rating Scale (HAM-A) and a sleep questionnaire. Quantitative EEG

revealed increases of delta activity during performance of the d2-test, the number identification and number connection tests in the fronto-temporal brain region. Higher theta activity was seen during relaxation and performance of the d2-test after intake of 50mg of Zembrin®. Statistically conspicuous increases of alpha1 spectral power were seen in the relaxed state. With respect to alpha2 spectral power, larger increases were observed in the centro-occipital region. Discriminant analysis of the EEG data revealed a projection of the Zembrin® data into the vicinity of the EEG data plot for a ginkgo-ginseng combination. Statistically significant improvement during performance of the arithmetic calculation test and number connection test was documented. The HAM-A anxiety score revealed a statistically significant decrease ( $p = 0.03$ ) after six weeks intake within the 50mg Zembrin® group. The results indicate that Zembrin® improves some aspects of cognitive function, and decreases anxiety in healthy older adults.

## PART IV

### KANNA AND MESEMBRINE-ALKALOIDS: POSSIBLE FUTURES

#### LEGAL HIGHS

Legal highs are typically sold by online Smart Shops and may be broadly defined psychoactive substances which have not (in some cases not yet) been proscribed by laws or regulations, and are used to elicit a desired state of mind which may be stimulated, euphoric, empathogenic or entactogenic, entheogenic, sedated or a combination. The substances may be isolated natural compounds, synthetic or semi-synthetic compounds, extracts of plants or fungi, or whole or minimally processed plant or fungal material. The first online sales of *Sceletium* plant material, originally from 40kg of plant material cultivated by Grassroots Natural Products for Pharmacare Ltd., began in 1999 by Om-Chi Herbs in Eugene, Oregon in the USA, and by Conscious Dreams in Amsterdam in the Netherlands, later to be followed by Botanic Art in the Netherlands. These online stores played a major role in introducing *kanna* to a wide international audience. It is now eighteen years later, and

there are many online Legal Highs and botanical supply stores selling fermented and unprocessed *kanna* as milled plant material and extracts. From about 2004, there seems to have been a marked increase in the use of *kanna* in the South African trance scene, where powdered *kanna* is used as a snuff, or mixed with marijuana for smoking to induce a “chilled” state of mind and to decrease anxiety in people who get more anxious while smoking marijuana. *Kanna* is used instead of MDMA by some people in the South African trance scene, and to reduce the come-down after an MDMA session by others. By 2017, *kanna* use had become part of the international trance and party scene, with use of *kanna* apparently being well known in Ibiza, Spain.

A recent development of serious concern is the online sale of concentrated to highly concentrated extracts sold as *kanna* which are of uncertain botanical origin, unknown total alkaloid content, unknown relative alkaloid composition and unknown stability. A search of *Sceletium* extracts on Alibaba.com shows a wide variety of “*Sceletium*” extracts, many produced in China (some accompanied by photographs of flowers that are definitely not *Sceletium* flowers). This includes some touted as “100:1” extracts (presumably a raw material to extract ratio, weight/weight) and some purporting to be “98% mesembrine” (Alibaba.com, 2017). There is already nascent legal and regulatory flagging of *kanna*, and overconcentrated extracts carry a potential for serious adverse events. The analysis of *Sceletium* alkaloids for future forensic toxicology and legislation purposes has already been described (Roscher et al., 2012), and the United Nations Office on Drugs and Crime (UNODC) issued a list of 20 plant-based substances of concern in 2013, including *Sceletium*. The metabolism of *Sceletium* alkaloids was investigated in rat urine and pooled human liver preparations (Meyer et al., 2015) because of the increasing popularity of *kanna* as a legal high, and the metabolites, especially in the urine, would be good analytical targets for forensic and legal purposes. *Sceletium* has already attracted the attention of the Drug Enforcement Agency (DEA) of the United States, featuring in a presentation by a forensic chemist at the DEA Special Testing and Research Laboratory with the title, “Novel Plant Hallucinogens and Plant-Derived Highs” (Dye, undated presentation). Surprisingly, Amazon.com has prohibited the sale of

*kanna* and cited it as an example of a plant-derived product that simulates the effect of illegal drugs (Amazon.com, 2017). An additional legal and regulatory threat is the potential for adverse reactions from adulterated *kanna*. During an investigation into the wide phytochemical variability of *kanna* available from online stores, the alarming discovery was made that one of the samples of *kanna* had been adulterated with the stimulant ephedrine (Lesiak et al., 2016).

Notwithstanding the forensic and regulatory flagging, the use of isolated pure mesembrine alkaloids may ultimately become more widely available to the general public via the rapidly growing vaping and electronic cigarettes industries, evidenced by two recent US Patent Applications for electronically heated aerosol systems filed by Philip Morris Products S.A., Neuchatel, Switzerland, with mesembrine given as one of the examples of active ingredients to be vaporized (Schneider J-C. et al., 2016; Thorens and Cochand, 2016).

## SUPPLEMENT

The first commercial supplement product containing *Sceletium* was put on the South African market in 2001 by a South African company I founded, Phyto Nova (Pty) Ltd. This product consisted simply of a low dose of 50mg tablets of milled cultivated *Sceletium tortuosum*, with the traditional uses stated as stress relief and mood elevation. The recommended dose was specified as one to two tablets daily. Tablets containing 25mg of the standardized *Sceletium* extract Zembrin® were first launched on the South African market in 2010. The recommended dose is 25-50mg taken once a day (containing 100-200 µg total mesembrine alkaloids). The tablets are used for stress, anxiety and mild to moderate depression. In South Africa, these tablets are popular during exam time, used by university students and matriculated school children for improving concentration and reducing stress while studying for exams. The South African National Defence Force has included tablets containing Zembrin® in its code of products that can be prescribed by military psychiatrists and physicians.

A highlight of the *Sceletium* project was the marketing authorization given to Zembrin® in 2014 by the Natural and Non-Prescription Health Products Directorate of Health Canada, issued

as Product Licence number 80052770 on 29 July 2014, for capsules containing 25mg extract, a daily dose of 100µg mesembrine alkaloids.

There are now many brands of tablets, capsules, tinctures and teas of functional food and dietary supplement products containing Sceletium plant material, Zembrin®, and other extracts on the market, mainly in the United States, with lesser sales in much smaller markets including Canada, South Africa, Malaysia and Japan. The cost of formally addressing the diverse national regulatory requirements has limited the international penetration of Sceletium supplements, and it is not clear if companies will be willing to invest in addressing these requirements in the face of increasing competition from what has essentially become a generic botanical dominated by internet sales of these products directly to consumers.

We are living in a fast-paced, highly stressed and uncertain world, challenged with electronic media competing for mindspace, and assaulted daily with news of dramatic geopolitical, economic, social, climatic and environmental changes. Simultaneously, we are on the threshold of the Fourth Industrial Revolution, which is fundamentally changing our lives, our work, our relationships and blurring the boundary between ourselves and our technologies. Low doses of mesembrine alkaloids, probably in the range of only 200µg-400µg and perhaps best in a sustained-release dosage form, have great potential to safely enhance the daily quality of people's lives. More than twenty years of work on this plant has shown me that we have not yet begun to realize the potential that supplements of Sceletium or Sceletium alkaloids hold for:

- reducing stress and situational anxiety
- enhancing well-being
- elevating mood in mild to moderate depression
- enhancing cognitive function
- reducing alcohol and drug abuse
- facilitating psychotherapy
- facilitating meditative and spiritual states

## MEDICINE

To date there have been no clinical trials on extracts of Sceletium

in a clinical population. Two recent clinical case reports are presented here, where extract *Sceletium tortuosum* Zembrin® was used by my wife Dr. Olga Gericke in her integrative psychiatric practice in Cape Town (Gericke et al., 2017).

#### CASE REPORT 1

A 40-year-old married housewife with two children, aged 6 and 9, was referred to Dr. Olga Gericke for medication review. Her history included recurrent major depressive disorder since age 17, postpartum depression and social anxiety disorder. For the previous eight years, she had been on citalopram 20mg per day, which had adequately treated her depression and social anxiety. However, the patient found the side effects difficult to tolerate: loss of libido, emotional blunting and weight gain. Two attempts to discontinue citalopram resulted in recurrence of her depressive symptoms within four months, necessitating resumption of the medication. During consultation, the patient stated she was determined to wean herself off citalopram. After being counseled on pharmaceutical and botanical treatment options, the patient opted for a trial of 25mg extract of *Sceletium tortuosum* (Zembrin®). Citalopram was reduced to 10mg daily for one week and then discontinued while starting 50mg of *Sceletium*, which was increased to a daily maintenance dose of 75mg. At one-month follow-up, she reported no anxiety/depressive symptoms, though she experienced occasional mild episodes of social anxiety, which she found easy to tolerate. Her libido had returned to normal, she felt much more in touch with her feelings and had lost two kilograms of weight. During the following month, her mood had slightly lowered, but this responded well to an increase of the *Sceletium* extract to 100mg per day. Eight months after initial assessment, she remained in remission on 100mg per day *Sceletium* extract Zembrin® with no side effects.

#### CASE REPORT 2

A 45-year-old married man, visiting South Africa from Europe, was referred to Dr. Olga Gericke by a general practitioner for assessment of depressive symptoms which



developed after the birth of the patient's child eighteen months previously. Two prior episodes of depression five years and seven years before were clearly associated with stressors and had resolved without treatment. He had seen a psychotherapist for two years in his country of origin. There was no history of medical illness and routine blood tests were normal. There was a family history of depression but no history of substance abuse. The patient had recently tried self-medicating with a combination product of *Sceletium tortuosum* and *Avena sativa*, but found it too sedating. Treatment was initiated with 50mg per day *Sceletium tortuosum* extract and increased to 100mg a day. In addition, the patient was seen for weekly supportive psychotherapy sessions. Within four weeks, his depressive symptoms remitted and he was discharged from the practice after six weeks when he was returned to his country of origin. He was advised to continue the 100mg *Sceletium tortuosum* extract daily and to seek psychiatric follow-up on his return home.

Standardized and characterized *Sceletium* extracts clearly have great potential as safe, effective botanical medicines for treating clinical anxiety and depression, and integrating extracts of *Sceletium* into psychiatric clinical practice has been described based on Olga's fifteen years of experience with *Sceletium* in her practice in Cape Town, and the clinical experience of Dr. Richard P. Brown, a psychopharmacologist and integrative psychiatrist in New York who has prescribed *Sceletium* in more than 30 patients during the past 4 years (Gericke et al., 2017).

While standardized *Sceletium* extracts have great potential to be used as botanical medicine to treat clinical anxiety and depressive states, it is not clear if this potential will ever be realized. The cost of developing the clinical evidence of safety and efficacy to achieve marketing authorization for a botanical medicine is prohibitive, the quality issues of polymolecular botanical medicines continue to be a major challenge, and the regulatory pathway to achieve registration as a botanical medicine is not as clear or as harmonized internationally as for single chemical entities. In the last two decades, the US Food and Drug Administration has only approved two botanical drugs; the first botanical drug approved by the FDA

was Veregen®, a treatment for genital and perianal warts that is derived from a green tea extract (*Camellia sinensis* Kuntze), and a number of years later the FDA approved Fulyzaq™, a drug for HIV-associated diarrhea, extracted from the latex of the South American tree (*Croton lechlerii* Müll. Arg) (Ahn, 2017).

Future approved medicines derived from *Sceletium* are more likely to be developed from isolated pure alkaloids, their metabolites, or from semi-synthetic derivatives. Pathways for the synthesis of mesembrine and related alkaloids have been described from the early 1960s. A review of the synthesis of mesembrine, for example, includes more than thirty described pathways, including isomer-selective synthesis (Zhao et al., 2010). While there is a fairly extensive literature on the chemistry and synthesis of these compounds, the pharmacology of isolated compounds has hardly been explored. The pharmacology of metabolites of these compounds presents a rich field for psychoactive new drug discovery.

Distillation of two decades of experience of indigenous uses, *in vitro* pharmacology, pre-clinical studies, anecdotal reports, clinical case studies and pilot randomized controlled clinical trials suggest that isolated *Sceletium* alkaloids (and their metabolites and analogues) have enormous potential for the development of rapidly acting psychoactive drugs with a low side-effect profile for:

- Major Depressive Disorder
- Generalised Anxiety Disorder
- Attention Deficit Disorder and Attention Deficit Hyperactivity Disorder
- Post-Traumatic Stress Disorder
- Mild Cognitive Impairment
- Neuroprotection
- Controlling appetite and craving in weight management programs
- Addiction management, including opioid addiction
- Chronic pain
- Schizophrenia

My hope is that this paper will stimulate further academic and pharmaceutical research to realize the potential of *Sceletium* extracts and mesembrine-type alkaloids for preventing, treating and

ameliorating diverse mental health diseases, and for enhancing the quality of life of all people.

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# Kratom (*Mitragyna Speciosa*) as a Potential Therapy for Opioid Dependence

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*Christopher R. McCurdy, PhD, BS Ph, FAAPS*

Department of Medicinal Chemistry, College of Pharmacy, University of Florida,  
Gainesville, Florida

Several psychoactive herbal products are widely available over the Internet with minimal control on their sale. Complicating this availability is the poor understanding of the chemical components and pharmacology of such products. Very little is known about specific chemical entities or combinations of chemicals present in these products. The availability of these products to adolescents and young adults has created a great concern for understanding the chemistry, psychopharmacology, and toxicology of these herbs. Use and abuse of these substances is difficult to measure, other than through anecdotal reports found on websites and through media reports. Particular interest has been generated around kratom (*Mitragyna speciosa* [Korth] Havil.), as it has been on the DEA (United States Drug Enforcement Agency) List of Drugs and Chemicals of Concern for over a decade (DEA, 2016). Kratom has been touted as a “legal high”, and the major alkaloid, mitragynine, has been thought to be responsible for its actions at opioid receptors (Babu et al., 2008). In addition, a minor alkaloid and oxidative product of mitragynine, 7-hydroxymitragynine, has also been reported to have potent agonist activity at opioid receptors (Babu et al., 2008). Although 7-hydroxymitragynine occurs in trace amounts in the natural plant, several marketed products are suspected to be adulterated with increased levels of this compound (Lydecker et al., 2016). According to the scientific literature, it is not clear if mitragynine has abuse liability, and has been reported to have mild analgesic properties most similar to codeine or non-steroidal anti-



inflammatory drugs (NSAIDs) (Macko et al, 1972). Conversely, 7-hydroxymitragynine (a minor plant constituent), when purified and pharmacologically tested alone, does show a conditioned place preference (drug-seeking behavior) in rodents, as well as potent analgesia (Matsumoto et al., 2008). To complicate matters, it is not entirely known if 7-hydroxymitragynine is produced by the plant, or is an oxidative byproduct of leaf drying, due to the low amounts in which it has been reported to occur in traditional fresh leaf extracts. Synthetic procedures have been published to convert mitragynine to 7-hydroxymitragynine (Takayama et al., 2002), but this involves specialty chemicals that are not commonly available to the public or clandestine laboratories. Nonetheless, from those commercially available products analyzed, it is clear that the levels of 7-hydroxymitragynine are in much greater concentrations than occur in nature (Lydecker et al, 2016).

Kratom has been linked to 16 deaths, although in each case the deceased individuals had multiple substances in their systems. It is important to note that not a single death has been attributed to kratom in Southeast Asia, where it has been traditionally used for over 100 years. In addition, the DEA had rightfully banned synthetic bath salts and synthetic cannabinoids (i.e., K2 or Spice) based on scientific evidence, removing them from the consumer marketplace and providing them a home in the list of Schedule I controlled substances. This void in the consumer market was filled with kratom products in gas stations, herbal shops, and the Internet. The DEA faced pressure from a small but vocal section of the public to ban kratom and place it in Schedule I. Even though very limited scientific information was available on kratom, in the fall of 2016 the DEA nevertheless announced their intention to place kratom, mitragynine, and 7-hydroxymitragynine into Schedule I of the Controlled Substances Act (DEA, 2016). This created a large push from those that have utilized kratom for control of pain and prescription opioid addiction to place pressure on the DEA as well. The result was unprecedented, with the DEA announcing a 30-day open comment period for the public. Over 23,000 written pleas were received by the DEA to reconsider this position (Federal register 2016). These communications came from the general public, legislators, and the scientific community involved in kratom

research. In addition, the Botanical Education Alliance published an 8-Factor analysis of kratom by Dr. Jack E. Henningfield that indicated kratom is *not* addictive (Pinney Associates, 2016). Moreover, it stated that the factors that appear important in maintaining kratom use appear more similar to those of normal caffeine intake. This report was submitted to the DEA & FDA in 2016. For the first time in history, the DEA withdrew their intention to place Kratom into Schedule I, though it still has the right to do so at any time (Federal Register, 2016). This manuscript aims to provide the current state of science around kratom.

Kratom is a tree native to Thailand, Malaysia, and other areas of Southeast Asia. The leaves of this tree have been utilized for many years by laborers for their stimulant effects (at low doses), and their ability to invigorate workers in harsh conditions (Jansen et al., 1988). Kratom has also seen much use as a replacement for opium due to its euphoric and sedative effects (at higher doses) (Jansen et al., 1988). Extracts and decoctions have also been noted as a method to alleviate opioid withdrawal. (Jansen et al., 1988; Boyer et al., 2007, 2008). Kratom was outlawed in Thailand through the Kratom Act in 1943; however, it remains a widely popular substance there (DEA, 2017; Jansen et al., 1988). It has been assumed that the ban in Thailand was due to the government's inability to generate tax revenue from the plant, although this is not documented. With the reports of its actions, and the fact that it is not controlled in much of the world, it was introduced to the Western world via the Internet and touted for its stimulant and opium-like effects. Indeed, according to an Internet supplier, sales are very good in the United States<sup>19</sup>.

<sup>19</sup> Salesperson at Naturalorganix.com. Personal communication 8/30/2017

Currently, kratom is not a controlled substance under federal law in the United States, and little information is known on its true pharmacological activities. However, six states have banned kratom as of July 2017: Alabama, Arkansas, Indiana, Tennessee, Vermont, and Wisconsin. It has also been made illegal in Sarasota County, Florida; San Diego, California; and Jerseyville, Illinois. In addition, it is illegal in many countries, including Australia, Burma, Denmark, Lithuania, Malaysia, Myanmar, Poland, Sweden, Thailand, and

Vietnam (Kratom Science, 2017).

Extracts of *Mitragyna speciosa* have been used in Thailand and Malaysia for many years for their opium-like effects and coca-like stimulant ability to combat fatigue (Jansen et al., 1988). It is interesting that the plant seems to have these apparently contradictory effects. Some early studies (Wray et al., 1907a; Wray et al., 1907b) indicated a similarity to cocaine in humans, but other studies (Jansen et al., 1988; Takayama 2004; Boyer et al., 2007) have shown opioid-like effects. In fact, kratom has long been promoted in these areas as a substitute for opium, and has also been used to wean addicts off morphine. Some recent clinical reports of kratom being utilized as a self-treatment for opioid withdrawal indicate the medical community is seeing patients who are using kratom (Jansen et al., 1988; Takayama 2004; Babu et al., 2008; DEA Public Affairs, 2016). The plant material and extracts are available on the Internet, making them easily obtainable by those who may want to experiment with such substances. Currently, as mentioned, there are no restrictions on this plant, extracts, or purified compounds in the majority of the United States.

Fortunately, there is some information in the literature about the chemistry and pharmacology of this plant. Some active alkaloids on opioid receptors have been identified from extracts of *Mitragyna speciosa* (Takayama et al., 2002) and are shown in Figure 1. These include: mitragynine (1), 7-hydroxymitragynine (2), and corynantheidine (3).

The studies that have been reported focus on the opioid-like effects of extracts and some of the pure chemicals that have been isolated. Many studies on these substances demonstrate effects that are reversible with naloxone, an opioid-receptor antagonist. It has been reported that extracts of *Mitragyna speciosa* can reduce pain in animal studies. Interestingly, little is known about the mechanism of the reported stimulant actions. A review of the literature demonstrates a wide variety of opioid activity and inconsistency in studies. These inconsistencies range from extraction procedures, binding affinity measurements, and antagonists utilized, as well as *in vivo* reports. These are all detailed below, and underscore the strong need to understand the actions of the extract and isolated natural products in a side-by-side

comparison in the same assays to more completely understand the chemistry and pharmacology of this species.

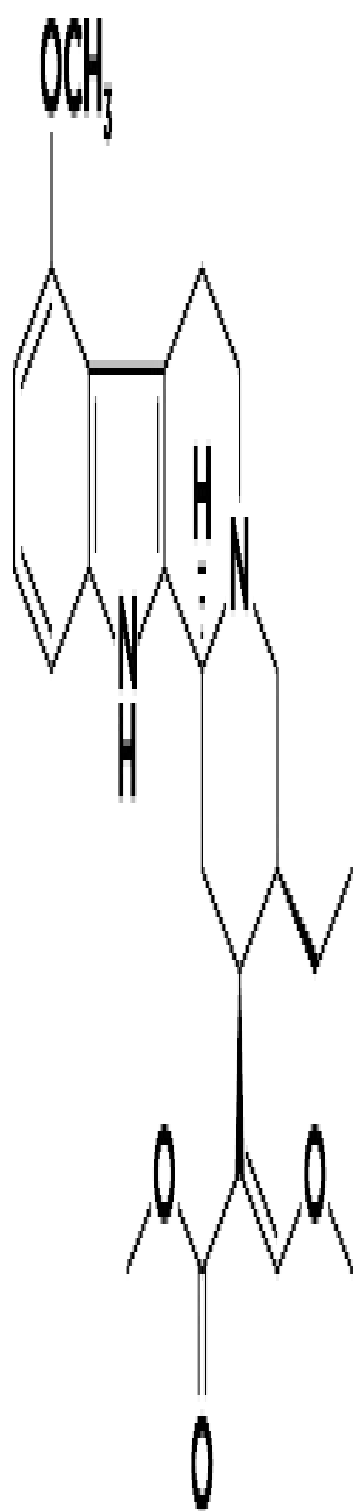
Isolation of some 40 alkaloids from this plant have focused on the most predominant alkaloid, mitragynine (1) (Adkins et al., 2011). Mitragynine, a corynantheidine alkaloid first isolated by Field in 1921 (Field 1921), has demonstrated opioid-receptor affinity and partial agonist activity. Interestingly, opioid-receptor affinities that have been reported in multiple studies are not consistent. In some cases, affinities for some opioid receptor subtypes have been reported by some and not found by others. This may be due to variations in the purity of compounds, receptor preparations, and radioligands utilized in these studies. However, it does lead to an ambiguity of the understanding of these naturally occurring chemical components. Of high interest are the most recent reports that demonstrate mitragynine as a partial agonist that has a G-protein signaling bias (Kruegel et al., 2016). This signaling bias has been hypothesized to result in fewer liabilities from mitragynine than other opioid ligands. Most notably, mitragynine and kratom do not cause significant respiratory depression in rodents, nor presumably in humans. This pharmacology may explain why there have not been any reports of overdose deaths from kratom alone, as unlike traditional morphine-based opioids, there seems to be little to no effect on respiration. If kratom has been listed as a cause of death, it is still suspect, as there are no controls on what products are sold. This lack of control and standardization makes the marketplace a “buyer beware” one. Moreover, it can be almost impossible to analyze a product for an adulterant that is not known. This has been evidenced by the rapidly changing landscape of compounds that are found in synthetic cannabinoid or bath salt preparations.

The first reports of pharmacological studies on mitragynine appeared in the literature in 1972 (Macko et al., 1972). Researchers at Smith, Kline and French (SKF) were interested in finding a novel analgesic that would have less liability than the currently utilized opioids (i.e. morphine). Their studies were the most comprehensive at the time and still remain as one of the more complete in the literature. A battery of animal studies were undertaken to investigate the analgesic potential and opioid actions of

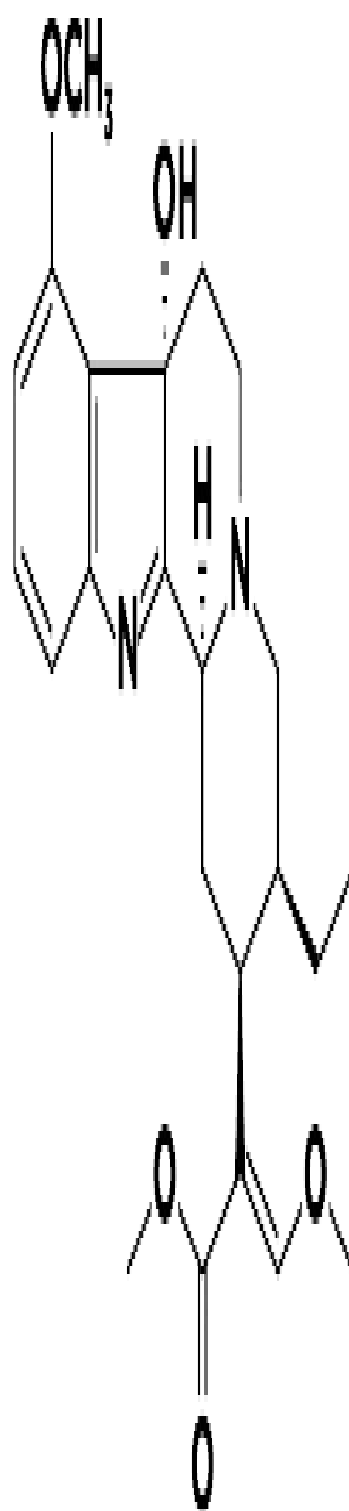
mitragynine. These studies did show that mitragynine had analgesic and antitussive properties comparable to codeine. Unlike codeine, mitragynine did not produce emesis or dyspnea, was not blocked by nalorphine, and had much less respiratory depression. Interestingly, it could suppress the opioid withdrawal syndrome. Moreover, it was noted that mitragynine was active only via the oral and intraperitoneal routes of administration (in an equal ratio), and was inactive via the subcutaneous route. It was hypothesized that the analgesic activity may be related to a metabolite, or that the bioavailability of mitragynine is influenced by the acidic conditions of the route of administration. It appeared that SKF decided to abandon further studies on this substance, most likely due to the weak analgesic potency when compared to traditional, marketed opioid pharmaceuticals.

Mitragynine seemed to be discounted for a number of years until the mid-1990s, when researchers in Japan began to study this compound and plant species again. By this time, it had been realized that nalorphine had mixed opioid agonist/antagonist actions, and may have confounded the results previously reported in the study carried out at SKF. The analgesic activity of mitragynine was again investigated in the tail-pinch and hot-plate tests, resulting in antinociceptive activity that was completely abolished by naloxone, a pure opioid receptor antagonist (Matsumoto et al., 1996a). This indicated the involvement of supraspinal opioid receptors in the analgesic actions of mitragynine and sparked a renewed interest in the pharmacology of this molecule.

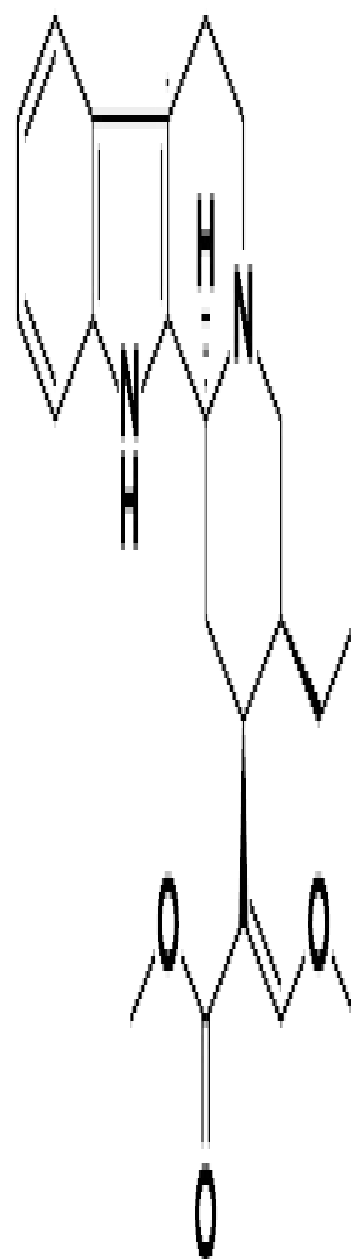
Shortly thereafter, the same group indicated the contribution of descending noradrenergic and serotonergic systems in the analgesic activities of mitragynine (Matsumoto et al., 1996b). This is similar to what is known with the actions of morphine. Utilizing the same paradigm in their previous study, the involvement of these systems was investigated by employing the  $\alpha_2$ -adrenoceptor antagonist idazoxan, and the 5-HT receptor antagonist cyproheptadine. Each of these agents significantly antagonized the analgesic effects of mitragynine. This work indicated that mitragynine may stimulate the release of endogenous norepinephrine and serotonin, similar to the actions of other opioid ligands.



MITRAGYNINE (1)



7-HYDROMITRAGYNINE (2)



CORYNANTHEDINE (2)

**Fig. 1** The opioid-active alkaloids isolated from *Mitragyna speciosa*.

Another study to elucidate the mechanism of action of mitragynine involved the 5-methoxy-N, N-dimethyltryptamine-induced head-twitch response in mice (Matsumoto et al., 1997). This study, again from the same researchers in Japan, seemed to echo the findings of the involvement of noradrenergic and serotonergic mechanisms in the actions of mitragynine. Indeed, mitragynine suppressed the effects of head-twitch in this assay, indicating possible agonist actions on adrenergic and antagonist actions on serotonergic systems.

The inhibition of electrically stimulated contraction in the guinea-pig ileum was also demonstrated to work through opioid mechanisms, as it was reversed by naloxone (Watanabe et al., 1997). This study did not employ any subtype-selective antagonists to indicate the possible opioid-receptor subtypes involved. Some understanding of the subtypes involved was revealed through a study of antinociception in mice, conducted by the same researchers. Their results indicated the involvement of MOP and DOP (Mu and Delta Opioid) receptors through the use of subtype-selective antagonists. They concluded that mitragynine has different selectivity than morphine for opioid-receptor subtypes, yet no receptor binding data was presented. It was much later that the same group published findings on the inhibitory effects of mitragynine on neurogenic contraction of the guinea-pig vas deferens (Matsumoto et al. 2005). The vas deferens is known to contain high amounts of DOP and MOP receptors. In this study, the effects of mitragynine were unable to be blocked by naloxone, leading to the conclusion that opioid receptors are not involved. The conclusion of these studies indicated that the inhibitory effects of mitragynine in this paradigm were through the blockade of calcium channels. This study was confounded by the fact that morphine could not inhibit electrically induced contraction in this assay, leading a reader to question the validity of the findings.

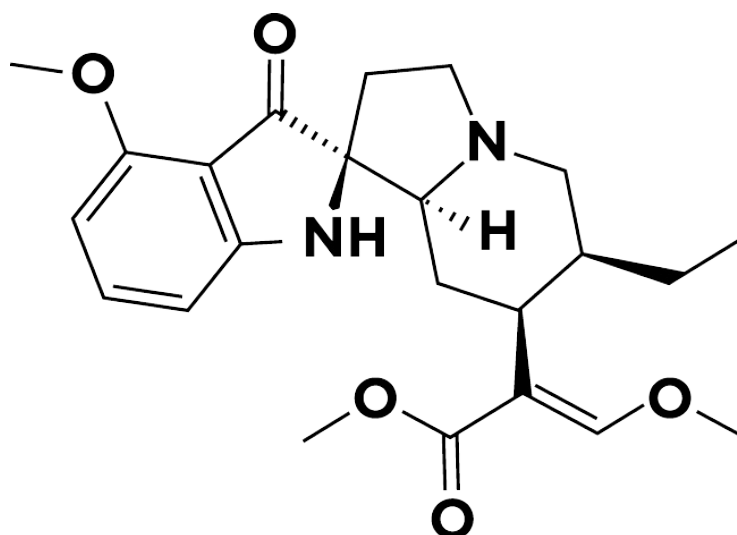


**Fig. 2** Structure of the microbial metabolite, mitragynine pseudoindoxyl.

The first receptor-binding data for mitragynine was presented in 2002 (Takayama et al., 2002). The binding affinities for mitragynine at the three opioid receptors were determined using guinea pig brain membranes and reported as pKi values. The data indicated that mitragynine is a MOP-selective opioid ligand with a pKi value of  $8.14 \pm 0.28$ , and a relative affinity of 88.7% for the MOP over the DOP and KOP receptors. The pKi values at the DOP and KOP were  $7.22 \pm 0.21$  and  $5.96 \pm 0.22$ , respectively. This report did not include functional data at each of the receptors, so it is difficult to relate it to the previously reported receptor selectivity studies that were conducted in mice. As previously mentioned, the *in vivo* study implicated the roles of the MOP and DOP in the actions of mitragynine. Taken together, these data are a bit inconsistent but still reasonable, since functional activities were not presented in the more recent report. The receptor-binding affinities described in this study also included other naturally occurring alkaloids from *Mitragyna speciosa*, and some semi-synthetic derivatives. Most of the natural products and semi-synthetic analogs had much less affinity than mitragynine. Although most of these compounds had less opioid receptor affinity, 7-hydroxymitragynine was 10 times more potent than morphine, and 40 times more potent than mitragynine in the guinea pig ileum assay. Surprisingly, this compound was not investigated in analgesic studies with mice so it was not determined if the activity was due to opioid receptors. The most interesting finding from this work was the inclusion of a previously reported microbial oxidative



metabolite of mitragynine, mitragynine pseudoindoxyl (Zarembko et al., 1974; Takayama et al., 2002) (4, Figure 2).

This compound had a higher affinity for mu-opioid receptors (pK<sub>i</sub> value 10.06 ± 0.39) and a similar relative affinity to morphine among the other opioid receptors (Takayama et al., 2002). Moreover, mitragynine pseudoindoxyl was 35 times more potent than morphine in the electrically stimulated guinea pig ileum assay. However, when mitragynine pseudoindoxyl was tested *in vivo*, the analgesic activity was less than that of morphine, but greater than mitragynine itself. The effects of mitragynine pseudoindoxyl were completely reversed by naloxone. Studies on this molecule have not appeared in the literature since this report. It may be due to the source of this molecule, as it is a metabolite of *Helminthosporium* sp. and therefore may be difficult to obtain.

This study (Takayama et al., 2002) also provided some insight into the structure-activity relationships of mitragynine, and in two reviews (Takayama 2004; Kruegel et al., 2016) on the chemistry and pharmacology of *Mitragyna speciosa* has included more information on semi-synthetic studies of mitragynine. This structure-activity-relationship information is summarized in Figure 3 (Adkins et al., 2011).

Essentially, all the semi-synthetic derivatives had less activity than mitragynine, indicating some important structural features on the natural product. First, the 9-methoxy seems to be important for agonist activity. When the methyl ether is cleaved to the phenol, a less active agonist is produced. When the oxygen is eliminated to produce the natural product corynantheidine (3), an antagonist is produced. Thus, it is interesting that modulation of functional activity may occur at this position. It is of chemical interest that this small change to the molecule may afford templates for novel opioid antagonists, potentially with superior bioavailability to currently marketed products. Next, it also appears that disruption of the b-acrylate moiety, albeit from a very limited study, leads to less active or inactive products. Finally, loss of the basic character of the tertiary amine abolishes activity. This seems to be consistent with other opioid-based alkaloids that require a protonatable nitrogen to form a salt bridge with a conserved aspartic acid residue in transmembrane III (TM III) of the opioid receptors.

Introduction of  $\alpha$ -OH increases activity

Acylation of OH decreases activity

N-oxide abolishes activity

Longer alkyl ethers abolish opioid activity

Removal of CH<sub>3</sub> decreases activity

Removal of OH creates antagonism

Acetylation decreases activity

inversion of stereochemistry  
abolishes opioid activity

ester hydrolysis or  
reduction to alcohol  
reduces activity

O replacement with  
NH abolishes activity

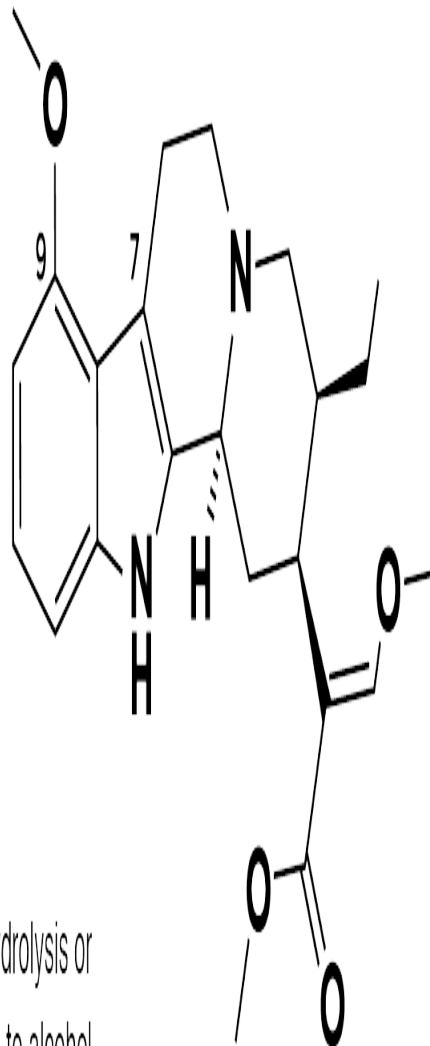


**Fig. 3** Known structure-activity relationships of mitragynine.

This result may indicate that mitragynine is binding in a similar mode to other known opioid ligands. However, reported comparisons of mitragynine and morphine (Takayama et al., 2002) do not indicate structural similarities, and hypothesize that mitragynine has a different binding mode than classical morphine-based ligands. It could be that some amino acid residues in the receptor are common to the affinity of both classes but some unique epitopes are involved with mitragynine recognition.

Although these studies have indicated some important structural features on mitragynine, detailed studies to elucidate the opioid pharmacophore are lacking. A few other alkaloids that have been isolated from the plant do not appear to have interesting profiles as opioid ligands, but only a few of the over 20 alkaloids have been subjected to receptor-binding studies. The C3 (quinolizidine bridge-head hydrogen) stereoisomer of mitragynine was reported to be 14-fold less active in the guinea pig ileum assay, yet no binding data was reported at opioid receptors (Takayama et al., 2002). Therefore, not all the alkaloids have been investigated nor have other non-alkaloidal ligands been characterized, and it is not entirely clear how important any of the stereochemistry is to the molecule. Moreover, no simplified analogs of mitragynine have been reported in the literature. Thus, there is a great need for a more complete understanding of the chemistry associated with *Mitragyna speciosa*.

From the reports in the literature on the naturally occurring alkaloids from *Mitragyna speciosa*, only a few of the alkaloids have been investigated for activity and some have been reported in separate studies, making them difficult to compare. More recently, the focus of literature studies has shifted to a minor component of the extract, 7-hydroxymitragynine (Ponglux et al., 1994; Matsumoto et al., 2004; Matsumoto et al., 2005). This is simply an oxidized form of mitragynine obtained from *Mitragyna speciosa*. The first report (Matsumoto et al., 2004) of the *in vivo* actions of 7-hydroxymitragynine also included receptor-binding data that was obtained under the same conditions as reported for the affinities of mitragynine and 7-hydroxymitragynine. Interestingly, 7-hydroxymitragynine displayed a higher affinity to

MOP than previously reported. Affinities for DOP and KOP were consistent with the previous report from the same group (Takayama et al., 2002). In this study, the tail-flick and hot-plate assays were utilized, and 7-hydroxymitragynine showed more potent effects than morphine in both tests. This is interesting since the affinity of 7-hydroxymitragynine is comparable to mitragynine and morphine. An interesting finding from this study was that 7-hydroxymitragynine was orally active and long-acting. It is now hypothesized that most of the opioid actions are a result of this compound and not mitragynine. However, the possibility of an active metabolite cannot be ruled out.

The tolerance and withdrawal symptoms of 7-hydroxymitragynine have also been studied (Matsumoto et al., 2005). In this report, the specific opioid-receptor subtypes responsible for its actions were also investigated. Tolerance developed to 7-hydroxymitragynine over time, as well as cross-tolerance to morphine. Similar to morphine, withdrawal symptoms were equally comparable upon naloxone-induced withdrawal of 7-hydroxymitragynine. It was determined that the analgesic activity of 7-hydroxymitragynine was mediated through MOP and partially through KOP. Attempts to overlay the compound with morphine were not successful, and it was concluded that 7-hydroxymitragynine may be interacting with opioid receptors in a different fashion than morphine. Overall, 7-hydroxymitragynine was shown to be a potent opioid receptor ligand that can potentially cause physical dependence.

An additional study on the effects of 7-hydroxymitragynine on gastrointestinal transit has demonstrated the involvement of MOP receptors in this action (Matsumoto et al., 2006). Interestingly, this study also investigated the receptor subtypes involved in the analgesic activity. This work came from the same group as the previous studies, and was consistent in demonstrating a MOP-selective activity. However, this time the KOP receptor was not shown to be involved. It had been previously reported by other researchers that mitragynine did not inhibit gastrointestinal transit, (Macko et al., 1972) but this study had noted limitations.

Because *Mitragyna speciosa* has been traditionally utilized to combat fatigue and promote the ability to work in harsh conditions, a study was undertaken to determine its effects on working memory

(Apriyani et al., 2010). This investigation involved the object-location task and the open-field test. In these paradigms, mitragynine was found to impair the cognitive function and decrease locomotion. The authors suggested this finding is similar to other mu-opioid agonists, and they further hypothesized that the memory impairment could be due to decreases in GABA neurotransmission. More studies would need to be carried out in more sophisticated paradigms to learn the effects of chronic use on working memory.

Many users of kratom, both traditional and recreational, have stated that ingestion of the plant material elevates mood and may have potential as an antidepressant. To test this idea, a study was carried out utilizing mitragynine in the mouse forced-swim test and the tail-suspension test (Idayu et al., 2011). It was determined that doses of mitragynine significantly reduced immobility in the forced-swim test and tail-suspension test, demonstrating antidepressant-like effects. Moreover, mitragynine significantly reduced corticosterone release, which is normally elevated in stressful situations. This study showed promising potential for the use of kratom as an antidepressant, and somewhat validated the anecdotal reports of human mood elevation.

Another study was published a few years later looking into the anxiolytic-like effects of mitragynine in the open-field and elevated plus-maze paradigms (Hazim et al., 2014). These studies were done in rats, in contrast to the above study that utilized mice. This work compared the efficacy of mitragynine versus a diazepam control. The findings support the human use of kratom as an anxiolytic, where mitragynine was shown to be effective, although less than diazepam, increasing exploration in both assays. Moreover, the investigators studied three neurological systems with antagonists pre-treatment. All antagonists tested were effective in blocking mitragynine's action. This indicated that the anxiolytic-like effects are possibly due to interactions among opioidergic, GABAergic, and dopaminergic systems in the brain. It was a bit curious that serotonergic systems were not investigated in this study.

Kratom has traditionally been utilized to wean addicts off opium, and two studies have appeared in the literature investigating mitragynine and its ability to attenuate morphine withdrawal

syndrome. The first study appeared utilizing zebrafish (Khor et al., 2011). Although not a commonly utilized model in opioid research, this proved to be an interesting study. Morphine was added to the water for a two-week, chronic-exposure paradigm. Mitragynine was shown to attenuate the majority of withdrawal behaviors, and real-time PCR analyses showed that it also reduced the mRNA expression of corticotropin-releasing factor receptors and prodynorphin in the zebrafish. A few years later, a study by researchers in Thailand showed an alkaloid-rich extract from *Mitragyna speciosa* was effective in attenuating naloxone-precipitated morphine withdrawal symptoms in mice (Cheaha; et al., 2017). Interestingly, their study was in direct contrast to the zebrafish study with regard to the effects of purified mitragynine. The study in mice failed to demonstrate efficacy for mitragynine alone in single-dose oral-administration studies. This is most likely due to the design of the study. To habituate the mice to morphine, doses were administered three times (50, 50, 75 mg/kg, respectively) a day for three days, and on the fourth day, mice were given a 50 mg/kg injection of morphine two hours prior to naloxone precipitation of withdrawal. In the studies that looked at ability for the alkaloid-rich extract or purified mitragynine, the mice were given only one dose of extract or mitragynine one hour after a dose of morphine and one hour prior to injection with naloxone. The only behavioral outcome that was considered for withdrawal symptoms was jumping behavior. Although various doses were examined, it is possible that a single dose of either test material would not be enough to attenuate the withdrawal effects. The authors concluded that another constituent of the alkaloid-rich extract may be responsible for the attenuation of effects seen, not mitragynine.

A group of researchers in Malaysia studied morphine-tolerance development in mice with a combination of mitragynine and morphine (Fakurazi et al., 2013). This study looked at a nine-day dosing regimen with both compounds, and evaluated the analgesic effects in the hot-plate test. Not surprisingly, the combination of morphine and mitragynine increased hot-plate latency. However, the combination of these two compounds did produce a significant reduction in morphine tolerance over morphine alone. The investigators looked at CREB-protein expression as well as liver and

kidney function tests, but did not see any significant changes in the combination-treated groups. Decreasing opioid-tolerance development is hypothesized to be one way of reducing the abuse or addiction potential of these agents, and certainly a way to avoid some of the side effects that can arise from increasing dosing regimens.

Another way to examine the abuse or addictive potential of opioids is through the conditioned place preference (CPP) paradigm. Two reports have appeared in the literature that are in overall agreement demonstrating that mitragynine causes a place preference, and that indicate a drug-seeking behavior is associated with mitragynine. It is interesting that the first study failed to demonstrate a statistically significant place preference for an extract of *Mitragyna speciosa*, but did show each dose of purified mitragynine to cause a place preference (Sufka et al., 2014). It is important to note that the error bars were quite large in these studies. The second study looked at CPP in a bit more detail, and looked directly at opioid-receptor involvement by the use of antagonists (Yusoff et al., 2017). This study was aimed at investigating whether the reinforcing effects of mitragynine were mediated by opioid receptors. This study demonstrated that naloxone was effective at blocking mitragynine CPP overall. Interestingly, the investigators also showed that the acquisition, but not the expression, of mitragynine place preference is mediated through opioid receptors. These findings add more support to the mu-opioid agonist activity of mitragynine.

Finally, an investigation was carried out to determine the discriminative stimulus properties of mitragynine in rats (Harun et al., 2015). Drug discrimination is a valid paradigm to compare substances, especially psychoactive ones. This work utilized rats that were trained to discriminate morphine from vehicle. Interestingly, the investigators also wanted to examine the stimulant properties (thought to be a result of mitragynine) by using a group trained with cocaine. Rats were able to discriminate between mitragynine and saline, similar to another group that was able to discriminate between morphine and saline. The dose required for mitragynine was 3-fold higher than that of morphine. Both mitragynine and 7-hydroxymitragynine individually substituted completely to morphine discriminative stimulus. This

suggests that there is pharmacological similarity between the two compounds. Interestingly, mitragynine also partially generalized to cocaine discriminative stimulus. Thus, both the opioid- and stimulant-like effects of *Mitragyna speciosa* can potentially be due to the major alkaloid, mitragynine.

All of the studies that have been conducted have shown that mitragynine and 7-hydroxymitragynine are opioid-receptor agonists. However, there are inconsistencies (as pointed out above) in these studies, making the interpretation of the entire body of pharmacological literature difficult to fully understand the pharmacology and chemistry associated with these compounds. Mitragynine and 7-hydroxymitragynine have been shown to work through opioid mechanisms *in vivo* and *in vitro* (Babu et al., 2008; Akins et al., 2011). They have also been shown to have activity in the serotonin and adrenergic systems (Matsumoto et al., 1996). This is not surprising upon review of the structure, which contains the tryptamine nucleus. One study that is completely lacking in the literature is the ability of mitragynine or 7-hydroxymitragynine, or extracts of *Mitragyna speciosa*, to be self-administered. Such a study would provide the most solid evidence for the abuse/addiction liability associated with the individual alkaloids or extracts. The fact that mitragynine alone interacts with multiple targets in the CNS, not to mention the full extracts' multiple activities, certainly helps to explain why the pharmacology is complex. However, it may be that this complex pharmacology has provided a natural antidote to opioid addiction. This remains to be seen, at least from a scientifically sound study and carefully controlled human clinical trial. There remains a great deal of scientific work that needs to be carried out on this plant species and its constituents to determine the chemical and pharmacological reasons that it is used traditionally and recreationally, to anticipate potential toxicities and potential therapeutic components. There seems to be great therapeutic promise to kratom.

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# The Ibogaine Project: Urban Ethnomedicine for Opioid Use Disorder

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Kenneth Alper, MD

*Associate Professor of Psychiatry and Neurology at the New York University School of Medicine*

## HISTORY

Ibogaine is a monoterpene indole alkaloid that occurs in the root bark of *Tabernanthe iboga* Baill. As a small molecule with apparent clinical effects in the alleviation of opioid withdrawal and diminution of drug self-administration, and an unknown and apparently novel mechanism of action, ibogaine offers an interesting prototype for drug discovery and neurobiological investigation.

In Gabon and elsewhere in West Central Africa, ibogaine is ingested in the form of *eboga*, scrapings of *Tabernanthe iboga* root bark as a psychoactive sacrament in the Bwiti religion for several centuries, and likely among Pygmies in much earlier times (Fernandez, 1982). The ritual aim of eating eboga has been conceptualized as “binding” across time through “the work of the ancestors”, and across space, socially on the basis of a common experience of a distinctive consciousness (Fernandez and Fernandez, 2001). In the colonial era, Bwiti offered a dignified realm of spiritual endeavor that supported psychological resistance to the anomie and dislocation imposed by the colonial presence, and became constellated with Gabonese national identity.

Outside of Africa ibogaine has been used most frequently for the treatment of substance use disorders, specifically for detoxification from opioids. Ibogaine has a storied past and an association with controversy, and the medical and nonmedical settings that have been collectively designated as a “vast uncontrolled experiment” (Vastag, 2005), or “medical subculture” (Alper et al., 2008).

Ibogaine has been classified as a hallucinogen and illegal in the US since 1967, and is similarly scheduled in 9 of the 28 countries presently in the European Union. As of this writing ibogaine is unregulated, i.e., neither officially approved nor illegal in much of the rest of the world. New Zealand, Canada, Brazil and South Africa have classified ibogaine as a pharmaceutical substance and restrict its use to licensed medical practitioners<sup>20</sup>. A systematic survey and description of the known settings of ibogaine use as of 2006 indicated that approximately 3,400 individuals had taken ibogaine, 68% of whom did so for the treatment of a substance-related disorder, 53% specifically for opioid detoxification (Alper et al., 2008). Now, a decade later the total number treated has likely increased several-fold.

**20.** Note added in proof by Dennis McKenna, ed.: Canada can be added to this list due to a recent classification of ibogaine as a prescription medicine by Health Canada. <http://www.hc-sc.gc.ca/dhp-mps/prodpharma/pdl-ord/pdl-ldo-noa-ad-2017-05-16-eng.php> (accessed 09/09/2017).

The ethnopharmacological paradigm of drug discovery begins with observational evidence of a clinical effect in an indigenous context of use, followed by subsequent Identification and isolation of the active agent, or possible synthesis of derivatives as candidates for development. With regard to ibogaine in the treatment of addiction, the indigenous context of this urban ethnomedicine is distinct from the use of *T. iboga* as a religious sacrament in Africa. The majority of participants in the ibogaine medical subculture are dependent on opioids. The sacramental alkaloid is used in the hydrochloride form, the ritual aim is opioid detoxification, and ritual space is a clinic outside the US, or an apartment or hotel room.

In June 1962 in Brooklyn (the exact date is not recalled), Howard Lotsof, 19-year-old heroin-dependent lay drug experimenter in an era which hallucinogens had not yet been regulated, serendipitously experienced the resolution of withdrawal following the use of ibogaine (Alper et al., 2001; Lotsof, 1985). Lotsof, an engaging and intrepid provocateur of scientific curiosity, credentialed only with an NYU film degree was eventually able to convince NIDA to support a project of research on ibogaine, with a total of approximately 2 million USD in direct cost support. During its existence from 1991-1996, the NIDA ibogaine project supported

preclinical contract work, including toxicology and pharmacokinetics that enabled a privately funded phase 1 study of single dosages of ibogaine for cocaine dependence that was approved by the FDA in 1993. This study ended in contractual and intellectual property disputes (Mash, 1997) and dosages of 1 and 2mg/kg were without reported adverse events (Mash, Kovera, et al., 1998). Data from that study regarding a possible effect of ibogaine on drug use is apparently unavailable. NIDA eventually terminated its ibogaine research program in 1996, and no subsequent clinical research with ibogaine has been conducted in the US.

Beginning in 2012, the National Institute on Drug Abuse (NIDA) has committed a total of over 6 million USD to support preclinical testing and chemical manufacturing and control work intended to enable clinical trials for the development of 18-methoxycoronaridine (18-MC), an apparently safer structural analog discovered by rational design (National Institutes of Health, 2012). 18-MC differs from ibogaine at three of the 21 positions on the ibogamine skeleton that defines the iboga alkaloid class (Figure 1) (Le Men and Taylor, 1965). NIDA has supported preclinical toxicology, pharmacokinetics and chemical manufacturing and control work, which now enables a phase I/II study, the next developmental step that awaits at the present time.

## IBOGAINE TREATMENT

### DOSING AND MONITORING

Ibogaine is used most frequently for detoxification from opioids, typically administered in the HCl form in a range of approximately 94% to 98% purity according to certificates of analyses. Crude extracts of *T. iboga* root bark vary with regard to estimated total alkaloid content, which is typically between 15% and 50%, about 25% to 50% of which might be expected to be ibogaine (Alper et al., 2008; Alper et al., 2012). Other iboga alkaloids co-occurring with ibogaine in *T. iboga* root bark include ibogamine, ibogaline, tabernanthine and voacangine (Bartlett et al., 1958), and are present to a variable extent in extracts (see Figure 1).

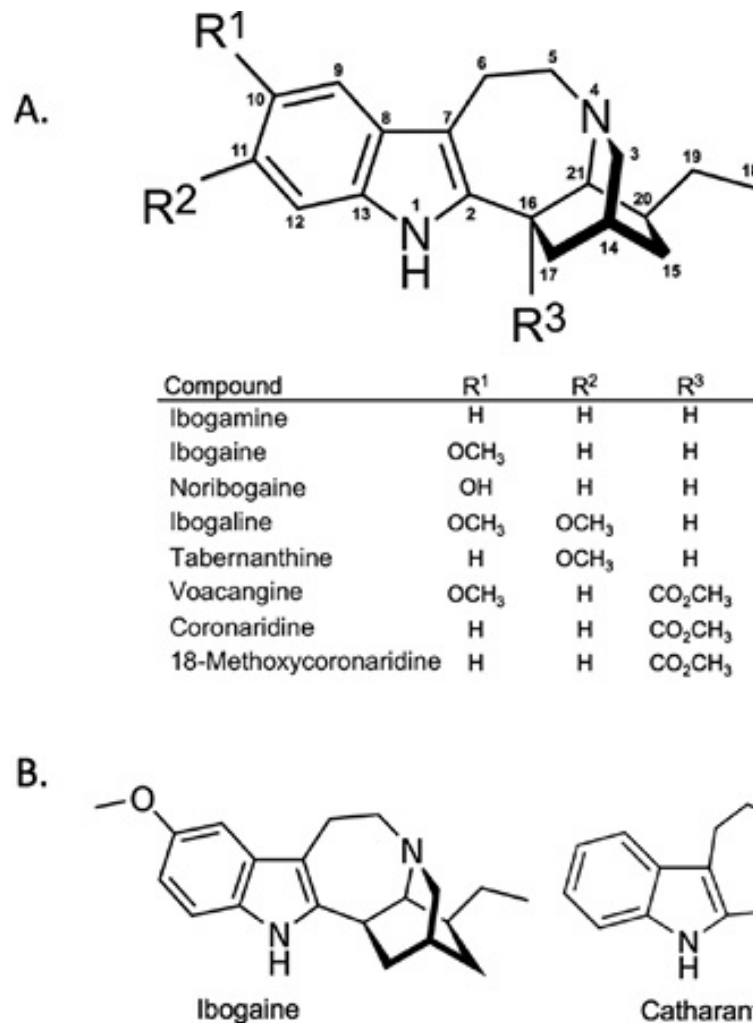


**Fig. 1** A. Ibogaine and other iboga alkaloids and structural analogues numbered using the Le Men and Taylor System (Le Men and Taylor, 1965). Ibogamine is the parent iboga alkaloid structural skeleton. Ibogamine, ibogaline, tabernanthine, voacangine co-occur with ibogaine in *T. iboga*. Noribogaine is ibogaine's major metabolite. Coronaridine also occurs naturally. 18-Methoxycoronaridine (18-MC) is a synthetic congener.

B. Ibogaine and catharanthine, another iboga alkaloid of pharmacological importance belonging to an opposite optical series.

As described in a recent observational study (Brown and Alper, 2017), the “test-flood-booster” opioid detoxification protocol presently in common use begins with a “test” dose of ibogaine on the order of approximately 3 mg/kg, typically administered in the morning after subjects had abstained from opioid use overnight, and begin to exhibit some initial signs of withdrawal. The providers appear to view the response to the test dose, which typically has some effect of reducing withdrawal signs as providing some indication of the degree of physical dependence on opioids. A “flood” ibogaine dose, typically four times the test dose, is given 2 to

12 hours following the test dose. Additional “booster” dosages of ibogaine of 3 to 5 mg/kg may follow the flood dose at intervals in a range from 1 to 16 hours, with the intention of either to alleviate residual or re-emergent withdrawal symptoms, or to increase the intensity of the psychoactive experience.

The total dosages of ibogaine administered in recent observational studies (Brown and Alper, 2017; Noller et al., 2017) are very similar to those used in prior treatments in the US in the 1960s and the Netherlands in the late 1980s (Alper et al., 1999), even though subjects in the present era use larger amounts of heroin that is of substantially greater purity (Drug Enforcement Administration, 2016). In the earlier era, nearly all of the total ibogaine dosage was administered at once. The test-flood-booster approach appears to be an adaptation intended towards maximizing dose efficiency in the face of severe levels of physiological dependence, and suggests that contemporary treatment providers perceive a dose ceiling, possibly due to a greater awareness of medical risk (Alper, Stajic, et al., 2012; Dickinson et al., 2016).

A set of clinical guidelines for detoxification from opioids with ibogaine has been developed by, the Global Ibogaine Therapy alliance (GITA), a group of physician and lay ibogaine treatment providers (Dickinson et al., 2016). Briefly, the guidelines recommend pre-treatment evaluation that includes a medical history, EKG, and electrolyte and liver function tests. Intravenous access, continuous pulse oximetry and three-lead EKG, monitoring of blood pressure are recommended throughout the treatment, with a medical professional (MD, nurse, or paramedic) certified in Advanced Cardiac Life Support (ACLS) present for at least the first 24 hours of the treatment. While the guidelines are unfortunately not followed across all of the varied settings in which ibogaine treatment is available, the emergence of an organized attempt by providers themselves to develop standards for ibogaine treatment is notable. A recent GITA conference in 2016 featured a training course in ACLS certification led by credentialed instructors.

## CLINICAL EVIDENCE OF EFFICACY

Ibogaine has been administered most often for opioid detoxification (Alper et al., 2008). A substantive effect ibogaine



treatment effect is reported in two early case series. In a series of 33 opioid detoxification treatment episodes in nonmedical settings with single mean dosages of 19.3 mg/kg, full resolution of opioid withdrawal signs and symptoms without drug seeking behavior over a 72-hour posttreatment interval was observed in 25 of 33 patients. Another study of 32 patients treated in a medical setting for the indication of opioid detoxification with fixed dosages of 800 mg reported the resolution of withdrawal of opioid withdrawal signs as indicated by physician-rated structured instruments at 24 hours, with sustained reductions in subjective ratings of withdrawal symptoms during the week following treatment as (Mash et al., 2001).

In two unpublished case series ibogaine appeared effective in opioid detoxification, and about one-third of subjects reported abstinence from opioids for periods of 6 months or longer following treatment. In a series of 52 outcomes assessed by interview following single dosages of ibogaine that became a basis for NIDA's decision to undertake its ibogaine project from 1991 to 1995, individuals reported cessation of use of the substances for which ibogaine treatment had been sought for 2 to 6 months in 30 cases (57%), and over 6 months in 17 cases (32%) (Alper, 2001). The other series, summarized in an academic thesis, is 21 subjects who responded to a Web-based questionnaire adapted from the European Addiction Severity Index at a mean interval of 21.8 months following treatment with ibogaine (Bastiaans, 2004). Of the 17 to 21 patients (81%) who identified opioids as the primary substance for which they had sought treatment, 5 reported abstinence from all substances, and another 9 reported abstinence from their primary substance of dependence while continuing to use alcohol or cannabis after treatment with ibogaine.

A recent prospective observational study reported on one-year follow up of 30 individuals treated with ibogaine for opioid detoxification with mean amount total of  $1540 \pm 920$  mg ibogaine HCl administered according to a test-flood-booster dosing scheme (Brown and Alper, 2017). The subjects in this study were heavy opioid users with histories of failure with conventional treatment. The subjects used mainly oxycodone ( $n=21$ ; 70%) and/or heroin ( $n=18$ ; 60%) in respective amounts of  $250 \pm 180$  mg/day and  $1.3 \pm$

0.94 g/day with a mean of  $3.1 \pm 2.6$  prior previous episodes of treatment for opioid dependence. The Subjective Opioid Withdrawal Scale (SOWS) (Handelsman et al., 1987) was used to assess detoxification outcome, and Addiction Severity Index Composite (ASIC) scores (McGahan et al., 1986) were used to assess posttreatment effects at 1, 3, 6, 9, and 12 months.

Assessed just prior to the test ibogaine dose, the pretreatment baseline SOWS score decreased a mean of 17 points from 31.0 to 14.0 at  $76.5 \pm 30$  hours following the initiation of treatment. This clinical effect of ibogaine on acute withdrawal symptoms appeared consistent with prior to be of a comparable order of magnitude to that of methadone reported in the original study that described the development and validation of the SOWS (Handelsman et al., 1987). In that study, subjects were administered the SOWS following two days of methadone stabilization, SOWS decreased by a mean of 18.7 points (from 24.3 to 5.6) in subjects who used opioid exclusively, and 8.7 points (from 23.1 to 14.4) in subjects who additionally abused other, non-opioid substances.

The numbers of subjects who reported no opioid use during the previous 30 days at respective posttreatment time intervals of 1 and 3 months were 15 (50%) and 10 (33%). This appears to be a substantive treatment effect in comparison to those reported in the published literature. For example, recent systematic reviews of studies of opioid detoxification without subsequent maintenance treatment found rates of abstaining from illicit opioid use of 18% at 4 weeks following detoxification with buprenorphine (Bentzley et al., 2015), and 26% at 6 weeks following detoxification with methadone (Amato et al., 2013). Figure 2 plots individual trajectories of the ASIC Drug Use score from pretreatment baseline to 1, 3, 6, 9, and 12 months. The figure indicates an apparently sustained posttreatment effect on opioid use in a subset of subjects. evident as trajectories characterized by large decreases from baseline to 1 month that are sustained at subsequent time points.

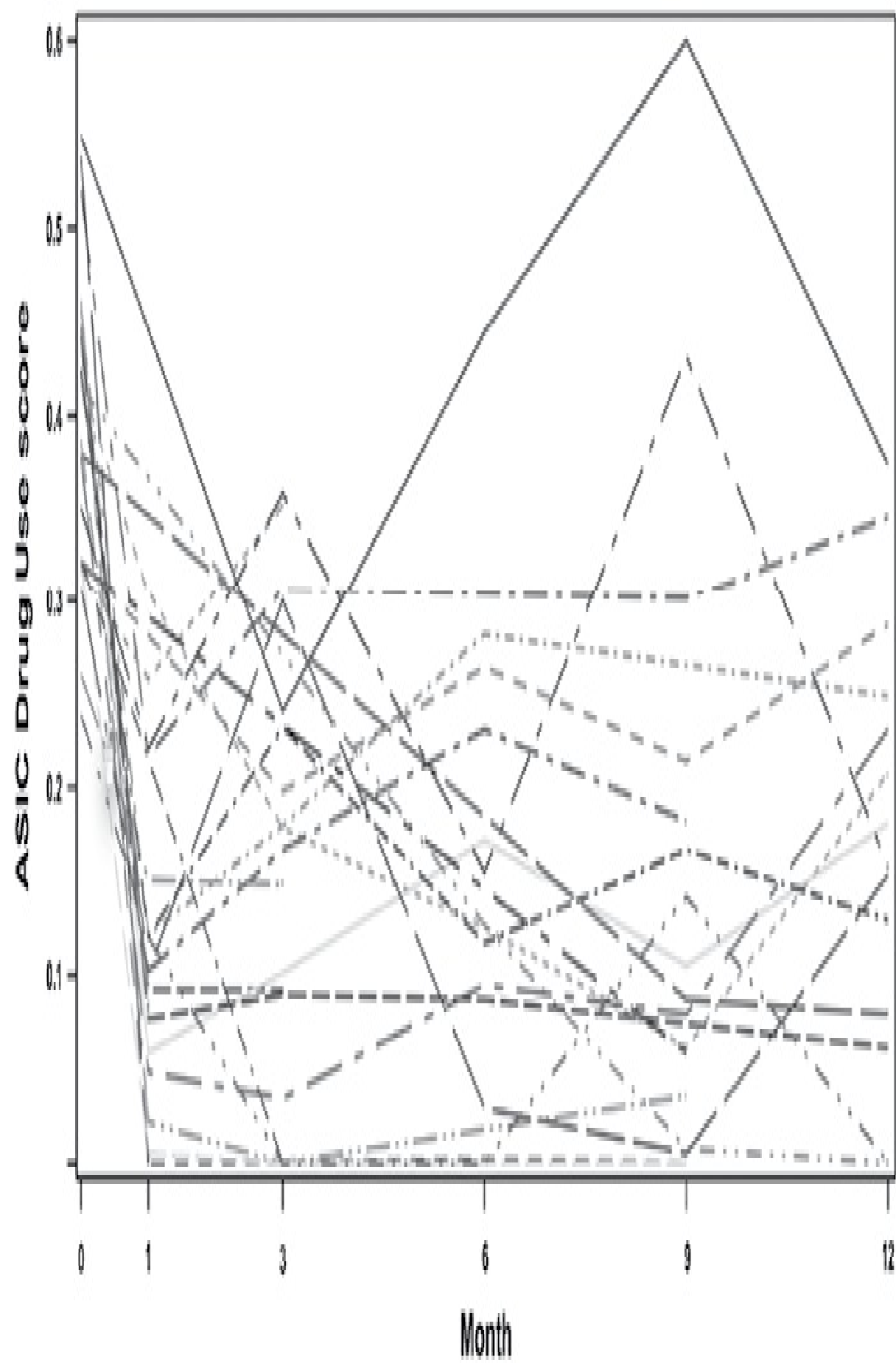


**Fig. 2** Individual trajectories of the Addiction Severity Index Composite Drug Use score in patients at 1, 3, 6, 9, and 12 month followup after opioid detoxification with ibogaine (Brown and Alper, 2017) (N= 30).

Other recent work, conducted in New Zealand with a design similar to that discussed immediately above on a smaller subject population (N=14) reported comparable outcomes regarding SOWS ASIC Drug Use scores in subjects followed up for one year (Noller et al., 2017). The study also included assessment with the Beck Depression Inventory that indicated progressive improvement throughout the interval of follow up.

Reported studies on ibogaine as treatment for substance use disorders have been uncontrolled and reliant on self-report without laboratory verification. While laboratory verification will be a necessary feature in future efforts to develop ibogaine or its structural derivatives, self-reporting in clinical research on substance use disorders can be accurate (Darke, 1998), particularly when there are no negative consequences to the subject for reporting use. Reported detoxification outcomes appear valid. The clinical expression of acute opioid withdrawal evolves acutely over a limited time frame, tends to be robust in its expression, and can be assessed accurately by lay providers in the settings in which ibogaine is administered (Alper et al., 2008). Patient self-reports also suggest a substantive, pharmacologically-mediated effect of ibogaine, especially in view of the lack of a significant effect of placebo in opioid detoxification (Amato et al., 2013; Gowing et al., 2017; Gowing et al., 2016).

## PRECLINICAL EVIDENCE OF EFFICACY

There are more than 50 published studies of ibogaine or its structural analogs 18-MC or noribogaine in animal models of drug self-administration or opiate withdrawal. Consistent with its apparent effect in opioid detoxification in humans, ibogaine administered intraperitoneally or intracerebrally to animals reduces naloxone- or naltrexone-precipitated opioid withdrawal signs, in rats (Cappendijk et al., 1994; Dzoljic et al., 1988; Glick et al., 1992; Parker et al., 2002), mice (Frances et al., 1992; Layer et al., 1996; Leal et al., 2003; Popik et al., 1995), and primates (Aceto et al., 1992; Koja et al., 1996). Single dosages of ibogaine administered to

rodents diminish self-administration of multiple abused substances including morphine (Belgers et al., 2016; Glick et al., 1994; Glick et al., 1996; Glick et al., 1991), heroin (Dworkin et al., 1995), cocaine (Cappendijk and Dzoljic, 1993; Glick et al., 1994; Glick et al., 1996; Maisonneuve and Glick, 1992; Sershen et al., 1994), amphetamine (Maisonneuve, Keller, et al., 1992), and alcohol (Rezvani et al., 1995), with normal responding for water. A recent meta-analysis of 30 animal studies of the effect of ibogaine on drug self-administration morphine, alcohol, or cocaine found a significant effect on drug self-administration across studies that was greatest at 24 hours but persisted for > 72 hours (Belgers et al., 2016). Sustained effects on morphine self-administration for even longer time intervals have been observed in individual animals (Glick et al., 1991).

Both ibogaine and 18-MC diminish an experimental pharmacological correlate of drug salience, the sensitized response of dopamine efflux in the nucleus accumbens in response to morphine (Maisonneuve and Glick, 1999; Maisonneuve et al., 1991) and nicotine (Glick et al., 1998; Maisonneuve et al., 1997). Ibogaine has had no significant on conditioned place preference, an animal behavioral model of drug craving (Belgers et al., 2016).

## SUBJECTIVE EFFECTS: PHENOMENOLOGY, NEUROPHYSIOLOGY, AND IBOGAINE AS A PSYCHOTHERAPEUTIC ADJUNCT

Historically, the use of ibogaine in the medical model began in the 1950s, when clinicians and researchers viewed ibogaine much as they did other compounds classified as hallucinogens. Some, such as Jan Bastiaans, MD (Snelders and Kaplan, 2002), Leo Zeff, PhD (Stolaroff, 2004), and Claudio Naranjo, MD (Naranjo, 1973), were interested in ibogaine as an adjunct to psychotherapy. Ibogaine, like other hallucinogens, was of interest as an experimental model of psychosis (Fabing, 1956; Salmoiraghi and Page, 1957; Schneider and Sigg, 1957; Turner et al., 1955). As with other hallucinogens, ibogaine may have also been investigated for military or intelligence purposes as a “truth serum”, or a means of “brainwashing” or incapacitating an adversary which was the focus the US Central Intelligence Agency project MKULTRA (Isbell, 1955; U.S. Senate,

1977).

The French chemist Robert Goutarel hypothesized that ibogaine produces a state with functional aspects shared by the brain states of REM sleep (Goutarel et al., 1993). Descriptions of subjective experiences associated with ibogaine have been designated as “oneiric” and likened to a “waking dream”, with interrogatory verbal exchanges involving ancestral and archetypal beings, and movement and navigation within visual landscapes. Another frequently described experience is panoramic memory, the recall of a rapid, dense succession of vivid autobiographical visual memories, which has been termed “the slide show.” Mechanistically, these subjective experiences associated with ibogaine possibly suggest functional muscarinic cholinergic effects, which are prominent in the mechanisms of dreaming and memory (Cantero et al., 2003).

Ibogaine is reported to enhance spatial memory retrieval in animals (Helsley et al., 1997; Popik, 1996), and produces an atropine-sensitive EEG rhythm (Depoortere, 1987; Schneider and Sigg, 1957). The atropine-sensitive EEG rhythm is regarded as an animal model of REM sleep and attributed to muscarinic cholinergic input from the ascending reticular activating system (ARAS) (Leung, 1998), and has been suggested to involve the inhibition of acetylcholinesterase (AChE) by ibogaine (Schneider and Sigg, 1957). More recent work indicates that ibogaine does not inhibit AChE (Alper, Reith, et al., 2012), suggesting the possibility that functional muscarinic cholinergic effect may be mediated by modulation of signaling downstream from the receptor itself.

Individuals who have taken ibogaine frequently report that memories and other mental representations which have previously been associated with troubling emotions such as fear, or shame, or anger are experienced with equanimity, allowing a reevaluation and reprocessing of their content (Heink et al., 2017). As memorably expressed by one individual reflecting on her ibogaine treatment for dependence on opioids, *“It’s as if all information in your brain file cabinet is shaken out of its drawers on to one big pile, looked at ‘objectively’ and put back in, untwisted from emotional trauma.”* (Lotsof and Alexander, 2001). Equanimity is also a prevalent theme in Bwiti. Ritual outcomes and transactions with ancestors involving the use of eboga are described (utilizing Fernandez’s translations)

with terms such as “even-handedness”, “tranquil-heartedness”, or “one-heartedness.” The quality of equanimity attributed to ancestral contact is evident in a Fang Bwiti poem (Fernandez, 1982), *“Joy, the ancestors give joyful welcome and hear the news. The troubled life of the born ones is finished.... All the misfortunes are shorn away. They leave. Everything clean. All is new. All is bright. I have seen the dead and I do not fear.”*

Narratives of individuals treated with ibogaine subjects appear consonant with themes of “one heartedness”, and “binding” to family and ancestors represented in Bwiti. A study that utilized ASIC scores found that Family/Social the most improved ASI composite factor apart from Drug Use (Brown and Alper, 2017). Lotsof provides a descriptive example of the clinical phenomenon of delayed benefit with ibogaine (Lotsof and Alexander, 2001), and suggests the interval of delay might correspond to the ongoing processing and behavioural integration of the psychoactive experience produced by ibogaine.

## TOXICOLOGY

### CARDIOTOXICITY

Ibogaine has been associated with fatalities (Alper et al., 2012; Koenig and Hilber, 2015). Ibogaine and its major metabolite noribogaine prolong the QT interval of the EKG. The QT interval corresponds to ventricular repolarization between cardiac contractions during which the electrical potential of the cardiac myocyte becomes more negative, inhibiting cell firing. With depolarization the electrical potential in the cardiac myocyte becomes more positive and excitatory, resulting in cell firing and the action potential that underlies ventricular contraction. With prolongation of the QT interval, cardiac myocytes may escape control of the cardiac conduction system and depolarize spontaneously. QT prolongation is viewed as correlate of cardiac instability, a loss of “repolarization reserve” (Roden and Yang, 2005), and is associated with polymorphic ventricular arrhythmias (PVTs) including Torsade de Pointes (TdP), a morphologically distinctive type of PVT that can progress to ventricular fibrillation and death (Kannankeril et al., 2010).

Repolarization of the cardiac myocyte depends importantly on the movement of positively charged potassium ions out of the cell through voltage-gated cardiac potassium channels. The protein that constitutes the pore of the channel is encoded by the human ether-ago-go-related gene (hERG), hence the term hERG channel, and hERG blockade is the major cause of drug-induced QT prolongation and TdP (Kannankeril et al., 2010). Ibogaine and its major metabolite noribogaine block the hERG channel with comparable potency (Alper et al., 2016; Koenig and Hilber, 2015). In a recent study, reported IC<sub>50</sub> values for 99.5% ibogaine produced by semisynthesis via voacangine, 95% ibogaine produced from extraction of *T. iboga*, and noribogaine were 4.09  $\mu$ M, are 3.53  $\mu$ M, and 2.86  $\mu$ M respectively. 18-MC produces substantially less hERG blockade (IC<sub>50</sub> > 50  $\mu$ M) (Alper et al., 2016).

The reported values for IC<sub>50</sub> for hERG blockade by ibogaine and noribogaine appear clinically relevant. The half-life (T<sub>1/2</sub>) of ibogaine in humans is estimated to be 4 to 7 hours (Kontrimavičiūtė et al., 2006; Mash et al., 2001), and the T<sub>1/2</sub> of noribogaine is apparently considerably longer than that of the parent compound, possibly on the order of days (Glue et al., 2015). In a sample of 24 subjects that were orally administered ibogaine dosages of 10mg/kg, mean peak blood levels for ibogaine and noribogaine respectively were 2.4  $\mu$ M and 3.2  $\mu$ M (Mash et al., 2001). From a postmortem series of 19 fatalities, the subset of 10 cases in which blood ibogaine levels were available, the mean was 7.6  $\mu$ M (range 0.77  $\mu$ M to 30  $\mu$ M), and in the two cases for which they were available, noribogaine levels were 13.4 and 18.8  $\mu$ M (Alper, Stajic, et al., 2012). Although the interpretation of levels from postmortem studies may be complicated by redistribution, and taking into account that ibogaine is 65% protein bound (Koenig et al., 2013), ibogaine or noribogaine may produce significant hERG channel blockade at clinically relevant concentrations (Koenig et al., 2013).

Bradycardia heightens the risk for fatal cardiac arrhythmia including TdP (Cubeddu, 2009) and has been observed following administration of ibogaine in medical (Mash, Allen-Ferdinand, et al., 1998) and nonmedical (Samorini, 1998) settings and in preclinical studies (Binienda et al., 1998; Dhahir, 1971; Glick et al., 1999; Schneider and Rinehart, 1957). Both laboratory models and



multiple clinical case reports indicate that hypokalemia is a particularly important factor in the genesis of arrhythmia associated with ibogaine (Koenig and Hilber, 2015). A case of TdP in the setting of severe depletion of potassium from serum and tissue stores due to the aggressive use of cathartics prior to ibogaine treatment, in which lengthening of the QT interval, bradycardia and ventricular tachydysrhythmias appeared to track potassium levels over an interval of 7 days. illustrates the importance of potassium in ibogaine-related cardiac arrhythmia, as well as the idiosyncratic hazards associated with the unconventional settings in which ibogaine is often administered (Shawn et al., 2012).

Drug-induced TdP is typically multifactorial, involving multiple determinants of cardiac rhythm instability in addition to hERG blockade (Kannankeril et al., 2010), which has been generally been the case with regard to fatalities temporally related to ingestion of ibogaine. Pre-existing cardiovascular medical comorbidities appear to have been particularly prominent in deaths temporally associated with the administration of ibogaine (Alper et al., 2012). The role of preexisting advanced medical comorbidities as contributing causes in ibogaine-related deaths may also be paralleling a general association of risk of fatal overdose with systemic disease (Darke et al., 2006). For example, ibogaine- related fatalities have been associated with cardiac hypertrophy and atherosclerotic disease (Alper et al., 2012), which are associated with chronic methamphetamine and cocaine use (Kaye et al., 2007; Knuepfer, 2003). Additional factors that commonly contribute to cardiac instability in chronic substance-related disorders include various co-ingestants, systemic medical conditions such as liver or respiratory disease, seizures, hypomagnesemia, or withdrawal from cocaine or alcohol (Cubeddu, 2009; Kannankeril et al., 2010; Levin et al., 2008; Otero-Anton et al., 1997).

## NEUROTOXICITY

Degeneration of cerebellar Purkinje cells were observed in rats given substantially larger dosages of ibogaine than those used to study drug self-administration and withdrawal (O'Hearn and Molliver, 1993). Ibogaine activates the release of glutamate by neurons in the inferior olive resulting in degeneration of the

Purkinje cells in the cerebellum, which are vulnerable to excitotoxic injury due to the redundancy of inputs to cerebellar Purkinje cells, an effect that may be potentiated by ibogaine's  $\sigma_2$  agonist activity (Bowen, 2001; O'Hearn and Molliver, 1997). Subsequent research found no evidence of neurotoxicity in the primate (Mash et al., 1998) or mouse (Scallet et al., 1996) at dosages which produced cerebellar degeneration in the rat, or in the rat at dosages used in studies of drug self-administration and withdrawal (Molinari et al., 1996). The FDA was aware of the work that indicated the neurotoxic effect of high dosages of ibogaine in the rat at the time it approved a phase 1 study in which humans received ibogaine (Alper, 2001). Clinical or postmortem evidence does not appear to suggest a characteristic syndrome of neurotoxicity (Alper et al., 2012).

## MECHANISM OF ACTION

### DISTINCT FROM MEDICATIONS KNOWN TO HAVE CLINICAL EFFECTS IN OUD

The mechanism of action of ibogaine is unknown and apparently novel and unexplained by actions of medications known to have clinical effects in opioid tolerance or withdrawal. Clinical observations suggest that ibogaine is not acting as an MOR agonist. Doses of ibogaine sufficient to detoxify individuals with severe physical dependence do not produce signs of overdose in opioid naïve individuals (Alper et al., 2008). If ibogaine were acting as an opioid agonist, it would not be tolerated by opioid-naïve individuals, because the methadone dosage of 60 to 100 mg per day that is used to stabilize withdrawal symptoms in the maintenance treatment of opioid dependent patients (Fareed et al., 2010) substantially exceeds the estimated LD<sub>50</sub> of 40 to 50 mg in humans who are not pharmacologically tolerant to opioids (Corkery et al., 2004).

Although ibogaine, its major metabolite noribogaine, and 18-MC bind with low micromolar affinity to the MOR, they are neither orthosteric nor allosteric  $\mu$  opioid receptor agonists assessed by [<sup>35</sup>S]GTP $\gamma$ S binding in cells expressing the  $\mu$  opioid receptor (Antonio et al., 2013). The potentiation of morphine analgesia by ibogaine in the animal model, without producing analgesia when administered alone, also suggests that ibogaine may alter signaling

through opioid receptors but is not itself an orthosteric agonist (Bagal et al., 1996; Bhargava et al., 1997; Cao and Bhargava, 1997; Frances et al., 1992; Schneider, 1957; Schneider and McArthur, 1956; Sunder Sharma and Bhargava, 1998). Although the potentiation of morphine analgesia without analgesia when administered alone might be consistent with an effect as allosteric MOR agonist, these compounds do not potentiate the activation of G proteins by morphine or DAMGO (Antonio et al., 2013), indicating they do not act as allosteric MOR agonists.

Some evidence suggests that ibogaine might possibly modify neuroadaptations associated with chronic exposure to opioids, such as the apparent reversal of analgesic tolerance to chronic morphine by ibogaine (Pearl et al., 1995; Schneider, 1957; Sunder Sharma and Bhargava, 1998). Ibogaine and noribogaine diminish tolerance in morphine-tolerant mice (Bhargava and Cao, 1997; Cao and Bhargava, 1997; Sunder Sharma and Bhargava, 1998), and dose-dependently potentiate the antinociceptive effect of morphine in morphine-tolerant but not in morphine-naïve mice (Sunder Sharma and Bhargava, 1998). Ibogaine has relatively selective effects on decreasing dopamine efflux in the nucleus accumbens (Pearl et al., 1996) and locomotor activity (Maisonnette, Rossman, et al., 1992; Pearl et al., 1995) in morphine-tolerant versus non-tolerant rats. Ibogaine's clinical effect of opioid detoxification without causing opioid overdose in non-tolerant individuals also suggests selectivity for neuroadaptations associated with prior exposure.

Ibogaine is an NMDA receptor antagonist (Popik et al., 1995; Skolnick, 2001), and NMDA antagonists such as memantine diminish signs of opioid withdrawal in preclinical models (Trujillo and Akil, 1994) and humans (Bisaga et al., 2001). However 18-MC, which lacks significant affinity for the NMDA receptor, is equally effective as ibogaine in animal models of opioid withdrawal (Cappendijk et al., 1994; Dzoljic et al., 1988; Glick et al., 2001; Glick et al., 1992; Panchal et al., 2005; Parker et al., 2002; Rho and Glick, 1998). Ibogaine has no significant affinity for the  $\alpha_2$  adrenergic receptor (Deecher et al., 1992; Sweetnam et al., 1995) or imidazoline I<sub>2</sub> site (MacInnes and Handley, 2002), indicating it does not act as an imidazoline  $\alpha_2$  adrenergic receptor agonist such as clonidine.

## DISTINCT FROM OTHER COMPOUNDS

## DESIGNATED AS “PSYCHEDELIC”

Although ibogaine is designated as a hallucinogen, and subsumed under the rubric of “psychedelics” it is pharmacologically distinct from the classical hallucinogens such as LSD, mescaline, or psilocybin, which are thought to act by binding as agonists to the serotonin type 2A (5-HT<sub>2A</sub>) receptor (Nichols, 2016). The 5HT<sub>2A</sub> receptor is non-essential for recognition of the ibogaine stimulus in drug discrimination studies (Helsley et al., 1998). Serotonin agonist or releasing activity does not appear to explain ibogaine’s effects in opioid withdrawal (Glick et al., 2001; Wei et al., 1998). There appears to be no clinical evidence apparent effect of classical hallucinogens in opioid detoxification, and in the animal model ablation of 90% of the raphe, the major serotonergic nucleus of the brain, does not significantly affect the expression of opioid withdrawal (Caille et al., 2002).

Although harmine does have an effect of diminution of antagonist-precipitated opioid withdrawal in rats, this effect is apparently due to its action of imidazoline I<sub>2</sub> receptor agonist (Aricioglu-Kartal et al., 2003). Ibogaine in contrast has no affinity at the I<sub>2</sub> receptor. Ibogaine does not inhibit MAOA (Nelson et al., 1979).

## THE A<sub>3</sub>β<sub>4</sub> NICOTINIC ACETYLCHOLINE RECEPTOR (NACHR), NEUROTROPHINS

The enhanced expression of glial-derived neurotrophic factor (GDNF) has been proposed to account for ibogaine’s effect on drug self-administration (He et al., 2005). Ibogaine increases GDNF expression *in vivo* and in cultured cells, and 18-MC reportedly does not (Carnicella et al., 2010), but both compounds are equally effective in animal models of drug self-administration (Glick et al., 2001). Ibogaine’s action as an allosteric antagonist of the α<sub>3</sub>β<sub>4</sub> nAChR is suggested to mediate its effect on drug self-administration (Glick et al., 2002), but does not appear to readily explain the prolonged effects that appear to persist beyond pharmacokinetic elimination (Pearl et al., 1997). Ibogaine’s major metabolite, noribogaine has a longer half-life than the parent compound (Baumann et al., 2001; Glue et al., 2015), and has been suggested to account for persistence of effects on drug self-administration and

withdrawal (Mash et al., 2016), although in the animal model the effect of ibogaine in reducing drug self-administration appears to persist beyond the elimination of ibogaine and noribogaine from serum or brain tissue (Pearl et al., 1997).

## ADENYLATE CYCLASE

Ibogaine may act downstream from receptor-coupled G protein activation to mediate effects on opioid withdrawal that are unexplained in view of its lack of agonist activity at the MOR. Adenylate cyclase (AC) is one plausible target of ibogaine. The MOR is negatively coupled to AC via G<sub>ai</sub>, and the inhibition of AC is a cardinal opioid agonist signaling effect, as is the AC “superactivation” or “overshoot” of increased production of cyclic adenosine monophosphate (cAMP) in opioid withdrawal (Christie, 2008; Nestler, 2001; Sharma et al., 1975). Ibogaine potentiates the inhibition of AC by morphine (Rabin and Winter, 1996), which may be consistent with its observed clinical effect in opioid withdrawal. The potentiation of morphine analgesia by Ibogaine and noribogaine, without analgesia when administered alone is also consistent with a possible effect of inhibition of AC in view of the upregulation of AC in pain sensitization associated with opioid withdrawal (Bie et al., 2005) and the analgesic effects of drugs that inhibit AC (Pierre et al., 2009; Zhuo, 2012). A hypothesis that iboga alkaloids could inhibit AC might explain why ibogaine does not itself produce signs of opioid overdose but potentiates the toxicity of co-administered opioids (Alper, Stajic, et al., 2012; Bhargava and Cao, 1997; Dhahir, 1971; MPI Research, 1996; Schneider and McArthur, 1956).

## WHAT IS IBOGAINE DOING IN THE PLANT?

### THE IBOGA CLASS OF MONOTERPENE INDOLE ALKALOIDS

Although there is some discussion among regarding the precise criteria for the term “alkaloid”, core attributes are containing a basic nitrogen as an electron donor in a ring or ring system. The term “true alkaloid” has been used to designate those alkaloids that derive from amino acid and share a heterocyclic ring with nitrogen

(Aniszewski, 2015). Indole alkaloids are true alkaloids and particularly well-adapted structurally for noncovalent interactions, including cation- $\pi$  interactions involving the ring system, and hydrogen bonds involving the nitrogen atom. G protein-coupled receptors (GPCRs) are typical targets of alkaloids, often involving aromatic side chains. Receptor binding tends to be diverse, with “off target” and toxic effects.

Alkaloids are formed in plants from pathways of synthesis of amino acids, and extend on amino acid scaffolds, as do neurotransmitters. The monoamine neurotransmitters may be regarded as alkaloids, just as tryptamine is an alkaloid, so is 5-HT (5-hydroxytryptamine, serotonin), as is auxin, an important plant hormone with a close structural relationship to 5-HT. Morphine, nicotine, cocaine, amphetamine, and the major classical hallucinogens are alkaloids.

Alkaloids were historically initially viewed as “secondary metabolites” – chemical detritus, the byproduct of primary metabolic processes such as photosynthesis or energy metabolism. The term secondary metabolites has been retained as generally synonymic with plant natural products, however alkaloids are now recognized as serving ecological aims mediating between the plant and its environment, such as chemical defenses against herbivores or pathogens, or attractants for pollinating insects (Hartmann, 2007). The ecological view is well-validated; however, an emerging view is that alkaloids may also serve functions within the plant itself as modulators of signaling pathways or gene expression (Aniszewski, 2015; Heinze et al., 2015; Neilson et al., 2013).

The phylogenetic lineage of many alkaloids tends to be narrow, as is the case with ibogaine, possibly due to evolutionary selection pressure for chemodiversity. The total number of all plant secondary metabolites is estimated on the order of 200,000 compounds (Neilson et al., 2013), with estimates of total number of alkaloids on the order of 20,000, occurring in quantities  $\geq 0.01\%$  of the dry plant weight in approximately 20% (Seigler, 1998) of the 405 families of flowering plants (The Plant List, 2013). Ibogaine is a monoterpene indole alkaloid (MIA), a pharmacologically important class of compounds formed by the condensation of the alkaloid tryptamine and the monoterpene secologanin. Estimates of the

number of MIAs are in the range of approximately 2000 to 3000 compounds, occurring predominantly in three plant families, Apocynaceae, Loganiaceae, and Rubiaceae (O'Connor and Maresh, 2006; Szabó, 2008). The iboga class of MIAs consists of about 100 compounds (Lavaud and Massiot, 2017) apparently limited to 5 of 410 genera within the Apocynaceae family (The Plant List, 2013), *Tabernaemontana*, *Tabernanthe*, *Catharanthus*, *Voacanga* and *Melodinus*.

## CROSS-KINGDOM COMMONALITY: PLANT AND ANIMAL HOMOLOGY

Plants lack many of the proteins targeted by drugs that are psychoactive in humans. Most approved psychopharmacological agents in clinical use (e.g., antidepressants, antipsychotics, some anxiolytics), as well as many drugs of abuse target GPCRs or monoamine transporters. Plants lack canonical GPCRs (Urano and Jones, 2014) such as opioid, dopamine, 5-HT or cannabinoid receptors, they lack monoamine transporters (Hoglund et al., 2005) at which cocaine or amphetamine act, and plants do not have pentameric ligand-gated ion channels (Jaiteh et al., 2016) – the targets of nicotine, benzodiazepines or ketamine.

Plants lack canonical GPCRS, but do share remarkable homologies regarding G proteins and effectors that are conserved in plants and metazoans. Figure 3 presents two examples of downstream signaling elements homologously present in plants and linked in humans to GPCRS that activate cardinal signaling pathways of psychoactive substances. In the case of the MOR, the respective transducer, effector, and second messengers present in both plants and animals are G $\alpha$ , adenylate cyclase, and cyclic AMP. In case of the 5-HT<sub>2A</sub>R they are G $\alpha$ , phospholipase A<sub>2</sub> and C, and arachidonic acid and inositol 1,4,5-trisphosphate. Clinical psychopharmacology does not generally target transducers and effectors, but plant alkaloids apparently do, and the identification of their targets may provide an interesting paradigm for drug discovery and neurobiological investigation.

A recent study provides an example of an endogenous plant alkaloid as a specific modulator of an effector in the plant itself (Heinze et al., 2015). *Eschscholzia californica* (Papaveraceae) and

*Catharanthus roseus* (Apocynaceae) express alkaloids which function as phytoalexins, compounds with antimicrobial activity against fungi and bacteria that are produced and accumulated by plants in response to infection. Microbial elicitors added to cultured cells from either plant increase the production of alkaloids by G $\alpha$ -dependent activation of phospholipase A2 (PLA2) to generate signaling molecules that code for the induction of biosynthetic enzymes downstream. The respective alkaloids in both of these evolutionary distant plants exert negative feedback to prevent their own overexpression by specifically targeting and inhibiting PLA2. PLA2 is present in metazoans and is an important downstream effector in the action of the classical hallucinogens, linked to the 5-HT2AR (Nichols, 2016), suggesting the possibility of a widely conserved, phylogenetically ancient signaling motif. Of note with regard to this present review, catharanthine (Figure 1), which occurs in *C. roseus* and inhibited *C. roseus* PLA2 in the study discussed above (Heinze et al., 2015), is an iboga alkaloid of pharmacological importance (van der Heijden et al., 2004).



## Signaling Element

### Opioids

### Classical hallucinogens

Receptor (GPCR)

$\mu$ -opioid receptor (MOR)\*

Serotonin 2A receptor (5-HT<sub>2A</sub>)\*

Transducer (G proteins)

G $\alpha^i$

G $\alpha^i$

Effector (enzymes)

Adenylate cyclase†

Phospholipase A<sub>2</sub>†, C†

Second messenger  
(cyclic nucleotides,  
lipids/phospholipids)

Cyclic adenosine monophosphate (cAMP)†

Arachidonic acid (AA)†,  
inositol 1,4,5-trisphosphate (IP3)†

\*occurs in animals, not in plants

†occurs in both plants animals

Fig. 3 Signaling elements linked to two mammalian GPCRs, the MOR and 5-HT<sub>2A</sub>R. Plants lack G-protein coupled receptors, but some downstream G proteins, effectors and second messengers are conserved among plants and metazoans.

## PLANT INTELLIGENCE

Plants have extraordinary capacities to sense and respond to their environment, but should they be regarded as intelligent? Intelligence is the capacity for learning, which involves the modification of programs of behavior or thought on the basis of prior experience (Trewavas, 2017). Learning is shaped by reinforcement in individuals within that individual's lifetime. Habituation may be viewed as an elementary form of learning but is limited to adaptations to manage the gain of environmental signals, and is shaped by repeated exposure to a habituating stimulus, such as leaf folding in response to mechanical disturbance (Gagliano et al., 2014). Intelligence differs from instinct, which is reinforced at the level of populations by adaptation and fitness over time spans of generations, and may be exemplified in plants as epigenetic memory in clonal plants (Latzel et al., 2016). Intelligence is distinct from consciousness, which has been defined as “global subjective awareness” (John, 2005), and may only be inferred, and not directly observed by the research investigator.

The example of the climbing behavior of *Passiflora caerulea* L, an experimental paradigm favored by Charles Darwin provides an example of plant intelligence that illustrates the capacity of plants to learn (Baillaud, 1962; Trewavas, 2005). The plant is presented with a support, which the tendril locates by circumnutation, a plant behavioural program of helical movement common in climbing plants that allows triangulation utilizing variations in light intensity registered by the moving tendril. The tendril finds the support each time it is moved to a new location. Locating the support requires some form of memory of the variations in light intensity over the trajectory of the circumnutatory movements (Trewavas, 2017). The tendrils appear to modify their search strategy with the progression of the experiment, and after the support is finally taken away altogether the plant appears to approach the last previous location of the support prior to it being removed.

Not only is the *Passiflora caerulea* plant itself apparently capable spatial learning, but *Passiflora incarnata* L. enhances spatial

learning when ingested by rats (Jawna-Zboinska et al., 2016). Both *P. caerulea* and *P. incarnata* contain multiple harmala alkaloids including harmine (Frye and Haustein, 2008). Harmine, as well as ibogaine both enhance spatial learning in the rat (Dos Santos and Hallak, 2017; Helsley et al., 1997; Popik, 1996). Alkaloids frequently accumulate most heavily in the parts of the plant that are growing, such as root tips. This has been viewed as consistent with a hypothesis of alkaloids as chemodefenses which are deployed more extensively in valuable, young growing plant tissue (McCall and Fordyce, 2010). However in the root system, which navigates, senses, and responds to its environment, the accumulation of alkaloids in growing tissue might also reflect a role of alkaloids of endogenous modulators of plant signaling in programs of behavior or growth and development.

## CONCLUSION

The iboga alkaloid structural skeleton appears to be a “privileged scaffold”, a term of medicinal chemistry for a basic molecular framework prototypic of a class of compounds on which systematic substitutions can be utilized to modulate therapeutic and toxic effects (Welsch et al., 2010). The effect of 18-MC in animal models of drug self-administration and opioid withdrawal is apparently equivalent to that of ibogaine (Maisonneuve and Glick, 2003), although its hERG blockade is much less (Alper et al., 2016), indicating the potential for isolating ibogaine’s therapeutic effect from its cardiotoxicity. With an unknown and likely novel mechanism of action, and a structure that evidently accommodates rational drug design, ibogaine may provide an interesting prototype for discovery and development of fundamentally innovative pharmacotherapy.

When a growing root tip meets a rock it cannot move, it revises its behavioral program. In this instance plants may output behavioral responses more intelligently than humans, who are prone to rigidly overdetermined repetitive behavior. It appears possible that possible that a restricted subset of plant alkaloids interacts with an evolutionarily ancient commonality, shared across signaling pathways in both plant and animal kingdoms that may mediate programs of plant adaptive behavior, growth or development in one

kingdom, and modify the pathological neuroadaptations of opioid dependence and linkages of motivational states to drug-related memories, representations or environmental cues. True intention, equanimity, distinct from the constraints of obsession and the pathological overattribution of salience, is both a cardinal spiritual goal and a desired outcome of pharmacological treatment of addiction. Recovery from addiction is often, typically, viewed by patients in spiritual terms. It is not entirely unexpected that a plant alkaloid used in an indigenous sacramental context may provide a valuable lead for discovery of pharmacotherapy for addiction.

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# Psychoactive Initiation Plant Medicines: Their Role in the Healing and Learning Process of South African and Upper Amazonian Traditional Healers

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*Jean-Francois Sobiecki, BSc Hons*

Research Associate, Univ. of Johannesburg;  
Founder, Khanyisa Healing Gardens Project, Johannesburg, South Africa

## ABSTRACT

There is an accelerating interest in strong acting psychoactive plants such as *ayahuasca* for healing and personal development. However, what has become apparent with initiating into South African traditional healing, and key literature sources from South America, is the importance not only of the strong mind ‘opening’ visionary plants but the equally significant utilization of subtle acting psychoactive plants that cleanse and strengthen the initiate healers, that are used in a sequence of initiation plant medicines both in the South African and South American traditional medicine systems. This paper explores and describes a cross cultural technology of healing with psychoactive initiation plants that are used in a sequential manner in order to take the initiate traditional healer through a process of self enquiry, growth and potential self-mastery. Understanding this sequential use of traditional initiation plant medicines and their physiological and psychological correlates could elucidate possible therapeutic mechanisms involved with the use of psychoactive traditional medicines and their potential applications in future medicine and healing. The connection is also made between the role of perturbation in the learning process healers engage and how psychoactive plants produce perturbation in the nervous system and what adaptive benefit this may have.

## INTRODUCTION

Little academic attention has been paid to the subject of psychoactive plants and their role in the initiation process of southern African traditional healers. Mentions of psychoactive plant use from the southern African anthropological and ethnobotanical literature are scant and anecdotal. One rare, early paper highlights the significance of plants used in the initiation and religious practices of the Sotho speaking people and their potential psychoactive properties (Laydevant, 1932). This lack of data on African psychoactive plant use in general, encouraged the author to conduct anthropological fieldwork from 1998 onwards, to document the role of psychoactive plants in the spiritual healing practices of the South African diviners (*Izangoma*) and herbalists (*Izinyanga*).

Some findings from conducting a literature review and long standing fieldwork included a preliminary inventory being published indicating over 300 species of plants being used for psychoactive purposes in southern African healing traditions (Sobiecki, 2002). A review of plants used in divination in southern Africa and their psychoactive effects was also conducted, that indicated that approximately 45% of the plants reported with uses in divination have other psychoactive uses (Sobiecki, 2008). Much of the traditional meanings and therapeutic significance of these plants remain undocumented and is in urgent need of study.

Having experienced a category of South African plant medicines called *ubulawu* and Ayurvedic *vamana* emesis therapy in Dharamsala in 2011, indicated that there is a common mechanism of action of using plant medicines to vomit and cleanse with in both the Ayurvedic and South African traditional medicine systems that has a corresponding psychoactive healing effect on the mind (Note: these are not emetics, but medicines that one manually cleanses with) (Sobiecki, 2012).

Thereafter, having completed my initiation using South African plant medicines with a masterful Northern Sotho African healer Mrs. Letty Maponya in 2012, provided valuable insights that what I had experienced through the use of initiation plants in South Africa paralleled what I had subsequently read about the *curandero* (shaman's) use of initiation plants in South America (Jauregui et al. 2011). In this paper they describe plants that were administered as

part of a particular sequence during the initiation process namely: (I) purification and cleansing (II) sensitivity and intuition; (III) strengthening; and (IV) protection and defence. I recognized this same sequence of plant medicines as what I had gone through with the African initiation plant medicine process.

The aim of this paper is to put forward the hypothesis that this same sequential use of initiation plant medicine categories in both the South American and South African traditional medicine systems indicates a cross cultural therapeutic technology of healing and self development by traditional healers from both South America and South Africa.

## METHODS

My training and initiation followed a long-time friendship and apprenticeship with a Northern Sotho healer and diviner Mrs. Letty Mamonyai Maponya. Having met Mrs. Maponya during my initial fieldwork in Johannesburg in 1998, to answer whether the *Izangoma* (South African diviners) were using psychoactive plants as part of their spiritual practices to induce trance states, Mrs. Maponya immediately offered to assist me where she could. This initiated a 15 year friendship and mentorship with her. It was only later towards the end of our relationship in 2012 (Mrs. Maponya passed over in 2013), that Mrs. Maponya finally agreed to facilitate a formal process of initiation with plant medicines for me during which time (approximately 3 months) I would come to realize the importance of the stages of medicine used in the initiation. I rented a cottage in Jeppestown, Johannesburg, so as to be close to my teacher to receive instruction. It was a time of introspection and isolation focusing on the self knowledge facilitated by the use of the initiation medicines.

## THE SOUTH AFRICAN TRADITIONAL MEDICINE

### INITIATION PROCESS

### CLEANSING MEDICINES

I started the initiation process using cleansing medicines, the purpose of which was to ritually let go of the past while preparing for the new to emerge. One key medicine I used to cleanse myself

with was *Elaeodendron transvaalense* (Burt Davy) R.H. Archer, or *Ingwavuma* (Zulu). I used the bark of this medicine, which is ground finely into a powder, to steam with, as well as a small quantity that is consumed as a decoction to vomit with. *Ingwavuma* is rich in tannins and flavonoids that not only cleans ritual pollution but is very effective in clearing diarrhea, impurities and pathogenic or toxic heat conditions from the body. Having cleansed myself sufficiently with this and other medicines for around two weeks made me feel energized and more confident. Mrs. Maponya advised me from the start of the 3 month period on behavioural and dietary restrictions: to not have sex or intimate relationships and to restrict social engagement (the energetic relationships with people would disturb my process of introspection and self-enquiry), as well as keeping a clean simple diet without stimulants. These restrictions are important in helping the initiate familiarize with the enhanced states of consciousness experienced and to help anchor new learnings. Jauregui et al., 2011, describes the significance of cleansing plants in the initiation of *curanderos*: “The first plants ingested during the diets are species that are well-known by the Amazonian societies and highly utilized in their traditional medicine due to their purgative, laxative, anthelmintic, and emetic properties. These plants are ingested by the apprentices at the start of the process so that they can purify themselves and prepare their bodies for meeting with the spirit of the vegetables or mothers of the plants.” From my experience, I learnt that strict monitoring by my teacher was essential throughout the initiation period to ensure correct dosages and administration methods of the medicines are used - too much *Ingwavuma* can negatively affect digestion because of its high tannin content, for example.

### MIND OPENING MEDICINES

The next stage of the initiation required that I use one species of *ubulawu* medicines that I call the ‘mirror *ubulawu*’, that is an initiation secret. *Ubulawu* is a preparation form of Southern African traditional medicine made from a number of different plant species that are all used to open the mind and that are described as “lucky medicines” by the indigenous people of Southern Africa (Sobiecki, 2012). The term *ubulawu* refers mostly to the roots of a variety of



plants that are ground and made into a cold water infusion that is churned with a forked stick to produce foam. The foam is eaten at night and the infusion is drunk on an empty stomach first thing in the morning and vomited with to cleanse the person. The foam is said to indicate saponins some of which are reported to be psychoactive. *Ubulawu* is used in traditional South African healing to open luck, and as my teacher said “all *ubulawu* opens luck.” I describe the term “lucky medicines” as an example of a metaphorical indicator of physiological actions from using psychoactive medicinal plants (Sobiecki, 2014), that is, using *ubulawu* medicines enhances dreaming, produces clearer thinking and produces more energy, and all of which are effects that are lucky to be experienced, which is why they are called “lucky medicines.” In the Nguni speaking groups of South Africa dreams are considered to belong to the domain of the ancestors (Sobiecki, 2008). A fundamental use of *ubulawu* in African healing traditions is to facilitate connection and communication with ones ancestors (deceased ancestral relatives) through dreams and/or intuitive feelings, that the medicines can help to access. Thus, these medicines are believed to be important tools to connect with one’s deceased ancestral spirits, (that incidentally my teacher equated with angels). Manton Hirst (1990, 1997), comprehensively describes the importance of *ubulawu* in the initiation of South African Xhosa diviners and the medicines’ role in their dreaming and ancestral connection. Having used the “mirror *ubulawu*”, I was expecting my dreams to be clearer but disappointingly this did not happen. However, what did happen was my intuition and sensitivity increased to the point I felt overwhelmed to be in any place with a lot of stimuli, e.g., shopping malls. I describe in Sobiecki (2012) how the cleansing action of vomiting with the *ubulawu* plant medicines, together with the psychoactive properties of the species used that are absorbed in the body, results in these effects. The importance of being clean in ones body so as to have good mental well-being and connection cannot be overstated in African traditional society and should be more utilized in western society. The culmination of using this medicine at twelve days was the feeling of being forced to face the deepest personal question of my life. I felt the intensity of emotions reaching a crescendo to the point that I wanted to run

away from my home I was renting close to my teacher for the initiation period. I stopped the medicine at this point after consultation with my teacher. Some of the *ubulawu* species used by various ethnic groups in southern Africa are described in a previous paper (Sobiecki, 2008). While the role of strong visionary medicines like *ayahuasca* used by the *curandero* healers to open the mind appears to predominate, there are also a number of plants that are also used to vomit with such as *Aristolochia cauliflora* Ule., to cleanse and open the initiate (Jauregui et al., 2011).

### STRENGTHENING MEDICINES

To help ground myself after this intense introspective stage of the process I was introduced to using a red strengthening mixture containing a plant called *Maytenus undata* (Thunb.) Blakelock, or *Dabulovalu* (Zulu). This medicine's name connotes "shock" and is used to relax a person. This and another tree that I cannot name at this stage, is used together as a strengthening medicine in order to help the initiates stabilize and strengthen after the intense opening period. This is similar to the use of tree medicines by the *curanderos* where Jauregui et al. 2011, explains: "The initiates need to strengthen themselves both physically and spiritually in order to move forward in the learning process, and therefore the diet should consist mainly of palos, the large rainforest trees, the jainoa onanti jihui, which means "tree that teaches" in the Shipibo-Konibo language." I also used during the initiation a powder made from Licorice (*Glycyrrhiza gabra* L.) that is eaten off the palm of the hand (to *kotha-Zulu*). The licorice medicine is called 'sweet mouth' and works as a tonic to calm and boost one's energy (Sobiecki, 2014). While the name "sweet mouth" and its traditional use to talk nicely may sound superstitious, its quick uplifting affects allows one to be calm and to speak easily and such behaviour is easily reflected by others through communicating owing to the well known mirror neuron phenomenon. Thus the name "sweet mouth" is not magical at all, but a metaphorical indicator of the physiological and psychological effects (Sobiecki, 2014), resulting from the tonic actions of the medicines. Together these medicines are used to assist in grounding the initiate after what can be an intense opening, and to help anchor the new insights into possible new learning's and

behaviour. It is worthwhile to note that some of the medicines used in the initiation process are considered a secret that requires a proper research project platform with ABS agreements in place for the local communities involved, in order to study these plants and their applications correctly.

## INITIATION PLANTS AS PERTURBATORY LEARNING TOOLS

In retrospect, this period of initiation involved a pragmatic approach to self growth and development through firstly; letting go of ones past through cleansing medicines, then opening to new knowledge through using *ubulawu* that encourages dreaming and enhanced intuition and sensitivity, and then finally absorbing and anchoring the new insights with red strengthening medicines. The hypothesis I make here is that this initiation medicine process is a pragmatic technology used to interrupt old patterns of behaviour and familiarize the initiate with enhanced states of awareness, self-enquiry, growth and potential self-mastery afforded by the psychoactive plant medicines and the ritual context. Other traditional healers have affirmed that the use of initiation plant medicines in this way is to achieve self-growth and mastery (Dr. Hlati, pers. comm, 2015).

At present, it appears that many westerners are focusing entirely on the opening class of medicines such as *Ayahuasca*, and are not familiar with the equally important cleansing and grounding medicines used in Amazonian and South African traditional healing systems demonstrated here. While *ayahuasca* has cleansing and purgative actions there are many other plants used in both traditions whose primary indication is to cleanse the body, thereby opening the mind through a gradual process of enhanced sensitivity and intuition. Thus, the subtle psychoactive affects of initiation plant medicines plays a significant role in psychological and spiritual healing in shamanic and other tribal societies.

What further significance may there be regarding the use of initiation plants in this sequence in terms of healing?

What I understood as part of my training and what my teacher Mrs. Maponya explained is “that too much power is not good for a

*twasa* (initiate), they must also relax.” I experienced this, in that following the power and intensity from the opening *ubulawu* medicines, one can ground and balance oneself with the relaxing red medicines that gives time for the insights and teachings to be absorbed and anchored.

This destabilizing (opening with *ubulawu* medicines) and then stabilizing (grounding with red medicines) reminds me of a number of other examples in the neuroscience field where perturbation has potential adaptive and therapeutic value.

For example, Dr. Froese proposes the possible selective benefits of mind alteration that he terms as the *interruption mechanism* as part of a self-optimizing spiking neural network model. In this study they found if the model ‘brain’ is subjected to occasional perturbations that profoundly alter its normal state of activity, in this case via the randomisation of its activity, synaptic plasticity spontaneously starts to reshape the network’s connectivity in a way that enhances coordination of neural activity (Froese, 2015). He goes on to say “This result is only based on an artificial model, but it is nevertheless suggestive: neuroscientists investigating the psychedelic state have found it to be associated with a similar disruption of normal activity, including cortical desynchronisation (Muthukumaraswamy et al. 2013) and increased disorder of neural activity (Carhart-Harris et al., 2014), and that these modified states of consciousness may have positive adaptive consequences by increasing integration between brain areas (Winkelman, 2010), providing users with functional adaptation of cognition (Müller and Schumann, 2011), and as influencing creativity (Dobkin de Rios and Janiger, 2003). Furthermore, Dr Carhart-Harris describes what he terms as elevated entropy with the use of psychedelic medicine that results in the breakdown of brain networks and that this is beneficial in interrupting familiarized conditioned learning (Carhart-Harris et al., 2014). These examples demonstrate that perturbation resulting from the action of psychoactive medicines and other stimuli can be advantageous in interrupting old behaviours while providing opportunities to initiate new behaviours.

From my experience, I propose that the ritual sequential use of psychoactive opening and grounding initiation plant medicines as

part of the South African traditional healers initiation provides such a perturbative process that fosters the disruption of old conditioned behaviours and offers the opportunity to familiarize with new insights that can translate, under certain conditions, into new learnings and behaviours with attendant personal growth and maturation, which is one desired outcome of a successful and completed initiation process of African traditional healers.

Thus, in summary, the perturbatory affects catalyzed by psychoactive initiation plant medicines is positively and pragmatically utilized in the initiation process of the traditional healers in Southern Africa and in South America towards healing ends.

### FUTURE RESEARCH

Much on the African traditional initiation plants and their cultural and corresponding scientific understandings is yet to be documented and investigated, and is one key reason for the inception of the Khanyisa Healing Garden Project, that aims to create a network of healing and research gardens between South America and South Africa to study these psychoactive plants and their application in medicine, healing and community health promotion through multidisciplinary collaborative projects.

Many of the plants in question are over-harvested and face eradication, without having been researched. Therefore, there is an urgent need for such documentation of this eroding knowledge and for new conservation strategies to be developed, which is a further objective of the Khanyisa project. The Khanyisa Project aims to establish sustainable working relationships with the local communities involved in the research through generating viable ethnobotanical tourism related to the African plant knowledge and establishing Access Benefit Sharing (ABS) agreements with research interest groups. This innovative project has much to offer in terms of integrating research, health promotion, conservation and community development relating to the use of psychoactive plants and furthering our understanding of healing consciousness with traditional plant medicine.

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# Psychoactive Australian Acacia Species and their Alkaloids

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*Snu Voogelbreinder*

Ethnobotanist, author of *The Garden of Eden: Shamanic Use of Psychoactive Flora and Fauna and the Study of Consciousness*

## INTRODUCTION

The genus *Acacia sensu lato* (Fabaceae, subfamily Mimosoideae) is one of the largest in the plant kingdom, with over 1,000 species native to Africa, the Middle East, Asia, Australia, the Pacific Islands and the Americas. Recent taxonomy has split the genus *Acacia* into several genera (*Acacia*, *Senegalia*, *Vachellia*, *Faidherbia*, *Mariosousa* and *Acaciella*), with *Acacia* controversially being retained for the Australian species<sup>21</sup> and their close relatives from Oceania, Southeast Asia, and the Mascarene Islands. Some *Acacia* spp. which are native to Australia have also been introduced in many parts of the world, either for erosion control, timber, tannin production, or ornamental purposes, and in some cases they have become invasive weeds following naturalisation.

**211.** A small group of *Vachellia* spp. are also native to Australia.

In Australia, the genus is numerous and widespread, with over 900 recognised species, known commonly as wattles. At certain times of year when there are mass-flowerings, these plants are such a noticeable feature of life in Australia that one species (*A. pycnantha* Benth., the golden wattle) became the national floral emblem, and the “green and gold” colours of the flowering plant have been used as national colours for sporting events. There is even a Wattle Day (1st of September), though for most people today this is a quaint artefact of the recent past. Since the early years of European colonisation, new Australians have exploited several species for tannin production and timber, and only relatively

recently have they begun to appreciate the food potential of wattle seeds. It is even less known that many *Acacia* spp. have properties which transcend the utilitarian.

## HISTORICAL USE OF AUSTRALIAN ACACIAS AS PSYCHOACTIVE AGENTS

Historical use of *Acacia* spp. *sensu lato* as psychoactive agents has been previously reported from Africa (Lehmann & Mihalyi, 1982; Watt & Breyer-Brandwijk, 1962) and possibly the Americas (e.g., Pendleton & Pendleton, 2008; Taylor, 1979, 1996). Certain species also have ancient traditions of sacred significance in Egypt, the Middle East, and India, and some scholars believe they may have once played an entheogenic-sacramental role in early religions (e.g., Dannaway, 2007; Graves, 1961; Newman, 2015; Shannon, 2008). This paper will focus on the psychoactive properties and related uses of native *Acacia* spp. *sensu lato* in Australia.

The first Australians and their indigenous descendants have made extensive use of Acacias, presumably for tens of thousands of years. Various species have been utilised for food (from the nutritious seeds, and sometimes the gum), medicine, and the manufacture of tools and ritual objects. These uses have been well documented (eg. Clarke, 2007; Cribb & Cribb, 1982; Latz 1995), but any traditional use of these plants as psychoactive agents in Australia remains obscure.

Since the colonisation of Australia by Europeans, Australian indigenous people have, in general, been quite open in sharing their plant knowledge with anthropologists, ethnobotanists, and other interested parties. However, they have withheld their knowledge of sacred ceremonial plant use to a large extent, as this is reserved for fully initiated men and women, who have their own gender-separate rituals and knowledge. Where such knowledge has been at least partly disclosed to an outsider, that person is generally sworn to secrecy, which has resulted in a paucity of public knowledge of indigenous Australian plant shamanism. In addition, many traditions have been abandoned and forgotten following more than 200 years of colonial settlement and subsequent massacres, breaking up of families, and forced assimilation. Despite this, in



some parts of the country these traditions have not been lost. Whilst there has been good work done to document any surviving knowledge of indigenous plant use in a number of publications, details regarding sacred ceremonial plants are at best only ever hinted at ambiguously in print, and are reserved for private oral communication. However, some other traditional uses of Acacias are suggestive of central nervous system (CNS) activity.

### SMOKING MEDICINES

Many plants have been (and still are) used medicinally and ritually in Australia by what is called “smoking”, but this is not smoking in the usual sense. It involves spreading fresh branches and foliage (and sometimes pieces of termite mound) on hot coals in a pit, with the patient or subject of the ceremony lying on a temporary bed frame constructed over the top, or sometimes lying directly on or next to the fuming foliage. Sometimes a wooden vessel is used to hold the coals and foliage, so that the smoke can be moved around and directed, as with “smudging”. Alternately, a person can simply stand by the pit, bathed in thick smoke. Smoking ceremonies are conducted in order to purify an area for ritual, or to cleanse a person before a long journey or important undertaking. Babies are traditionally exposed to smoke from various *Acacia* spp. or other plants after birth; in that case, they may be held and wafted briefly through the smoke, although sometimes mother and child may sleep overnight next to the fuming foliage. The purpose of this is to make the newborn child and its mother strong; in the case of the mother, squatting over the smoke and fumes of some species also serves to alleviate postpartum bleeding.

*A. ligulata* A. Cunn. ex Benth. is of ritual and spiritual importance to Warlpiri women, and the phyllodes are used in smoking ceremonies to treat a wide variety of illnesses. *A. dictyophleba* F. Muell.<sup>22</sup>, *A. pruinocarpa* Tindale, and *A. lysiphloia* F. Muell. phyllodes are used as smoking medicines in northern Australia for newborn babies and their mothers (Aboriginal Communities, 1988; Bindon, 1996; Clarke, 2007; Latz, 1995; Low, 1990; Smith, 1991). Probable sedative or narcotic activity is suggested by a different use of smoke on Groote Eylandt: “excited and uncontrollable” children are sometimes held head-down in smoke from the phyllodes of

(what is probably) *A. pellita* O. Schwarz, to quieten them (Levitt, 1981). Although not known to be a smoking medicine, *A. acuminata* Benth. has been used as a sedative inhalant – the Noongar of s.w. Western Australia sometimes inhale the vapours from crushed flowers “to relax the mind for a good night’s sleep” (Hansen & Horsfall, 2016).

**22.** This use of *A. dictyophleba* might instead refer to *A. melleodora* Pedley (Butcher et al., 2001).

In southeast South Australia, the Tangane used to rub emu fat over their bodies and smoke themselves with fresh branches of an *Acacia* spp. before fighting. The context in which this anecdote was related gives the impression that this preparation helped make a warrior strong, brave, and calm in the face of angry (and therefore unbalanced) foes. Another more interesting ritual use of “smoked” *Acacia* can be mentioned here, as it has previously been published, is presumably no longer practiced, and the species used was not identified. Some Tangane men could reputedly vanish and travel large distances in one night for secret purposes – sometimes malicious sorcery – by means of a practice translated as “walking with magic shoes”. For the Tangane, this involved wearing shoes made from bark of a *Leptospermum* sp. and human hair, with the feet and insides of the shoes smeared with a mixture containing death adder (*Acanthophis antarcticus* Loveridge) venom, as well as skin and hair from a corpse, whilst “standing in the dense smoke of a fire made of green wattle branches” (Tindale, 1937). Known in central Australia as “kurdaitja”, such “magic shoes” are well known, although they were made of emu feathers stuck together with blood and hair, and were generally written about as being worn when literally sneaking up on a sleeping victim at night to ritually murder them (Spencer & Gillen, 1899). Less commonly, such shoes have reportedly been “used by the “Doctors” when seeking out the evil being who has swallowed the rain, and thus caused droughts” (A.W. Howitt, in Etheridge, 1894). Tindale’s report appears to be unique in mentioning an associated use of plants and snake venom, shoes made from bark and not feathers, and explicitly stating that the practitioner vanishes and travels impossible distances rather than sneaking about physically.

## PAIN MEDICINES

Some species have also been applied topically to relieve pain. In northern Australia, the Ngarinyman heat phyllodes and branches of *A. lysiphloia* on hot coals, and apply them to sore muscles or joints as an analgesic (Aboriginal Communities, 1988; Smith, 1991; Smith et al., 1993). The Gurindji heat the phyllodes in water and use them as a wash to treat muscle pain and stomach ache (Wightman et al., 1994). The Mudburra use the same species “to ward off spirits who are annoying people.” For this, the branches are heated and held on the temples and forehead. *A. monticola* J.M. Black may be used in the same way (Wightman et al., 1992). An infusion of the phyllodes and pods of *A. auriculiformis* A. Cunn. ex Benth. is used as an analgesic wash to relieve body pains (Low, 1990). Seeds of *A. pruinocarpa* are used to treat headaches (Latz, 1995). On Groote Eylandt, a species which is probably *A. pellita* is used for the same purpose. Phyllodes and seeds are used externally to relieve body pains, and heated phyllodes are also applied to the forehead for headaches (Levitt, 1981). *A. difficilis* Maiden phyllodes are heated and “applied to chest, back, or ears to relieve pain” (Brock, 1988). Bark strips from *A. holosericea* A. Cunn. ex G. Don are tied around the head with the inner bark against the skin to relieve headache (Aboriginal Communities, 1988). In the Pilbara region of Western Australia, phyllodes and twigs of *A. ancistrocarpa* Maiden & Blakely and *A. trachycarpa* E. Pritz. are used as a wash to treat headaches, and heated and applied externally to treat internal pain (Reid, 1977). Phyllodes and twigs of *A. translucens* A. Cunn. ex Hook. are also made into a wash to relieve headaches. A tea of *A. dictyophleba* phyllodes is drunk to treat headaches, coughs and colds. A decoction of *A. ligulata* bark has been used to treat “dizziness, nerves and fits” (Bindon, 1996). It remains to be seen if any of these uses indicate narcotic effects. At least some of the analgesic applications may be effective due to anti-inflammatory rather than neurological activity. The uses of *A. lysiphloia* and *A. monticola* by the Mudburra in the Northern Territory, and *A. ligulata* in Western Australia certainly suggest some kind of CNS activity is involved. These species may prove useful in the search for more effective psychiatric medicines.

## FISH POISONS

Numerous species have been used as fish poisons, which temporarily stun freshwater fish without rendering them inedible. For this purpose, plant parts are crushed, thrown into a water hole and agitated, or placed in a mesh bag made from plant fibres and used like an oversized toxic tea bag. After a short time, stunned or asphyxiated fish rise to the surface where they are easily caught. Species used in Australia as fish poisons include *A. auriculiformis* (phyllodes), *A. binervata* DC. (phyllodes), *A. colei* Maslin & L.A.J. Thomson (bark, phyllodes), *A. decurrens* Willd., *A. falcata* Willd. (bark), *A. hemignosta* F. Muell. (bark, phyllodes), *A. holosericea* (branches, phyllodes, pods, seeds), *A. longifolia* (Andrews) Willd. (phyllodes), *A. melanoxylon* R. Br. (bark, twigs), *A. oncinocarpa* Benth. (bark, phyllodes), *A. pellita* (pods, seeds), *A. penninervis* Sieber ex DC. (bark, phyllodes), *A. pulchella* R. Br., *A. salicina* Lindl. (bark, twigs, phyllodes), *A. tumida* F. Muell. ex Benth. (pods, seeds) and *A. verniciflua* A. Cunn. (Brock, 1988; Cribb & Cribb, 1982; Hamlyn-Harris & Smith, 1916; Hurst, 1942; Maiden, 1889, 1913; Marrfurra et al., 1995; Sadgrove, 2009; Smith, 1991; Webb, 1948; Wightman et al., 1994). The ichthyotoxic pharmacology of *Acacia* spp. is poorly understood, but is presumed to involve tannins and saponins reducing the amount of oxygen available to the fish (Sadgrove, 2009); any alkaloids present might also affect the central nervous system (pers. obs.). Tannic acid in water has been found to cause “marked physiological disturbance” and death in fish at concentrations of 1:10,000 (Hamlyn-Harris & Smith, 1916). Saponins extracted from “*A. cunninghamii*” pods (note: this may no longer be an accepted name; see comments below under *A. concurrens* Pedley) “produced total insensibility of the leg” and muscle paralysis when injected into the leg of a frog. Injection of an extract of one pod into the arm of a human resulted in pain, swelling, nausea, and shivering; an extract of two pods also resulted in headache, mydriasis, and paralysis of the eye muscles (Lauterer, 1897). Applied topically to mucous membranes, saponins from *A. delibrata* A. Cunn. ex Benth. pods act as an irritant, and applied to the heart, muscle, or nerves of a frog, they resulted in paralysis of those parts (Bancroft, 1887).

## ALKALINE ASH SOURCES FOR CHEWING WITH TOBACCO AND PITURI

Selected *Acacia* spp. (such as *A. auriculiformis*, *A. aneura* F. Muell. ex Benth., *A. beauverdiana* Ewart & Sharman, *A. calcicola* Forde & Ising, *A. coriacea* DC., *A. estrophiolata* F. Muell., *A. hakeoides* A. Cunn. ex Benth., *A. kempeana* F. Muell., *A. ligulata*, *A. omalophylla* A. Cunn. ex Benth. or *A. cambagei* R.T. Baker, *A. pruinocarpa*, and *A. salicina*) are burned to produce a fine, alkaline ash for chewing with tobacco or pituri/pitcheri (*Nicotiana* spp., *Duboisia hopwoodii* F. Muell.), to aid in alkaloid release. The part used is usually the phyllodes, bark, or twigs, varying from species to species (Aiston, 1937; Johnston & Cleland, 1933; Latz, 1995; Maiden, 1922; Marrfurra et al., 1995; Meggitt 1966; Reid, 1977; Smith, 1991). In the Lake Eyre district, *A. salicina* used for ash production is itself called “pitcheri”. In the case of this species, the young branch tips were cleaned of damaged and diseased growth. To make the ash, the tips “were tied in bundles, ignited over the fire, and then allowed to burn out while held over a wooden bowl” (Aiston, 1937). One report claimed that in Woorabinda, Queensland, *A. salicina* ash is “smoked to produce “drunkenness, drowsiness, or dopiness, and finally deep and lengthy sleep””, but this is most likely a confusion with the drug the ash is mixed with (Webb, 1969). Nevertheless, pituri is rarely if ever smoked, and would not require alkaline ash to be added when doing so. Furthermore, attempting to smoke ash by itself would be a futile exercise. This strange report is intriguing despite its apparent inaccuracies.

## COFFEE AND TEA SUBSTITUTES

*Acacia* spp. were experimented with by early colonial settlers as substitutes for coffee and tea, due to local shortages of those imported stimulants. However, it appears that these plant parts were used not because of any caffeine- or theophylline-like effects, but simply because they could be used to prepare beverages that looked, tasted, and/or smelled a little like the real thing in the absence of anything better. Certainly, some wattle seeds have a coffee-like aroma when roasted. Ludwig Leichhardt and his “convict

companion” Mr. Phillips trialled numerous plants as coffee substitutes in Australia’s early colonial days. Their experience with the bushfire-roasted seeds of an *Acacia* sp. in Expedition Range, Queensland, is worth quoting:

“Mr. Phillips (who was always desirous of discovering substitutes for coffee[...]) collected these seeds, and pounded and boiled them, and gave me the fluid to taste, which I found so peculiarly bitter that I cautioned him against drinking it; his natural desire, however, for warm beverage, which had been increased by a whole day’s travelling, induced him to swallow about a pint of it, which made him very sick, and produced violent vomiting and purging during the whole afternoon and night. The little I had tasted acted on me as a lenient purgative, but Mr. Calvert, who had taken rather more than I did, felt very sick.”

The species used was not recorded (Leichhardt, 1847), but was possibly *A. bidwillii* Benth. (*Vachellia bidwilli* (Benth.) Kodela) (Fensham et al., 2006). Mature seeds of *A. murrayana* F. Muell. ex Benth. were roasted and used as a coffee substitute by early European settlers (Latz, 1995), and seeds of *A. victoriae* Benth. are currently used as such (Ariati et al., 2007), although a stimulant effect has not been noted.

Leaves of *A. decurrens* and phyllodes of *A. suaveolens* (Sm.) Willd. were used as tea substitutes by early settlers (Low, 1989). No stimulant effect has been mentioned, although the phyllodes of *A. suaveolens* contain phenethylamine (White, 1944a, 1951, 1954). *A. iteaphylla* F. Muell. ex Benth., which is very close to *A. suaveolens*, has a bitter taste at some times of the year and may also prove to contain phenethylamines. The phyllodes (harvested in March) make a reasonable substitute for Japanese green tea, in a dose of 1 tablespoon finely chopped and dried phyllodes steeped in just-boiled water. A higher dose (2 tab.) decocted for 10 minutes had a less agreeable taste. This tea appears to have some mild stimulant activity, but further experimentation is required to eliminate the placebo effect (personal observations, 2017). Root shavings of *A. georginae* F.M. Bailey are said to be used as a tea substitute in modern times (Latz, 1995), but again, no stimulant effects have been reported. As some specimens of *A. georginae* can produce

dangerous levels of sodium fluoroacetate (see below), drinking tea made from this species is not recommended.

## MODERN NON-TRADITIONAL USE OF ACACIAS AS PSYCHOACTIVE DRUGS

In 1965, the first report of the isolation of N,N-dimethyltryptamine (DMT) and N-methyltryptamine (NMT) from an Acacia species – *A. maidenii* F. Muell. – was published in a scientific journal (Fitzgerald & Sioumis, 1965), followed shortly by another which reported the isolation of DMT from *A. phlebophylla* H.B. Will. (Rovelli & Vaughan, 1967), both Australian species. Several other journal papers followed over the next decade, reporting the finding of these alkaloids in other Acacia species from Africa, Asia, and Oceania. These reports arrived at a time in Western history that saw a large increase in public curiosity about psychedelic drugs, yet they remained obscure footnotes in the phytochemical literature for more than 20 years, apparently unnoticed by anyone who might wish to make use of the information by extracting the alkaloids for human use. This may be due to the fact that DMT itself remained an obscure and unpopular psychedelic agent until at least the late 1980s, but despite the information being published in science journals rather than popular books or articles, it is still surprising that it took so long for academically-inclined drug enthusiasts to notice these papers and spread the information into the wider culture, as would occur rapidly today.

Several publications which emerged in the early 1990s raised awareness of the fact that some Acacias contain DMT. The first was a scientific text book (Collins et al., 1990), followed by popular nonfiction books more specifically about psychoactive plants and drugs (eg. Ott, 1993). Around the same time, several university students in Australia had stumbled across this information in the journal papers by Fitzgerald & Sioumis (1965) and Rovelli & Vaughn (1967), and the work of Collins et al. (1990). In 1992, one of these anonymous researchers published a report on successful experiments in extracting and smoking the alkaloids from *Acacia maidenii* bark. The investigator had first tried smoking the bark

itself, with very mild effects (Anonymous, 1992). Early the following year, another researcher posted a report to an internet newsgroup detailing the first documented use of a decoction of *Acacia phlebophylla* phyllodes, drunk after having swallowed ground *Peganum harmala* L. seeds. This produced powerful psychedelic effects in two human subjects (C.G., 1993). Later that year, another anonymous person consumed the same combination with one of the original bioassayists, and this was written up and posted to an internet newsgroup (Anonymous, 1993). All of these reports were soon reproduced on various websites as the Internet grew over the 1990s (e.g., Michael from Melbourne, 1992). At this time, experimentation with what have become known as “ayahuasca analogues” – the combining of plants not traditionally used in *ayahuasca*, but which contain monoamine oxidase (MAO)-inhibiting  $\beta$ -carboline alkaloids (such as harmine and harmaline), and DMT – was in its infancy. In the United States, a small number of people had been experimenting with *Desmanthus spp.* root and *Phalaris spp.* leaves in combination with *Peganum harmala* seeds prior to 1993 (Appleseed, 1993; J.G., 1992), but this was not widely known until Jonathan Ott published his book *Ayahuasca Analogues*, by which time he had performed his own bioassays with the *A. phlebophylla*/*P. harmala* combination (Ott, 1994).

In the mid-1990s, a period of intense investigation into the psychoactive properties of *Acacia* species began, not by sanctioned academics, but by interested amateurs in many parts of the world, particularly Australia. Initially, much of the focus by drug enthusiasts was on *Acacia phlebophylla* – which has a fairly reliable DMT content with few other alkaloids present, if any – and *Acacia maidenii*, which has proven to be a less reliable source of DMT due to variation within the species, and with an NMT content often higher than that of DMT. This limited focus quickly led to some negative impacts on both species in the wild. *Acacia phlebophylla* is found only on Mt. Buffalo in Victoria, Australia, and the population has suffered both from overharvesting, and widespread galling caused primarily by a rust fungus, *Uromycladium sp.*, which was adversely affecting the health of much of the population by the late 1990s (Heinze et al., 1998). Since then, an extensive bushfire at Mt. Buffalo appears to have destroyed the infected material, and the



species is currently regenerating well. This granite-loving species has also proven difficult to cultivate to maturity outside of its natural habitat; however, this author is aware of several successes.

*Acacia maidenii* suffered partly due to ignorance – as the initial report by Fitzgerald & Sioumis (1965) detailed extraction of alkaloids from the bark, many people assumed that this was the only part of the plant to contain alkaloids. Subsequently, wild and cultivated plants were crudely decorticated by people hoping to extract tryptamine alkaloids, and many trees were killed outright by this treatment, not all of them even correctly identified. To this day, similar episodes continue to occur, and are documented and discussed by concerned “Acaciaphiles” on internet discussion forums and in private. This has most often been the case with *Acacia obtusifolia* A. Cunn. (the first “new” species to have been discovered as a source of tryptamine alkaloids by the underground researcher then known as E, and later publicised by Mulga (1996a)), and more recently, *Acacia acuminata* Benth., plus a very rare species which will not be named here. Unfortunately, the financial profit and peer-group status that can be derived from a plentiful supply of DMT or mixed *Acacia* alkaloids have been seized upon by a small minority of people, and those who buy these alkaloid extracts are apparently mostly unaware of the ecological destruction that may be associated with their production.

Due to these issues, some Australian underground researchers decided to begin to share some of what they had learned about *Acacias*. These people hoped to encourage others to learn sustainable harvesting techniques; to shun commercial trade in *Acacia* alkaloids; and to explore a variety of other species in order to take the pressure away from threatened species such as *Acacia phlebophylla*. These efforts appear to have been somewhat successful, although there are still incidences of overharvesting in the wild and death of plants due to bark removal. Also, the discovery that root bark of some species can contain high levels of alkaloids has sometimes led to trees being killed by root bark harvesting from living plants *in situ*, or whole plants being uprooted and ground up for alkaloid extraction (Kelly, 2012; Nen & Nickles, 2014; personal communications).

## METHODS OF INVESTIGATION AND USE

Amateur researchers have investigated species which had no previously published chemical analysis, and species which had been reported as alkaloid-positive in published chemical screenings but not explored further. Some have approached this by performing acid/base or straight-to-base alkaloid extractions, and/or thin-layer chromatography and spot tests on all species they can obtain. Some have learned to narrow down the field of inquiry by taste, chewing a small sample of the plant and comparing it to samples known to contain tryptamines. Another method used is the “burn test”, lighting a dried phyllode or leaf briefly and smelling the smoke for traces of indolic aromas associated with the presence of tryptamines. Some other researchers who believe they have a kind of sensitive spiritual connection to these plants select species to assay based on intuitive feelings, allegedly with a high degree of success. Amateur researchers have been hindered by lack of affordable access to laboratory equipment used to identify alkaloids with a high degree of certainty. Due to this, with much of the early amateur work in particular, identification of any alkaloids present in a sample was subjective guesswork following autoingestion – generally as a smoked or vapourised crude alkaloid extract – and basic, preliminary analysis with thin-layer chromatography and spot tests using plant samples with known alkaloid content for comparative reference. Occasionally, some researchers have been able to get alkaloid samples analysed by professionals using GC-MS equipment. Through all of these approaches, amateur researchers working in a legal grey area have vastly increased the knowledge of Acacia alkaloids, in a period where such work has almost disappeared from mainstream academia. The risks involved have been not only of a legal nature, but include the potential dangers of experimenting with human ingestion of plants or plant extracts of poorly known or unknown chemical content.

Acacia alkaloid extracts are usually vapourised in a glass pipe, or mixed with other herbs – sometimes Cannabis – and smoked in a water pipe or cigarette, in the same manner as DMT has been used in the last fifty years worldwide. DMT has been evaporated from a solvent solution onto carrier herbs (usually parsley) for smoking since the 1960s. However, since the early 2000s, herbal blends for

smoking Acacia alkaloids, with the novel inclusion of *Banisteriopsis caapi* (Spruce ex Grisebach) Mort. leaves (with their MAO-inhibiting  $\beta$ -carboline alkaloid content), have become a popular means of consumption, and are known as “changa” (pronounced with a hard “g”). The addition of *B. caapi* leaves boosts the effectiveness of the Acacia alkaloids, and makes it easier to inhale an effective dose by extending the window of administration time. Mullein herb (*Verbascum* spp.) added to the blend also makes the smoke milder and easier to inhale and hold in the lungs. A variety of other herbs may also be included to modify the flavour and perhaps the effects (Palmer, 2015). This approach has been taken on in other parts of the world, using tryptamine-containing source plants other than *Acacia* spp., such as *Mimosa tenuiflora* (Willd.) Poir. non Benth.

The oral ingestion of Acacia decoctions (or alkaloid extracts) in combination with an MAO-inhibitor (usually *Peganum harmala* seeds, *Banisteriopsis caapi*, or *Passiflora* spp.) is much less common than smoking, but does occur in Australia (Cakic et al, 2010; personal communications and observations). As already stated, *A. phlebophylla* has been used in this way by a small number of people since at least 1993 (C.G., 1993; Ott, 1994). In addition, *A. obtusifolia* has been used in this way since 1993; *A. maidenii* has been used in this way since the mid-1990s; *A. acuminata* has been used in this way since the late 1990s/early 2000s; and in more recent years, *A. floribunda* (Vent.) Willd. and other species have been occasionally used as well. *Ayahuasca* ceremonies held with small groups of people in Australia now frequently use DMT-containing Acacias or their alkaloid extracts in place of more traditional DMT-containing additives such as *Psychotria* spp. However, because of their high tannin content<sup>23</sup>, brews using Acacia spp. (rather than an alkaloid extract thereof) are often very astringent and more difficult to keep down for long compared to brews using *Psychotria* spp. They can also result in particularly powerful and challenging experiences – physically and mentally – depending on the alkaloid composition. In some cases with *A. obtusifolia*, this has led to speculation of the presence of 5-MeO-DMT, which has not been confirmed. The alkaloid/s responsible for the unpleasant physical effects of some Acacias when consumed

with an MAO-inhibitor (MAOI) has not been determined. Caution is advised in casually boiling up unknown *Acacia* spp. and ingesting them orally with or without an MAOI. Not all species contain DMT, and many contain non-tryptamine alkaloids of unknown pharmacology, as well as unidentified alkaloids which might be toxic, or dangerous in combination with an MAOI.

**23.** Some people have found that adding an egg white to an unreduced, acidic decoction attracts many of the tannins – as well as a small proportion of the alkaloids present – and after the egg white congeals, it can be filtered out through a cloth or decanted.

## GENERAL SUMMARY OF RECENT DISCOVERIES

Underground researchers in Australia have made a number of significant discoveries (not including the specifics of alkaloid content in different species):

- \* Foliage and twiggy branches can be used instead of stripping bark from the main stem or main branches. These parts generally may contain useful concentrations of similar or identical alkaloids to the bark, and represent a much more sustainable source of alkaloids. Fallen phyllodes collected from beneath a plant can also retain significant alkaloid content if they have not begun to degrade (nen888, 2011-2013). This is also highly sustainable, but care should be taken to leave some on the ground to feed the plant and soil biota.

- \* Alkaloid content may be highly variable even amongst plants growing in the same wild population, and at different times of year. Some species have been found to contain alkaloids only in an occasional individual specimen; some individuals may be more or less alkaloid free for most of the year, yet produce high concentrations of alkaloids occasionally. Even at that time, another specimen of the same species growing nearby may still contain no detectable alkaloids. Heavy rain appears to minimise alkaloid content for a short period afterwards, but this is not always the case (personal communications).

- \* *Acacia* alkaloid extracts comprised of a mix of indole alkaloids have transitioned from being regarded as “impure” by those seeking DMT, to being appreciated in their own right, and sometimes preferred to pure or near-pure DMT. Many users have reported that such alkaloid mixtures have subjective effects that are gentler and

longer-lasting than DMT alone while still being very powerful, and may bring about an experience that is easier to assimilate and learn from (personal communications and observations).

\* One researcher investigated non-DMT fractions from some such alkaloid mixtures and found that NMT (tentatively identified) is psychoactive when smoked or vapourised and inhaled (60 mg+), with psychedelic effects that are much less visual than those of DMT, and with a longer duration of 45-70 minutes. The researcher has described this alkaloid as a “spatial entheogen” (nen888, 2011a).

\* Some Acacia alkaloid extracts containing mainly tryptamines and a smaller proportion of phenethylamines can result in a greatly extended duration of psychedelic effects when smoked/vapourised (nen888 pers. comm., 2017).

\* Some Acacia spp. have been found to be mildly psychoactive when chewed, or drunk as a decoction, with no further MAO-inhibitor required (personal communications). In some cases, this is likely to be due to samples containing both tryptamines and  $\beta$ -carbolines (endlessness & nen888, 2011-2012), although the possible role of flavonoids or other non-alkaloidal constituents in MAO-inhibition (e.g., Dixon-Clarke & Ramsay, 2011) should be explored. It must be noted that chewing large amounts of fresh plant matter is potentially risky due to the cyanogenic compounds present in many species, which might occasionally occur at levels toxic to humans. However, many species probably only contain these compounds at levels problematic to ruminants eating large quantities, and even then, some species appear not to contain the enzymes necessary for the liberation of hydrocyanic acid (Everist, 1981; Hurst, 1942).

\* Seeds of some species (*A. acuminata* ssp. *burkittii* (F. Muell. ex Benth.) Kodala et Tindale, *A. maidenii*, *A. pendula* A. Cunn. ex G. Don., *A. podalyriaefolia* A. Cunn. ex G. Don) have been bioassayed via smoking, and are claimed to be mildly psychoactive (t st tantra et al., 2009).

## ALKALOIDS IN THE GENUS ACACIA

Alkaloids are common in the genus Acacia, and where they occur, several different classes of alkaloids have been identified. Simple

phenethylamines are well represented, such as phenethylamine, N-methyl-phenethylamine, tyramine, and hordenine. Claims of the presence of mescaline, amphetamine derivatives and tetrahydroisoquinolines in some North American species (*A. berlandieri* Benth. (Clement et al., 1997), *A. rigidula* Benth. (Clement et al., 1998)) remain controversial and unproven, although the tetrahydroisoquinoline calycotomine has been found in the Indian species *A. concinna* (Willd.) DC. (Gupta & Nigam, 1971). Less common alkaloids include pyridines such as nicotine (which requires further confirmation), histamine derivatives, and the spermidine alkaloid (-)-acacine, so far found only in *A. myrtifolia* (Sm.) Willd. (Nichols, 1983). The most attention has recently been focused on species which contain indole alkaloids, including N,N-dimethyltryptamine and other tryptamines, and a variety of  $\beta$ -carboline derivatives. It is these species which are most sought after by neo-shamans and other modern sacramental drug users, although species containing mainly phenethylamines may also prove to have psychoactivity in humans.

Other phytochemicals found in *Acacia* spp. include tannins/flavonoids, terpenes/saponins, cyanogenic glycosides, imino acids, and polysaccharides (Clarke-Lewis & Dainis, 1967; Everist, 1981; Kunii et al., 1996; Maslin et al., 1998; Seigler, 2003; Tindale & Roux, 1969, 1974). At least one species (*A. georginae*) can contain dangerous levels of the toxin sodium fluoroacetate (Everist, 1981; McEwan, 1978; Peters et al., 1965). Seeds of *Acacia* spp. contain carbohydrates, fatty acids, proteins, amino acids, non-protein amino acids, and imino acids (such as albizziine, djenkolic acid, pipelicolic acid, and others), and sometimes alkaloids, saponins, and oxalates. Some of the proteins present are protease inhibitors with anti-nutritional effects, which are greatly diminished by brief roasting, along with any saponins and oxalates present (Ee & Yates, 2013; Evans et al., 1977; Kunii et al., 1996).

## ALKALOIDS IN AUSTRALIAN NATIVE ACACIA SPP.

In general, the presence of indole alkaloids is concentrated in the section *Juliflorae*, species of which bear multi-nerved phyllodes and spike inflorescences on mature plants. However this class of alkaloids is also encountered less commonly in other sections of the

genus. Only a small portion of the 900+ *Acacia* spp. in Australia have been investigated chemically. Below is presented a summary of investigations into the alkaloids of *Acacia* spp. native to Australia. Introduced species that have become naturalised, such as *A. farnesiana* L. (*Vachellia farnesiana* (L.) Wight & Arn.) and *A. nilotica* spp. *indica* (Benth.) Brenan (*Vachellia nilotica* spp. *indica* (Benth.) Kyal. & Boatwr.), are not included. Several native species that contain tryptamines have been excluded for conservation reasons, due to their rarity. One of these species is not only rare but has a high concentration of alkaloids, and has already been subject to much exploitation in the space of a few years. The rare *A. phlebophylla* has been included because it is now firmly established in the literature.

Note: all species analysed by E.P. White were growing in New Zealand, unless stated otherwise. It is uncertain if a nonnative environment can influence the alkaloid content of Acacias, which are known to form symbiotic relationships with *Rhizobium* spp. bacteria to fix nitrogen. Also, White's identification of alkaloids should be taken as inconclusive, because he failed to identify DMT in several species which are now known to often contain it as a major alkaloid. Some of White's yields of tryptamine may have actually consisted of a mixture of indoles, including DMT.

***Acacia acinacea*** Lindl. (gold-dust wattle) – Stems and phyllodes yielded 0.04-0.07% alkaloids in Feb., 0.79-0.82% in Dec.; ripe seed pods yielded 0.08% alkaloids; seeds contained 0 traces of alkaloids. The alkaloid mixture consisted largely of phenethylamine (White, 1951).

***Acacia acuminata*** Benth. **ssp. *acuminata*** (mungart, raspberry jam wattle) – Yielded 0.72% alkaloids from stems and phyllodes of a “broad-leaf” form (harv. Oct.), consisting mostly of tryptamine. A “narrow-leaf” form (either of ssp. *acuminata* or ssp. *burkittii* – see below) yielded 1.5% alkaloids from stems and phyllodes (harv. Oct.), consisting mostly of tryptamine, as well as smaller amounts of phenethylamine, and another unidentified non-volatile base (White, 1957). In an alkaloid screening, phyllodes of a plant from a nursery in Victoria gave strong positive results (Collins et al., 1990). TLC/GC-MS analysis of the “narrow-leaf” and “small-seed” varieties found phyllodes to contain 0.6-0.8% DMT, and up to

1.6% in bark; young phyllodes contained almost entirely tryptamine (J.J., 2007). Another phyllode sample of the “narrow-leaf” variety (harv. Feb.) yielded 0.9-1% alkaloids, found by GC-MS to consist mainly of DMT, with traces of 2-methyl-1,2,3,4-tetrahydro- $\beta$ -carboline (2-methyl-TH $\beta$ C) and an unidentified peak. Phyllodes from the “broad-leaf” variety (harv. Jun.) yielded c.1% alkaloids, found by GC-MS to consist of mainly tetrahydroharman, as well as (in decreasing concentration) DMT, tryptamine, 3-methyl-quinoline (tentative), harman, N-methyl-phenethylamine, and phenethylamine. Preliminary TLC assay tentatively showed DMT, NMT, and 4 unidentified spots, although NMT did not show up in the GC-MS analysis (endlessness & nen888, 2011-2012). A decoction of 50 g phyllodes from this same specimen had mild psychedelic activity lasting c.90 minutes, taken orally with no additional MAOI (nen888, 2011-2013).

**Acacia acuminata ssp. burkittii** (F. Muell. ex Benth.) Kodala et Tindale (*A. burkittii* F. Muell. ex Benth.) (gunderbluey, Burkitt’s wattle, fine leaf jam wattle, sandhill wattle) – See ssp. *acuminata* above for an analysis on an indeterminate specimen which might have been ssp. *burkittii* (White, 1957). TLC/GC-MS analysis found ssp. *burkittii* to be very variable in content, with the bark of wild plants yielding 0.2-1.2% DMT, and phyllodes yielding under 0.1% alkaloids, mostly NMT (J.J., 2007).

**Acacia adunca** A. Cunn. ex G. Don. (*A. accola* Maiden & Betche) (Wallangarra wattle, cascade wattle) – Stems, phyllodes, and flowers (harv. Aug.) yielded 3.2% alkaloids, which appeared to consist of c.70% N-methyl-phenethylamine, with smaller amounts of phenethylamine (White, 1957); phyllodes from Queensland yielded 2.4% N-methyl-phenethylamine (Fitzgerald, 1964a).

**Acacia alpina** F. Muell. (alpine wattle) – Suspected of containing DMT based on human bioassay of 30-40 g dry phyllodes with 4 g *Peganum harmala* seeds (nen888, 2011-2013). Rovelli (1967) detected no alkaloids.

**Acacia auriculiformis** A. Cunn. ex Benth. (marra, northern black wattle, ear-pod wattle) – Phyllodes have tested positive for alkaloids (Aboriginal Communities, 1988); others have tentatively identified 5-MeO-DMT in stem bark (harv. Apr.) by TLC (Trout ed., 1997). Phyllodes were found to contain small amounts of 2-OH-



pyridine, 3-OH-pyridine, 4-OH-pyridine, 2-MeO-pyrazine, 6-methyl-3-pyridazinone, 1,1,3,3-tetramethylbutylamine, 2-methyliminoperhydro-1,3-oxazine, and 4-methyl-2-oxopentanenitrile, as well as numerous non-nitrogenous compounds (GC-MS) (Ibrahim et al., 2015). Aerial parts have also yielded 0.01% auriculose, a flavan glycoside with mild CNS-depressant activity (Sahai et al., 1980). An ethanol extract of fresh phyllodes from Indian plants (harv. Jun.) improved memory and inhibited brain acetylcholinesterase in rats (Sharma et al., 2014).

**Acacia baileyana** F. Muell. (Cootamundra wattle) – Leaves from plants growing in California yielded 0.02% alkaloids in late March [80% tetrahydroharman, 20% tryptamine], and 0.028% in early October [tryptamine only]; July collections yielded no alkaloids (Repke et al., 1973). Stems, leaves, flowers, and seeds from plants growing in New Zealand (harv. Mar., Aug.) were shown to contain small amounts of alkaloids (White, 1944a). Ripe and unripe pods have yielded c.0.02% unidentified alkaloids, with ripe and unripe seeds showing only traces (White, 1951). Seeds might contain DMT and 2 other indoles (all tentative) in small amounts (TLC) (Trout ed., 1997). One amateur researcher claimed to have extracted DMT from the bark (EsKaTaRi, 2010), but based on descriptions of the psychoactive effects of the smoked alkaloid/s at a reported dose of 200-300 mg, there is no reason to think DMT was present in the extract unless the dose was actually 20-30 mg or less. Several people have experimented with smoking the leaves, the effect of which has been described by one person as “somewhere in between tobacco and weed” (Cannabis) (maxzar100, 2009; personal observations).

**Acacia binervata** DC. (two-veined hickory) – Phyllodes yielded c.0.2-0.3% alkaloids; may contain DMT based on reagent-positive reactions, compared with *Psychotria viridis* Ruíz et Pav. leaf as a reference standard (nen888, 2011-2013). Another researcher obtained no alkaloid yield from the bark, despite it having an alkaloidal taste (chocobeastie, 2011-2012). One screening detected no alkaloids in phyllodes (harv. Jun.) (Smolenski et al., 1973).

**Acacia buxifolia** A. Cunn. (box-leaf wattle) – Stems and phyllodes (harv. Dec.) from a variety slightly different than the

norm yielded 0.65% alkaloids; seeds yielded 0.09% alkaloids; pods yielded 0.58% alkaloids. The alkaloid mixture appeared to consist largely of phenethylamine (White, 1951).

**Acacia cardiophylla** A. Cunn. ex Benth. – Stems, leaves, and flowers (harv. Oct.) yielded 0.03% alkaloids; stems and leaves yielded 0.02-0.06% alkaloids (highest in Mar.). The alkaloid mixture appeared to contain tryptamine and phenethylamine (White, 1957). In an alkaloid screening, leaves and stems from Mitcham, Victoria gave negative results (Collins et al., 1990).

**Acacia caroleae** Pedley (narrow-leaf currawang) – Phyllodes have yielded alkaloids, mainly DMT (subjective identification from vapourisation) (nen888, 2011-2013; nen888 pers. comm., 2017).

**Acacia colei** Maslin & L.A.J. Thomson (Cole's wattle) – Has been claimed to contain high concentrations of DMT (Kruszelnicki, 2005), but it is unclear where Kruszelnicki obtained this information, which may be based on misidentification of the closely related *A. neurocarpa* (see below), or simply false. Plants believed to be true *A. colei* have not yet yielded alkaloids (Palmer pers. comm., 2011).

**Acacia complanata** A. Cunn. ex Benth. (flat-stemmed wattle, weeping wattle) – Phyllodes and stems from south Queensland yielded 0.3% N-methyl-tetrahydroharman, and traces of tetrahydroharman (Johns et al., 1966). Another sample yielded 0.22% alkaloids from phyllode and stem (Collins et al., 1990). Bark has been claimed to contain DMT based on at least one reported successful extraction. Attempts have been made to utilise *A. complanata* alkaloids as an oral MAOI, in order to allow for the activity of orally consumed tryptamine alkaloids from *A. obtusifolia*. 100 mg of alkaloids in HCl salt form extracted from the foliage did not activate tryptamine alkaloids taken orally, but did seem to potentiate and lengthen the effects of smoked *A. obtusifolia* alkaloids (Mulga, 1996b). Another person found no oral activation of DMT using up to 1000 mg of *A. complanata* alkaloids (Torsten, 2008). A decoction of 20 phyllodes from a bitter-tasting specimen had sedative effects in one person (nen888, 2011-2013).

**Acacia concurrens** Pedley (curracabah) – Evaporated ethanol tincture of branch bark was reported to be psychoactive when taken orally with an MAOI (seldom, 2012); identification of the plants

needs to be confirmed, as this species is readily confused with the closely related *A. crassa* Pedley, *A. leiocalyx* (Domin) Pedley, and *A. longispicata* Benth., which all used to be grouped under *A. cunninghamii* Hook. f., now an invalid name (Butcher et al., 2001). As such, it is not known which species under that name was found to contain saponins in the unripe seed pods, described as “a strong poison for the muscles and nerves and producing local anaesthesia very much like cocaine”, as well as having irritant properties (Lauterer, 1897). It is also unclear whether Lauterer’s cocaine comparison was in reference specifically to the saponins isolated from this plant, or to “saponin” in general, as the diversity of saponins was poorly known at that time, and Lauterer’s writing style was imprecise in this case.

**Acacia cultriformis** A. Cunn. ex G. Don (knife-leaf wattle) – Phyllodes and stems yielded 0.07% alkaloids in Feb., 0.06% in Apr.; an August assay found 0.02% alkaloids in stems, 0.02% in phyllodes, and 0.04% in seeds. The alkaloids appeared to include phenethylamine (White, 1944a). Stems and phyllodes from two separate plants (harv. Dec.) yielded, respectively, traces and 0.02% alkaloids, and unripe seed pods yielded 0.04% alkaloids; this appeared to consist mainly of tryptamine (White, 1951). Stems and phyllodes (harv. Jul.) yielded 0.02% alkaloids, consisting partly of tryptamine, and a phenethylamine-like base (White, 1957). TLC analysis showed tentative presence of 5-MeO-DMT in phyllodes, twigs, and flowers (Trout, ed., 1997).

**Acacia cyclops** A. Cunn. ex G. Don (western coastal wattle) – Bark and phyllodes from a specimen growing in South Africa yielded a small amount of unidentified alkaloids, which were psychoactive on vapourisation, with a slow onset (roughly two minutes) and lasting about twenty minutes. Effects were psychedelic in character but not as visual as DMT, and the extract possibly consists of NMT and other alkaloids. Bark from a different specimen harvested after heavy rain yielded no alkaloids (PrimalWisdom, 2011). In Australia, people have had variable results, with low or absent yields of what seem to be tryptamine alkaloids (subjective i.d., plus TLC assay of unspecified plant parts in one case) (nen888, 2011-2013; shanedudddy2, 2013).

**Acacia dallachiana** F. Muell. (catkin wattle) – Phyllodes may

contain DMT based on limited human bioassays of vapourised alkaloid extracts (nen888, 2011-2013; nen888 pers. comm., 2017), although some attempts at extraction obtained no alkaloids (chocobeastie, 2011-2012).

**Acacia dealbata** Link (silver wattle) – Leaf from Queensland plants (harv. Jun.) gave weak positive results in alkaloid screening (Webb, 1949). Stems, leaves (harv. Nov.), and seeds were found to contain <0.01% alkaloids which were not identified (White, 1944a). Plants growing in Portugal yielded 0.58-1.9% unidentified alkaloids from aerial parts, with highest yields from acetone extracts and lowest from ethanol extracts (Luís et al., 2012). Has been claimed to contain DMT (EsKaTaRi, 2010)<sup>24</sup> in some specimens, not others (Palmer pers. comm., 2011).

<sup>24</sup>. See comments for *A. baileyana* by this source regarding the questionable subjective identification of DMT.

**Acacia difformis** R.T. Baker (wyalong wattle, drooping wattle) – Tryptamines including 5-MeO-DMT were tentatively detected (TLC) in young plants initially misidentified as *A. implexa* Benth. (Trout, ed., 1997), though specifics are currently under review due to discovery of a data mix-up (Trout pers. comm., 2017).

**Acacia effusifolia** Maslin & Buscumb (*A. coolgardiensis* ssp. *effusa* R.S. Cowan & Maslin) – Bark yielded 0.4-0.5% alkaloids, phyllodes yielded 0.2% alkaloids, consisting mainly of NMT, as well as DMT; exposed plants seem to contain more NMT, as well as norharman (TLC) (J.J., 2009).

**Acacia elata** A. Cunn. ex Benth. (mountain cedar wattle) – Branches and bark yielded c.0.3% alkaloids, consisting of DMT, 5-MeO-DMT, NMT, N-formyltryptamine (tentative), and  $\beta$ -carboline (GC-MS). The alkaloids were strongly psychedelic when vapourised in doses of 30-50 mg, lasting up to 45 minutes. An alkaloid extract from a flowering specimen had much milder, non-visionary effects with a meditative quality (nen888, 2011-2013). An early analysis found <0.01% alkaloids in stems, leaves (harv. Mar. & Nov.), and seeds, which were not identified (White, 1944a); unripe pods were found to contain traces of alkaloids, with none in the bark or unripe seeds (White, 1951).

**Acacia excelsa** Benth. (ironwood, rosewood) – Phyllodes and

stems gave positive tests for alkaloids (Collins et al., 1990); TLC analysis of unspecified parts found 5-MeO-DMT and unidentified tryptamines (J.J., 2009).

**Acacia falcata** Willd. (burra, hickory wattle) – Phyllodes and twigs from young, flowering trees yielded 0.025% alkaloids, which were psychoactive on vapourisation, but with unusual non-psychedelic effects that lasted up to 45-60 minutes. The dose (c.20mg) consisted of the entire crude alkaloid extract, so effects of higher doses are unknown (nen888, 2011-2013). An early analysis found <0.01% alkaloids in phyllodes and stems (harv. May), which were not identified (White, 1944a); “insignificant” alkaloid concentrations were found in stems/phyllodes (harv. Apr., Dec.), stems/phyllodes/flowers (harv. Jul.), and ripe seeds/pods. One sample of phyllodes (harv. Jul.) contained no alkaloids (White, 1957).

**Acacia fimbriata** A. Cunn. ex G. Don. (fringed wattle, Brisbane golden wattle) – Phyllodes and bark (harv. Mar.) tested positive for alkaloids (Webb, 1949); in a later screening, phyllodes (harv. time unspecified) also tested positive for alkaloids (Collins et al., 1990); phyllodes and twigs appear to contain phenethylamines, based on reagent colour reactions, and compared with similar colour reactions with *A. harpophylla* (see below) (nen888, 2011-2013).

**Acacia flavescens** A. Cunn. ex Benth. (yellow wattle, red wattle) – Bark has been claimed to have “strongly psychoactive” properties (Anonymous, 2015), with no reference or supporting information.

**Acacia floribunda** (Vent.) Willd. (gossamer wattle, sally wattle) – Phyllodes yielded 0.07-0.08% alkaloids; stems yielded 0.04-0.19% alkaloids; stems/phyllodes combined yielded 0.06-0.16% alkaloids; and flowers yielded 0.15-0.98% alkaloids. Phenethylamine was isolated as a minor component (White, 1944a). In follow-up work, tops (harv. Apr.) yielded 0.18% alkaloids, consisting mostly of tryptamine, with traces of phenethylamine; flowers (harv. Sep.) yielded 1.18% alkaloids (0.82% from an undated harvest), consisting of +/- equal quantities of tryptamine and phenethylamine (White, 1944b); bark has yielded traces of an alkaloid that was not identified (White, 1951). Using TLC/GC-MS, phyllodes were found to contain mostly DMT (usually less than

0.1%); bark yielded up to c.1% alkaloids, with 0.3-0.5% DMT, slightly less NMT, and small amounts of tryptamine, harman, and norharman (J.J., 2007). A specimen infected with galls gave particularly good yields of tryptamines (personal communication, 2011).

**Acacia harpophylla** F. Muell. ex Benth. (brigalow) – Phyllodes and twigs from Queensland yielded 0.6% alkaloids (phenethylamine and hordenine in a 2:3 ratio) (Fitzgerald, 1964b); another screening found 0.1% alkaloids in phyllodes and 0.3% in bark (Collins et al., 1990). Bark from branchlets (harv. Jun.) tested strongly positive for alkaloids, though bark of the stems tested negative (Webb, 1949). One screening detected no alkaloids in phyllodes and stem bark (harv. Apr.) (Smolenski et al., 1973). An alkaloid extract from phyllodes taken orally (dose not recorded) was reported to have sedative effects (nen888, 2011-2013; nen888 pers. comm., 2017).

**Acacia holosericea** A. Cunn. ex G. Don (soap bush, silver-leaved wattle) – Bark from Queensland has yielded 1.2% hordenine (Fitzgerald, 1964b); plants from another Queensland location yielded 1.22% alkaloids from the bark, and phyllodes and stems gave weak positive reactions for the presence of alkaloids (Collins et al., 1990). Two other screenings detected no alkaloids in phyllodes and stem bark (harv. Jul.) (Smolenski et al., 1973), or in phyllodes, bark, and root (harv. time not specified) (Aboriginal Communities, 1988). The identity of the plants assayed in all cases may be in question, as this species has often been confused with the similar *A. colei*, *A. neurocarpa* (both of which were only distinguished from *A. holosericea* after these reports), and *A. cowleana* (Maslin & Thomson, 1992).

**Acacia kettlewelliae** Maiden (buffalo wattle) – Phyllodes and stems yielded 1.3% alkaloids in Apr. and 1.88% in Oct., which appeared to consist of more than 92% phenethylamine, with no tryptamine (White, 1957); phyllodes from central Victoria yielded 0.9% N-methyl-phenethylamine (Fitzgerald, 1964a).

**Acacia latior** (R.S. Cowan & Maslin) Maslin & Buscumb (*A. coolgardiensis* ssp. *latior* R.S. Cowan & Maslin) – Found to contain roughly equal amounts of NMT and DMT in phyllodes in some samples, though many samples had no observable tryptamines

(TLC). Very variable in morphology and alkaloids. (J.J., 2011).

**Acacia leiocalyx** (Domin.) Pedley **ssp. leiocalyx** (curracabah, early flowering black wattle) – Stem bark yielded 0.3-0.4% unspecified tryptamine alkaloids (nen888, 2011-2013). Others have had no success in extracting alkaloids from this subspecies (seldom, 2014). Alkaloid content appears to fluctuate greatly, possibly depending on weather (Borris, 2012-2013).

**Acacia leptostachya** Benth. (*A. argentea* Maiden) (slender wattle, Townsville wattle) – Phyllodes have yielded 0.03-0.6% N-cinnamoyl-histamine (Fitzgerald, 1964b).

**Acacia linifolia** (Vent.) Willd. (*A. linearis* (J.C. Wendl.) J.F. Macbr.) (flax-leaved wattle, white wattle) – Stems and phyllodes were reported to contain phenethylamine (White, 1944a), but the plants analysed were later found to have been *A. prominens* (see below). Stems, phyllodes, and flowers of genuine *A. linifolia* (harv. Apr., Sydney) yielded 0.03% of an alkaloid that was not identified (White, 1951). Stems and phyllodes from Sydney plants contained “insignificant concentrations of alkaloid” in Oct. (White, 1957).

**Acacia longifolia** (Andrews) Willd. *ssp. longifolia* (sallow wattle, Sydney golden wattle) – Tops from plants growing in New Zealand (harv. Nov.) yielded 0.12% alkaloids; c.1% was obtained from tops with an unspecified harvest time; flowers (harv. Sep.) yielded 0.186% alkaloids. In both, phenethylamine was identified as a minor constituent, and though tryptamine-like bases seemed to be present, tryptamine itself was not detected (White, 1944b), except in some samples of flower spikes (White, 1951). Tops and flowers combined have yielded up to 0.01% phenethylamine; in one sample, it only comprised 9.2% of the total alkaloids. Stems and phyllodes collected at various times in New Zealand yielded 0.02-0.29% alkaloids; there was no clear correlation between yield and month of harvest. From an Oct. harvest, stems yielded 0.15% alkaloids, phyllodes 0.06%, and flowers 0.14-0.29% (White, 1944a). Bark (harv. Apr.) yielded 0.03% alkaloids; seeds yielded 0.01% alkaloids (White, 1951). Material from Australia (location not specified) was found to contain N-cinnamoyl-histamine, 3-OH-dec-2-enoyl-histamine, and other histamine-amides in the phyllodes (from 0.2% total crude alkaloids) (Rovelli, 1967). Plants growing naturalised in California yielded N-cinnamoyl-histamine and N-decadienoyl-

histamine. Respectively, phyllodes (harv. late Jan.) yielded 0.0038-0.004%/0.0225-0.024%, phyllodes (harv. Mar.) yielded 0.0067%/0.027%, bark (harv. late Jan.) yielded 0.015%/0.0175%, and pods (harv. at maturity in Jul.) yielded 0.09-0.17%/0.06-0.112%. Seeds (harv. Jul.) and flower spikes (harv. in Mar., fresh) contained traces of these two compounds (Repke, 1975). However, independent psychonauts have verified that at least some examples of this species can produce DMT and other alkaloids. Up to 0.3% DMT (as well as what may be tryptamine) has reportedly been obtained from aerial parts, with highest yields in winter (E, 1996; nen888, 2011-2013). Also, in 1995, a friend succeeded in obtaining DMT (subjective i.d.) from the bark of *A. longifolia* ssp. *longifolia* from Victoria. This was successfully smoked by six people (pers. comms.). Phyllodes have also rarely been used in *ayahuasca* analogues in New South Wales, although caution is advised when consuming decoctions of specimens of unknown alkaloid content (nen888, 2011c; nen888 pers. comm., 2017). Although heavy rain is often associated with low alkaloid yields, with this species one person obtained higher yields of alkaloids, including DMT, from material harvesting during heavy rain, and lower yields with proportionally less DMT present from material harvested 2 weeks after the last rain (acacian, 2014).

***Acacia longifolia* ssp. *sophorae*** (Labill.) Court (*A. sophorae* (Labill.) R. Br.) (coast sallow wattle) – Alkaloid screening in Australia revealed strong presence of alkaloids in the phyllodes (Collins et al., 1990). Specimens from Mentone, Victoria, were found to contain N-cinnamoyl-histamine, 3-OH-dec-2-enoyl-histamine, and other histamine-amides in phyllodes (from 0.1% crude bases in May, 0.03% in Jan.) (Rovelli, 1967). A form of *A. longifolia* close to ssp. *sophorae* yielded 0.15% crude alkaloids from unripe pods, 0.07% from stems and phyllodes (harv. May), and none from seeds; the alkaloids apparently included phenethylamine (White, 1944a). In the “informal” literature, some forms have been reported to contain tryptamine alkaloids. One specimen was claimed to have yielded DMT, 5-MeO-DMT, gramine, and histamine derivatives at levels of 0.6% in bark, and 0.15% in phyllodes, in an elusive unpublished analysis (E pers. comms., 1999-2001; E 1996). Alkaloids extracted from plants growing in California were found to



contain DMT as a minor alkaloid in both bark and phyllodes, a faint spot possibly corresponding to NMT, and a major component that was not identified (TLC). GC-MS follow up of the same extract confirmed the presence of DMT and NMT (as well as numerous unidentified peaks), but could not identify the major alkaloid, which was possibly a phenethylamine (Siebert, 2017). Branch bark from one specimen of a more erect, tree-like variety from NSW yielded c.0.5% alkaloids, including mainly DMT (subjective i.d.). Seed pods have also yielded alkaloids including tryptamines (nen888, 2011-2013). Success in obtaining tryptamine alkaloids from this subspecies has been highly variable, from many attempts by different people over the last two decades (pers. comms.).

**Acacia longissima** Hort. ex H.L. Wendl. (*A. linearis* Sims) (narrow-leaf wattle) – Phyllodes yielded 0.2-0.3% alkaloids, including DMT (subjective i.d.) (nen888, 2011-2013). Plants from Springbrook, Queensland, yielded 0.25% alkaloids from phyllodes and 0.02% from bark; the identity of the alkaloid/s was not reported. As *A. linearis* Sims, phyllodes gave positive results in alkaloid screening; however these plants were from the same source as the plants analysed as *A. longissima* (Collins et al., 1990), suggesting that the *A. linearis* analysis was on *A. linifolia* (syn. *A. linearis* non Sims, see above). Less than 0.01% alkaloids were detected in stems and phyllodes (harv. Jul., Oct.), and seeds (White, 1944a). One screening detected no alkaloids in phyllodes and stem bark (harv. May) (Smolenski et al., 1972).

**Acacia mabellae** Maiden (Mabel's wattle, black wattle) – Phyllodes and twigs from a tree in east NSW yielded unidentified psychoactive tryptamines (subjective i.d. from vapourisation) (timeloop, 2012).

**Acacia macradenia** Benth. (zig-zag wattle) – Claimed to have “tested positive for tryptamine content” (translated from Polish – <http://herbarium.o-700.pl/Akacje.html>), but no details were given for the source of this information, and it is yet to be publicly verified.

**Acacia maidenii** F. Muell. (Maiden's wattle) – Bark yielded 0.36% DMT, and 0.24% NMT (Fitzgerald & Sioumis, 1965), though a later screening found a slightly higher yield of 0.71% total alkaloids. Bark extracted for pharmacological testing yielded 0.13%

alkaloids, consisting of DMT and NMT (Collins et al., 1990). Younger trees are said to give the best yields (E, 1996). Others have had little success with obtaining DMT from this plant, due to quite variable yields. The common form with broader, more falcate phyllodes appears to be +/- deficient in alkaloids. The phyllodes of useful varieties are said to sometimes contain greater levels of alkaloids than bark (Mulga, 1996a; nen888, 2011-2013; pers. comms.); in an early alkaloid screening, the phyllodes gave a strong-positive reaction (Rovelli, 1967). Phyllodes and bark from Tamborine, Queensland (harv. Jun.) tested strongly positive for alkaloids (Webb, 1949). 5-MeO-DMT was tentatively detected in wood (weak positive) and twigs (TLC) (Trout, ed., 1997).

**Acacia mangium** Willd. (hickory wattle, black wattle) – Rumoured to contain psychoactive alkaloids, though documented extraction attempts by amateur researchers have been inconclusive so far (nen888, 2011-2013). Phyllodes and bark gave weak positive test for alkaloids (Collins et al., 1990), although one screening detected no alkaloids in stem bark (harv. Jul.) (Smolenski et al., 1973).

**Acacia mearnsii** De Wild. (*A. decurrens* var. *mollis* Lindl.) (black wattle) – Yielded <0.01% unidentified alkaloids from seeds (White, 1944a), 0.02% from stem, leaf, and flower (harv. Oct.), and none in galls (White, 1951); leaf and stem of one sample from Healesville, Victoria, gave negative results in alkaloid screening (Collins et al., 1990). However, bark from one specimen in northern Victoria (harv. Dec.) yielded 1.2% alkaloids including DMT (subjective i.d. following vapourisation), though the same tree yielded no alkaloids four months later (chocobeastie, 2011-2012). Branch bark from another specimen in central Victoria (harv. Dec.) yielded c.0.4-0.5% unidentified tryptamines (nen888, 2011-2013; nen888 pers. comm., 2017).

**Acacia melanoxylon** R. Br. (mugerabah, blackwood) – Phyllodes and stems (harv. Apr., Aug.) were found to contain <0.01% alkaloids (White, 1944a); phyllodes and stems from one Victorian location gave negative tests for alkaloids, though young phyllodes from another Victorian location gave strong positive results (Collins et al., 1990). Bark and seeds in one sample were alkaloid free, but pods yielded 0.03% unidentified alkaloids (White,

1951). Many people have attempted to extract tryptamine alkaloids from this variable species, mostly without success. However, one large fallen tree in NSW, growing near *A. maidenii*, yielded 0.6-0.7% tryptamine alkaloids (subjective i.d.) (nen888, 2011-2013). Plants growing in Portugal yielded 0.41-1.8% unidentified alkaloids from aerial parts, with highest yields from methanol extracts and lowest from hydroalcoholic extracts (Luís et al., 2012).

***Acacia mucronata* ssp. *longifolia*** (Benth.) Court (*A. mucronata* var. *dissitiflora* Benth.) (narrow-leaf wattle) – Alkaloids were detected in the phyllodes (Collins et al., 1990), and also in an unspecified variety of the species, which gave a slightly stronger reaction (Rovelli, 1967). Young plants 6-8 months old yielded c.0.3-0.4% crude alkaloids from phyllodes and stems; phyllode alkaloids consisted of tryptamine, NMT, and 2-methyl-TH $\beta$ C as the main alkaloids, with lesser amounts of harmine, possibly N-formyl-NMT, and 6 unidentified peaks; twig alkaloids contained mainly tryptamine, with (in decreasing concentration) harmine, NMT, possibly N-formyl-NMT, oleamide, 2-methyl-TH $\beta$ C, tetrahydroharman, indole, harman, tryptophol, and several unidentified peaks and possible solvent contaminants (TLC/GC-MS) (endlessness & nen888, 2011-2012). A decoction of 50-60 g phyllodes from the same specimen had mild psychedelic effects when taken orally with no additional MAOI. Stem bark from another specimen yielded 0.4-0.6% alkaloids, including DMT, NMT, tryptamine, and  $\beta$ -carboline (GC-MS) (nen888, 2011-2013). Phyllodes of some specimens appear to sometimes contain DMT and other alkaloids (E pers. comms., 1999-2001).

***Acacia multisiliqua*** (Benth.) Maconochie – Low amounts of DMT & NMT were detected in bark of one specimen, with no tryptamines detected in other samples (TLC) (J.J., 2011).

***Acacia myrtifolia*** (Sm.) Willd. (myrtle wattle, red-stemmed wattle) – Phyllodes and stems yielded 0.76% crude bases, including (-)-acacine (a new spermidine alkaloid), and traces of unidentified alkaloids (Nichols, 1983). Alkaloid yield did not vary seasonally in plants from the Dandenong Ranges (Vic.) (Rovelli, 1967). Stems and phyllodes from Sydney, Australia (harv. Apr.) did not yield any alkaloids (White, 1951). Another screening detected no alkaloids in phyllodes (harv. Jun.) (Smolenski et al., 1973).

**Acacia neurocarpa** A. Cunn. ex Hook. (*A. holosericea* var. *neurocarpa* (A. Cunn. ex Hook.) Domin) – Claimed to be a good source of DMT (subjective i.d.) (Palmer pers. comm., 2011). Has been confused with *A. pellita* (Maslin & Thomson, 1992).

**Acacia neurophylla** W. Fitzg. – Hybridises with *A. acuminata*, and is represented by two subspecies – ssp. *neurophylla* and ssp. *erugata* R.S. Cowan & Maslin. The former is very variable, and some specimens may represent new species or subspecies. Plants from the *A. neurophylla* complex were found to contain mostly DMT in the bark, with phyllodes containing mostly harman and norharman, with only traces of DMT or no DMT (TLC/GC-MS) (J.J., 2007).

**Acacia obtusifolia** A. Cunn. (blunt leaf wattle) – A variable species which has sometimes been confused with *A. maidenii*, *A. longifolia* ssp. *longifolia*, and *A. orites* in the field (pers. comms.). Bark has yielded 0.15% alkaloids, though their identities were not reported (Collins et al., 1990); in northeast NSW, 0.15-0.2% has typically been isolated (E pers. comms., 1999-2001), though others have achieved higher yields of 0.4-0.5%. Fresh young phyllodes yielded c.0.07% alkaloids (Mulga, 1996a). Dried phyllodes from different locations have yielded 0.15-0.3% alkaloids, consisting mostly of NMT with lesser amounts of DMT and traces of  $\beta$ -carboline, according to two commissioned analyses (GC-MS) (E pers. comms., 1999-2001; nen888 pers. comm., 2017), although TLC performed on an extract of another phyllode sample (using pure reference standards) observed mostly DMT with lesser amounts of NMT (Siebert, 2017). Preliminary TLC analysis of one bark extract revealed the presence of at least five alkaloids, including what were very tentatively identified as DMT, 5-MeO-DMT, and bufotenine. At some times of year, plants from the same patch yielded an extract seemingly comprised of DMT and a larger quantity of NMT (E pers. comms., 1999-2001). In one array of extracts, initial analysis by GC-MS found all to contain mainly DMT, with traces of bufotenine in an orange-coloured summer extract, and higher levels of bufotenine in darker-coloured extracts; a second analysis of the darkest sample found no bufotenine, but did find 1,2-dimethyl-TH $\beta$ C (Trout, 2005). Any bufotenine present might not have been detected in this second analysis due to

technical issues (Trout, pers. comm., 2017). Another analysis of stem bark extract by HPLC-MS found DMT as the major alkaloid by far, with traces of tryptamine, possibly NMT, and unidentified  $\beta$ -carbolines; no 5-MeO-DMT or bufotenine was observed (Mulga, 2005). Another analysis (TLC/GC-MS) using plants from various sources also found no 5-MeO-DMT or bufotenine. In general, bark contained mostly DMT, with lesser amounts of NMT, tryptamine, harman and norharman; phyllodes contained mostly NMT, with lesser amounts of DMT (J.J., 2007). A form from south NSW (harv. Mar.) yielded 0.6-0.7% alkaloids from twigs, 0.4-0.5% from phyllodes, and 0.5-0.6% from bark; alkaloids appeared to consist almost entirely of DMT, with traces of 2-methyl-TH $\beta$ C, and possibly 3-methylquinoline; traces of DMT N-oxide were also detected in the twig extract. The phyllode and bark extracts indicated the presence of small levels of NMT (TLC) which appear to be co-chromatographing with DMT in the GC-MS analysis of these samples due to its low concentration. Another south NSW specimen (harv. Mar.) yielded 0.3-0.4% alkaloids from twigs, consisting mostly of DMT, with traces of 2-methyl-TH $\beta$ C, harmine, and possibly 3-methylquinoline (TLC/GC-MS) (endlessness & nen888, 2011-2013).

**Acacia orites** Pedley (mountain wattle) – Has on occasion been confused with *A. obtusifolia* and *A. longissima* (see above). Some underground researchers have reported obtaining alkaloids that might be  $\beta$ -carbolines (E pers. comms., 1999-2001).

**Acacia oxycedrus** Sieber ex DC. (spike wattle) – Phyllodes and stems from Victoria gave positive tests for alkaloids in a screening; another sample yielded 0.16% unidentified alkaloids (Collins et al., 1990; Rovelli, 1967). Some samples have yielded useful quantities of tryptamine alkaloids including DMT (subjective i.d.), although others have yielded no alkaloids. Branch and stem bark of a naturally occurring hybrid (possibly x with *A. longifolia* ssp. *longifolia*, or *A. mucronata*) has yielded 0.3-0.7% alkaloids, including DMT (subjective i.d.) (nen888, 2011b, 2011-2013).

**Acacia phlebophylla** H.B. Will. (Buffalo sallow wattle) – Phyllodes (harv. May) gave a strongly positive result in alkaloid screening; “leaves and tops” harvested later (Aug.) yielded 0.3% DMT as apparently the sole alkaloid (or at least the major alkaloid

by far) (Rovelli, 1967; Rovelli & Vaughan, 1967). A recent TLC/GC-MS analysis estimated phyllodes to contain up to 0.6% DMT, though the youngest growth was much less potent (J.J., 2007). Young phyllodes contain mostly tryptamine (TLC) (J.J., 2009).

**Acacia podalyriaefolia** A. Cunn. ex G. Don (Queensland silver wattle) – Bark from Ipswich, Queensland, yielded 0.12% alkaloids; stems and phyllodes yielded 0.28% alkaloids (Collins et al., 1990); stems and phyllodes (harv. Feb.) yielded 0.11% alkaloids, which appeared to contain phenethylamine (White, 1944a); stems and phyllodes (harv. Nov.) yielded 0.29% alkaloids, which appeared to consist mainly of tryptamine, with smaller amounts of phenethylamine (White, 1957); stems and phyllodes collected after flowering yielded 0.11% alkaloids, consisting mostly of tryptamine, with no phenethylamine (White, 1951); seeds and pods yielded 0.11% alkaloids, also consisting mainly of tryptamine, with smaller amounts of phenethylamine (White, 1957). Phyllodes harvested at an unspecified time yielded (w/w) 0.06% tryptamine (Balandrin et al., 1978). One screening detected no alkaloids in phyllodes and stem bark (harv. Sep.) (Smolenski et al., 1973).

**Acacia polystachya** A. Cunn. ex Benth. – Bark yielded 0.35% N-cinnamoyl-histamine (Fitzgerald, 1964b).

**Acacia pravissima** F. Muell. (Oven's wattle, wedge-leaf wattle) – Stems (harv. Aug.) yielded 0.13% alkaloids; phyllodes (harv. Aug.) yielded 0.31% alkaloids; stems/phyllodes combined (harv. Mar.) yielded 0.44% alkaloids. This appeared to consist largely of phenethylamine (White, 1944a). Tops (harv. Jan.) yielded 0.69% crude alkaloids, consisting mostly of phenethylamine (White, 1954).

**Acacia prominens** A. Cunn. ex G. Don (*A. praetervisa* Domin) (Gosford wattle, golden rain wattle) – Stems/phyllodes yielded 0.2-0.65% alkaloids (highest found in Aug. and Dec.); stems and phyllodes separately (harv. Aug.) yielded 0.17% alkaloids each; seeds yielded 0.04% alkaloids. Phenethylamine appeared to be the major alkaloid (White, 1944a, 1951). Stems and phyllodes from both a small and a large tree yielded 0.23% and 0.25% alkaloids, respectively (harv. Aug.); this consisted of c.50% phenethylamine and c.20% N-methyl-phenethylamine (White, 1957). Flowering tops of a horticultural variety yielded 1.8% alkaloids, consisting mostly of

what was tentatively identified as phenethylamine and N-methyl-phenethylamine. Other samples of tops yielded 1.11-2.38% crude alkaloids. Both types varied in which alkaloid was predominant at different times, though no definite correlations could be determined (White, 1954). *A. hakeoides* A. Cunn. ex Benth. was reported to contain phenethylamine (White, 1944a), but the plants analysed were later determined to have been *A. prominens* (White, 1951).

**Acacia provincialis** A. Camus (wirilda, swamp wattle) – Bark and phyllodes of plants growing in Bolivia yielded varying quantities of unidentified alkaloid/s, not DMT but apparently a tryptamine or tryptamines (subjective i.d.). The effects of the alkaloid/s were psychedelic when vapourised or snuffed, with a slow onset peaking after 20-30 minutes and lasting up to an hour (yatiqiri, 2011). A very variable species, formerly classified under *A. retinodes* (see below) (O’Leary, 2007).

**Acacia pruinosa** A. Cunn. ex Benth. (frosty wattle) – Tops have yielded 0.04% alkaloids, consisting mostly of tryptamine, with small amounts of phenethylamine (White, 1944b); stems and leaves (harv. Feb.) yielded 0.03% alkaloids; (harv. May) 0.09% alkaloids; and (harv. Oct.) 0.02% alkaloids (White, 1944a); stems, leaves, and flowers (harv. Aug., Dec.) yielded 0.02% alkaloids from both samples; no alkaloids were found in seeds or unripe pods (White, 1951, 1957).

**Acacia pycnantha** Benth. (golden wattle) – Less than 0.01% alkaloids were detected in phyllodes and stems (harv. Apr.), and stems, phyllodes, and flowers (harv. Sep.) (White, 1944a). An alkaloid screening did not reveal the presence of alkaloids in the phyllodes of the “weeping variety” (Rovelli, 1967). A small amount of what may have been DMT (subjective i.d.) was extracted from phyllodes, but the small quantity was only sufficient for mild threshold effects (pers. obs., 1996). Attempts at extracting alkaloids from this species by amateurs have had variable results, usually with low or absent yields, but occasional plants have given good yields of alkaloids including DMT (subjective i.d.) (nen888, 2011-2013). Small stems of one specimen yielded c.0.1% alkaloids which were described as an “easy smoke with meteorically intense effects” (seldom, 2014). Phyllodes have shown acetylcholinesterase-inhibiting activity (Subhan et al, 2014).

**Acacia retinodes** Schltdl. (wirilda) – Phyllodes and green twigs from 3-year-old plants cultivated in the Netherlands yielded 0.01% nicotine. However, the identity of the plants was not certain, as they had not flowered (Fikenscher, 1960). Phyllodes of plants from Melbourne gave a small yield of a single major alkaloid which did not correspond with nicotine; also, phyllodes of plants from Mornington Peninsula [Vic.] gave a very low yield of an alkaloid that could not be identified in comparison to the reference standards (which were phenethylamine, hordenine, NMT, DMT, tetrahydroharman, and N-methyl-tetrahydroharman) (Rovelli, 1967). Stems and phyllodes (harv. Apr.) and seeds were found to contain <0.01% alkaloids (White, 1944a); in another assay, stems, phyllodes, bark, ripe and unripe seeds, and unripe pods contained no alkaloids (White, 1951). The identities of the plants used in all of these assays remains uncertain, as the very variable *A. retinodes* has now been split into *A. retinodes*, *A. provincialis* (see above), and *A. uncifolia* O’Leary (O’Leary, 2007).

**Acacia spectabilis** A. Cunn. ex Benth. (mudgee wattle, pilliga wattle) – Leaf and bark (harv. Jun.) gave strong positive results in some alkaloid screening tests (Webb, 1949); leaves and stems yielded 0.21-0.35% alkaloids, consisting of 60-72% phenethylamine, with traces of a non-volatile base and no tryptamine; leaves and bark (harv. Jun.) were rich in alkaloids (White, 1957).

**Acacia suaveolens** (Sm.) Willd. (sweet wattle) – Stems and phyllodes yielded 0.7-0.89% alkaloids; stems (harv. Sep.) yielded 0.07% alkaloids, phyllodes 0.69%, seeds 0.01%, and unripe seed pods 0.05-0.17%. Stems, phyllodes, and flowers (harv. Apr., Sydney) yielded 0.97% alkaloids. The alkaloid mixture in all cases appeared to consist mainly of phenethylamine (White, 1944a, 1951). Tops (harv. Nov.) yielded 1.1% crude alkaloids, consisting mostly of phenethylamine (White, 1954).

**Acacia vestita** Ker Gawl. (hairy wattle, weeping boree) – Stems and phyllodes gave different alkaloid yields at different times – 0.03-0.04% (Jan.), 0.28% (May), 0.08% (Jul.-Aug.), and 0.12% (Oct.); this consisted of up to 83% tryptamine, with traces of a non-volatile base (White, 1957).

**Acacia victoriae** Benth. (gundabluie, narran, arlep, bramble wattle) – Alkaloid screening of phyllodes and stems was negative in



spot tests (Collins et al., 1990), though Rovelli (1967) obtained a weak-positive reaction with the phyllodes (Rovelli, 1967). Young plants were tentatively found to contain DMT in aerial parts (1-year-old seedling), and 5-MeO-DMT in roots (2-year-old seedling) (TLC) (Trout, ed., 1997). Stem bark from specimens in South Australia yielded tryptamine alkaloids consisting mainly of DMT, possibly with some 5-MeO-DMT (subjective i.d. from vapourisation) (nen888, 2011-2013).

In broad alkaloid screenings, a number of other Australian *Acacia* spp. were found to contain alkaloids which were not identified – *A. amblygona* A. Cunn. ex Benth. (phyllodes and stems; only detected in some tests), *A. aneura* F. Muell. ex Benth. (0.009% in phyllodes), *A. angusta* Maiden & Blakely (0.08% in phyllodes and stems) (Collins et al., 1990), *A. aulacocarpa* R.S. Cowan & Maslin (phyllodes harv. Jul., weak-positive; none in Jan.) (Webb, 1949), *A. beauverdiana* Ewart & Sharman (phyllodes and stems) (Collins et al., 1990; Rovelli, 1967), *A. cedroides* Benth. (Aplin & Cannon, 1971), *A. conferta* A. Cunn. ex Benth. (phyllodes harv. Jun., weak-positive) (Webb, 1949), *A. cowleana* Tate (phyllodes), *A. deanei* (R.T. Baker) Welch, Coombs & McGlynn (leaves and stems) (Collins et al., 1990), *A. decora* Rchb. (phyllodes harv. Jun.; traces in stems and phyllodes harv. Mar., Apr., & Oct.) (Webb, 1949; White, 1957), *A. decurrens* Willd. (<0.01% in stems and leaves harv. May; 0.02% in Feb.; none in Dec.; weak-positive in leaves harv. Jun.) (Webb, 1949; White, 1944a, 1951), *A. doratoxylon* A. Cunn. (0.06% in phyllodes and stems) (Collins et al., 1990), *A. drumondii* Lindl. (<0.01% in leaves and stems harv. Feb., none in Aug., or in flowers) (White, 1944a, 1951), *A. estrophiolata* F. Muell. (phyllodes) (Aboriginal Communities, 1988; Collins et al., 1990), *A. filifolia* Benth. var. *pedunculata* C.A. Gardn. (Aplin & Cannon, 1971), *A. flexifolia* A. Cunn. ex Benth. (traces in stems, phyllodes and flowers harv. Jul.) (White, 1957), *A. fragilis* Maiden & Blakely (Aplin & Cannon, 1971), *A. gilbertii* Meisn. (leaves), *A. gonophylla* Benth. (phyllodes) (Collins et al., 1990; Rovelli, 1967), *A. heteroclita* Meisn. (phyllode) (Rovelli, 1967), *A. howittii* F. Muell. (reported incorrectly as *A. vestita* Ker Gawl.; <0.01% in stems and phyllodes harv. Feb.-May; no alkaloid in other assays of stems, phyllodes, ripe seeds, and pods) (White, 1944a, 1951), *A. implexa* Benth. (moderate to strong

positives in phyllodes and unripe pods, negative in bark, harv. Nov.; weak positive in phyllodes, in some tests, harv. Dec., and unspecified) (Rovelli, 1967; Webb, 1949), *A. iteaphylla* F. Muell. ex Benth. (phyllodes positive in one assay, negative in others) (Rovelli, 1967), *A. ixiophylla* Benth. (phyllodes, harv. Jun.) (Webb, 1949), *A. juncifolia* Benth. (0.008% in phyllodes), *A. kybeanensis* Maiden & Blakely (phyllodes), *A. latipes* Benth. (phyllodes), *A. leichhardtii* Benth. (0.007% in phyllodes and stems), *A. leiophylla* Benth. (phyllodes) (Collins et al., 1990), *A. leprosa* Sieber ex DC. (<0.01% in stems and phyllodes harv. Feb., stems/phyllodes/flowers harv. Sep.) (White, 1944a), *A. leptocarpa* A. Cunn. ex Benth. (0.09% in phyllodes; some tests negative) (Collins et al., 1990), *A. lineolata* Benth. (Aplin & Cannon, 1971), *A. loxophylla* Benth. (phyllodes) (Rovelli, 1967), *A. lunata* G. Lodd. (phyllodes harv. Jun., strong-positive) (Webb, 1949), *A. lysiphloia* F. Muell. (phyllodes; some tests negative) (Aboriginal Communities, 1988), *A. maitlandii* F. Muell. (phyllodes), *A. neriifolia* A. Cunn. ex Benth. (1.3% in phyllodes, 1.2% in bark) (Collins et al., 1990), *A. nervosa* DC. (phyllodes) (Collins et al., 1990; Rovelli 1967), *A. paradoxa* DC. (0.01% in tops; as *A. armata* R. Br., plants in New Zealand gave no alkaloid from stems and phyllodes harv. Mar., or stem, phyllodes, and flowers harv. Oct., though ripe pods contained traces) (Collins et al., 1990; White, 1951), *A. pendula* A. Cunn. ex G. Don. (phyllodes, bark), *A. penninervis* Sieber ex DC. (phyllodes and bark harv. Jun.; phyllodes gave stronger reaction) (Webb, 1949), *A. rhodoxylon* Maiden (phyllodes and stems) (Collins et al., 1990), *A. rupicola* F. Muell. ex Benth. (traces in stems, phyllodes, and flowers harv. Jul.) (White, 1957), *A. salicina* Lindl. (phyllodes harv. Nov., weak-positive; has also given negative results) (Aplin & Cannon, 1971; Collins et al., 1990; Webb, 1949), *A. saligna* (Labill.) H.L. Wendl. (<0.01% in stems and phyllodes harv. Feb.; traces in stems and phyllodes harv. Apr., as *A. cyanophylla* Lindl.) (White, 1944a, 1957), *A. semilunata* Maiden & Blakely (phyllodes; some tests negative) (Collins et al., 1990; Rovelli, 1967), *A. shirleyi* Maiden (identity uncertain; phyllodes harv. Jun.) (Webb, 1949), *A. simsii* A. Cunn. ex Benth. (0.03% in phyllodes), *A. stenoptera* Benth. (phyllodes) (Collins et al., 1990), *A. stricta* (Andrews) Willd. (<0.01% in stems and phyllodes harv. Feb. & Aug., also in seeds;

another assay found none in stem, phyllodes, flowers, ripe seeds, or pods) (Collins et al., 1990; White, 1944a, 1951), *A. subcaerulea* Lindl. (Aplin & Cannon, 1971), *A. terminalis* (Salisb.) J.F. Macbr. (as *A. discolor* (Andrews) Willd.; 0.03% in stems, leaves and flowers harv. Feb.; traces in stems and leaves harv. Apr.-May, traces in flower spikes) (White, 1951), *A. tetragonophylla* F. Muell. (root bark; phyllodes negative) (Aboriginal Communities, 1988; Collins et al., 1990), *A. torulosa* Benth. (phyllodes, not in bark) (Collins et al., 1990), *A. triptera* Benth. (phyllodes and branches harv. Jun.), *A. ulicifolia* (Salisb.) Court (as *A. juniperina* nom. illeg.; phyllodes and stems harv. Nov., strong-positive) (Webb, 1949), *A. umbellata* A. Cunn. ex Benth. (0.013% in phyllodes) (Collins et al., 1990), *A. urophylla* Benth. (phyllodes) (Aplin & Cannon, 1971; Collins et al., 1990), *A. verniciflua* A. Cunn. (traces in stems and phyllodes harv. Feb.; another Feb. harv. gave no alkaloids, as have others from unspecified harv. times) (Collins et al., 1990; Rovelli, 1967; White, 1951), *A. verticillata* (L'Hér.) Willd. (<0.01% in phyllodes and stems harv. Sep., as well as in seeds and flowers; other assays of stems, phyllodes, seeds, and pods yielded no alkaloids; moderate positive in phyllodes in another assay, none detected in bark) (Collins et al., 1990; White, 1944a, 1951), *A. viscidula* Benth. (phyllodes and stems harv. Nov.) (Webb, 1949), and *A. xiphophylla* E. Pritz. (Aplin & Cannon, 1971).

### CLOSING REMARKS

The recent growth of interest in *Acacia* spp. as a source of DMT reflects a growing interest in consciousness expansion and direct spiritual experience that has been occurring globally for some time. However, this increased interest has also brought with it greed and commercial exploitation. Many users of *Acacia* alkaloid extracts have no idea of the source, or whether it was produced sustainably. To them it is just DMT (even when it is a mix of alkaloids), and they may not even know what an *Acacia* is. Some of the species being commercially (and illegally) exploited are extremely rare and may be threatened with extinction in the wild if current practices continue or increase. Regardless of legality, the use of these plants will continue, but it is hoped that all people doing so can learn to tread lightly and discreetly. If these substances are shared

respectfully through friends with no profit motive, and people cultivate plants and use sustainable harvesting methods, scenes of trees killed by bark-stripping could be a thing of the past. This author calls for DMT users to boycott the sale and purchase of Acacia alkaloid extracts, as well as non-propagative plant parts, and to show respect to the plants from which they are trying to learn.

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# From ‘There’ to ‘Here’: Psychedelic Natural Products and Their Contributions to Medicinal Chemistry

## [Keynote]

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*David E. Nichols, PhD*

Division of Chemical Biology and Medicinal Chemistry,  
Eshelman School of Pharmacy, University of North Carolina, Chapel Hill, NC

### ABSTRACT

This review will be an excursion that considers each of the major types of psychedelic agents: tryptamines, ergolines, and phenethylamines. The review will feature natural product templates (“there”), and show how each template evolved through chemical structural modification that led either to optimized potency or unique psychopharmacology (“here”). Each chemotype has at some point in time been the focus of attention by medicinal or natural products chemists. For example, in the “modern” era, Western attention to psychedelics was first directed to mescaline, a simple trimethoxy-substituted phenethylamine produced by the peyote cactus, *Lophophora williamsii*. Anthropological studies have indicated the use of peyote by Native North Americans was ongoing as long as 5700 years ago. Following the identification of mescaline as the active component in peyote by Heffter in 1897, it was then synthesized in 1919 by Späth. More than four decades would then pass before the prodigious efforts of Alexander Shulgin led to a variety of ring-substituted analogues of mescaline. Part of Shulgin’s inspiration derived from his knowledge of the structures of essential oils. Additional medicinal chemistry efforts led to extremely potent congeners of mescaline. Similar, although less productive, studies occurred with simple tryptamines, and with the tetracyclic ergolines. Each of these chemotypes will be discussed, and it will be

seen how natural products played a significant role in bringing psychedelics of various types to the present moment (“here”).

## INTRODUCTION

Although the focus of this symposium is on the “ethnographic search” for psychoactive drugs, what I plan to show in this presentation is what medicinal chemists do once a lead compound has been identified from a natural source. My talk will highlight the development of the classic (serotonergic) psychedelics, beginning with tryptamines, proceeding to phenethylamines, and ending with ergolines. I will note which portions of the molecule are essential for activity, and which can be modified to effect changes in its qualitative and/or quantitative actions. This review will not be an encyclopedic compendium, which would probably take an entire book, but will highlight some of the more important structural elements and approaches to understanding the medicinal chemistry of psychedelics.

## TRYPTAMINES

Tryptamines are naturally occurring compounds that have been employed in religious and shamanic practices for millennia. There are three basic types of tryptamines that are psychoactive, and they are all *N,N*-dimethylated tryptamines, either with no substitution on the indole ring, with a 4-hydroxy substituent, or with a 5-oxygen substituent.

The simplest psychoactive tryptamine is *N,N*-dimethyltryptamine, or DMT. It occurs widely throughout nature and is produced by many plants. Several species of *Mimosa* are native to eastern Brazil, and are known as Jurema or Jurema Preta. The dried root bark of *Mimosa tenuiflora* has been shown to contain 1-1.7% DMT, and is referred to as “Black Jurema” (Jurema Preta) (Schultes and Hofmann, 1979). DMT is not orally active, but was employed as a snuff. When ingested orally, DMT is deaminated by monoamine oxidase enzymes in the liver. However, it is rendered orally active when administered with inhibitors of monoamine oxidase. The most well-known example is that of *ayahuasca*, which is a decoction prepared by boiling pounded vines of *Banisteriopsis*

*caapi* with leaves of *Psychotria viridis*. The latter contain DMT, whereas *Banisteriopsis caapi* contains beta-carbolines that inhibit monoamine oxidase. *Ayahuasca* was incorporated as a sacrament by two syncretic churches, the *União do Vegetal* (UDV), and the *Santo Daime*, and has become popular in recent years for those wishing to have a legal psychedelic experience by traveling to various sites in South America, primarily Peru, where *ayahuasca* is administered in various rituals.

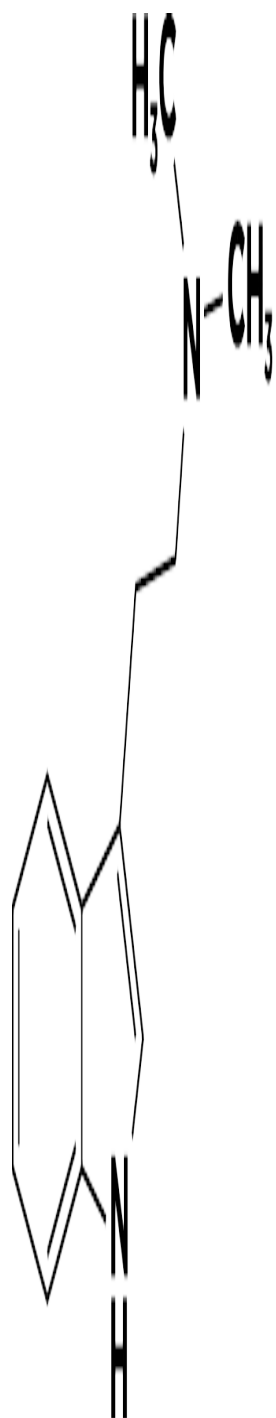
Perhaps next in structural complexity is 5-hydroxy-*N,N*-dimethyltryptamine (bufotenine). Bufotenine is likewise not orally active. Seeds and pods of *Anadenanthera peregrina* served as the basis of one of the most widely used shamanic inebriants in South American Andean cultures. Evidence for this use has been recovered from archeological sites at least four millennia old. Seeds were roasted, pulverized, and inhaled through the nose as cohoba or *yopo* snuff, or were smoked in pipes or as cigars (Torres and Repke, 2006). Seeds contain up to 7.4% bufotenine (5-hydroxy-*N,N*-dimethyltryptamine), 0.16% DMT, and 0.04% 5-MeODMT. Based on the amounts of snuff used, bufotenine was likely the most active component, although its psychoactivity still remains controversial.

Whereas the hallucinogenic activity of bufotenine is still controversial, its *O*-methyl derivative, 5-methoxy-*N,N*-dimethyltryptamine (5-MeODMT) is extremely potent, although again lacking oral activity. This tryptamine is found in the red bark resin of *Virola theiodora* or *Virola elongata* and is used by the Yanomamo to make a potent snuff known as Epená (Schultes and Hofmann, 1980). Recently, a fad has developed for smoking the venom of *Bufo alvarius* (the psychedelic toad of the Sonoran desert). This toad secretes a toxin in its parotid gland that contains significant concentrations of 5-MeODMT. In fact, the dry weight of the parotid and tibial glands may include as much as 15% 5-MeODMT (Weil and Davis, 1994). Although the secretion of the parotid gland is quite toxic if ingested orally, when smoked, the toxic components are evidently destroyed.

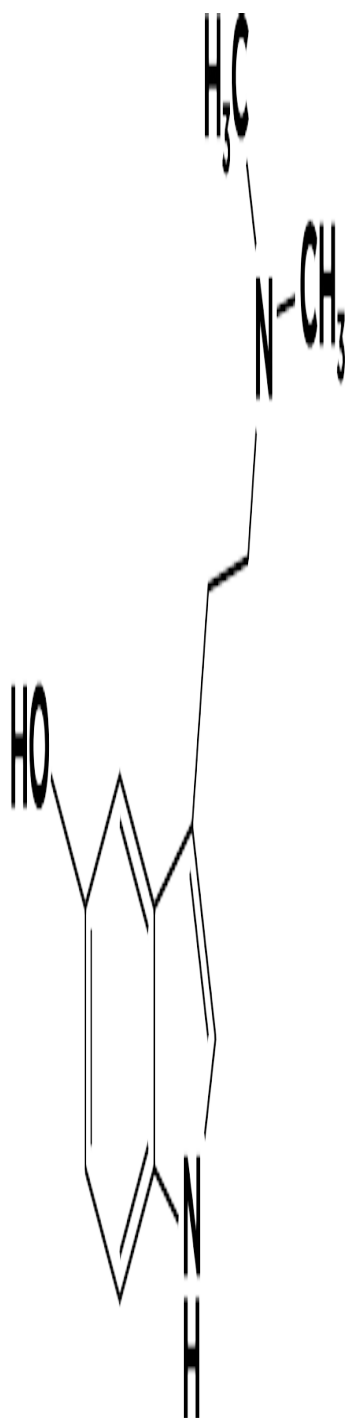
Whereas DMT and 5-MeODMT are not active orally, substitution with a 4-oxygen substituent confers oral activity on the molecule. Although Richard Evans Schultes clarified the correct botanical identity of psychedelic (hallucinogenic) mushrooms used for

various rituals in ancient Mexico (Schultes, 1940), Western attention on these natural products was heightened by a May 13, 1957 *Life Magazine* article titled “Seeking the Magic Mushroom”, by banker and amateur mycologist R. Gordon Wasson. In this story, he recounts travel to Southern Mexico and meeting with a *curandera* named Maria Sabina and her daughter, who allowed him to participate in a ceremony where *Psilocybe* mushrooms were ingested. They emerged from the experience “awestruck,” having “expected nothing so staggering as the ... astonishing effects of the mushrooms” (Wasson, 1957).

These remarkable mushrooms had been named *teonanacatl* by the Aztecs, which roughly translates to “divine flesh.” Although Spanish missionaries had made concerted efforts to destroy all traces of “pagan” worship involving these mushrooms, nonetheless, more than 200 mushroom stone effigies had escaped destruction and were discovered by later explorers. Chemical investigations by Dr. Albert Hofmann at the Sandoz laboratories revealed that the active component of *Psilocybe* mushrooms was psilocybin, with lesser amounts of psilocin, its dephosphorylated analogue (Hofmann et al., 1958), as shown below:



N,N-dimethyltryptamine



Bufotenine



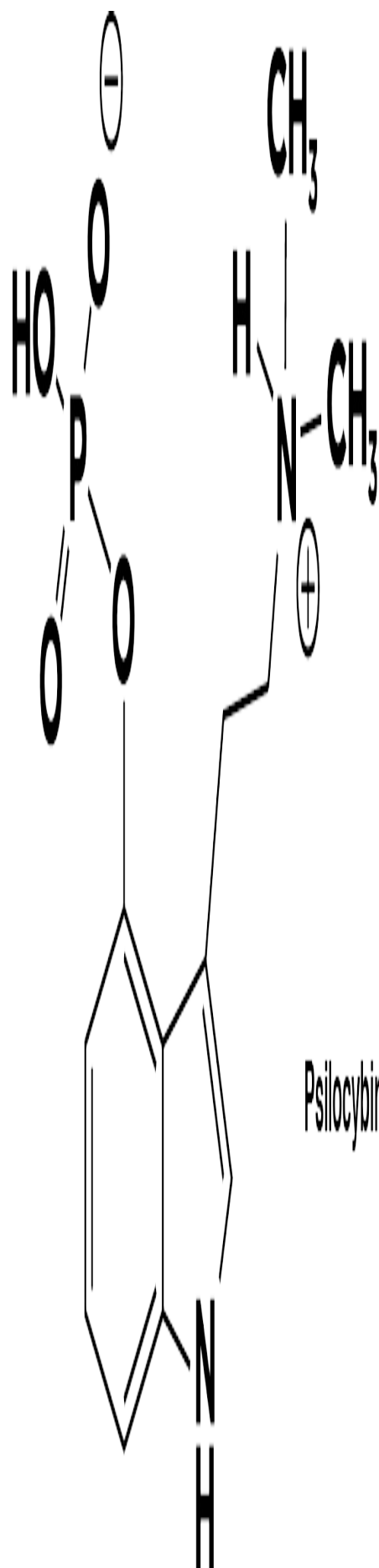
5-Methoxy-DMT

**Fig 1.** Three naturally occurring tryptamine chemotypes that are not orally active.

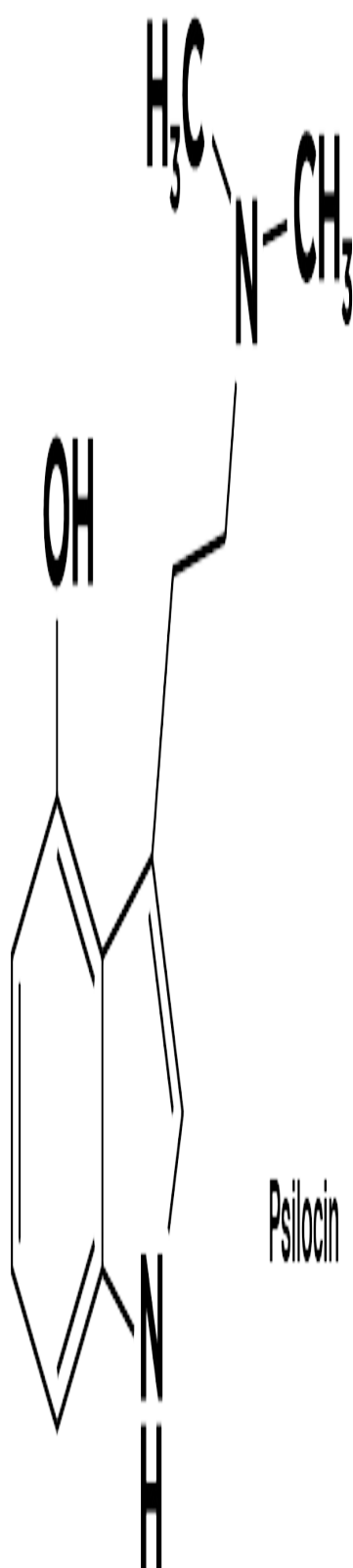
Although most of the literature published on the so-called magic mushrooms has largely dealt with their use by indigenous South American peoples, there is some evidence that their use may go much further back into history. For example, the ancient ritual in Eleusis, Greece, which was part of that culture for about 2000 years, employed a drink known as *kykeon*, whose important ingredients have been lost to history. There have been many debates as to what type of psychoactive material might have been in the beverage, and some have speculated, based on barley being one of the components, that some form of psychoactive ergot may have been included in the drink (Wasson et al., 1978). By contrast, Berlant (2005) has argued that a type of psilocybe mushroom may have been the key ingredient in *kykeon*.

The identification of the ancient Vedic Soma, praised for its effects in the Rig-Vedas, also remains elusive. Although Wasson has argued persuasively that only the mushroom *Amanita muscaria* fits the physical description of the central component of Soma (Wasson, 1968; Wasson and Ingalls, 1971), there is no solid evidence that ingestion of this mushroom actually has the sort of psychoactive properties that would be expected of Soma. Recently, however, diggings were carried out in 2009 by an expedition of the Institute of Archaeography and Ethnography, Siberian Branch of the Russian Academy of Sciences, at 31 Xiongnu tumuli dated from the late 1st century B.C.E. to the early 1st century A.D. of the Noin-Ula burial ground in Mongolia (Polosmak, 2010). The expedition discovered preserved embroidered woolen textiles that filled a narrow space between the chamber's wooden walls and the coffin. The partially restored textiles depict an altar scene, with men in it who are speculated, from their style of clothing, to be Indo-Scythians or Indo-Parthians, performing a ritual indicating that they acknowledge a form of Zoroastrianism, with the symbol of a sacred fire altar. A king or possibly the priest is shown holding a mushroom in his hands that appears to belong to the family *Strophariaceae*, with an external appearance similar to *Psilocybe cubensis*.





Psilocybin



Psilocin

**Fig 2.** The chemical structures of orally active psilocybin and psilocin.

An interesting feature of psilocybin and psilocin is the fact that they are orally active, whereas the other tryptamines discussed earlier are only active by insufflation, or if combined with a monoamine oxidase inhibitor. Psilocybin is dephosphorylated in the body to psilocin, so the latter molecule is the one of most interest. We addressed this issue in a study published in 1981, where we compared the solution side chain conformations of bufotenine with psilocin, as well as experimentally measuring their octanol-water Log P values, and the pKa values of their amines (Migliaccio et al., 1981). 360 MHz  $^1\text{H}$  NMR spectra were recorded in  $\text{CDCl}_3$  for bufotenine and psilocin freebases. Whereas spectral analysis indicated that the side chain of bufotenine preferred to exist in the *trans* conformation, the side chain of psilocin freebase highly favored the *gauche* conformation, indicating that the adjacent 4-hydroxy group was somehow influencing the side chain conformation. If the effect was purely a nonbonded steric one, the side chain would not be expected to favor conformations where it was folded closer to the 4-OH substituent.

The nature of this stabilization was therefore of some interest; it was speculated that it might result from an intramolecular hydrogen bond. Energy minimization using Hartree-Fock 6-31G\* potentials (freebase in vacuum) revealed that intramolecular hydrogen bonding is likely in one *gauche* side-chain conformer of psilocin. The side-chain amino to 4-oxygen hydroxyl distance is 1.88 Å, with other bond angles and distances nearly ideal. The minimized structure is shown in figure 2.

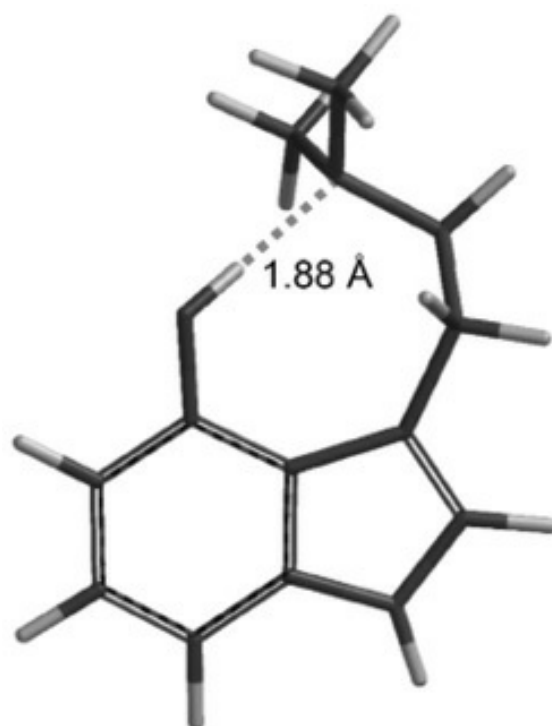


**Fig 3.** Energy-minimized structure of psilocin freebase.

The consequences of this intramolecular hydrogen bond are manifested as reduced basicity for the amino nitrogen of psilocin (pKa 8.47) compared to bufotenine (pKa 9.67), as well as increased hydrophobicity for psilocin (Log P 1.45) compared to bufotenine (Log P 1.19) (Migliaccio et al., 1981). At a physiological pH of 7.4, only about 0.5% of bufotenine will exist in the unprotonated (unionized) form, whereas about 8% of psilocin will exist in the unprotonated form. Recognizing that it is the unprotonated form of a base that is transported across membranes, psilocin therefore will more readily penetrate into the brain. The experimental Log P value of psilocin also indicates a more favorable lipid solubility than bufotenine. That may reflect the fact that to cross membranes, not only will the amine have to be unionized, but it must also undergo loss of solvation, and the intramolecular hydrogen bond will partially compensate for that in psilocin.

A final factor that is also likely important for the oral activity of psilocin relates to the mechanism of action for monoamine oxidase, which deaminates other tryptamines, such as DMT and 5-MeODMT, in the liver. Possible mechanisms in the first step of the deamination reaction are: 1. a single-electron transfer mechanism, and 2. a nucleophilic mechanism (Gaweska and Fitzpatrick, 2011). Importantly, with either mechanism, the first step involves access of

the enzyme's flavin cofactor to the electrons of the basic amino group. In psilocin, however, the electrons are engaged in the intramolecular hydrogen bond with the phenolic 4-OH group, and would be less available for donation to the flavin cofactor of MAO.



1. "X" - Aromatic ring substitution
2. Side chain substitution at  $\alpha, \beta$
3. N-substitution (R groups)

**Fig 4.** Possible sites for structural modification of tryptamines.

## STRUCTURAL MODIFICATIONS OF TRYPTAMINES

Conceivably, tryptamines could be modified on the aromatic portion, in the side chain, or on the nitrogen atom. It has been found that no substitutions on the aromatic portion of the molecule other than hydrogen (DMT), or 4-OH, or 5-OCH<sub>3</sub> lead to active molecules. Thus, medicinal chemists have explored the effect of small alkyl groups on the side chain and a variety of different alkyl groups on the nitrogen.

A methyl group attached to the alpha side chain position has proven to give the most active compounds, with the enantiomer having the *S* configuration being more potent than the *R* isomer. 5-methoxy-AMT is the most potent simple tryptamine that has been reported (Shulgin and Shulgin, 1997).

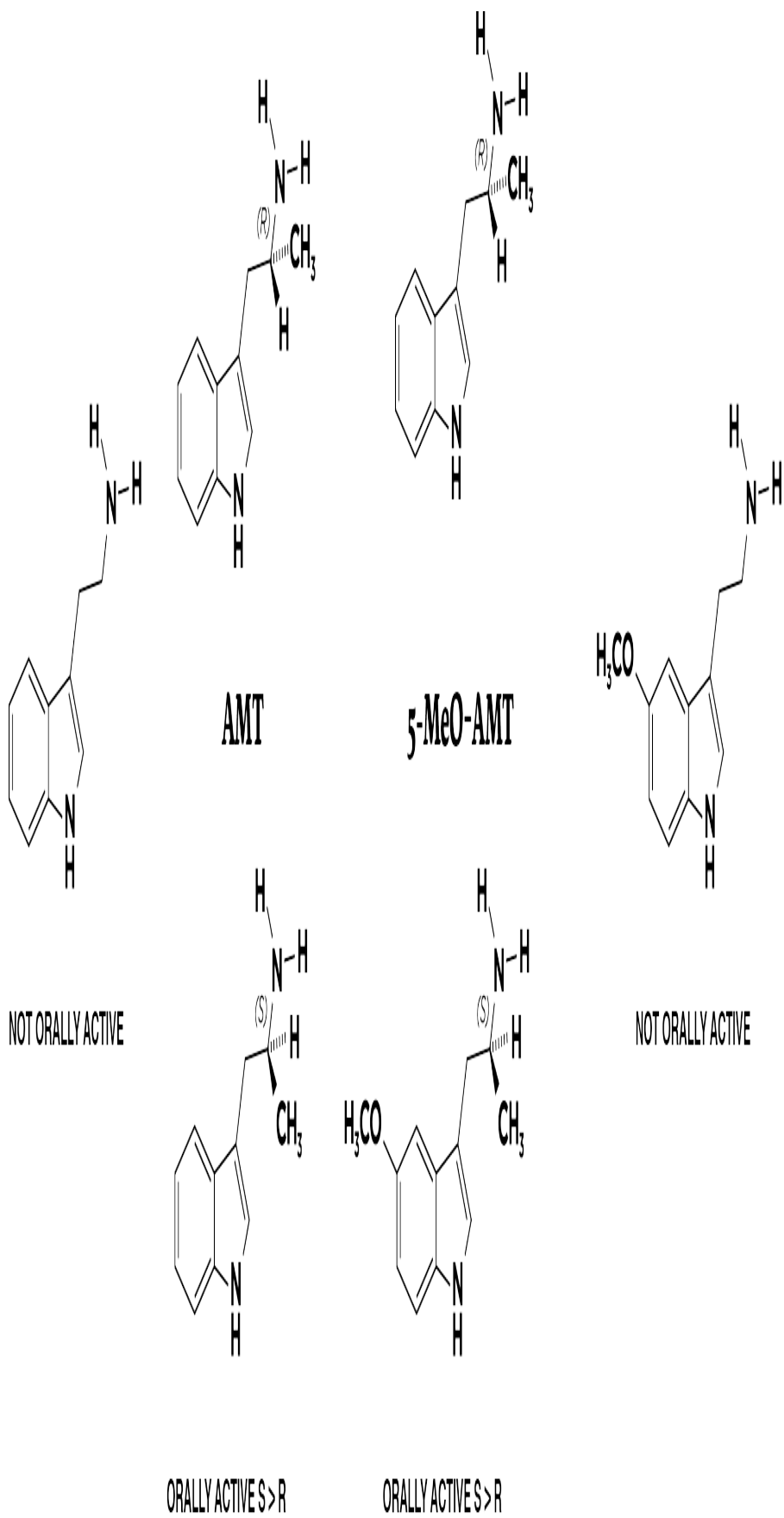
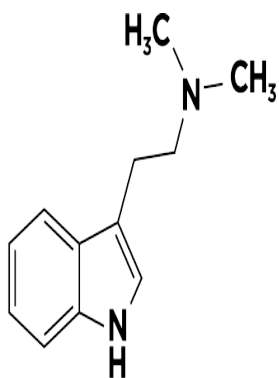


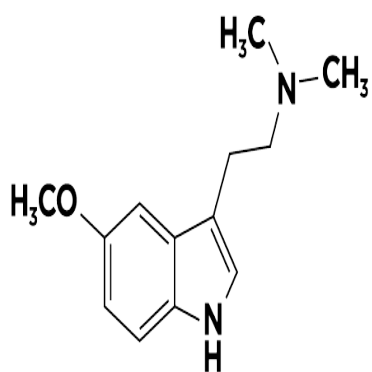
**Fig. 5** Tryptamines with an alpha-methyl in the side chain.

Although simple *N*-methylated tryptamines (DMT and 5-MeODMT) are not orally active, introduction of larger *N*-alkyl groups on the basic nitrogen leads to oral activity. In particular, an *N*-isopropyl group confers good oral activity. Figure 6 illustrates dosages and approximate duration of action for a variety of *N*-substituted tryptamines (Shulgin and Shulgin, 1997)

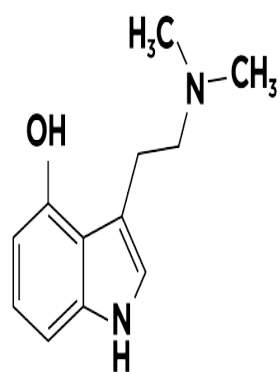




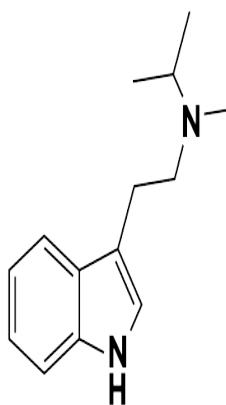
60-100 mg Smoked  
Up To 1 hours



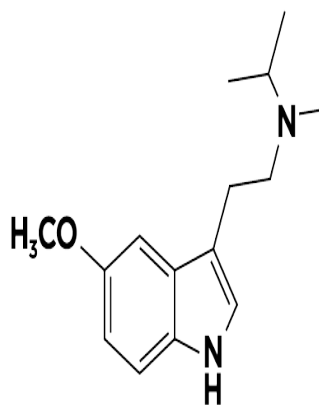
6-20 mg Smoked  
1-2 hours



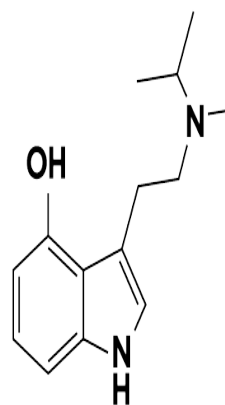
10-20 mg Smoked  
3-6 hours



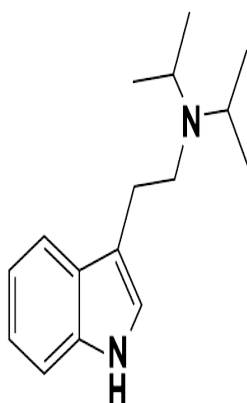
10-25 mg po  
3-4 hours



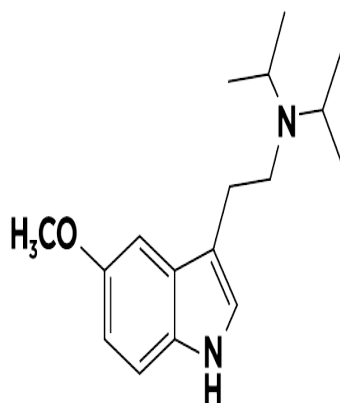
4-6 mg po  
4-6 hours



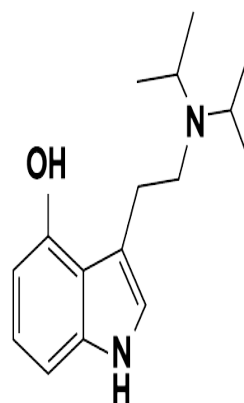
12-25 mg po  
4-6 hours



25-100 mg po  
6-8 hours



6-12 mg po  
4-8 hours

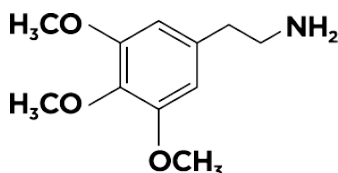


15-20 mg po  
2-3 hours

**Fig. 6** Tryptamine structures with approximate oral doses and durations of action.  
(Shulgin and Shulgin, 1997)

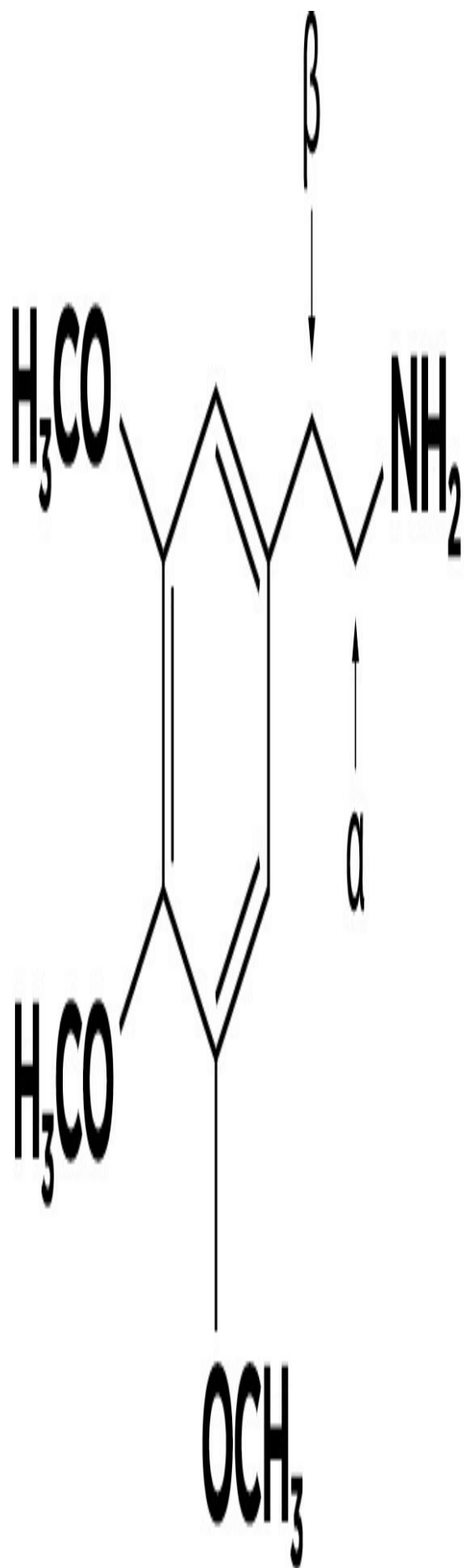
## PHENETHYLAMINES

Although several naturally occurring tryptamines serve as templates for structural modification, only a single phenethylamine was available as a natural psychedelic. Dr. Arthur Heffter first identified mescaline, a simple phenethylamine, as the active component of the peyote cactus, *Lophophora williamsii* (Heffter, 1898). He isolated the various alkaloids present in the cactus, and in self-experiments found mescaline to be the compound that produced the psychoactive effects and colored visions characteristic of peyote. This cactus is native to the American Southwest and Northern Mexico and has been used for millennia by the indigenous peoples in that region. Analysis and radiocarbon dating of two peyote samples from a cave on the Rio Grande River, in Texas, were found to date between 3780–3660 B.C.E (El Seedi et al., 2005). This evidence supports the use of peyote by Native North Americans as long as 5700 years ago (Bruhn et al., 2002). Today, peyote is a sacrament used by the Native American Church in its all-night religious services.



## MESCALINE

Although mescaline has relatively low potency, requiring a dose of about 250-400 mg of the sulfate salt, it served as the prototype for the phenethylamine-type psychedelics. Several hundred phenethylamines have been synthesized and tested as of today. As with the tryptamines, there are several sites for structural modification. Although the tryptamines are active psychedelics when they are tertiary amines, the phenethylamines generally do not tolerate N-substitution. Thus, the modifications can be carried out on the ring substituents as well as the side chain.

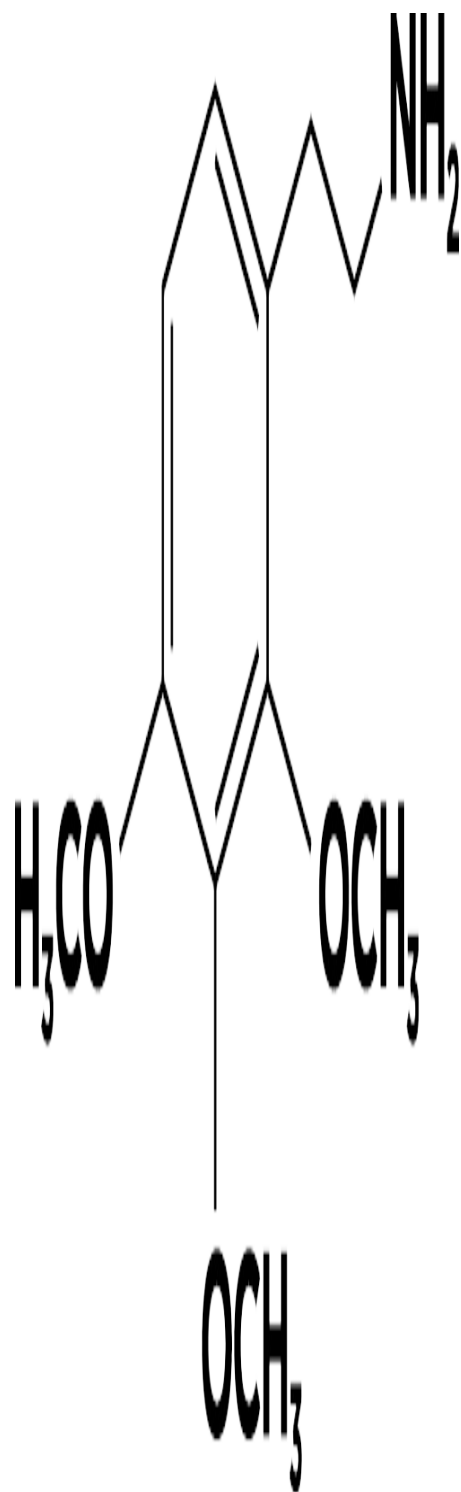


1. Aromatic ring substitution

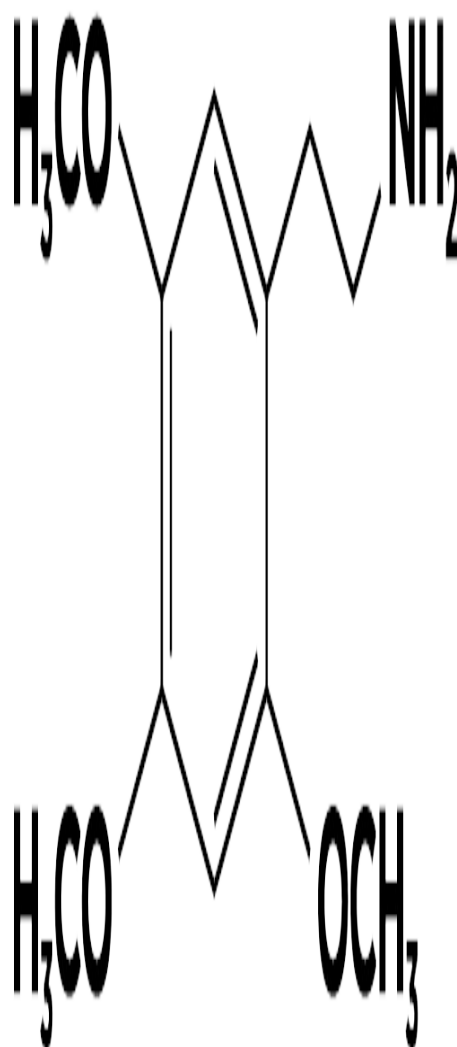
2. Side chain substitution at  $\alpha, \beta$

**Fig. 7** Mescaline, with locations where structural variation has been studied.

The earliest modifications were to change the orientations of the methoxy groups. Those changes led to inactive compounds, such as 2,3,4-trimethoxyphenethylamine (Slotta and Heller, 1930), and 2,4,5-trimethoxyphenethylamine (Dittrich, 1971)(Fig. 8). At least in the case of 2,3,4-trimethoxyphenethylamine, it was found to be very quickly metabolized *in vivo* compared with mescaline, and that could be the explanation for its lack of activity (Demisch and Seiler, 1975). Similar studies of 2,4,5-trimethoxyphenethylamine have not been carried out, but rapid deamination *in vivo* might also account for its lack of activity.



2,3,4-trimethoxyphenethylamine



2,4,5-trimethoxyphenethylamine

**Fig. 8** Inactive mescaline isomers.

Interestingly, however, replacing the 4-methoxy of mescaline with higher-order alkoxy groups such as ethoxy, propoxy, and isopropoxy, led to compounds substantially more active than mescaline. In addition, 4-alkylthio substituents also led to highly active compounds (Fig. 9) (Shulgin and Shulgin, 1991).

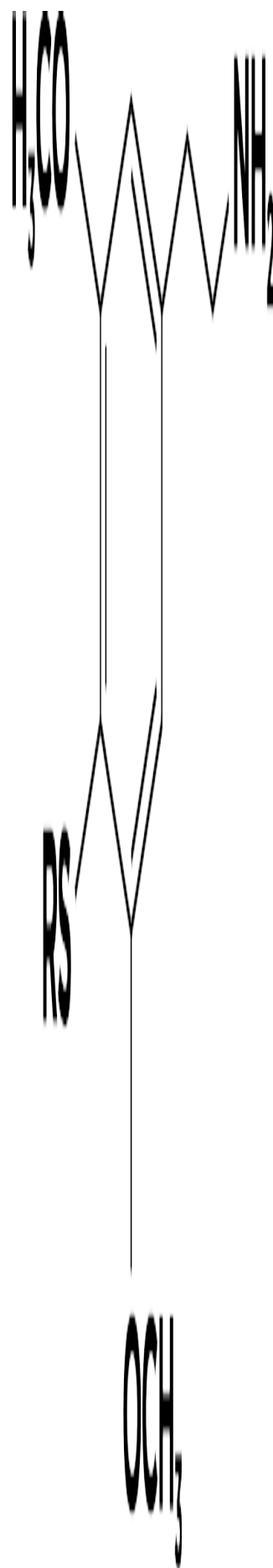
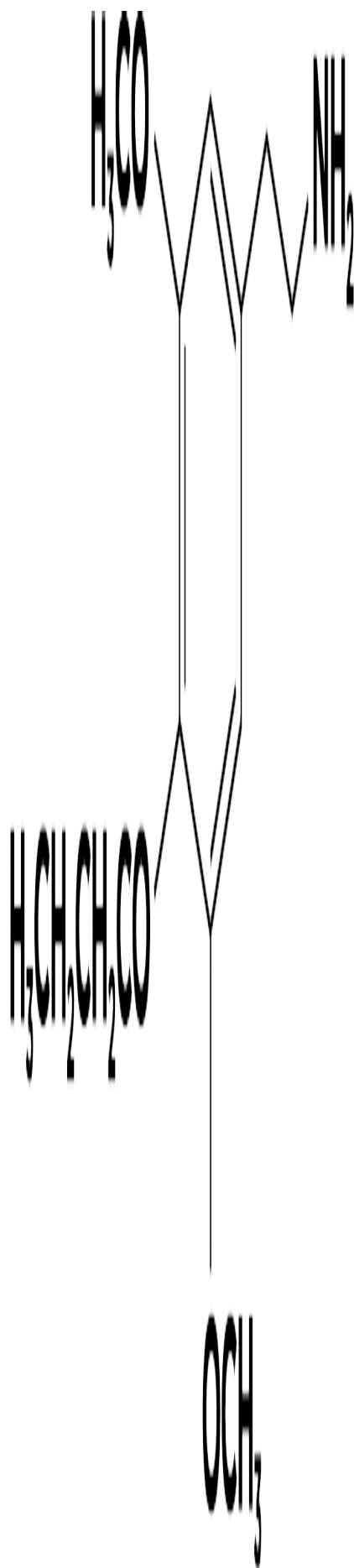
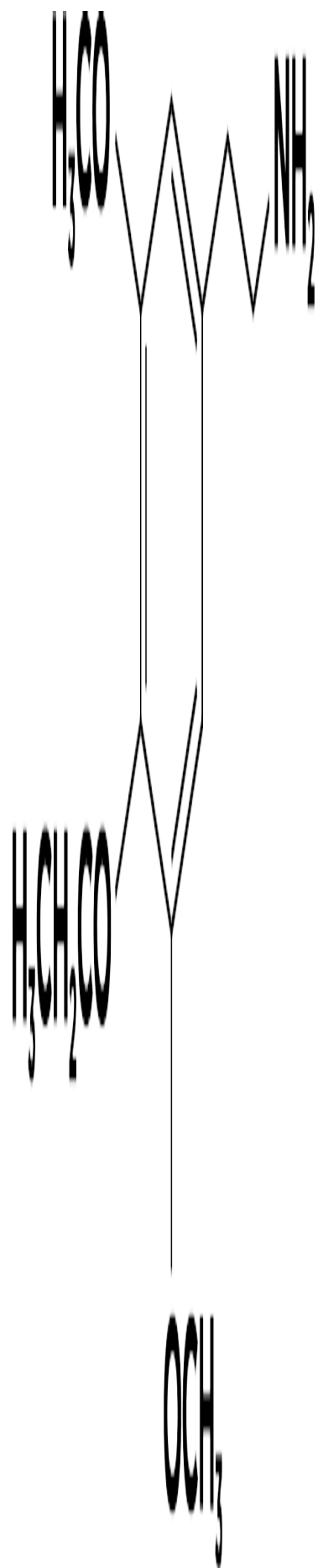
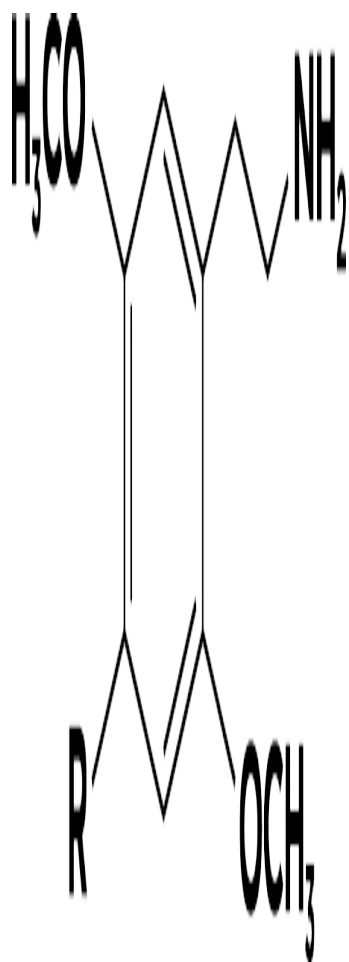


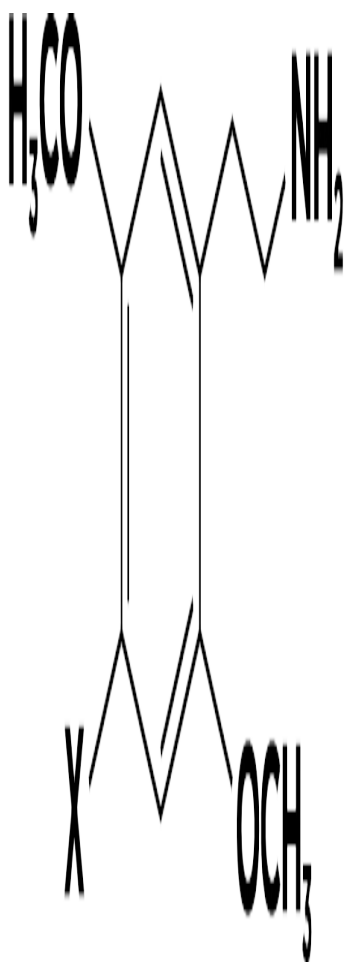
**Fig. 9** Mescaline analogues with higher potency than mescaline.

Larger alkoxy groups replacing the 3-methoxy of mescaline did not lead to active compounds, although certain compounds with an alkylthio replacing the 3-methoxy did retain activity. Although 2,4,5-trimethoxyphenethylamine was not orally active, when the 4-methoxy was replaced by alkyl, halogen, or alkylthio groups (Fig. 10), surprisingly, the compounds were orally active and quite potent (Shulgin and Shulgin, 1991).

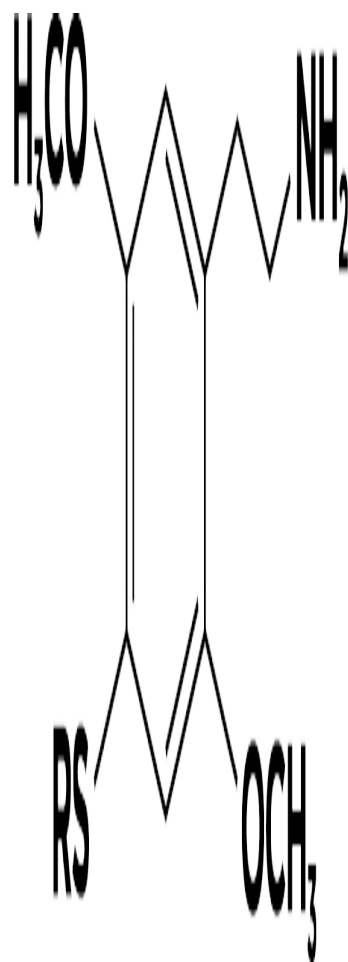




R=CH<sub>3</sub>: 2C-D  
R=Et: 2C-T2



X=Br: 2C-B  
X=I: 2C-I

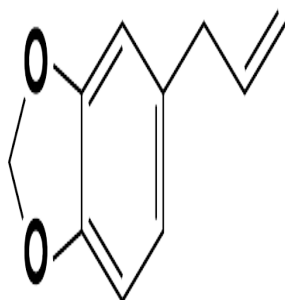


R=Et: 2C-E  
R=nPr: 2C-T7

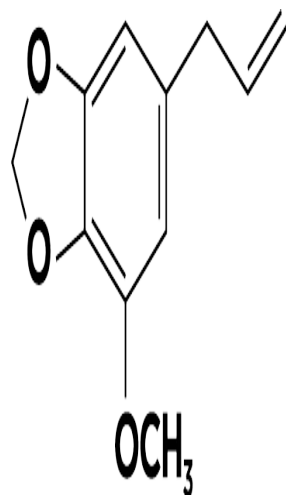
**Fig. 10** Potent, orally active 2,4,5-substituted phenethylamine psychedelics.

These compounds are all active within dose ranges averaging between 6-30 mg, depending on the substituent. Although it has not been studied, it seems possible that the enzyme that deaminates the side chain readily attacks a molecule with a 4-methoxy, whereas compounds with a hydrophobic 4-substituent may not be substrates for the enzyme. Many of these phenethylamines also have a fairly long duration of action (e.g., 12-15 hours).

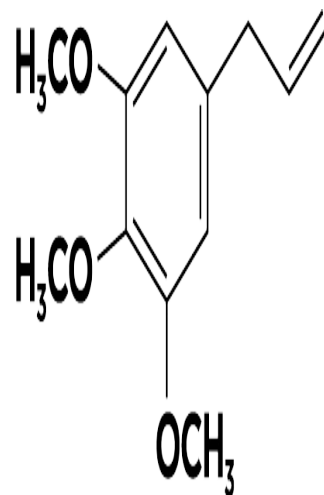
A number of essential oils provided ideas for a variety of ring substitution patterns, as illustrated in figure 11.



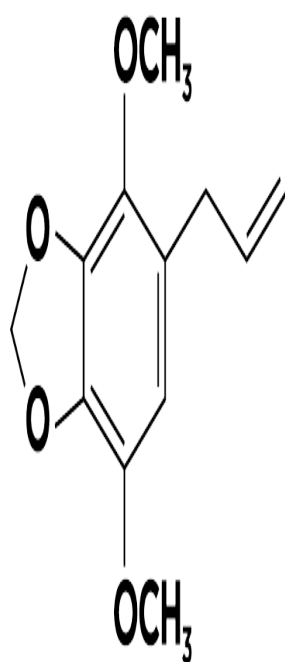
Safrole  
(sassafras)



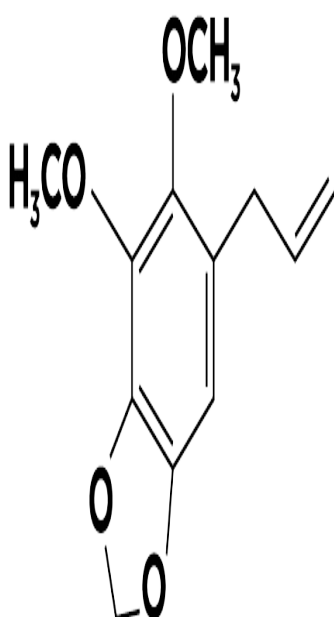
Myristicin  
(nutmeg)



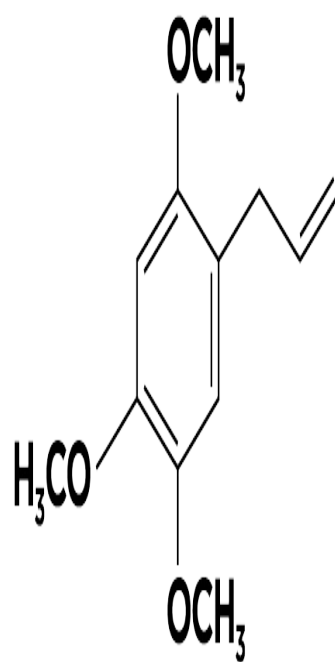
Elemicin  
(nutmeg/mace)



Apiole  
(parsley)



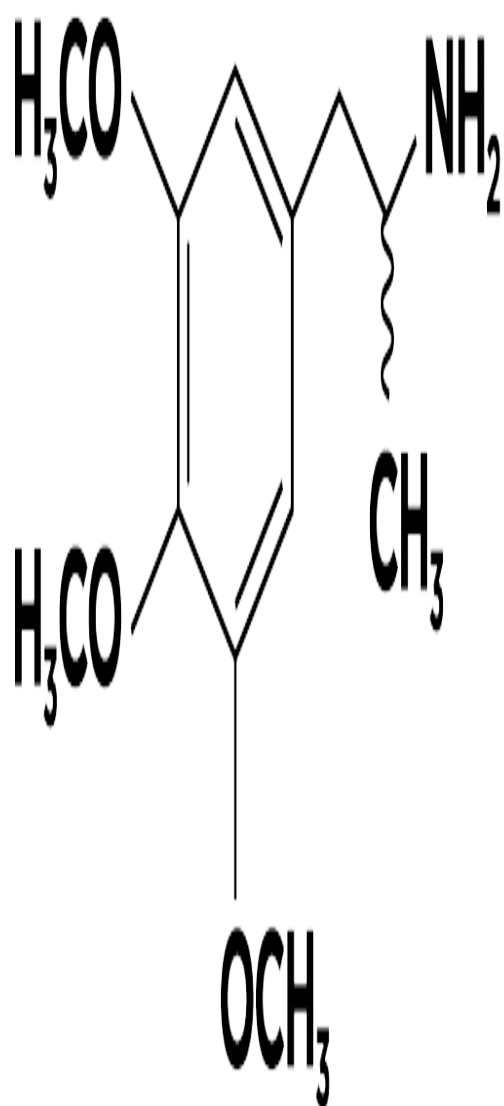
Dilapiole  
(dill)



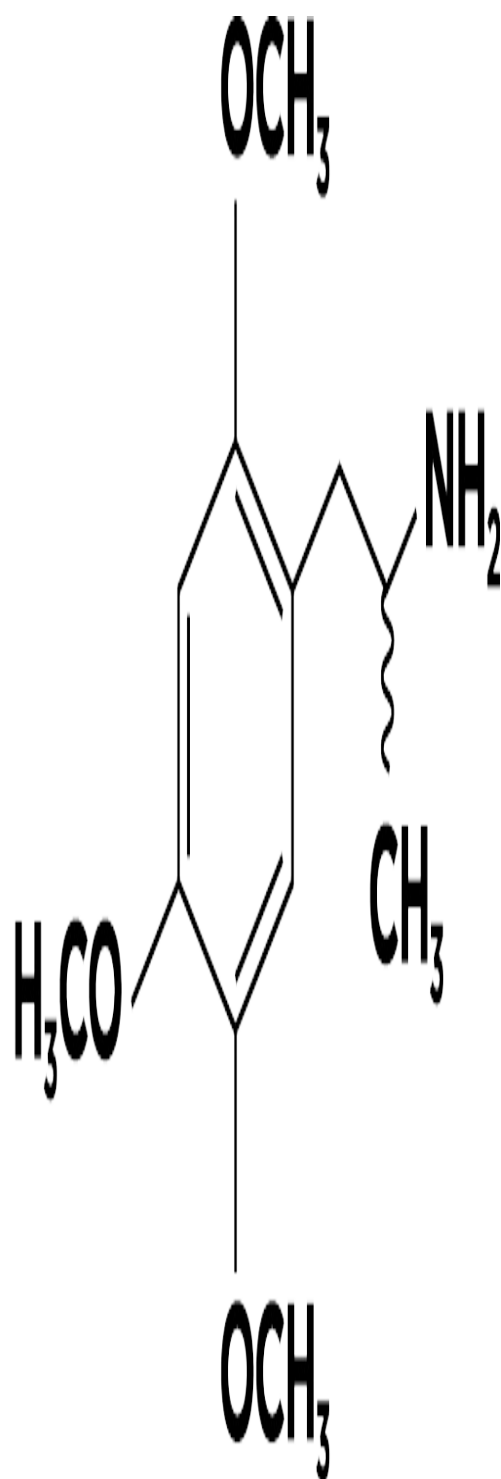
α-Asarone  
(from Calamus)

**Fig. 11** Essential oils with substitution patterns that inspired novel psychedelics.

In addition to changes in ring-substitution patterns, it was also found that placing a methyl group at the alpha side-chain position gave active compounds (Fig. 12). These compounds are often referred to as substituted amphetamines, based on the fact that amphetamine itself has an alpha-methyl, which prevents rapid deamination by monoamine oxidases. The first such compound was 3,4,5-trimethoxyamphetamine (TMA), shown in figure 12. TMA has about twice the potency of mescaline (Peretz et al., 1955). TMA-2 has more than ten times the potency of mescaline, in spite of the fact that the non-methylated 2,4,5-trimethoxyphenethylamine is inactive! A large number of substituted amphetamine psychedelics have now been prepared and tested, and those experiments and testing results are detailed in the Shulgins' book, *PIHKAL* (Shulgin and Shulgin, 1991). It is also known that it is the *R*-(-)-enantiomers of the substituted amphetamines that are most potent, as contrasted with amphetamine or methamphetamine, where it is the *S*-(+)-enantiomer that is most potent as a stimulant (Dyer et al., 1973; Nichols et al., 1973; Shulgin, 1973).



TMA



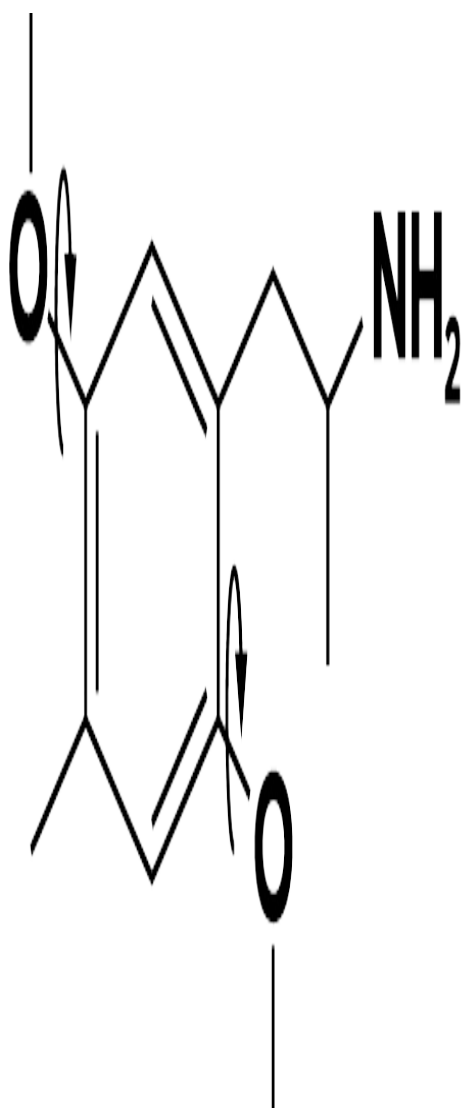
TMA-2

**Fig. 12** Structures of phenethylamines with an alpha-methyl in the side

Although the addition of the alpha-methyl to the side chain likely prevents metabolic deamination, it also enhances the efficacy of the molecules. That is, the unsubstituted phenethylamines are partial agonists, but their alpha-methyl congeners have significantly higher intrinsic activity at the PLC signaling pathway (Parrish et al., 2005).

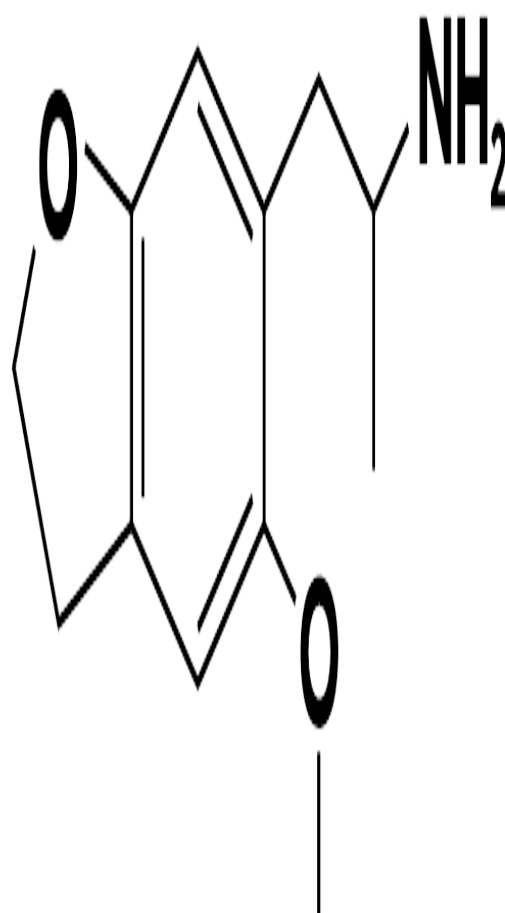
Extension of the alpha-methyl to an alpha-ethyl abolishes activity (Standridge et al., 1976). Incorporation of the side chain into a trans-cyclopropylamine also leads to active compounds (Aldous et al., 1974; Cooper and Walters, 1972; Nichols et al., 1979; Pigott et al., 2012), but the corresponding cyclobutylamines are inactive (Nichols et al., 1984).

In addition to studies of the ring substituents and substitutions on the side chain, several studies have indicated that the methoxy groups must have a particular orientation, presumably to interact with polar residues within the receptor. Early on, we prepared a compound we called ABF, shown in figure 13, and found that in a rat drug discrimination assay, it had very little activity when compared with DOM, a congener with freely rotating methoxy groups.



DOM

DD ED50 0.9  $\mu$ M/kg



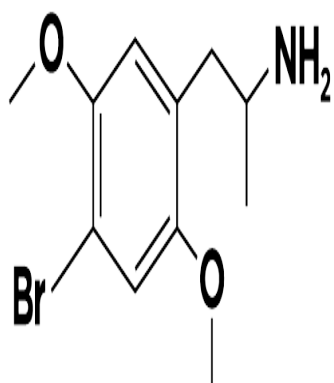
ABF

DD ED50 7.0  $\mu$ M/kg

**Fig. 13** The DOM molecule, with flexible methoxy groups, and the first benzofuran molecule with a constrained “methoxy.” ED<sub>50</sub> values are from the two-lever rat drug discrimination assay in rats trained to discriminate LSD from saline. ABF can be seen to be much less potent.

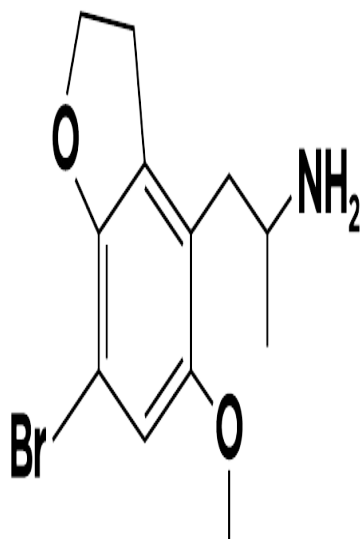
This led us to prepare several series of compounds where the methoxy groups were tethered in an orientation that was “anti” with respect to the 4-substituent. To that end, we made the series of compounds in figure 14 to illustrate the active orientation of the methoxy groups, and that the oxygen at the 2-position fits into a more sterically restricted location in the receptor. Activities listed below each compound represent the ED<sub>50</sub> value in rats trained to discriminate 0.08 mg of LSD tartrate from saline in the two-lever drug discrimination assay (Monte et al., 1996; Nichols et al., 1991; Schultz et al., 2008; Whiteside et al., 2002).





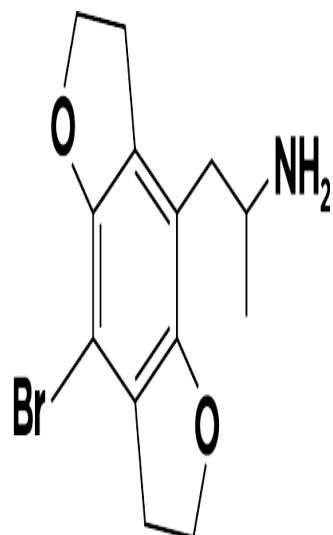
**DOB**

DD ED50 1.1  $\mu\text{M/kg}$



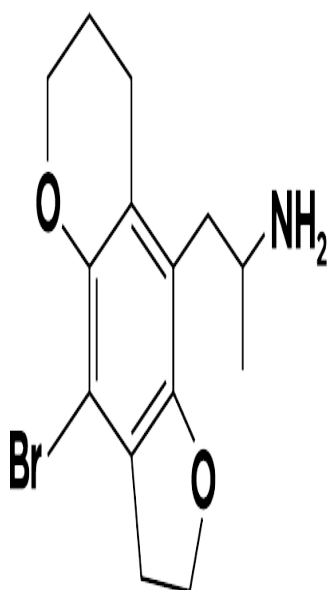
**SBF**

DD ED50 0.9  $\mu\text{M/kg}$



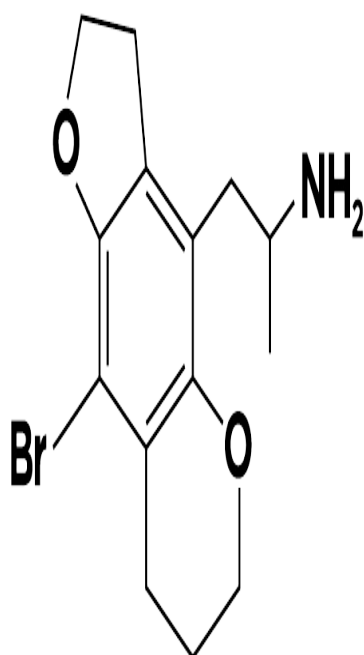
**BromoFly**

DD ED50 0.06  $\mu\text{M/kg}$



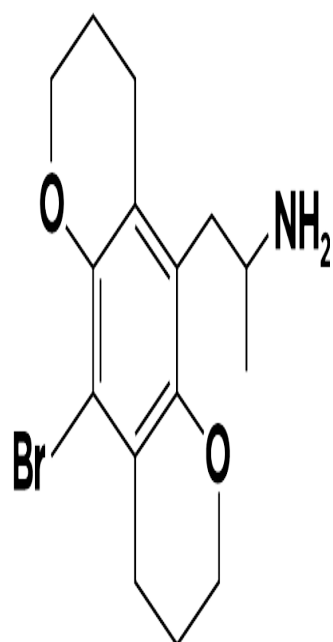
**2F5P**

DD ED50 0.4  $\mu\text{M/kg}$



**2P5F**

DD ED50 1.2  $\mu\text{M/kg}$



**DPA**

DD ED50 1.2  $\mu\text{M/kg}$

**Fig. 14** Phenethylamines with constrained “methoxy” groups, comparing their potency to the flexible molecule DOB. Five-membered furan congeners were more potent than the corresponding six-membered pyran compounds.

When either the 3- or 5-methoxy groups of mescaline were similarly tethered, the resulting compounds were inactive (Monte et al., 1997). They had higher affinity at the 5-HT<sub>2A</sub> receptor than mescaline, but their efficacy was markedly diminished. When the compound “bromofly” was made fully aromatic (i.e., double bonds were introduced into both of the furan rings) the molecule was even more potent, comparable to LSD in the rat drug discrimination assay (Parker et al., 1998).

Based on extensive design of rigid analogues of psychedelic amphetamine-type molecules in this author’s laboratory over many years, it may be concluded that the active binding conformation of these molecules at the 5-HT<sub>2A</sub> receptor can be represented by Figure 15 (see, for example McLean et al., 2006). The side chain is proposed to reside in a plane nearly perpendicular to the plane of the aromatic ring. The 5-methoxy oxygen may be a hydrogen-bond acceptor from serine 5.42 in the receptor.

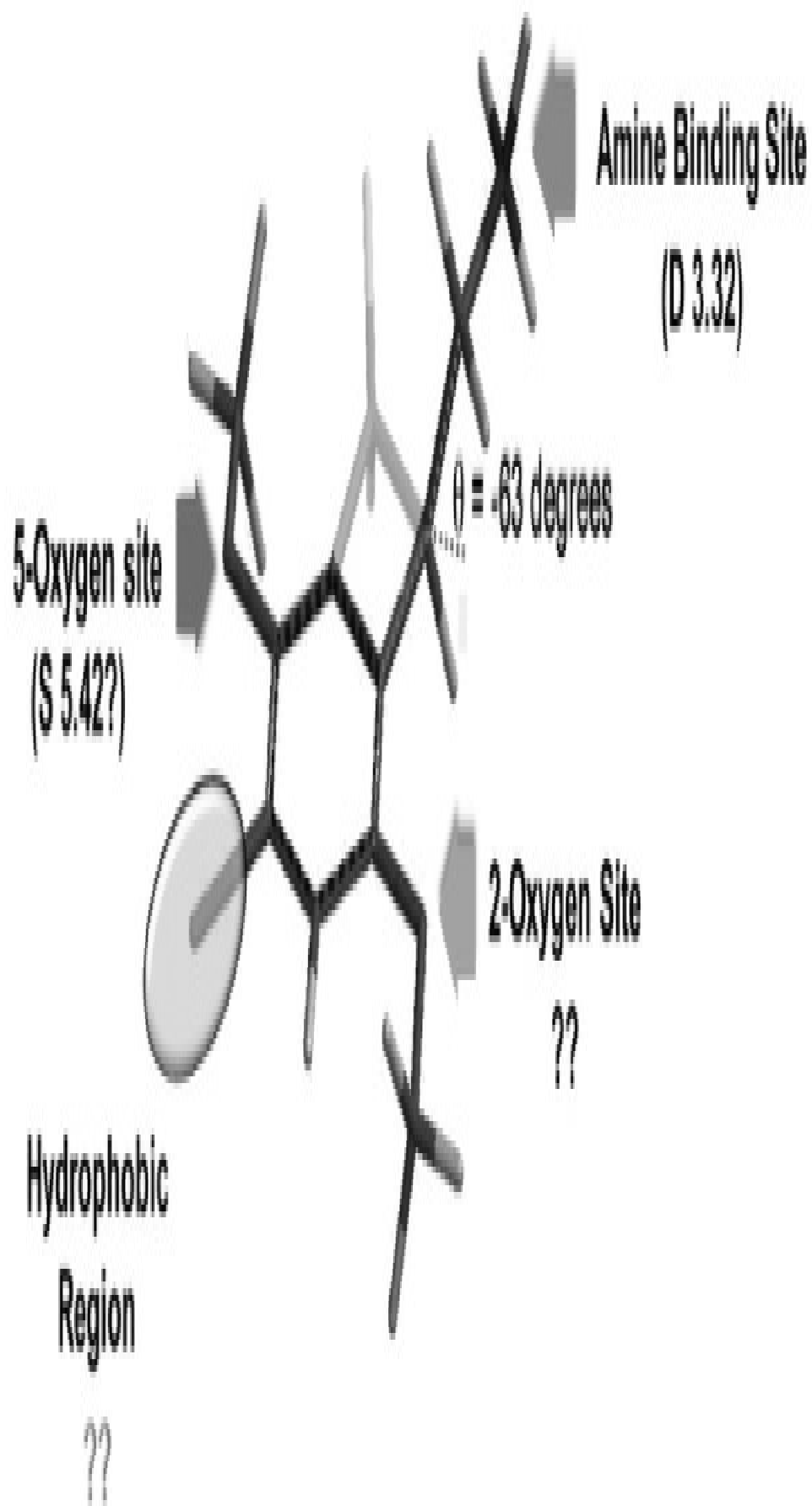
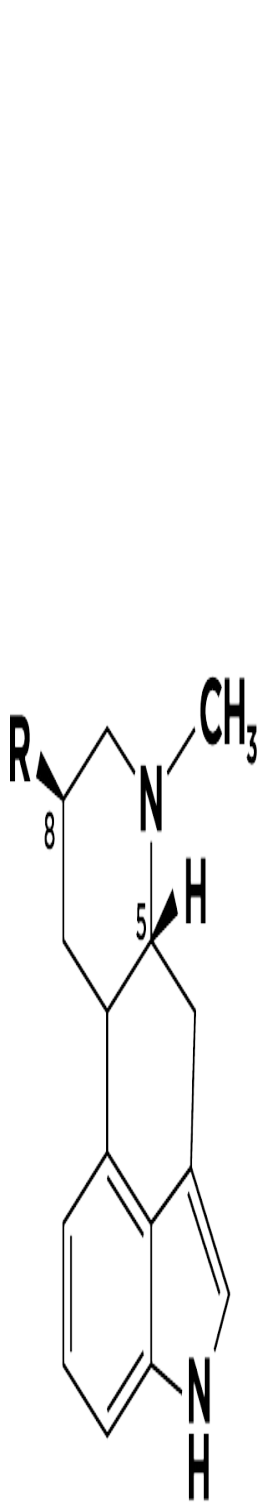


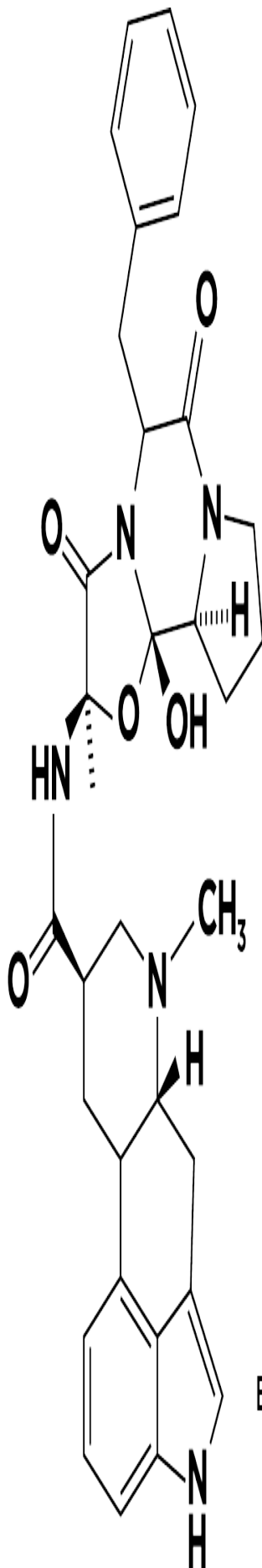
**Fig. 15** Proposed active binding conformation for psychedelic amphetamines.

## ERGOLINES

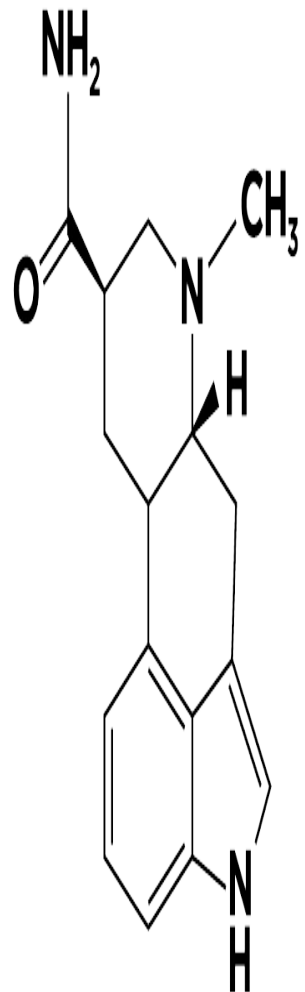
Ergolines have a tetracyclic nucleus with an indole aromatic system as its key pharmacophore. Naturally occurring ergot alkaloids have the R stereochemistry at the 5-position, as shown in figure 16, and the R configuration at the 8-position.



Generic Ergoline



Ergotamine



Lysergamide (ergine)

**Fig. 16** Structures of a generic ergoline, ergotamine, and lysergamide.

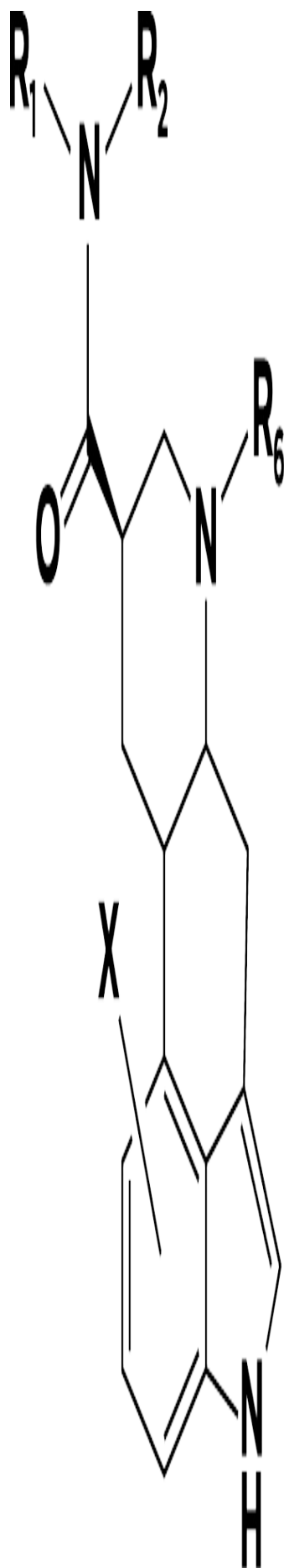
The substituents at the 8-position can vary, but most typically are complex cyclic peptoid-like moieties, such as in ergotamine. Ergotamine and similar ergot alkaloids are produced by the ergot fungus, most notably *Claviceps purpurea*, which can parasitize rye and barley, and is visible as dark curved and enlarged black growths, known as sclerotia, emerging from the grain stalk. The ergot alkaloids are very potent vasoconstrictors, and ingestion of breads containing significant amounts of ergot can cause prolonged peripheral vasospasms and vasoconstriction, ultimately leading to gangrene. Symptoms of ergot poisoning include burning sensations in the fingers and toes, and hallucinations. Once gangrene sets in, the fingers and toes become necrotic, and take on a black, charred appearance. More than 40,000 people died from an epidemic of ergotism during the Middle Ages. Ergotism was referred to as St. Anthony's fire, due to the intense burning sensations in the limbs and the charred appearance of gangrenous fingers and toes. St. Anthony was the patron saint of ergotism victims.

In spite of the toxicity of ergot alkaloids, if the substituent at the 8-position is a simple amide, as in lysergamide (ergine), the vasoconstrictor pharmacology is markedly reduced, and instead, ergine can produce a mild hallucinogenic intoxication. Indeed, *Rivea corymbosa* (*Turbina corymbosa*) is a species of morning glory native throughout Latin America, from Mexico as far south as Peru. Their seeds contain ergine, were employed by the Aztecs for their intoxicant effect, and were known as *Ololuiqui*.

*Ipomoea violaceae* and *Ipomoea tricolor* are other species of morning glory whose seeds contain ergine. The former have white flowers that open at night, and the latter are commonly known as heavenly blue morning glories.

Knowledge of the psychoactive properties of the seeds from these flowers and the nature of their chemistry was unknown when Albert Hofmann first synthesized the diethylamide of lysergic acid, LSD-25, in 1938, but he later determined that the active principle was ergine (Hofmann and Tschertter, 1960), and was thus chemically related to LSD.

Research on lysergic acid derivatives has focused on three areas of the molecule, as shown in figure 17.



1. Amide alkyl substitution (R<sub>1</sub> & R<sub>2</sub>)
2. N(6) substitution
3. Aromatic ring substitution

**Fig. 17** Areas for structural modification in lysergic acid amides.

Although in theory, substituents could be introduced into the aromatic system, in practice the synthesis of such analogues is extremely difficult. The total synthesis of lysergic acid itself was considered by natural products chemists to be a sort of “Mount Everest” of chemistry. The first total synthesis, by Kornfeld et al., in 1956, was a tour de force at the time, and was not amenable to the synthesis of derivatives substituted in the aromatic ring(s) (Kornfeld et al., 1956).

One productive approach was to examine the effect of various alkyl groups attached at N(6) of LSD. Hashimoto et al. (1977) had previously studied the anti-serotonin and oxytocic activities of several of these compounds in rat uterus. The N(6) ethyl, propyl, and allyl compounds were more potent in that regard. We resynthesized a series of these analogues, and tested them in the two-lever drug discrimination assay in rats trained to discriminate saline from 0.08 mg/kg of LSD tartrate. In this assay, the ethyl, propyl, and allyl analogues were all more potent than LSD (table 1) (Hoffman and Nichols, 1985). These three compounds were subsequently reported to be at least as potent as LSD in humans, with the N(6) ethyl being somewhat more active than LSD itself (Shulgin and Shulgin, 1997).

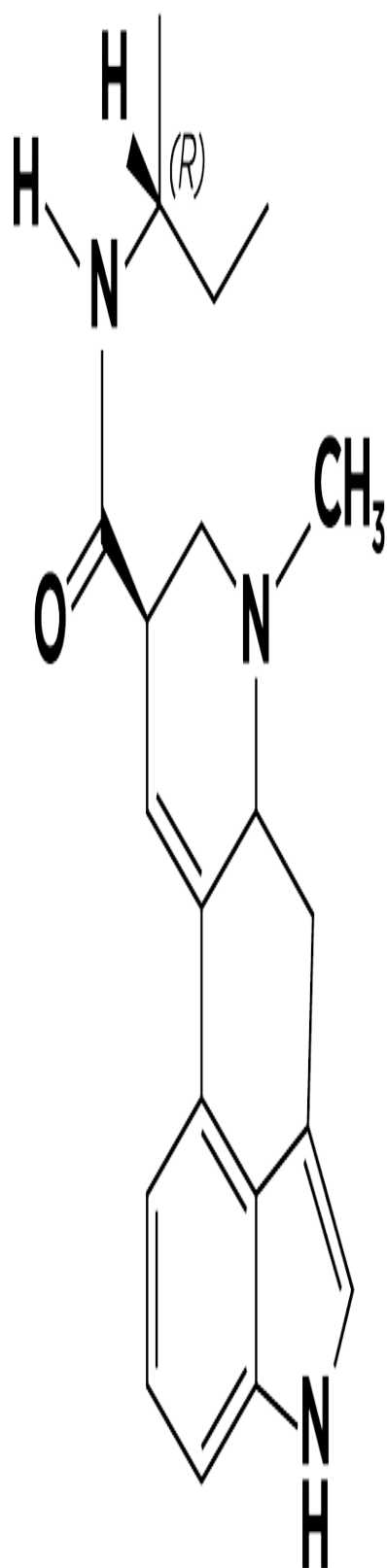
**Table 1.** Potency comparison of N(6)-alkyl-norLSD derivatives in the rat two-lever drug discrimination in rats trained to discriminate LSD from saline. ED50 values are in mM/kg.

| <b>R</b>                                   | <b>ED50</b> | <b>Potency *</b> |
|--------------------------------------------|-------------|------------------|
| H                                          | No Sub      | NA               |
| CH <sub>3</sub> (LSD)                      | 0.046       | 1.00             |
| CH <sub>2</sub> CH <sub>3</sub> (Ethlad)   | 0.020       | 2.30             |
| C <sub>3</sub> H <sub>7</sub> (ProLad)     | 0.037       | 1.24             |
| CH <sub>2</sub> CHCH <sub>2</sub> (ALLAD)  | 0.013       | 3.54             |
| CH(CH <sub>3</sub> ) <sub>2</sub> (iPrLAD) | 0.10        | 0.46             |
| C <sub>4</sub> H <sub>9</sub> (BuLAD)      | 0.357       | 0.13             |
| CH <sub>2</sub> CH <sub>2</sub> Ph         | No sub      | NA               |

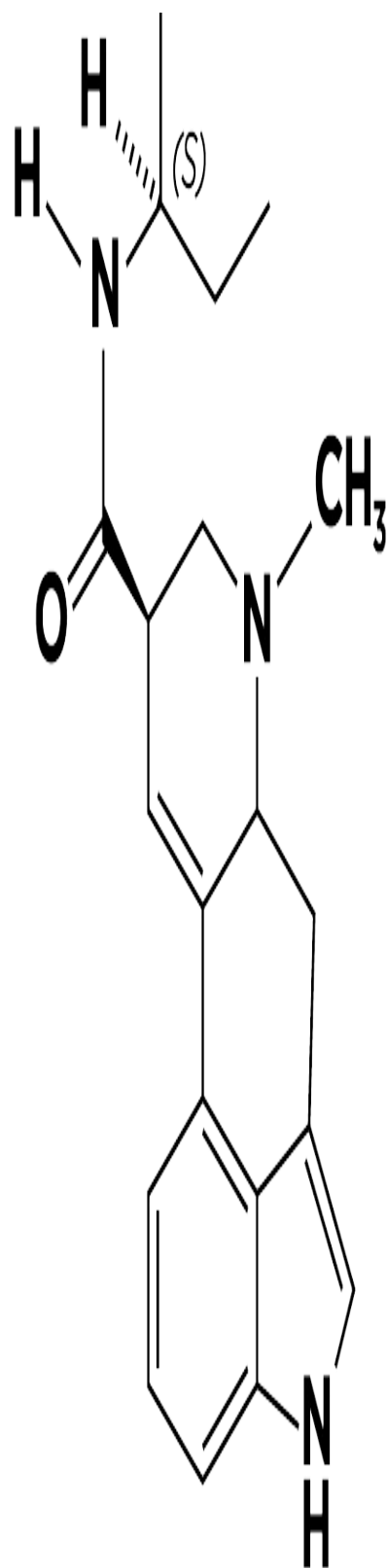
A large number of different amides of lysergic acid have been studied over the years. Generally, any structural change from the N,N-diethyl, no matter how minor, leads to a dramatic loss in



potency (e.g., see Pfaff et al., 1994). The high potency of LSD thus seems to depend specifically on the *N,N*-diethylamide moiety. We hypothesized that there might be a particular region of the receptor that was highly complementary to the diethylamide moiety. Our first simple experiment asked the question, “Is this region of the receptor stereochemically defined?” If the amide binding region was within the orthosteric binding site, and given that the receptor is made exclusively of L-amino acids, we predicted that a lysergic acid amide with a chiral substituent might show stereoselective effects. We thus prepared lysergic acid amides of *R* and *S*-2-aminobutane (Oberlender et al., 1992), shown in figure 18.



DD ED50 33 nmol/kg

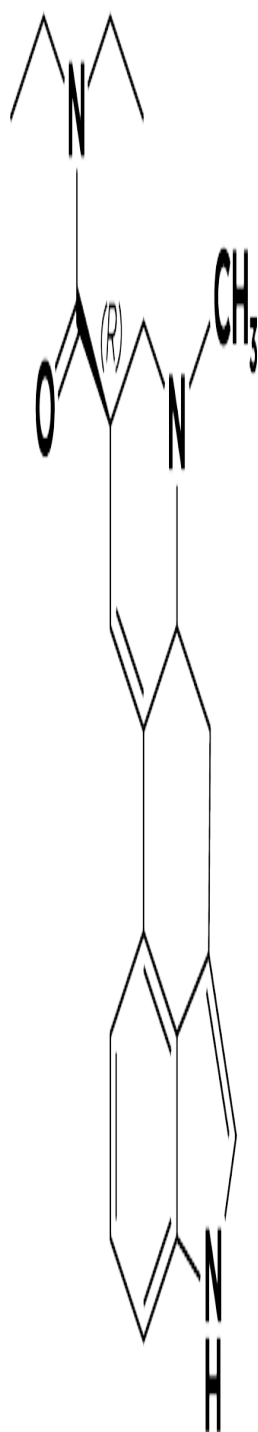


DD ED50 124 nmol/kg

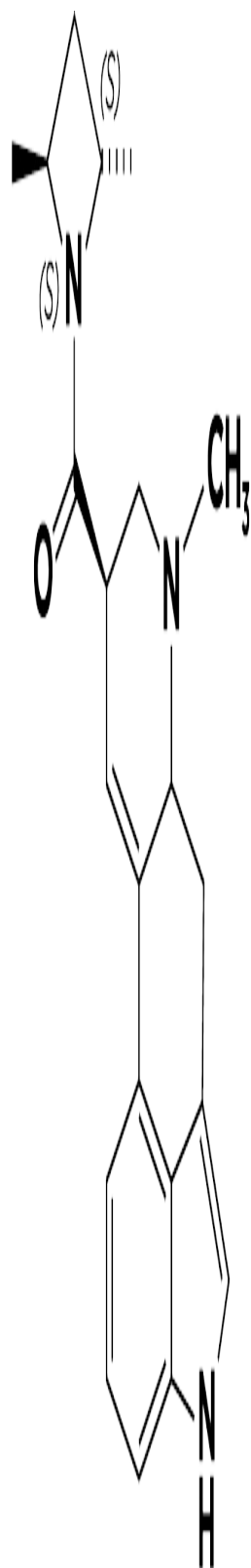
**Fig. 18** Comparison of the behavioral potency of the lysergic acid amides of *R* and *S* 2-butylamine. ED<sub>50</sub> values are from the two-lever drug discrimination assay in rats trained to discriminate LSD from saline.

Shown below the two stereoisomers are the ED<sub>50</sub> values in the two-lever drug discrimination assay in LSD-trained rats. Clearly, the stereoisomer with the 2-butyl substituent having the *R* configuration is approximately four times more potent than the stereoisomer with the *S* configuration in the 2-butyl substituent. This finding clearly indicated that the amide substituent engaged stereoselective elements of the receptor.

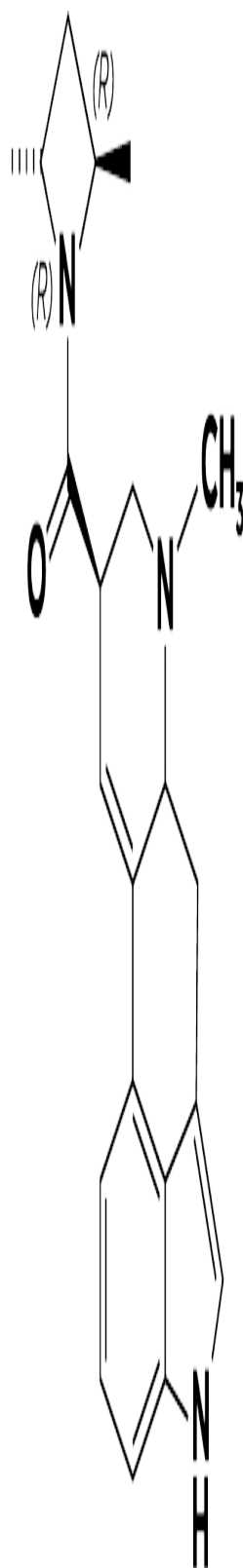
We next rigidified the diethylamide moiety of LSD to provide the *cis*-meso, *trans-S,S*-, and *trans R,R*-dimethylazetidines, shown in figure 19 (Nichols et al., 2002). Testing in the rat two-lever drug discrimination assay revealed that the stereoisomer with the *S,S*-dimethylazetidine had activity most similar to LSD itself.



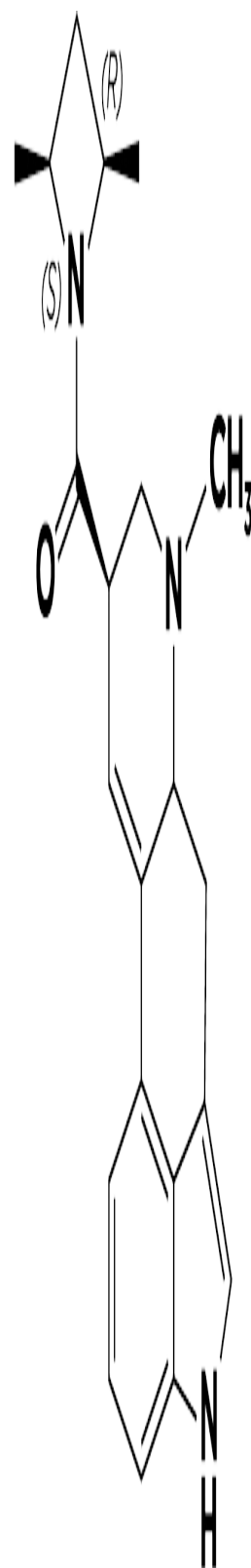
DD ED50 45 nmol/kg



DD ED50 25 nmol/kg



DD ED50 134 nmol/kg



DD ED50 115 nmol/kg

**Fig. 19** Comparative potencies of LSD and the stereoisomers of lysergic acid amides prepared from the three possible 2,4-dimethylazetidines. Values are from two-lever drug discrimination assays in LSD-trained rats.

Virtual docking of LSD into a homology model of the human 5-HT<sub>2A</sub> receptor indicated that the diethylamide likely interacted with a portion of extracellular loop 2 (EL2), which connects the extracellular end of transmembrane helix 4 to the extracellular end of helix 5. John McCorvy, a senior graduate student working in my laboratory, then prepared receptors with mutations in EL2: L228A, L228V, L229A, L229S, L229I, A230L, and A230N (McCorvy, 2012). Comparing their affinities to displace [<sup>3</sup>H]LSD in each of the receptors showed that LSD and the *S,S*-azetidide most closely resembled each other, and also that the polar mutation L229S had the most dramatic effect on each azetidide stereoisomer. Thus, we proposed that the *S,S*-azetidide represented the binding conformation of the more flexible diethylamide groups of LSD, and further, that residue L229 in EL2 directly interacted with the diethylamide moiety of LSD.

In 2017, it was possible to obtain the x-ray crystal structure of LSD bound within the serotonin 5-HT<sub>2B</sub> receptor (Wacker et al., 2017). The *S,S*-azetidide stereoisomer could essentially be superimposed on the LSD molecule in the crystal structure, where the dark structure in figure 20 is LSD, and the grey structure that of the *S,S*-azetidide.



**Fig. 20** Superposition of lysergic acid *S,S*-azetidide onto the crystal structure conformation of LSD bound in the serotonin 5-HT<sub>2B</sub> receptor (Wacker et al., 2017).

In the same report, it was experimentally observed using cloned human 5-HT<sub>2A</sub> receptors that LSD had a very slow association rate with the 5-HT<sub>2A</sub> receptor at 37 °C, and an even slower dissociation rate, requiring several hours for the LSD molecule to be completely dissociated from the receptor. It was seen that EL2 folds over the bound LSD molecule, essentially “trapping” it in the receptor so that it only dissociates with great difficulty. Furthermore, LSD was found to be a highly biased ligand, markedly recruiting  $\beta$ -arrestin2 relative to G protein-mediated signaling.

Molecular dynamics simulations in the same report indicated that EL2 was not very mobile, consistent with the receptor-binding experiments. However, when L229 was mutated to L229A, the receptor kinetics of LSD were changed dramatically, with a rapid on and off rate. In addition,  $\beta$ -arrestin2 recruitment was also markedly attenuated in the L229A mutant, suggesting that the long residence time of LSD in the receptor was correlated with its bias for  $\beta$ -arrestin2 recruitment.

## CONCLUSIONS

Natural products of the tryptamine, phenethylamine, and ergoline types are exemplified in nature. Medicinal chemists have exploited these natural product chemotypes to develop structure-activity relationships. Active tryptamines have largely been confined to ring-unsubstituted or 4- or 5-oxygenated molecules, with most of the structural variation being in larger alkyl groups attached to the basic nitrogen atom, comprising a relatively small number of new molecules. By contrast, following mescaline as the single prototype for psychedelic phenethylamines, literally hundreds of novel molecules have been synthesized. A large variety of ring substituents have been examined, with some compounds approaching the potency of LSD. The binding orientations of the methoxy groups have been determined, and the active side-chain conformation has been proposed. Finally, starting with lysergic acid amide and lysergic acid diethylamide, it has been found that replacing the N(6)-methyl of LSD with ethyl, allyl, or propyl leads to

compounds with potency in humans similar to LSD. The diethyl groups of LSD have been rigidified as stereoisomeric 2,4-dimethylazetidines to map their binding orientations at the receptor. In addition, the crystal structure of LSD bound within the serotonin 5-HT<sub>2B</sub> receptor has recently been determined, which validated the prediction that the lysergic acid amide of the S,S-dimethylazetidine would be the active conformation. It was also discovered that extracellular loop 2 of the receptor folds over LSD after it binds, resulting in a very long receptor occupancy, as well as a bias for beta-arrestin 2 signaling relative to signaling via G proteins.

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# MEXICO & CENTRAL AMERICA

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# Fertile Grounds? – Peyote and the Human Reproductive System

## [Keynote]

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*Stacy B. Schaefer, PhD*

Professor Emerita Department of Anthropology,  
California State University, Chico, California

### ABSTRACT

This paper examines the ingestion of the mind-altering peyote cactus, (*Lophophora williamsii*, endemic from the borderlands of Texas to Central Mexico), its medicinal properties, and how it may interact with the human reproductive system, specifically in women. The influence of peyote on pregnancy will be discussed through scientific studies involving peyote alkaloids such as mescaline, as well as qualitative data collected through ethnographic interviews with indigenous women from the Huichol Indian culture in Mexico and members of the Native American Church (NAC) in the United States. The paper will briefly compare the practice of peyote consumption by pregnant Huichol women, and ayahuasca tea consumption by pregnant ayahuasca church members. From personal perspectives informed through bioassays and participant/observation in Huichol and NAC peyote ceremonies, the topics of menstruation and fertility will be examined. Information grounded in biomedical and fertility research will be presented to hypothesize the interplay that may occur between peyote alkaloids, the nervous and endocrine systems, and the human reproductive system. Peyote, its medicinal qualities, and the interrelationship between peyote and women, specifically through pregnancy and the female reproductive system, are the themes highlighted in this paper. This report may have broader implications for other serotonergic entheogens.

## INTRODUCTION

In 1967, the first Ethnopharmacologic Search for Psychoactive Drugs conference served as a landmark in the multidisciplinary quest to discover and explore novel psychoactive plants and drugs. Just one year later, American anthropologists Peter T. Furst and Barbara G. Myerhoff were the first outsiders to participate in and document a Huichol peyote pilgrimage to Wirikuta, the sacred desert in the Mexican state of San Luis Potosí, led by the Huichol Indian shaman apprentice, Ramón Medina Silva. The Norwegian explorer and anthropologist Carl Lumholtz was the first to note this annual pilgrimage in the 1890's (Lumholtz, 1900, 1902). However, although he never had the opportunity to join Huichols on their sacred journey to the peyote desert, he did have an opportunity to eat peyote when trekking with some Huichol companions in their sierra homelands, where native shrines, sacred caves, and god-houses dot the countryside. He writes:

Under ordinary circumstances the plant (peyote) was nauseating to me; but now, when I was thirsty and tired, I could, rather to my surprise, swallow the cool, slightly acid cuts (sections of peyote) without difficulty. I found them not only refreshing, quenching my thirst and allaying hunger, but also capable...of taking away any sense of fatigue, and I felt stimulated, as if I had had some strong drink. ... during the night I suffered from the after effects of the drug, which when my eyes were closed, showed themselves in colour visions consisting of beautiful purple and green flashes and zigzags... (Lumholtz, 1902: 178-179)

Barbara Myerhoff also shared her narrative of the first time she consumed peyote. She writes:

.....after an inestimable period of time I began to be aware of a growing euphoria; I was flooded with feelings of goodwill. With great delight I began to notice sounds...Time and space evaporated as I floated about in the darkness and vague images began to develop...I sat concentrating on a mythical little animal...the little fellow and I had entered a yarn painting and he sat precisely in the middle of the composition.

I watched him fade and finally disappear into a hole ...  
(Myerhoff, 1974: 43-44)

This event took place prior to the pilgrimage she and Furst would take with Ramón and his extended family to “hunt”, harvest, and consume this mind-altering cactus that enables Huichols to intimately commune with their gods. This pioneering work resulted in Myerhoff’s 1974 ethnographic book *Peyote Hunt: The Sacred Journey of the Huichol Indians*, and Furst’s 1969 documentary movie *To Find Our Life: The Peyote Hunt of the Huichols of Mexico*.

Now let’s fast forward to 1987. I was a doctoral student in anthropology at UCLA working under the guidance of Johannes Wilbert, the same mentor who had supervised the research of Furst and Myerhoff. That year, I myself participated in the peyote pilgrimage with a large group of Huichols from the San José temple. Participating in this pilgrimage was a transformative experience, for not only did I gain a much more intimate understanding of my companions and their peyote traditions and beliefs, but the experience was an important event in my own personal development. It was challenging to participate in as well as document the journey. The authorities of the temple group had granted me permission to photograph the journey, and I was even instructed at times by the leading shaman as to what subjects would be important for me to include.

Weeks later, when I returned to the community to share copies of the photographs, one of my Huichol companions abruptly walked up to me, obviously disturbed, and in an assertive manner told me: “You *tewaris* (outsiders), you come on the pilgrimage, take photos, you even eat the peyote. But you never ask ‘why’ to the peyote. You never ask ‘why’. Well, I am going to tell you why: Peyote is everything. It is the crossing of the souls. It is everything that is. Without peyote, nothing would exist.”

Initially, I was taken aback by this confrontation, but in retrospect, I welcomed it because his challenge motivated me to learn everything I could about this innocuous-looking, yet powerful, entheogenic cactus. Since then, I have participated in three more peyote pilgrimages to Wirikuta, and in many peyote ceremonies in the Sierra. For over eight years, beginning in 1993, I also learned

about peyote from the Mexican-American “dealers” in South Texas, who are federally licensed to sell peyote to members of the Native American Church (NAC), and from NAC members. I have participated in more than two dozen NAC meetings in the “Peyote Gardens” of South Texas. Over the years since that first remarkable peyote pilgrimage, I am reminded that there will always be more to learn about this enigmatic plant.

In 1996, I began initial research on the topic of pregnancy and peyote, providing Huichol and Western scientific perspectives, and I published a seminal article on this subject (Schaefer, 1996b). At that time, I learned about the origin and spread of ayahuasca churches in Brazil and beyond, which led me to a preliminary inquiry into the use of ayahuasca during pregnancy, and to a comparison with peyote. This paper summarizes what is known to date on this topic, and provides an interesting comparison between two major entheogenic families, the phenethylamines (peyote) and tryptamines (ayahuasca), relative to women’s health.

## METHODOLOGY

It may be useful to the reader to provide an overview of the methodologies of cultural anthropology. As a cultural anthropologist, I have been trained to carry out qualitative ethnographic fieldwork. For me, this has involved living with Huichol family members on their ranches, learning from the women to become a master weaver on the Huichol back-strap loom, forming kinship ties as a godmother to various children in the family, and accompanying the family in their domestic and religious traditions. These activities have spanned the years from 1977 to the present.

My research approach is called participant/observation; it includes partaking of peyote within this cultural context, and conducting formal and informal interviews with my many Huichol consultants. This kind of fieldwork is an immersive experience; learning the language of Huichol ideas, concepts, and metaphors is necessary to decoding the information they have shared with me. This is to discern the emic perspective, the cultural viewpoint of the group being studied.

Another component to my research methodology brings an etic



perspective to the study, and incorporates the knowledge and information that Western science can provide about the world, nature, humans, life, and even death. Scientific inquiries can bring meaningful explanations along Western ideological lines to the questions addressed. In my research, I incorporate the etic approach primarily through the scholarly literature and in consulting with experts in pertinent fields of study.

Both the objective and the subjective perspectives can be integrated to provide a holistic understanding of the world, and in many ways explain the same phenomena; perhaps the only difference is in the language by which these phenomena are conveyed. This is what has been termed “natural modeling” by Johannes Wilbert in his discussion of tobacco shamanism (Wilbert, 1987). I have utilized the methodologies described above to understand the peyote plant from various levels. These include ethnobotanical knowledge held by botanists, chemists, and Huichol shamans; the preparation and consumption of peyote as it was observed and discussed by Huichol consultants; the integration of tobacco and other desert-dwelling plants as experienced by shamans and understood by medical doctors and botanists; peyote visions expressed by Huichol pilgrims and explained by neurobiologists; and cultural traditions and the meaning attributed to the peyote experience as seen by Huichol participants and Western psychologists (Schaefer, 1996a, 2004, 2005, 2011).

## PEYOTE: THE PLANT

Peyote is a low, grey-green, spineless cactus that naturally occurs in harsh landscapes which include both the Tamaulipan thorn scrub habitat from South Texas across the Mexican border, as well as the Chihuahuan Desert from West Texas south to San Luis Potosí, Mexico (Fig. 1). The oldest evidence of peyote and its importance to prehistoric peoples comes from ancient sites from Coahuila, Mexico, to the Lower Pecos region of Texas. Necklaces of dried peyote strung beadlike on fiber cord have been found associated with burials in rock shelters that date from 800 A.D. to as far back as 6000 B.C. (El-Seedi et al., 2005). Along the Pecos River in West Texas, peyote samples dating to around 5000 B.C. were discovered in the Shumla Caves. After careful analysis, researcher Martin Terry

and his team were intrigued when they discovered that these samples were composed of a mixture of peyote and other plant material, and appear to have been intentionally created as plant effigies (Terry et. al., 2006). This region is filled with spectacular rock art; the artists appear to have most likely been proto-Uto-Aztec speakers. Some of the themes in the rock art along the Rio Grande River north of Eagle Pass, Texas, may include renderings of powerful peyote-related experiences and beliefs (Boyd and Dering, 1996, Boyd, 2003, 2016). Light, compact, and potent, peyote could very well have been a trade item along with other precious goods, such as salt and obsidian, that were carried along the pre-Columbian trade networks (Weigand, 1981).



**Fig. 1** Peyote (*Lophophora williamsii*) collected in Wirikuta and placed in votive bowls.  
Photo by Stacy B. Schaefer

Through the centuries, this precious psychoactive cactus was considered to be sacred by many indigenous people, and called the “devil’s root” by Spanish missionaries and other Christian officials. Known by the Aztecs as “peyotl” in the Nahuatl language, “hikuri” by the Huichol Indians, and “medicine” by many Native American tribe members, its botanical name is *Lophophora williamsii* (Lem. Ex Salm-Dyk) J. M. Coult.<sup>25</sup> Peyote contains more than 60 alkaloids, yet little is known about the effects many of these have on the human body. Phenylethylamines and tetrahydroisoquinolines make up more than half of the naturally occurring chemical compounds in the plant. Mescaline (3,4,5-trimethoxyphenethylamine) was identified by chemist Arthur Heffter in 1897 as the principal alkaloid responsible for peyote’s

mind-altering effects. Research on isoquinoline alkaloids indicates that they, or other monoamine oxidase inhibitors (MAOIs) in the tissue of peyote, may enable normally orally inactive compounds to become orally active (Shulgin & Perry, 2002; Bruhn et. al., 1978).

**25.** Most indigenous groups that use peyote have a name for this revered plant in their own language.

## PEYOTE AS MEDICINE

With its abundance of alkaloids, peyote is like a virtual pharmacy. It is no wonder that this plant is also used for medicinal purposes. Richard Evans Schultes, who became renowned for his research and publications on psychoactive plants, began his lifelong career in the 1930s with his field study of peyote among the Kiowa Indians. In his groundbreaking article, “The appeal of peyote (*Lophophora williamsii*) as medicine”, he wrote of the therapeutic value of peyote that he learned from Native Americans (Schultes, 1938). Peyote is said to provide relief from pain and fevers, and it is used to treat scorpion stings and snake bites. Poultices made from peyote are applied externally to arthritic joints, cuts, and bruises. Juice from the peyote has been used as eye drops to treat cataracts. It is taken as a tonic to stimulate energy, allay hunger, and promote feelings of well-being (Schultes, 1938, Anderson, 1996, Schaefer, 2015b). Another salubrious benefit of peyote is as a treatment for intestinal problems. Scientific studies have discovered that some of the peyote alkaloids (ex., hordenine) have antibiotic qualities, inhibiting the growth of penicillin-resistant strains of the bacterium *Staphylococcus aureus* (McCleary et al., 1960; Rao, 1970).

Laboratory research also indicates that peyote appears to increase immune response to cancerous tumors (Franco-Molino et. al., 2003). In this study, 50 g of *Lophophora williamsii* was macerated, treated with 50 mL of methanol, and filtered. This methanol extraction of peyote was added to *in vitro* murine lymphocytes and macrophages, and human peripheral blood mononuclear cells (HPBMCs), and applied directly to murine and human tumor cell growth. The results showed that “a methanol extract of peyote cannot only potentiate some immune parameters, but also directly kill tumor cells” (Franco-Molino et al., 2003). Citing research by Sissors and Voss (1978), which indicated that mescaline inhibits *in*

*vitro* murine lymphocyte proliferation, Franco-Molino et al (2003) suggest from the results of their study that there “might be some immunostimulatory compounds in peyote’s extract whose concentration might exceed that of a potential inhibitor of lymphoproliferation, such as mescaline.” The authors also noted that the peyote extract activated murine leukocytes as well, and increased signals to proteins in human mononuclear cells that are known to be “extremely potent inflammatory molecules” that are “involved in acute and chronic inflammation” (ibid).

Indeed, the term “medicine” used by Native Americans for peyote is most appropriate. It has medicinal qualities, but it is not a “drug” that some fear can be abused. Numerous studies have demonstrated that it is not addictive. In fact, peyote consumption, especially within a religious context such as NAC ceremonies, can be beneficial in the rehabilitation of individuals from alcohol and drug abuse (Halpern et al., 2005, Calabrese, 1997, Schultes, 1938). Also, one must not overlook the positive influence that peyote experiences may have on individuals, which in turn can lead to greater spiritual awareness and meaning in their lives.

## PEYOTE AND PREGNANCY

The Huichol pilgrimage to the peyote desert is a formidable journey that enables pilgrims to “find their lives.” There are many layers of meaning for this trip, some formalized in traditional myths. My female consultants recounted to me an origin myth of the first peyote pilgrimage, and one of my companions drew a picture to visually tell the story, which involves three women, the Earth Goddess (Utüanaka), the Goddess of Peyote (Wiri’uwi), and the Blue Corn Goddess (Yuawime) (Fig. 2). One day, while Utüanaka was weaving on her loom, the design of the path to Wirikuta appeared, and the road manifested before them. These women traveled to the entrance of the peyote desert. The Deer Messenger, Kauyumarie, accompanied them. Utüanaka and Wiri’uwi were allowed to enter this sacred place, where they encountered peyote and consumed it. Yuawime stayed behind. The two goddesses who entered became pregnant while in Wirikuta. Utüanaka returned to share the wonders of peyote with her community, and showed them how to make the pilgrimage to

Wirikuta. Wiri'uwi remained in Wirikuta and became the Mother of Peyote.



**Fig. 2** Drawing of the myth of the original pilgrimage to Wirikuta by Estela Hernandez. The two women on top are the goddesses Wiri'uwi, and Utüanaka with babies in their wombs. The seated woman below is the goddess Yuawime, who was not fertile and could not enter the sacred peyote desert. Photo by Stacy B. Schaefer

This theme of peyote and pregnancy is also ever present in the daily lives of Huichol women. Some Huichol women may be pregnant and consume peyote while on the pilgrimage or in ceremonies in their communities. On my first peyote pilgrimage with the San José temple group, I noticed that various women were pregnant. One woman, who was the wife of the leading shaman, was eight months pregnant. Another woman was six months along, and a third woman was two months into her pregnancy. All of these women ate large quantities of peyote because, as I later learned, they were either shamans or learning to become shamans. I found out that these mothers did not experience any complications when giving birth, and that by all appearances their babies were healthy and well adjusted. I continued to be involved in the ceremonies of this temple group, and I came to know these babies and watch them grow from childhood to adulthood. They are active members in the community and beyond, and have their own families. During their reproductive years, many Huichol women are pregnant on average every other year. For Huichol women, as it is for the men, following cultural traditions inevitably involves consuming peyote in ritual contexts. Peyote may be consumed fresh, dried, or powdered and mixed into a beverage. Women, like their male counterparts,

consume peyote throughout their lifetimes, even when pregnant.

I spoke with various Huichol women about the practice of ingesting peyote during pregnancy. One said that it was best to wait until the second trimester to do so, because in the first three months the baby was in a very delicate state and could abort. Several others commented that they consumed peyote during all stages of their pregnancy, and they and their babies did not experience any ill effects. Another explained that to ensure that there will be no problems or complications, the shaman provides prenatal care throughout the pregnancy by palpating the woman's stomach, healing with power wands, dreams, prayers and offerings to the gods for the mother and the baby in her womb.

The Huichol women whom I interviewed about their peyote experiences while pregnant all agreed that the babies in their wombs felt the effects of the peyote. One female shaman who specializes in fertility and childbirth told me:

The baby is naturally much purer than others, the gods are helping it, like the fire and the deer, like the shaman who blesses the fire and blesses the sun...for this reason when the mother eats peyote she knows everything that is happening and the baby knows too...the baby feels the same as the mother...when a woman is pregnant even the baby inside receives messages from the deer, messages from the peyote...the baby always feels the same as a person...the baby cannot talk, it communicates without words, only with its '*iyari*', heart memory (a kind of genetic memory of the soul).

A second woman described that first there is a quiet period. Her husband, speaking for her, said yes, her baby was "drunk" with the peyote and the two could communicate their thoughts telepathically. "My wife said that when this happened to her, that the baby remained in the womb, but their '*iyaris*' went up to the sky to Niwetüka (the goddess who cares for the souls to be born). When the effects of the peyote wore off, her heart memory returned to her body, and that of her fetus returned to its place in the womb."

After this quiet period, the fetus can become very active and move in the womb; some women say the baby is "dancing" inside. One other female shaman described her sister's peyote experience in the eighth month of her pregnancy:

At first it hurts. Then the baby inside is real quiet. Then it moves around a lot. The baby is 'inebriated' with the peyote also but does not know how to communicate well. My sister said that when she was pregnant and "traveling with the peyote", that although the baby was inside of her, she saw it right in front of her eyes. She didn't talk with the baby. She communicated with the gods to see that everything was all right, that the baby was formed well and there was nothing wrong with it.

Female shamans, because of their spiritual calling, may consume more peyote than other Huichol women; consequently, their children, while *in utero*, are more likely to experience peyote's effects than others' babies in the womb. A female shaman shared with me her thoughts, "I always like to eat peyote. It doesn't matter if I am pregnant ... If I feel well I like to eat it. There in Wirikuta, the people pray to the gods, and for some the gods give them the prize (a child) that has the design of a shaman...a clearer of fields...or a deer hunter ... that's how they are born. I think it happens like this because it is a custom that will never be lost."

This female shaman recounted her peyote experience in Wirikuta when she was two months pregnant with her son:

(In Wirikuta) I thought we would eat a lot of peyote, to see what we could encounter to learn more about our customs. So I ate eight large peyotes, and the peyote was strong. I got dizzy and then 'inebriated with the peyote.' I never thought I was pregnant. Kauyumarie (the deer messenger) appeared like a person, and told me how I was feeling ... he was talking to me from his heart. ... I think that Kauyumarie was talking (to my son in my womb). ... Afterwards, the shamans said that he was given to me in Wirikuta by the gods, with our goddess Wiri'uwi, the mother of peyote, so that our customs will not be lost...That is why he was born, why they gave him to me in Wirikuta, with me eating peyote, that's why he is peyote. I think he is peyote. He likes to eat peyote a lot ... that's how (some) are born.

Let us turn from the emic perspective of Huichol women to scientific studies and neurobiology. Research shows that when

peyote is ingested, the mescaline in the plant functions like naturally occurring transmitters in the brain. Depending on the dosage, mescaline can inhibit, or block, the chemical transmission of impulses between nerve cells at synaptic receptor sites in the central nervous system. This affects the manner in which impulses are transmitted in the brain, and how the brain processes these signals. Mescaline has the same basic monoamine structure as the neurotransmitters norepinephrine, serotonin, and dopamine. Norepinephrine is abundantly concentrated in the limbic system of the brain, the site where emotions such as love, hate, joy, and sadness are stimulated. Greater clarity of thought can be induced by the release of norepinephrine. As norepinephrine neurons descend to the spinal cord, they play an important role in regulating behavioral responses to sensory stimuli influencing the muscles in the arms and legs (Snyder, 1996). The serotonin system affects sleep, mood, appetite, and depression, as well as sensorimotor processes. The release of serotonin causes the secretion of growth hormones, and it acts as a vasoconstrictor, stimulating the smooth muscles. Dopamine pathways are related to reward-behavior responses and hormonal release. Dopamine neurons are linked to motor abilities, and serve to maintain thoughts and perceptions in accord with the reality of one's mundane environment (Snyder, 1996: 209).

So how does ingestion of peyote by a pregnant woman affect her fetus? Laboratory research in the 1960s and 1970s was carried out to determine the risks of taking psychedelic substances during pregnancy. This was at a time when propaganda circulated widely, prompting public concern that verged on hysteria. For example, unfounded claims were disseminated about the health dangers of "psychedelic drugs", especially LSD, and the alleged chromosomal damage that could influence future generations. During this time and in this social climate, laboratory studies were conducted on mescaline and fetal development (Gerber, 1967; Maickel and Snodgras, 1973; Shah, 1973; Taska and Schoolar, 1972) using pregnant laboratory rats, mice, hamsters, and monkeys, which were injected with varying doses of mescaline and then euthanized to examine the results. In some cases, a radioactive carbon isotope was incorporated in the injected mescaline to trace where it traveled in



the body. The animals used in the various experiments ranged in their pregnancies from the eighth day of gestation, as in one study with hamsters, to the fifteenth day of gestation in the study of mice, to the third semester in the monkey study. The amount of mescaline injected into the animals also varied among the studies.

This research demonstrated that mescaline could cross the placental barrier in each case. Some restrictions in the passage of mescaline to the fetus were noted, indicating that the fetus did not receive as high a dose of mescaline as the mother. However, once the mescaline entered the fetus, its distribution to the central nervous system did not appear to be restricted, and the brain tissue rapidly accumulated mescaline in high concentrations. The action, it was suggested, may have been due to the partially developed blood-brain barrier in the fetus. The younger the fetus was in its development, the greater the amount of mescaline that passed to the brain. The metabolism of mescaline in the fetal brain was slower than in the brain of the mother. Upon examination of the maternal tissues, mescaline was found in high concentrations in the kidney, liver, and spleen, with relatively low amounts in the brain. This result was attributed to the well-developed protective blood-brain barrier of the mother. Also noteworthy was that among the maternal tissues, the uterus was capable of storing mescaline for longer periods of time than other tissues studied, and the uterine smooth muscle had a great affinity for mescaline. Congenital malformations of the fetus were found only in one study, on hamsters on the eighth day of pregnancy that were injected with 0.45 to 3.25 mg/kg of mescaline.

While these laboratory studies ascertained that mescaline can cross the mother's placental barrier and the blood-brain barrier of the fetus, these animal experiments did not precisely replicate the dose/response of peyote consumption or its effects on a human mother and her fetus (Fig. 3). In addition to mescaline, there are an abundance of other alkaloids in peyote, and little is known about how they interact in the human body. The manner in which mescaline was administered to the animals by injection does not replicate typical human ingestion of peyote. Likewise, there are physiological differences between people and these research animals. The dosage of mescaline administered, the stage of fetal

development, and the marked differences that exist in the gestation periods of mice, rats, hamsters, monkeys, and human beings are all important considerations.

| animals  | study        | dose ammount                       | eq. dose for 55kg. woman |
|----------|--------------|------------------------------------|--------------------------|
| hamsters | Greber 1967  | 0.45 mg                            | 24.75 mg                 |
| hamsters | Greber 1967  | 1.33 mg                            | 73.15 mg                 |
| hamsters | Greber 1967  | 3.25 mg                            | 178.75 mg                |
| monkeys  | Taska 1972   | 5 mg/kg <sup>14</sup> C-mesc.      | 231.4 mg                 |
| mice     | Shah 1973    | μmol/kg <sup>14</sup> C-mesc.      | 96.8 mg                  |
| rats     | Maickel 1973 | 0.50 μmol/kg <sup>14</sup> C-mesc. | 27.5 mg                  |

**Fig. 3** Dosages of mescaline given to the laboratory animals in the various reports and how these correspond to equivalent dosage for a 55 kg. woman. I am grateful to Jonathan Ott for helping calculate these dosages.

To date, the only scientific study that examined human subjects who consumed peyote and its effects on their offspring was conducted by Dorrance et. al. (1975). The research compared lymphocyte chromosomes of 57 Huichol Indians with a lifelong and generational history of peyote ingestion to 50 peyote-naïve Huichol control subjects and ten laboratory control animals. The results indicated that no association could be made between multigenerational consumption of peyote and abnormalities in lymphocyte chromosomes (Dorrance et. al, 1975: 301-302). Also noteworthy in this report was the clinical opinion of the physician responsible for the treatment of the Huichols in the study, who stated that despite the common use of peyote by pregnant Huichol women, there was no evidence for any increase in congenital malformations among their offspring (ibid: 302).

If some Huichol women ingest peyote during their pregnancy, and scientific studies on mescaline show that it can cross the placental and blood-brain barriers, it is worth contemplating what effects this may have on the baby's cognitive development while in the womb. Beginning at three months and onward, the primary sensory areas in the neocortex of the fetus' brain begins to develop. The tactile

senses, followed by the visual and then auditory centers begin to develop. At twenty-four weeks of development, many of the neurons in the brain are present. At this stage, the eyes are light sensitive and the fetus reacts to sound. By the third trimester, the brain of the fetus develops rapidly, causing sensory and behavioral capacities to expand (Berk, 2006: 86).

Due to the nature of such research, we have a limited understanding of the processes of cognitive development in a fetus. Researchers turn to the cognitive development of infants and newborns to try to assess what may be occurring while *in utero*. Theoretically, internal and/or external stimulation of the neocortex of the fetus may help with the connection of neurons in the brain. Along these lines, it is also theorized that the reason newborns sleep so much, and that 50% of this is REM sleep, is because they do not get the stimulation they need from the environment in the waking state. REM provides the stimulation necessary in young infants for development of the central nervous system that they do not get in an alert state (Berk, 2006: 130; DiPetro et. al., 1996; de Weerd and van den Bossche, 2003). Professionals believe that the earlier in its life a baby receives ongoing stimulation, the better its nervous system will develop; this includes cognitive and reflex abilities, etc. (Gary Montgomery, 1996, personal communications).<sup>26</sup> (Fig. 4). Laboratory studies indicate that the younger the fetus, the greater the amount of mescaline that can cross the partially developed blood-brain barrier. Could that mean that two-month-old babies in the womb are exceptionally stimulated from the peyote the mother ingested? Could such episodes at various stages in development influence the cognitive development, even the neurological networking, of the fetus to the point where the baby literally perceives the world differently than those who have not had this experience? Huichols say that babies who have received peyote while in the womb are more predisposed to becoming shamans.

**26.** I have consulted over the years about this topic with Gary Montgomery, PhD, Professor of Psychology, who has for several decades focused his research on child development at the University of Texas-Pan American (now University of Texas-Rio Grande Valley).

It should also be noted that Huichol children consume peyote, first via their mothers' milk, and then by eating small amounts. Some children show an affinity for peyote and seek it out. It is never forced upon children. Upon reaching adolescence, they are given specific peyote plants selected by family members to ingest as a kind of "rite of passage."



**Fig. 4** Mother and child in the peyote desert. Photo by Stacy B. Schaefer

Peyote is also ingested by women in smaller doses during childbirth. Women I have interviewed say that it helps alleviate the pain of childbirth, quickens the delivery, and results in less blood loss in the birthing process.

#### PARALLELS WITH AYAHUASCA AND PREGNANCY

Some pregnant members of ayahuasca churches drink the entheogenic brew of ayahuasca (*Banisteriopsis caapi* and *Psychotria viridis*), also known as *daime*, as a sacramental tea. One Brazilian woman who was a devout member of the *Santo Daime* Church, Yatra W. da Silveira Barbosa, spoke with me (personal communication, 1996) about pregnancy and the ritual use of ayahuasca. She explains:

[Ayahuasca] doesn't affect the physical development of the fetus. The children in the forest who were born with *daime* and received *daime* from their mother throughout her whole pregnancy, they have a very special character, they are more observant, they are very wise ...

Yatra also conveyed that during childbirth the mother drinks ayahuasca, and other women who are present for the delivery also partake.

During the labor, they invoke the entities to come and do the labor, deliver the child. When the baby is delivered, it is under these circumstances and it is already around these entities and these people around them. And the child, the first thing they put in its mouth, even before the mother's milk, is a drop of *daime*. That means that they are born in this other dimension ... <sup>27</sup>

**27.** Yatra da Silveira Barbosa was instrumental in bringing ayahuasca and the *Santo Daime* Church to Amsterdam. While living in Amsterdam, she founded the organization Friends of the Forest, dedicated to conservation of the Brazilian rainforest, the indigenous people, and the scientific study of ayahuasca. When I interviewed her in 1996, she related that women in Amsterdam who were initiated into using ayahuasca for religious purposes were also drinking ayahuasca throughout their pregnancies. She described the first baby that received ayahuasca *in utero* and at birth in the Netherlands. During the mother's labor in the hospital, up to five women from this group were present. Clandestinely, they gave ayahuasca to the mother during the delivery, and they all sang as the baby was born. A small amount of ayahuasca was put on a piece of cotton that was then put on the tongue of the newborn. The women called this baby "Star Baby", because it was the first baby born in this way in the Netherlands.

Also, according to Silveira Barbosa, in Brazil and the Netherlands, Church babies are baptized two or three weeks after birth with salty water, honey water, and ayahuasca on their tongues. Henceforth, they drink ayahuasca during meetings. The mothers give their babies ayahuasca - the amount is determined by their size - and then the mothers drink it.

Anthropologists Marlo Eakes Meyers and Matt Meyers, who carried out fieldwork in Brazil and participated in the Universal Light Christian Illumination Center - Alto Santo, discuss ayahuasca and pregnancy. They report that pregnant women are supervised, as are other special members, by the Godmother of the church.<sup>28</sup> Some women may take smaller amounts of ayahuasca during their pregnancy than they normally would (Eakes Meyer and Meyer, 2013: 197). Brazilian anthropologist Beatrice Labate (2011) interviewed one woman who was a member of the *Santo Daime* Church, and her consultant also stated that smaller doses of ayahuasca are ingested by pregnant women. She reported:

**28.** Marlo Eakes Meyer and Matt Meyer are former students of mine at California State University, Chico. We had numerous conversations about entheogens, including peyote among the Huichols, my research on pregnancy and peyote, and what I had learned about pregnancy and ayahuasca as presented in this paper. Upon completing their MA degrees in Anthropology, Matt Meyer continued in the PhD program at the University of Virginia, conducting fieldwork in Brazil on ayahuasca religion for 15 months from 2002-2007 (Meyer, 2014). Marlo accompanied him in the field with their children. Together, they

became interested in the use of ayahuasca by pregnant women, and summarized their preliminary findings in the article by Eakes Meyer and Meyer (2013). I received a draft copy of this article written in English; later it was translated into Spanish for publication.

*Daime* gives women a profound experience of pregnancy and a strong contact with the baby in her womb ... And children who take *Daime* are normal, healthy, and intelligent. At this point, there are many families who have used *Daime* in the church for several generations, and in general they are healthy, happy, prosperous, and well balanced.

Another woman, Vera Fróes, who is a Brazilian historian and member of the *Daime* church Colônia Cinco Mil, wrote about her own experience taking *daime* during childbirth. Her description of the event, as discussed and translated from Portuguese to English by Eakes Meyer and Meyer (2013, in Fróes, 1988) is as follows:

I started to ingest the liquid at 7 in the morning, and from there took another dose every half hour ... I felt the contractions accelerate quickly; I had never felt that before, and by two in the afternoon, already suffering a lot, the *mirações* (visions) gave me relief [from pain] ...

At that moment I had a vision of Our Lady giving me the cup and saying:

‘Take it, my daughter, it is your last dose.’

Believing what I saw and heard, I grabbed the cup and drank. Right afterwards I entered into labor, and the baby began to ‘crown.’ The time had arrived, and Marco, who was singing the hymn ‘Sol, Lua, Estrela,’ wanted to help me, but it depended all on me...the *Daime* achieved true miracles in women’s childbirth. I saw that all the spirits who were helping me turned and looked at the spirit that would incarnate in the baby, a burst of light lit up everything and the baby cried, I felt an indescribable happiness, was in harmony with all the world, floating on clouds of light.

Eakes Meyer and Meyer relate that church members look favorably upon pregnant women who ingest *daime*. This same sentiment is held for infants and older ones. Having intimately experienced *daime* in the womb or as babies, they are sometimes

considered by church members to be enlightened, for they truly are children of the Queen, meaning the Virgin Mary who is “Queen of the Forest” (Eakes Meyer and Meyer, 2013; Froes, 1988: 198).

Cultural practices allow pregnant Huichol women and ayahuasca church members to ingest peyote or the ayahuasca brew, respectively. This is viewed by some as a special kind of initiation and a favorable way to bring a child into the world.<sup>29</sup> It would appear that this is not a maladaptive practice. Care is taken in these situations to safeguard the health and development of the fetus. Likewise, the mothers are consciously aware that their actions enable the babies in their wombs to experience the effects of the sacramental plants and commune with the spirit world as they understand and perceive it to be. In both practices, these plants are intentionally taken during childbirth to quicken the delivery and assuage the pain. Some Huichol women relate that consuming peyote also reduces the blood involved in childbirth. In the case of some female ayahuasca church members, drinking this tea during childbirth also opens a doorway for their own direct communication, as well as that of their newborns, with spiritual beings, such as the Virgin Mary.

**29.** This paper does not advocate for or against the ingestion of entheogens during pregnancy. It is important to not only note that the practice does exist, but also to understand the processes at work on many levels.

In scientific terms, both peyote and ayahuasca interact with the same serotonergic system. Stimulation of serotonin receptors, particularly 5HT<sub>2</sub>, induces vasoconstriction in the uterus, which causes blood vessels to constrict the flow of blood; hence, a lesser amount of blood is shed during the delivery process. Serotonin also interfaces with the smooth muscle in the uterus and can induce contractions (Pharmacorama.com Drug Knowledge, accessed 07/12/2017). Peyote or ayahuasca taken during childbirth, or to induce it, interact with the 5HT<sub>2</sub> serotonin receptors, which in turn can enable greater ease in parturition.

## MENSTRUATION, FERTILITY, AND PEYOTE

Having examined the topic of peyote consumption during pregnancy and at childbirth, let us turn to peyote and fertility and

revisit the Huichol myth of the origin of the pilgrimage to Wirikuta, the peyote desert, with the three women who made the journey – Utüanaka, Wiri'uwi, and Yuawime. Before entering Wirikuta, they stopped at a lake to leave offerings. Kauyumarie, the deer messenger, looked to see if they had fertile wombs. Utüanaka and Wiri'uwi were menstruating. They washed themselves in the lake and the water turned red from their menstrual blood. To this day, this sacred place is called Haa Xuretü Mayema, “where there is red water.” Utüanaka and Wiri'uwi were allowed to enter Wirikuta. Yuawime was infertile, and so she stayed behind and became a mountain in the western part of the Sierra.

Interestingly, Huichol couples that go on the pilgrimage may do so in hopes of having children. I have observed some women receiving healings by shamans in Wirikuta in order to become pregnant and bear children.<sup>30</sup> One Huichol woman I know told me with great excitement that she and her husband had wanted to have another child, but were unsuccessful until they went on the pilgrimage to Wirikuta. During one pilgrimage on which I participated, a couple was desperately seeking to have a child. Upon entering Wirikuta and after ingesting peyote, the woman began to menstruate. The shaman who was overseeing the healing of this couple told me that this was a good sign for preparing the woman to become pregnant. I also began to bleed in Wirikuta earlier than anticipated in my menstrual cycle, and participated with this woman in a ritual in which a lock of hair at the crown of the head was cut by the shaman to “calm the heat from the menstrual blood.” Otherwise, it is believed that the blood will spoil the peyote.<sup>31</sup> This was not the first time I discovered that consuming peyote on the pilgrimage, or during peyote ceremonies in the Huichol Sierra, often caused me to bleed, even when it was out of sync with my cycle.

**30.** There is a scene in Furst's 1969 documentary video, *To Find Our Life: The Peyote Hunt of the Huichols of Mexico*, in which the leading shaman, Ramón Medina Silva, is curing a Huichol woman on the pilgrimage so that she may become pregnant.

**31.** In Huichol culture, menstrual blood is perceived as “hot,” and menstruating women are seen as very powerful yet dangerous. There are various taboos forbidding menstruating women from carrying out certain kinds of tasks, such as preparation of ceremonial foods and drink, or working in the cornfield. On the peyote pilgrimage, menstruating women must tell the shaman so that he or she can perform the hair-cutting ritual to “neutralize” the “heat” they emit. Otherwise, it is believed that the pilgrims are put into grave danger,



because the peyote will spoil because of their blood.

Later on in South Texas, when I began to participate in peyote ceremonies conducted by members of the NAC, I had the same experience. According to NAC traditions, menstruating women should not enter the tipi to participate in the meeting. Being very respectful, I made a point of adhering to this taboo. Despite my vigilance, at times I discovered that in the middle of the night or the early morning hours of the ceremony, I would unexpectedly begin to bleed. Afterwards, other women who had been in the meeting also commented that they, too, had begun to bleed. I was puzzled by my response and that of other women of reproductive age, and sought to find a cause and effect between consuming peyote and the monthly cycle.

## THE INFLUENCE OF PEYOTE ON REPRODUCTIVE HORMONES PROGESTERONE

I contacted various specialists in women's reproductive health. First, I spoke with Dr. Erica T. Wang, MD and OB/GYN reproductive specialist at Cedars Sinai Medical Center in Los Angeles, California. She was not well-versed about peyote or mescaline, but she told me that, if she had to guess what was occurring, she would say that peyote is stimulating the release of progesterone. Progesterone is a female hormone that prepares the uterus for pregnancy and helps maintain a fertilized egg. It causes the uterine lining to thicken and is essential before and during pregnancy (Healthline.com, accessed 7/02/2017).

I also spoke with Nurse Practitioner and Advanced Practice Midwife Maria Victoria Mangini, who practices in the San Francisco Bay area of California and is knowledgeable about peyote. She responded to my inquiry by mentioning the work of Russell Marker, a chemist who discovered that local people in Orizaba, Veracruz, Mexico, used a wild yam in the genus *Dioscorea* as a gynecological medicine. Marker was able to extract the compound diosgenin from the yam and further synthesize it into progesterone. Progesterone has been used to treat menstrual problems, difficult pregnancies,

and gynecological cancers (Redig, 2003, Hahn et al., 2009). Ms. Mangini emphasized the fact that Russell Marker took indigenous people's folk medicine seriously.

Juanita Nelson, another certified professional midwife who is director of Community Midwives in Durango, Colorado, has been involved with the NAC for more than 20 years, during many of which she was the wife of a prominent roadman (religious specialist of the NAC). In her response to my questions, she concurred with what the other two specialists had told me by saying that she believes peyote alkaloids activate the release of progesterone. Ms. Nelson explained that she can empirically validate what I related above; she has seen it happen over and over again. If a woman is close to menstruating and she eats peyote, then she will get her period. If a woman is off cycle, she will also bleed. However, if a woman is ovulating or just finished with her period, she will not bleed. Ms. Nelson went on to say that in her experiences and observations at NAC meetings, pregnant women who eat peyote have very little problem with miscarriage, and that it helps establish the placenta and maturation of the fetus.

## ESTROGEN

Estrogen is another essential hormone in the reproductive endocrine system. It has multifaceted effects on the hypothalamus and can rapidly alter the firing of neurons (Kelly et al., 2005). Estrogen and serotonin receptors are found to coexist in a variety of tissues. The activation of estradiol at E2 beta receptor sites stimulates an increase in serotonin receptor 5HT2a (Getz, 2013; Rybaczyk et al., 2005). Serotonin also functions as a hormone that can physiologically affect systems outside the central nervous system. It would seem that estrogen could also be triggered in response to ingestion of mescaline and other peyote alkaloids.<sup>32</sup>

**32.** An interesting variable to consider is the age of a woman. Pre-menopausal women will have an abundance of estrogen and serotonin in circulation. As women age past their reproductive years, estrogen levels decline. This, in turn, leads to a decline in serotonin receptors, and may also lessen the amount of serotonin stored in the body (<https://neuroendoimmune.wordpress.com/2013/10/29/thought-you-knew-everything-about-estrogen-what-about-its-effects-on-the-nervous-system/>).

## OXYTOCIN

Oxytocin, a hormone produced in the hypothalamus and stored in the posterior lobe of the pituitary gland, plays a role in sexual reproduction, childbirth, and breastfeeding (Smith, accessed 7/20/17; Yang et al., 2013). Studies have shown that serotonergic transmission via 5-HT<sub>2a</sub> receptors stimulates the release of oxytocin into the bloodstream (Saydoff et. al., 1991). Mescaline and MDMA are both molecules in the phenethylamine family. Research points to the interaction MDMA has with the release of oxytocin (Kirkpatrick et al., 2014a, 2014b). The same release of oxytocin secretions in the body may also occur with mescaline. Perhaps the “heart-opening” emotions numerous people attribute to eating peyote could mean, in scientific terms, the release of oxytocin into the body’s system.

## PROLACTIN

Prolactin is a hormone in the anterior lobe of the pituitary gland that also promotes the production of breast milk (Smith, accessed 7/20/17). Oral administration of mescaline has been found to affect 5-HT<sub>2a</sub> receptors and trigger the secretion of prolactin more than fourfold above baseline level. Human Growth Hormone (HGH) secretion was also stimulated (Demisch and Neubauer, 1979). It is interesting to point out that mescaline and other peyote alkaloids can be transmitted to babies and children via their mothers’ milk. Huichol women are well aware of this, and have remarked to me that they will, at times, notice that their babies appear to be affected (Fig. 5). In one case, the nursing child on his mother’s lap contentedly quieted down, and after a while tried to grasp at things in the air that were not visible to his mother or to me.



**Fig. 5** At a Huichol temple peyote ceremony (Hikuri Neixa) the mother, who has consumed peyote for the last couple of days, nurses her baby. Photo by Stacy B. Schaefer

## DISCUSSION

As we have seen, the ingestion of peyote alkaloids may influence the production of hormones in the endocrine system via the neurons in the nervous system. The endocrine and nervous systems are linked via the hypothalamus and adjacent pituitary gland. Together, they are responsible for producing hormones, directly or indirectly, that are released and transported throughout the body (Sargis, 2015).

Progesterone- and estrogen-binding neurons are concentrated in the hypothalamus, and along the ascending monoamine neuron systems that innervate the hypothalamus and adjacent areas. Dopamine and norepinephrine systems, as well as the Raphe Serotonin System, are interlinked with the hypothalamus region (Moore, 1986: 13)(Fig. 6).

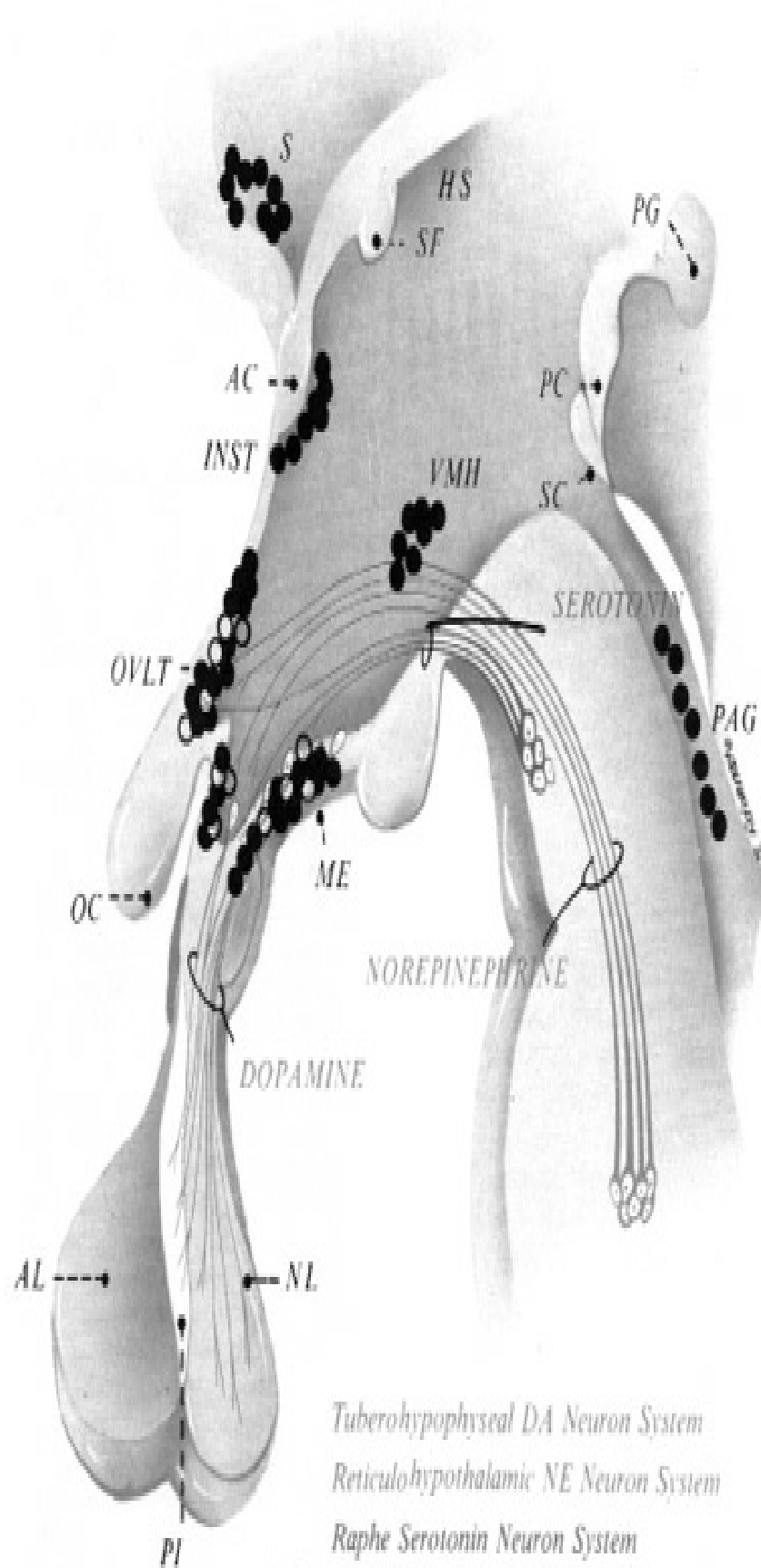


**Fig. 6** Estrogen and progesterone-binding neurons in the hypothalamus and surrounding areas (Moore 1986:13).

Seeking possible explanations for the association I observed between peyote consumption and the unexpected onset of bleeding within hours, I contacted neurobiologist Adam Haberstadt, an adjunct professor in the Department of Psychiatry at UCSD. His response was as follows: “Such an effect isn’t surprising – there are 5-HT<sub>2a</sub> receptors in the hypothalamus that regulate hormonal secretion, so the effects that you observed are likely occurring as a consequence of this action...” (personal communication via email April 20, 2017). Another idea offered by pharmacologist and medicinal chemist David E. Nichols, PhD, (personal communication, June 8, 2017) was to examine the modulation of neurotransmitter release, that is “the process by which a given neuron uses one or more chemicals to regulate diverse populations of neurons..” See also <https://en.wikipedia.org/wiki/Neuromodulation>

Along this line of reasoning, perhaps neurotransmitters from neurons potentiated by mescaline and/or other peyote alkaloids at 5-HT<sub>2a</sub> receptor sites can diffuse to nearby hypothalamus areas. In response, this action could possibly potentiate the process discussed by Hoffman et al. (2016), in which neurotransmitters enter into the circulatory system and travel to reach distant target organs such as a woman’s ovaries.

In addition to activity in the brain, one can look to other leads to understanding peyote’s effects on the body. It is worth revisiting the results of animal studies that showed that the uterus is capable of storing mescaline for longer periods of time than other tissues studied, and that the uterine smooth muscle has a great affinity for mescaline both before and during pregnancy (Shah et al., 1973). In fact, 5-HT<sub>2a</sub> receptors have been documented in the uterus (Sonier, 2005). Research has shown that many hallucinogens can cause constriction in the umbilical veins of humans (Gant, 1970; Dyer & Gant, 1973). Nair (1974) documented contraction of umbilical arteries by mescaline, and mescaline was found to stimulate uterine contractions (Jacques, 1976). Although dated as a result of legal and political realities in the intervening years, in the future such research might lead us to alternate avenues to understanding the

observed effects that peyote and ayahuasca have on the female reproductive system.

## CONCLUSION

The integration of Western science and indigenous empirical knowledge is crucial to advancing our understanding of the world. We have much to learn from cultures such as the Huichol that are wise and experienced in the use of entheogenic plants. We need to listen closer to their myths, and strive to more deeply understand their perspectives, their rituals, and their practices. People such as the Huichols have acquired intimate knowledge of peyote and its effects. They have developed and fine-tuned a complex, elaborate worldview that provides members with tools and traditions to heal their bodies, promote fertility, manage healthy pregnancies, and raise their babies. In all of these actions they expand their understanding of consciousness and human existence.

Clearly, there is much to learn about the interactions of mescaline and other entheogens on the human neuroendocrine system. The activation of 5-HT<sub>2a</sub> and other receptor sites can stimulate the endocrine system via the hypothalamus/pituitary complex in the brain as well as in the reproductive system, including the uterus. Hopefully, this paper will inspire further thought and study in this fertile field of research with entheogenic plants, including peyote, and contribute to our understanding of the complex nature of “being human.”

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# Mescal, Peyote and the Red Bean: A Peculiar Conceptual Collision in Early Modern Ethnobotany

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*Keeper Trout*

Self-taught ethnobotanist, scholar and author of *Trout's Notes*; active with Cactus Conservation Institute and Shulgin Archives Project

## ABSTRACT

Most people think of a fiery alcohol rich drink when they hear the word mescal/mezcal. That thought is correct but there is a larger picture, as the name “mescal” has been applied to three quite different plants. Scientific carelessness, puritanical propaganda, and government overreach have confused peyote and the frijolillo with each other and with agave, all under the name “mescal.” This paper employs extensive archival research of newspapers, scientific publications, and government documents to identify the sources of these confusions and, where possible, to draw a more disentangled history of these plants, so that they may be more easily understood on their own terms and in relation to each other.

1. Our three “mescal” plants, will be presented in the order of their appearance in the historical record:
2. Maguey: *Agave* spp. (Agavaceae)
3. Peyote: *Lophophora williamsii* (Lem. ex Salm-Dyck) J.M. Coult. (Cactaceae)
4. Texas mountain laurel AKA the red bean: *Dermatophyllum secundiflora* (Ortega) Ghandi & Reveal (Leguminosae) (This is the presently accepted synonym. *Calia secundiflora* (Ortega) Yakovlev,

*Sophora secundiflora* (Ortega) DC, and *Sophora speciosa* Benth. have also appeared in pertinent published phytochemical or toxicological accounts.)

5. For reasons that will become clear, the name “mescal” came to be applied to the latter two of these plants only by virtue of their reputation as intoxicants and, in the case of *Lophophora williamsii*, also known as peyote, accompanied an ‘education’ effort meant to establish such a reputation.

### AGAVE SPP. AS “MESCAL”

The first candidates referred to as ‘mescal’ and ‘the mescal plant’ were the *Agave* species that now go by the common name “maguey” and, in English, “century plant.”

This is the original mescal.

Since antiquity, the hearts of the maguey (i.e. the bases of the stems) have been roasted in earth ovens to prepare an important sugary food (Castetter, 1935). In addition to being a foodstuff, cooked agave hearts serve as a sugar source enabling production of fermented drinks and the distilling of a liquor named mezcal (Bruman 2000). In fact, the word “mescal” derives from the Nahuatl word “mexcalli”, a word that combines “metl” (agave) with either “ixcalli” (stew) or “ixca” (to bake) to mean “cooked agave” (*Random House Dictionary* 2017). In early occurrences of the name ‘mescal’ in Hispanophone literature, its loanword status was indicated through its spelling. As the name gained wider acceptance and use, the spelling shifted to the current “mezcal.”

It was a common practice among the Spaniards to assign names to indigenous peoples based on common foods, practices or geographic features, rather than by the names those peoples already used to describe themselves. Several different groups found themselves indicated by their practice of roasting and eating the mescal plant.<sup>33</sup>

**33.** For example:

The Mescales were noted to be in Coahuila in 1760 by García.

The Mescal [a singular or plural noun] were encountered by Massanet in 1688 about fifty miles north of the Rio Grande in South Texas (see Massanet 1691 or Portillo 1888).

Mescale/Mescales were recorded as being on both sides of the Rio Grande in the 17th century (de Leon 1689 (1905) and National Park Service (NPS) 2002, citing Wade 1999).

A Coahuiltecan-language group in south Texas was known as the Mescalero in 1691 (Hodge 1912 citing Terán 1691-1692).

Mescalero apaches were recorded with that name by 1724 (NPS 2002, citing Rivera 1945:6).

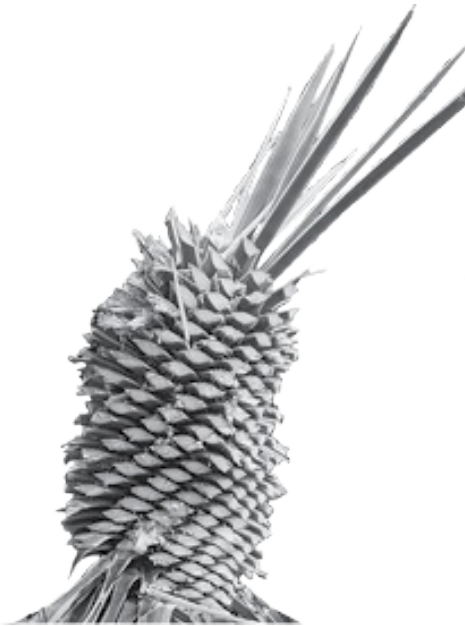


**Image 1** Agave heart with most leaves removed.

It is important not to confuse mescal as is associated with *Agave* spp. with mescal beans. *Agaves* do not possess beans. The 2017 *Random House Dictionary* describes the phrase “mescal bean” as an “Americanism” that first appeared in use during 1855-1860, but did not include a reference. The only point of publication we could locate around that time frame was in a 1854 Grand River Times account of a peculiar musical review, penned by George Horatio Derby (writing as “John Phoenix”), of a symphony titled *The Plains*. This piece of prose appears to have coined the phrase “mescal beans.” His satirical “review” continued to be re-run in newspapers for many years (example, the 1875 *Helena Weekly Herald*), and was eventually published in Stedman & Hutchinson 1891.



**Image 2** *Agave parryi*. Images from Creative Commons. *Agave parryi* was a favorite food of some of the Apache groups including the Mescalero according to Castetter, 1935.

A small excerpt:

The symphonie [sic] opens upon the wide and boundless plains in longitude  $115^{\circ}$  W., latitude  $35^{\circ} 21' 03''$  N., and about sixty miles from the west bank of Pitt River. These data are beautifully and clearly expressed by a long (topographically) drawn note from an E flat clarionet. The sandy nature of the soil, sparsely dotted with bunches of cactus and artemisia, the extended view, flat and unbroken to the horizon, save by the rising smoke in the extreme verge, denoting the vicinity of a Pi Utah village, are represented by the bass drum. A few notes on the piccolo call the attention to a solitary antelope, picking up mescal beans in the foreground. The sun, having an altitude of  $36^{\circ} 27'$ , blazes down upon the scene in indescribable majesty.

Ignore, for a moment, the glaring problems with those “mescal beans”: plugging those coordinates into Google Maps generated something that is worth noticing.

Derby's coordinates place his fictional mescal bean-eating antelope less than fifty miles away from the Mescal Range. The Mescal Range in eastern San Bernardino County are named after cooked hearts of the locally abundant *Yucca mohavensis* (Gudde &

Bright 2004), in the aforementioned Hispanophone tradition.



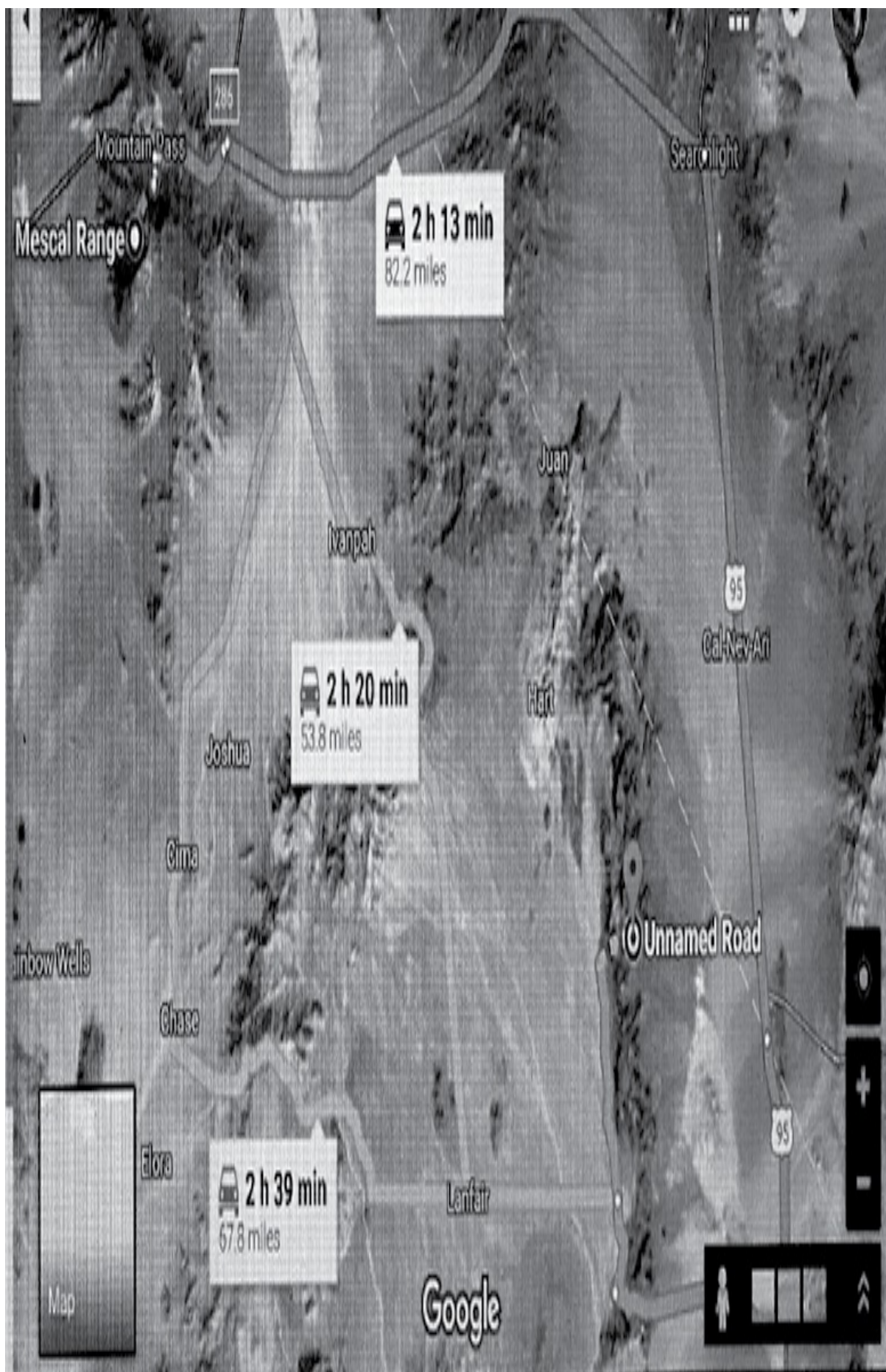


**Image 3** Google map of the Mescal range in Eastern San Bernardino County, California.

A short review of the aforementioned troubling details can help illuminate what Derby meant, and, for our discussion more importantly, what Derby did not mean when creating the phrase “mescal beans”:

- Derby certainly can't be speaking of beans from an *Agave* spp or a *Yucca* spp. Only leguminous plants produce beans.
- Peyote can be ruled out as it is not referred to as mescal beans in print until several decades later, in 1888.
- The red-bean can also be removed from consideration as it is not recorded with the name mescal beans until a few years after peyote.
- Which leads us to the conclusion that the “antelope, picking up mescal beans in the foreground” does not clearly refer to anything real.

Stedman & Hutchinson (1891) claimed that the symphony *The Plains* was first performed at San Diego's Odeon theatre in 1855. Derby lived in California, so, while the name choice may be a coincidence, it is at least plausible he was familiar with the Mescal Range and that his “mescal beans” were coined based on that name.

Despite those problems concerning the phrase mescal beans, our next mescal was somehow ascribed as actually having beans but it is unknown how or why the word beans came to be applied to something that does not look anything like beans.

### LOPHOPHORA WILLIAMSII AS “MESCAL”

In 1888, E.E. White referred to our second mescal designate, *Lophophora williamsii* (Peyote), as the “mescal bean,” and James Mooney called it “the mescal plant” in 1891. These two names create a particularly problematic point of shared identity, which we will examine in some detail. White (1888) sources his term from “white people” in Oklahoma, whereas Mooney appears to have gotten his information from one of his Kiowa friends in 1891, while engaged in field research on their calendar history. The Smithsonian Bureau of Ethnology later assigned him to specifically study the peyote

religion (Owen, 1921).

Something very peculiar happened here.

The peyote plant had been known in print by the name peiotl or peyotl (the ancient name in the Nahuatl language) and then peyote (the Spanish derivative of the Nahuatl name), ever since the Spanish invaders of Mexico began writing about the plant (examples: de Cárdenas, 1591, Hernandez 1651). Despite their widespread and common use in print for both the plant and the drug up to and through the 1800s (a few examples: de León, 1611; Massanet, 1691; Morfi, 1778; Orozco y Berra, 1864), for a few decades in the USA starting in the 1880s, peyote became known as mescal, the mescal plant, mescal beans and mescal buttons (in various spellings):



**Image 4** Mescal buttons, Anon., *The Mitchell Capital*, 1906.

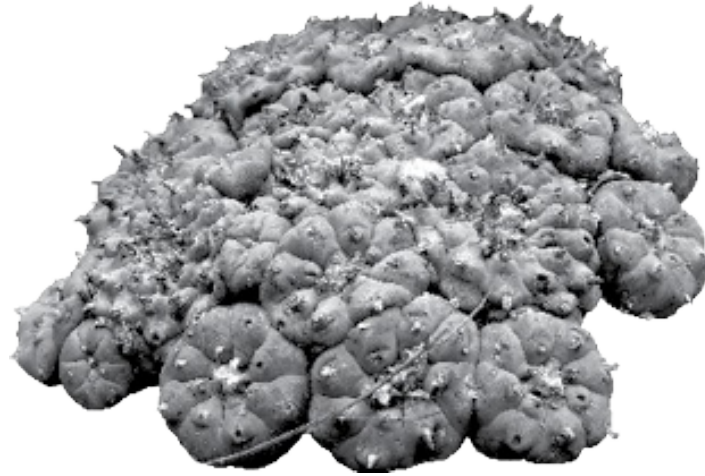


**Image 5** *Lophophora williamsii* in the Peyote Gardens.

### SUMMARY OF EARLY APPLICATIONS OF THE TERM “MESCAL” TO LOPHOPHORA WILLIAMSII.

1. (1885 is given as the date of first use, but no reference has included details of that use. We presently suspect this date may be erroneous.)
2. 1887 Briggs – Muscale buttons. (This was also used by Lewin and by Hennings in 1888, and by Rusby in 1894.)
3. 1888 White – Mescal bean.
4. 1891-1893 Mooney – Mescal and as the Mescal plant. Mooney’s first use of “Mescal” appears to have been in a presentation and in a personal letter during 1891.
5. 1894 Heffter – Mezcal. (Heffter “corrected” muscale to mezcal on the basis both of ‘muscale’ not being a proper Spanish word and of the term’s reference to an intoxicant. Heffter then coined mezcaline. Mescaline was thus derived from mezcal, and reflects Heffter’s belief that peyote was intoxicating.)
6. 1895 Prentiss & Morgan – Mescal buttons. (Prentiss & Morgan obtained their material from Mooney, as did Weir Mitchell, Wylie and Ewell.)

It is valuable to consider why the particular name “mescal” rather abruptly appeared, as the history of this name illuminates an enduring part of peyote’s story. Sources such as Turner (2010) claim that “the term [mescal] came to be applied indiscriminately to other intoxicants, or perceived intoxicants.” However, as far as we can determine, “mescal” appears to have been applied to just three “intoxicants”: peyote, the red bean and, as a misspelling of mezcal, the distilled alcoholic beverage.

“Mescal buttons” are more understandable than “mescal beans,” but dense levels of confusion almost typify this small area of study.

Whether buttons or beans, some clarity can be obtained through historical context and that era’s political environment.

Despite the fact that peyote had been known to botanists for almost half a century, confusion about the plant’s identity was abundant when it first came to the attention of medical, chemical, and pharmaceutical science. Parke, Davis & Company’s documented distribution of dried peyote to several prominent researchers as “muscale buttons” was only part of this confusion: Parke, Davis & Company was initially unaware that it was a dried cactus (See Bender, 1968; Bruhn & Holmstedt, 1978; and Stewart, 1987).

Those opposing indigenous use of peyote also added to the confusion. Missionaries and religious organizations vehemently condemned peyote as it compounded their universal opposition to alcohol and other intoxicants with their vilification of quasi-pagan and indigenous religious ceremonies and dances. These organizations campaigned for legislation against the mescal bean, despite often not knowing what it was they opposed.<sup>34</sup> How much of their confusion was genuine and how much was disingenuous is anyone’s guess.

**34.** For example:

“A new narcotic to tempt mankind. Mescal a drug which surpasses hashish and furnishes devotees dreams more entrancing than De Quincey’s” (Anon. 1904 *The Washington Times*).

“A rare variety of the plant [*Agave*] called “Button Mescal” is found in the Rio Grande valley which is a powerful narcotic, and is now being investigated by the agricultural department at Washington, D. C.” (Anon. 1895 *Arizona Republican*).

“The mescal bean is not a bean at all. It is a small circular blossom from a plant in Mexico.



The blossom is dried” (Anon. 1898 *Wichita Daily Eagle*).

“The buttons are the seed pods of a variety of the century plant called bayote” (Anon. 1916 *The Topeka State Journal*).

“It is related by federal officials [...] the Indians succeeded for many years in concealing the true quality of the beans. They led the white people to believe that they used the beans to season certain kinds of stews which they made” (Anon. 1909 *The Yakima Herald*).

A surprising degree of confusion about peyote still persists today. Mescal’s “Definition 5” at Memidex.com, for example, offers that “The button-shaped top of the mescal cactus [is] a source of psilocybin” (Accessed in 2017). Likewise, the University of Maryland’s CESAR tells us that “Peyote (*Lophophora williamsii* or *Lophophora diffusa*) is a spineless cactus with small protrusions called “buttons” that are used for psychoactive hallucinogenic purposes. Mescaline, an amphetamine, is the principal active psychedelic compound in peyote” (Accessed in 2017, last updated in 2013).

There are at least two leading possibilities for how peyote became known as mescal. These are not mutually exclusive, nor do they preclude the existence of additional reasons, including a speaker or writer’s deliberate attempt to cause confusion:

Possibility 1: This may have been an instance of the “tastes like chicken” phenomenon, where people choose a “best fit” drawn from a limited range of experience and belief to describe something novel.

Example: “The fact that a wild state of intoxication can be produced by chewing a few of the beans and swallowing the juice causes them to be called ‘mescal’ beans by many Mexicans” (Anon. 1909 *The Yakima Herald*). Likewise, Safford (1922) offered a variant, proposing that the name referred to the beverage mezcal fortified with peyote.

Possibility 2: During their rise to power, prohibitionists saw political value in peyote being perceived as an intoxicant. Many of these prohibitionists were Christian reformers who wished to eliminate all traditional religions, and saw similar political value in its ceremonial use. Missionaries of this time actively tried to obliterate indigenous cultures and their religious practices as a matter of policy: the assimilation and transformation of all Native

Americans into hard-working and prosperous Christian farmers was a core plank in their political and religious platform (Keller, 1983). This neatly dovetailed with the campaign against alcohol and all intoxicants: peyote found itself referred to as Indian dope, Indian cocaine, the dope bean, the jag bean, the drunk bean, the bean drunk, the booze bean, whiskey root and dry whisky in addition to the common misnomer ‘mescal bean.’ We will look at a number of instances in which peyote was deliberately confused with alcohol and other drugs, as well as where it was linked variously with a sinister and spurious religion, violence, immorality, and insanity for this specific purpose.

Examples: “The craze for mescal has been growing rapidly on the reservations, being identified with the development of a secret cult which is half religion and half a sort of freemasonry” (Anon. 1912, *The Continent*). Gertude Bonnin made the accusation that an “unscrupulous organization, through its agents, is promoting the Peyote cult, under a religious guise, solely for the easy money gotten from their superstitious victims” (1917: 39).

Consider some comments from that period and overlay them onto the ongoing effort to eliminate the use of all intoxicants worldwide. The goal was not just to ban alcohol – it included everything from coca to cocoa. While national Prohibition never saw a large majority of support (McGirr 2015), this was a popular and well-funded campaign that operated on a national level through several different religious organizations, and which was financed both by some of the leading capitalists and, what are mistakenly referred to as, the “idle rich” of the day, such as Herbert Walsh, so it proved to be highly effective. (The prohibition movement is too complex for adequate treatment here, beyond touching upon its relevance to peyote and mescal. See the afore cited McGirr (2015) for an in-depth and well-referenced discussion of prohibition’s larger scope and history.) Efforts to ban peyote were inseparable from alcohol and other addictive drugs in the minds of the prohibitionists.

Activities intended to educate the public that peyote was a dangerous intoxicant persisted during the decades that followed and the opposition to peyotism<sup>35</sup> has not stopped<sup>36</sup> [see endnote 1]. Early comments that its effects were the same as or stronger than alcohol were common (ex. *Yakima Herald*, 1909). Some accounts

such as the 1909 *Brownsville Daily Herald* confusedly asserted, “These beans ... are not only a strong intoxicant but contain opium and cocoaine [sic] as well.” while *The Spokane Press* (1909) claimed, “The bean, chewed, results in an exaltation of spirits similar to that action that follows a combination highball of cocaine and whisky with a dash of champagne.” Other sources such as the 1913 *El Paso Herald* referred it as being akin to hasheesh, “with visions which make a strong appeal to the aboriginal sense of the supernatural.” The *Medical World* (1907:201) invoked opium, digitalis and strychnine in their description of its effects.

**35.** Peyotism: A religious practice that is based on the sacramental use of peyote.

Peyotist: A person using peyote within a religious context and regarding it as sacrament.

**36.** As examples, see Bromberg, 1942; Bromberg & Tranter, 1943; Tranter, 1942; Davis, 1961; ProjectKnow 2017.

In his 1911 annual report Commissioner of Indian Affairs Robert G. Valentine asserted “The physiological and toxic action of peyote places it in the same general class with opium, cocaine, Indian hemp and chloral hydrate. ... It is needless to say that peyote is a greater enemy to civilization, especially to the Indian race, than whiskey.” It is not coincidental that Valentine was a committed prohibitionist.

Peyote use was purported by Agent McShoridge to first drive the user insane and then kill them. Unsubstantiated claims of actual deaths can be found in the testimony presented to Congress (see the 1918 peyote hearings for many examples) as well as in the media. Some of the claims pushed the limits of belief considering that insanity and death seem at odds with something gaining in popularity.

Interestingly a couple of the errors appearing in prohibitionist news copy during that period persisted into modern times forming the basis of urban legends about smoking peyote or the hairs being active or toxic.<sup>37</sup>

**37.** From Anon. 1918 *Free Trader Journal*: “In the center is a little tuft of cotton. This cotton is more highly charged with the stuff that makes users wild than any other part of the plant, ... Its effect is more like insanity than intoxication. The mescal buttons are also smoked. ... A few whiffs of mescal smoke and the smoker becomes completely insane. The drug works more quickly when smoked than in any other way, and the effects last longer.”



The 1911 report of Commissioner of Indian Affairs Robert G. Valentine also contained a telling spot of honesty concerning the motivations being religious in basis. “Even if the physiological effects of this drug were not serious, its use would have to be prohibited for the same sociological reasons as have led the Government strongly but tactfully to modify Indian dances. As is well known, exercises which the Indian consider of a religious nature are made the occasion of taking the drug. These meetings are held as often as once a week.”

Spaulding (1915) spoke similarly when commenting that efforts to prevent the use of peyote existed “chiefly because it is believed by some of those interested in the Christianizing of the Indians that it has a tendency to make them revert to their primitive condition and to their heathen beliefs.”

James Mooney captured the dilemma nicely in a 26 October 1920 letter to Joseph Thoburn, “This is the native Indian religion ... which I have defended before Congress committees and other bodies, for such defense and stand have been recalled from Oklahoma by Dr. Fowkes on demand of Cato Sells and the local agent. ... They are oppressed, persecuted and vilified by interested missionaries and officials who fear the development of Indian initiative as a danger to their own monopoly of religious and economic control.”

The rejection of the validity of the peyote faith for being just a form of deviant drug taking wearing a spurious mantle of religious respectability was quite commonplace.<sup>38</sup>

### **38. Examples:**

Becker, 1921, “The evil effects of this drug cannot be questioned, although there is much propaganda to allow the Indians to retain this drug.”

Daiker, 1914 “The great cry of those in favor of its use is that the Office is attempting to interfere with their religious liberties, but in my opinion the religious feature is being used as a cloak to cover its general use by the Indians.”

Valentine, 1908:14, “Apparently for the purpose of justifying the use of this narcotic, a religious cult has been built up based on its use.”

Herbert Walsh (1920:53-54) made an often repeated claim that if a

peyote church could legally exist surely so could a “whiskey church”, Mabel Luhan compared peyotism with the religious defense of hashish, cocaine or morphine (Stewart, 1987), while the Indian Leader (1917) took this a step further with their comment averring that “there would be nothing to prevent setting up in any of our cities a pagan temple, with prostitutes offering themselves under the name of religion as ministers to lust.” Perhaps the most incredulous dismissal appeared on page 4688 of the 1921 Congressional Record where the peyote debate included a particularly interesting comment by Representative Chalmers on the subject of the conscientious practice of the peyote religion. “I would remind the gentleman that some mothers conscientiously and religiously believe that they are doing the right thing when they sacrifice their offspring to the alligators, religiously.” It is difficult to argue with anyone who is willing to make a statement like that.

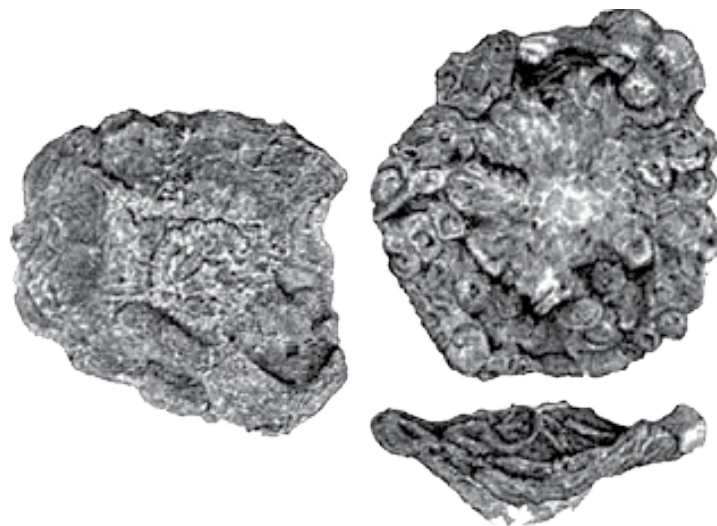


**Image 6** Prentiss & Morgan’s Mescal buttons

The dire prediction that the Winnebagos were facing actual extinction, due to their use of peyote, appeared in many newspapers across the USA during 1906. The accompanying media barrage coincided with several Protestant womens’ groups coming together to declare that they were waging a “War on Mescal” (example: 1906, *Norfolk Weekly News Journal*).

It is difficult to imagine any other outcome considering that the story headlines were then declaring: “Drug killing off Winnebago Indians – Victims of Mexican Bean dying at startling rate – ...Will be extinct in few years – Introduced but a year ago habit has seized

men and women alike – 700 in an orgie [sic].”

It is worth reflecting on how any average American with no better information would have received the news accounts including this sort of content. That headline was drawn from *Abbeville Press & Banner* in 1906 but this was a popular news story that year and versions appeared in many newspapers over a period of a few months.

A larger account in *The Mitchell Capital* (1906) added the absurd claims that: “Fearless of the horrors of insanity; resolutely facing racial extinction; conscious of inevitable physical decline; courting death itself in the practice of strange and weird religion ... Men and women who were among the brightest and most intelligent Indians on the reservation ... are now dull of comprehension, driveling idiots who chatter like monkeys, speaking neither English nor their native tongue intelligently.”

This included only a minute sampling from the era of the “mescal bean” to illustrate the consistency of the overall message about peyote that was intended.

Charges of wanton behavior, loss of morality, and sexual inappropriateness were abundant and persisted in the media for many years. In 1961 an article by Davis appeared damning peyote to be “America’s baffling sex buttons” and purported it to be used in “Indian sex rites.”

Similarly, the 1909 *Rural New Yorker* ran the headline “Getting Drunk on Beans - The demoralizing Mescal and its Effects,” whose article read: “A friend who observed one of these ceremonies in Indian Territory told me that the Indians divide themselves into two squads during this part of their ceremony, one-half of them remaining sober to restrain those who eat the mescal buttons from killing themselves or each other. This gives a good idea of the excitement produced by this intoxicant.”



**Image 7** Columbus Commercial, Anon. 1913.

Despite the period's leading anthropologists' and ethnobotanists' work to defend peyotism's religious legitimacy, the opposition continued unabated. In his 1920 annual report, Commissioner of Indian Affairs Cato Sells commented, "Scientific investigation of the nature of this narcotic drug shows conclusively its dangerous effects. ... [Medical] scientists say that peyote has no medicinal value and if habitually used results in the derangement of both mental and physical structure. Its defense as a religious rite is largely fictitious, the promoters of its use having seized upon this idea in an attempt to prevent or delay prohibiting legislation." Dissenting scientists and laypeople were generally dismissed, belittled, or simply ignored. This has remained the case. The presence of such commentary in religious publications is scarcely surprising but trivializing and even contemptuous comments were and still are casually included in mainstream publications and peer review journals, contemporary or bygone.

As examples, an image of Frank Takes Gun appearing in *TIME* (1959) holding a depiction of a peyote ceremony was entitled "For some a hangover after the service."

Similarly a 1975 issue of the journal *Human Behavior* included an article concerning peyote being evaluated in the treatment of alcoholism. Notice the density of pejorative and trigger wording contained within the brief excerpt below.

"Hair-of-the-Dog is an alcoholic. But as with other American Indians who receive treatment for problem drinking in a program by the US Public Health Service Indian Hospital, Clinton,

Oklahoma, he is learning to get his buzz from peyote instead of a bottle of Ripple.”

Participants were said to “pop an average dozen mescaline-packed peyote buttons apiece” (Anon. 1975).

Their wording might be anticipated if this was a religious tract rather than a peer review journal.

Dismissive and antithetical comments were not limited to written articles, James Mooney’s recognition of the legitimacy of the peyote religion led anti-peyotists to successfully demand his removal.

Herbert Walsh 1919 expressed a sentiment, then common to this camp, suggesting that Mooney was “anxious to see the Indians retain their old ways and be regarded as interesting ethnological specimens for the study of scientists. It does not look well for a representative of one branch of the Government (Ethnological Bureau) to try to interfere with the work of the Indian Bureau in its endeavor to advance the cause of civilization among these Indians.”



**Image 8** This image is worth considering as a potential hook for the intended audience.

After first being banned from two reservations, followed by a request for his recall by Agent Stinchecum at Anadarko, Mooney was recalled to Washington. Senator Robert L. Owen (Oklahoma) wrote letter protesting Mooney’s removal and defending his integrity, but it likely fell on deaf ears when it reached Commissioner Sells. Becker (1921) included a comment illuminating how Mooney was regarded by those forces. “... [They]

waged a losing fight for their religion [and] had no legal protection as a religion, until a representative of the Smithsonian Institution at Washington, for reasons not yet clear, started active propaganda among the various tribes to arouse a new enthusiasm in peyote and the Indian dance. ... The harm of reviving the pagan practice became so apparent that the United States Government sent officers out to investigate and ordered white agitators from the reservation.” It is worth reflecting that during this period Mooney had specifically been assigned by the Bureau of Ethnology to study the peyote religion (Owen, 1921).



**Image 9** Davis 1961

While the religious use of peyote was clearly part of anti-peyotist objections, the prejudices held against peyote were also based on the erroneous assumption that peyote was no different from alcohol or other addictive drugs.

The so-called third “Great Awakening,” following the 1859-1860 revivalist craze, stimulated a lasting activist imperative whose core goals included achieving the prohibition of all intoxicants worldwide. In a syndicated news flash extolling the progress of the Women’s Christian Temperance Union (WCTU), Clarence True Wilson clarified their intentions that “Prohibition is a World Movement. The evil it aims to remove is worldwide in extent and as old as the human race. ... [The] downward tendency of human nature is to seek excitement in the sub-cellar of its being, and the



biggest task we have is to get folks to move upstairs. ... For people of every clime and age have found methods of gratifying this lower propensity with intoxicants” (Wilson, 1910).

Wilson listed opium, coca, cocaine, alcohol, hashish, Datura, fly-agaric, betel, tobacco and mescal beans as well as yaupon [*Ilex vomitoria* Aiton], tea and cocoa as pernicious influences from which humans needed compulsory liberation. The sentiment was captured nicely in a quip from R.G. Watermulder in 1914: “[Peyote] then appeals to his craving for leadership and to the lust of the flesh. And today we have a new semi-religious movement among our Indian people, with peyote as a fetish that is worshipped, as something extra ordinarily supernatural. ... I stand appalled and cry, ‘O God, we will fail in all our work unless thou dost set these men free-and then they shall be free indeed-and use us to set them free.’ ”

One prohibitionist summed it up simply: “When we know we’re right, the trouble comes in convincing the other fellow and the other fellow’s fellows” (*American Advance*, 1911). As this quote demonstrates the speakers are clearly of a mindset that lack of agreement is only an indication that more convincing or coercion is required.

And there’s the rub. While temperance refers to the use of personal self-control to limit intoxicant ingestion, the goal of a prohibitionist is instead achieving legislation to implement their religious ideology through force of law by declaring what they consider sins to be crimes. This line of thought was captured succinctly in a comment appearing in Kinney (1922) “... the only right way to deal with an evil is to outlaw it.”

Their contemporary H.L. Mencken (1914) offered some lucid observations about what was then occurring: “The new Puritanism is not ascetic but militant. Its aim is not to lift up the saint but to knock down the sinner. ... Differing widely in their targets and working methods, these various Puritan enterprises have had one character in common: they are all efforts to combat immorality with the weapons designed for crime.” It was not a casual word choice when the biographer of Special Agent William E. Johnson complimented his dedication to the ‘temperance’ cause with the comment, “He is a good soldier of Jesus Christ” (McKenzie, 1920). The personally-held Christian militant imperative may well have

remained the strongest driving force of anti-intoxicant activity even after perception of the subject matter had been transformed into one of public health and safety.

Lisa McGirr (2015) produced a very well researched study of prohibition that largely served as the basis for the following analysis.

The Prohibitionists' decades-long campaign to eradicate the nation's then-legal drug and alcohol sales, production, and distribution finally succeeded, despite the actual population being very divided on this subject. A majority of the country did not actually favor Prohibition but the contest was close enough that a good showing at the polls could take a majority of the votes; especially if the naturalized immigrant turnout was low. Achieving Prohibition required many years of persistent effort accompanied by having success with getting their supporters elected or appointed into positions of influence and policy making. An under-appreciated part of those successes was the huge increase in the ranks of enforcement personnel and support staff, creating a large body of professional enforcers and enablers. A dramatic expansion of the federal government's power in national law enforcement accompanied this and led directly to the creation of the modern federal legal machinery (McGirr, 2015).

After establishing legislative dominance at the end of the 19th century, the Prohibitionists implemented a number of policies over the course of the next three decades that not only gave birth to the modern federal legal system but turned mass incarceration and prison building into a boom industry, setting the conditions and providing the impetus for the modern war on drugs. By 1930 over half of the federal prison population was there for drug or alcohol offenses, and by 1935 half of that same population was there specifically on narcotics violations (McGirr, 2015).

Special courts, overcrowding in prisons (some states reported having two prisoners for every bed), armed vigilante goon squads (sometimes comprised of the Ku Klux Klan) assisting law enforcers, and the shooting of unarmed suspects all became commonplace in the aftermath of the Volstead Act, commonly known as the National Prohibition Act (See US Congress, 1919). Prohibitionists ran roughshod over basic civil rights in their zeal to shut down alcohol



production and distribution, conducting door to door warrantless searches in immigrant and minority neighborhoods. At law enforcement's behest, President Hoover set the tone for a "tough on crime" approach that has never disappeared from favor. (McGirr, 2015).

Kinney quoted President Warren G. Harding from 1922: "In another generation I believe that liquor will have disappeared not only from our politics but from our memories." Echoing this unrealistic view (or, perhaps, statement of intent?), a 1922 article in *The Evening World* described the word 'whiskey' as "obsolete" in American English. It added that a cactus known as whiskey root was "also obsolete," adding, despite that "it still grows" (Anon., 1922, *The Evening World*).

During Prohibition, as now, unrealistic expectations were the norm. Sound bites that are still familiar today began appearing during this era: "We hope and believe the raids by Federal and local officers mark the definite beginning of the end of the dope traffic in the United States." Harry J. Anslinger, 8 December 1934. Other headlines from 1929 to 1935, also gleaned from the *Dope Chronicles* which sadly omits the venues and most of the dates: "Federal machinery limited in combatting drug traffic declared Anslinger," "Victory in War on Dope," "Situation is well in hand" – Dr. Mott, "Drastic Rules to Curb Trade in Narcotics," "Drastic Jail Terms Urged in Dope Evil," and "Congress Will Rush Dope Bill" (Silver, 1979).

Enforcement laid heaviest on small producers and operators in urban poor, minority, and immigrant communities, who could not afford to pay for protection like the larger producers and distributors for whom Prohibition often proved a highly lucrative period. (McGirr, 2015) It is also clear that in some cases the laws were sought less as a ban on the drugs and more as a tool to control people who used those drugs: laws targeting cannabis were enforced in Mexican communities, cocaine in African-American communities, and peyote in Native American reservations.

Peyote drew malicious attention from multiple directions. Opposition to peyote and peyotists was organized on a national basis by several prohibitionist societies and related organizations, including the Indian Rights Association, whose spear-fronts were

active at both the state and federal level. They enjoyed an almost seamless working relationship with the various agencies involved in the 'welfare' of indigenous people, which lasted until John Collier entered the picture in the 1930s (see *Daily* 2004). As was also true of law enforcers such as Johnson and Anslinger, each of those groups lobbied, issued press releases, wrote articles for popular magazines and news syndicates<sup>39</sup>, and, through assorted (often rural) Protestant churches, conducted national letter writing campaigns to garner public sentiment and pass legislation. (See *American Advance*, 1911; Bonnin, 1917; Bromberg, 1942; Bromberg & Tranter, 1943; *Daily*, 2004; Ellis, 1918; Friends of the Indian, 1914; Home-Missions-Council, 1920<sup>40</sup>; Indian Rights Association, 1918; McGirr, 2015; McKenzie, 1920; Tranter, 1942; Wilson, 1910.) Valentine (1912) complained that the amount of mail received by his office had nearly tripled in the prior decade. In addition to letter writing campaigns, appearance of news items and submissions of articles to popular magazines, some stand-alone publications were also produced and distributed. Gertrude Bonnin published a booklet "The Menace of Peyote" which was widely read and promoted. Bonnin was an active peyote opponent who moved to Washington for several years so as to be able to devote adequate time to congressional lobbying. Another active lobbying force on capitol hill, Herbert Walsh and the Indian Rights Association, produced a similar but larger work in 1918 entitled "Peyote; An Insidious Evil." *The Outlook* 1917 described that book as having been prepared to spare busy congress people the need to spend time reading through the voluminous submissions in the peyote hearings of that year (US Congress, 1918). State laws most commonly appeared in the wake of perceived failures by the federal authorities to suppress peyotism. An underappreciated part of this picture was the federal mandate to convert the Indian nations to Christianity combined with the Bureau of Indian Affairs, the Board of Indian Commissioners and the employees of all reservations being largely comprised of a membership drawn from the missionary ranks who shared a common belief that traditional Native American religious practices, including the use of peyote, impeded the acceptance of Christianity. [Becker, 1921; Valentine, 1911] The "Indian Nations" were governed by the Board of Indian Commissioners who, since their inception,

had been drawn entirely from the ranks of missionaries and religious leaders (Keller, 1983) with the following well-defined understanding of their duties and obligations to their “wards.”

**39.** Then, as now, the domestic syndicated press organizations were owned by conservative Christians.

**40.** Robert D. Hall, commented in the report from the thirteenth annual meeting of the Home Missions Council, “... it rests with the Christian citizens of this country to see that Congress votes right on this matter. The women of America are largely responsible for prohibition.. American Christian womanhood is asked to bring all pressure possible to bear upon the members of Congress to vote for the suppression of peyote at the present session of Congress.” (1920:89). See also comments therein by G.A. Watermulder on page 159).

“... the duty of the [government] being to protect them, to educate them in industry, the arts of civilization, and the principles of Christianity; ...” (Board of Indian Commissioners, 1869).

When John Collier tried to introduce a sense of moderation and respect for indigenous culture<sup>41</sup>, the attacks were expanded both by the missionary groups and by BIA employees in an attempt to remove him from office or at least negate his influence (*Daily* 2004).

**41.** John Collier’s act that drew the most furor was Circular 2970, in which it said, “No interference with Indian religious life or ceremonial expression will hereafter be tolerated. The cultural liberty of Indians is in all respects to be considered equal to that of any non-Indian group.”

That Collier’s shift in policy would cause problems for him seems unsurprising as his opposition included the people in charge of the reservations.

The results of that mandate to Christianize Native Americans created a long-lasting legacy of misguided efforts aimed at the destruction of indigenous culture and religion in general, not just peyote.

## DERMATOPHYLLUM SECUNDIFLORUM AS “MESCAL”

To round up the last member of our trio, another mescal bean appeared on the scene. Mescal beans became applied to *Dermatophyllum secundiflorum* at some point after the name was associated with peyote.

The Oklahoma Session Laws of 1899 that illegalized the activity of

“Medicine men” also outlawed Mescal beans in Section 2: “That it shall be unlawful for any person to introduce on any Indian reservation or Indian allotment situated within this Territory, or to have in possession, barter, sell, give, or otherwise dispose of, any “Mescal Bean,” or the product of any such drug, to any allotted Indian in this Territory: Provided, That nothing in this Act shall prevent its use by any physician authorized under existing laws to practice his profession in this Territory.” These laws did not provide an appropriate definition of the phrase “mescal bean,” and contributed to the existing confusion between the red bean and peyote. Definitional complaints along these lines in 1907–1908 left the ban unrenewed.



**Image 10** Chief Special Agent William E. “Pussyfoot” Johnson. Image from Anon., 1912, *Sunday Oregonian*.

The exact point of appearance of the common name “mescal bean” might be unclear but it is demonstrable that the red bean was being called by that name by 1907 as the following comment from Stewart 1987 illustrates. “After August 21, 1907, [Special Agents] Shell and Johnson had no excuse for confusing the terms “peyote” and “mescal,” for Special Agent R.S. Connell, then at Rosebud, South Dakota, brought to their attention the difference between the

mescal bean, *Sophora secundiflora*, ... and peyote, *Lophophora williamsii*". During the 1907 struggle against the ongoing anti-peyotist activity, Quanah Parker testified to the Medical Committee of the Constitutional Convention (in Oklahoma) "that mescal beans were poison and peyote is an herb learned from the Mexican Indians to the Lipan Apache, then Comanche, Kiowa, etc." (Stewart, 1987). Nevertheless, a number of authorities ignored this clarification and continued to call peyote "mescal," "the mescal bean" and "the mescal button."



CHIEF QUANAH IN HIS EVERYDAY

**Image 11** Quanah Parker dressed appropriately in Brownell 1907.

Undaunted by the continuing confusion, Kansas state legislators seized the bull by both horns. Legislation sailed through both the State House and Senate under the following title: “An act relating to *Lophophora williamsii* or Peyote (Pellote) and *Agava* [sic] *americana* (commonly known among the Kansas Indians as mescal); prohibiting the use or possession thereof, traffic therein, and providing penalties for the violation of this act.” This act was made state law in 1920, and Arizona and South Dakota enacted almost identical laws in 1923. Evidence that bad laws die hard can be found in modern-day Dodge City Code 2014 (Dodge City, Kansas), which echoes Kansas’ precedent: “11-404. PEYOTE; MESCAL BUTTON; INDIAN HEMP; CANNABIS. It shall be unlawful for any person to plant, cultivate, protect, harvest, cure, prepare, barter, sell, give away or use, or offer to sell, furnish or give away, or to have in his or its possession peyote (pellote), botanically known as *Lophophora williamsii*; or *Agave americana*, commonly known as mescal button; ... or any compound, derivative or preparation of the above-mentioned plants. (K.S.A. 65-4127a; 65-4127b; Code 1983, 20-137)” page 11-6. At least this one spelled *Agave* correctly.





## Image 12 The Red Beans.

Now that we have gotten to an actual red bean, it seems like a good time to clear up some related misconceptions. An influential 1976 paper by Adovasio & Fry further contorted the conceptual relationship between peyote and the red bean. Based on archeological finds, they speculated that psychotropic drug use had followed a logical and sequential path from more toxic to safer choices. They proposed that the Mexican buckeye, *Ungnadia speciosa* Endl. (Sapindaceae), had been succeeded by the red bean, *Dermatophyllum secundiflora* (Leguminosae), which was then eventually replaced by peyote, *Lophophora williamsii* (Cactaceae). This hypothesis has somehow become accepted as fact, despite it including a number of disturbing deficiencies which have not been previously addressed and must be considered:

1. The data presented in Adovasio & Fry's paper appear to be inadequate to support its conclusion. If there was more data, they did not mention it; in any case, it is not possible to consider what may have been omitted.
2. Their oldest reported find apparently yielded only the red bean: they said its presence in the strata was continuous from 8440 BC – 1040 AD. *Ungnadia* was not mentioned.
3. Most of the other sites listed had both the red bean and buckeye. No reported site showed only the *Ungnadia* seeds, and neither empirical data nor any indication of relative proportions were given, outside of a single inadequate comment that the proportion was higher in the older finds.
4. The only example of *Lophophora* was reported at their youngest date. Other ancient peyotes were known to exist, but none were slated for dating. Mardith Schuetz (1963) commented that the Pecos River Focus represented the most archaic culture known in Texas,

estimating their age to be “at least” 5000 years, and possibly up to 7000 years. Schuetz added that both peyote and the red bean had been found together in the Shumla Caves, “suggesting contemporaneity or overlapping of mescal and peyote cults.” Adovasio & Fry, who were familiar with her paper, omitted this overlap. We will return to the significance of the Shumla cave excavations in a moment.

5. Use of buckeye as a drug is, at best, implausible. We will return to this below.

Details of the evidence presented in Adovasio & Fry:  
Some facts concerning this ancient peyote:

1. Taylor (1956) determined the age of the Cuatro Ciénegas (CM79) peyote indirectly, based on pieces of matting that was believed to be in the same context.
2. Taylor and Adovasio & Fry both reported the Cuatro Ciénegas site to date from 810–1070 AD. Terry et al., (2006) corrected these dates to 1070–1280 AD, reflecting direct radiocarbon dating of the peyote.
3. The peyote buttons strung on a cord clearly show that ‘best’ harvesting practices were already known and being employed by this date.
4. Bruhn, et al., (1978) reported a chemical analysis of the material.
5. In more recent times there has been investigation into an even older discovery of ancient “peyote.”

Members of the 1933 G.C. Martin Expedition from the Witte Museum in San Antonio reportedly found the specimens in the Shumla Caves of Val Verde County in Texas. It is believed that the specimens came from Cave #5, but the excavation details were

inadequately documented. For sake of context, all of the Shumla Caves sites are located within the same few miles as the Val Verde County sites mentioned in Adovasio & Fry (see map in Story & Bryant, 1966), and date to the same time frame.

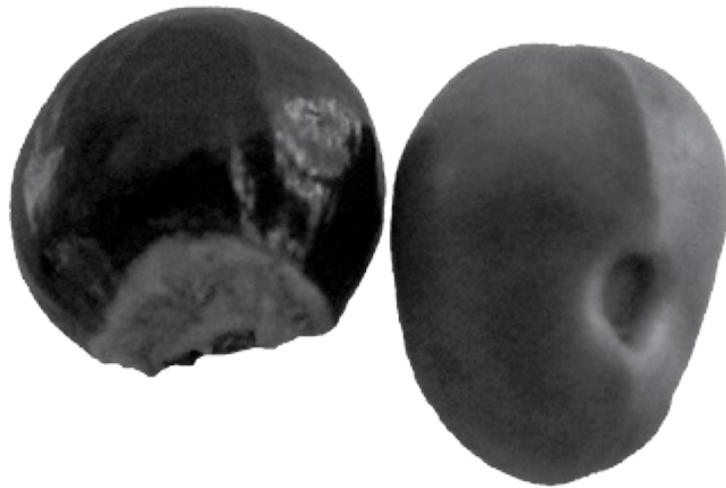


**Image 13** *Dermatophyllum secundiflorum*.

Several dates have been given for the Shumla Caves peyotes. Peter Furst slipped an estimated date of 7000 BC for the specimens into a 1989 book review (not mentioning how many were sacrificed or how many remained). The full data from the UCLA Radiocarbon Lab on the Shumla Caves specimen(s) were never retrieved, due to the fatal illness of the technician who did the work and the laboratory's subsequent closing. El-Seedi et al., (2005) and Bruhn et al., (2002) reported two of the remaining Shumla Caves peyote artifacts to average 5700 years old. In both of those cases the published values could be extrapolated as representing the age for all of the artifacts. Radiocarbon dating destroys what it evaluates so it can be a stretch of faith when applying the results to additional materials found in archaeological excavations, even when not inadequately documented as was the case with the Witte expedition to the Shumla Caves.

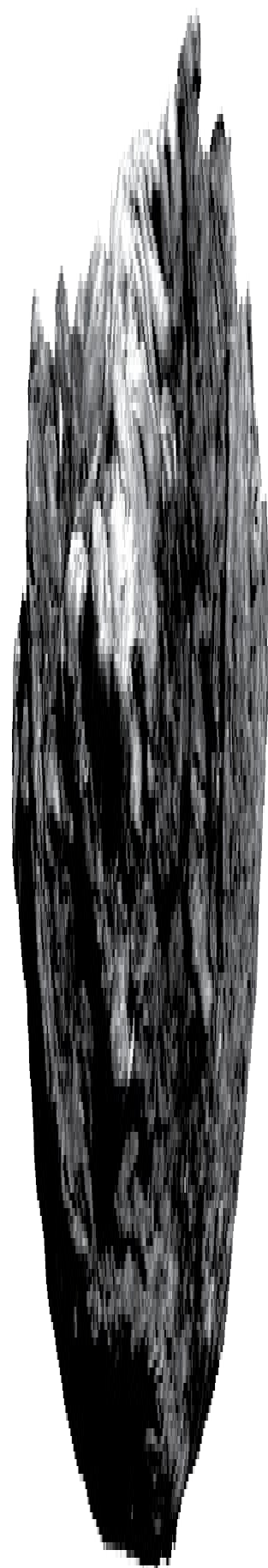


**Image 14** Dried *Lophophora williamsii*.

Terry et al., (2006) established that the three remaining Shumla Caves peyote artifacts were made in two different time periods, each in the range of 4200–3950 BC.

You might have noticed the word artifacts. The most amazing observation in the study by Terry et al., (2006) was that these specimens were not specimens of whole peyote crowns, contrary to reports by Bruhn et al., (2002). There are no signs of ribs, areoles, or any evidence of any vascular structures as are normally present on peyote buttons.

When examined under magnification, these were discovered to have been manufactured; incorporating what is assumed to be peyote but showing a random fibrous internal composition that looks a lot like the wood in chip-board.

Was this an archaic pharmacist's preparation? That would seem to strain credibility and is probably more than a little controvertible.

What is known without any controversy is that these were artifactual items (Terry et al., 2006) incorporating what is assumed to be peyote, based on the reported presence of mescaline (Bruhn et al., 2002; El-Seedi et al., 2005), along with a fibrous plant material binder (Terry et al., 2006). These archaeological artifacts were shaped from some sort of dough to represent a peyote crown that had been cut at ground level. The oldest two of the three remaining artifacts were partially made with non-cactaceous C3 plant material, and the third was made entirely from CAM plants (Terry et al., 2006; with added elements from unpublished data of Martin Terry, Karen L. Steelman, Tom Guilderson and Phil Dering 2003).

As far as learning anything more, the obstacles appear nearly insurmountable. There are no more specimens of this type known and the likelihood of anyone recovering any additional specimens seems remote even if they exist.

All went unrecognized as artifacts, rather than actual peyote buttons, until the Terry et al., examinations. Even El-Seedi et al., referred to the Witte artifacts as "peyote buttons, i.e. the dried tops of the cactus." It is worth noting, though, that El-Seedi's odd comment describing Carolyn Boyd as being someone "who also accepted this identification," as well as Furst's reference to them as "shriveled" (in a 2003 conversation with Jon Hanna) and the

peculiar descriptor of “mummified” in Martin (1933) suggests that many may have noticed that something seemed odd.

Of the effigies once at the Witte Museum, two were completely consumed during Furst’s inadequately published dating attempt (Hanna 2003). Bruhn’s group hollowed out the backs of two of the remaining three.

The latest radiocarbon dates obtained by the Texas A&M group determined at least two different makers created the three surviving effigies of peyote at times separated by several human generations, and using different binder choices (Terry et al., 2006). Nothing further can be known about the other two peyote artifacts. It is also unknown how many there may once have been: there appear to have been at least five, yet Martin (1933) mentioned just one. Schuetz (1963) said that the Shumla Caves peyote was commonly encountered with the red bean. What is also known is that out of all of the specimens reported to have been recovered in a handful or so of archaeological excavations only these two examples appear still to be in the possession of their respective museums. (We refer to the eight whole buttons, originally nine, recovered by Taylor from CM79 and which are housed in the Smithsonian, and to the three ancient manufactured specimens from the Shumla Caves still housed by the Witte Museum.) Peyote specimens were historically common targets of thefts from museum holdings and from herbaria, seriously hampering historical research concerning the plant (Martin Terry, pers. comm., 2012).

The most peculiar datum of all was made by El-Seedi et al.: they report observing 2% mescaline, with no other identifiable alkaloid. To still have 2% mescaline left after six millennia would require a far higher original level, especially as a large percentage of the artifact is the inert fibrous binder. We have many questions without answers in that area.

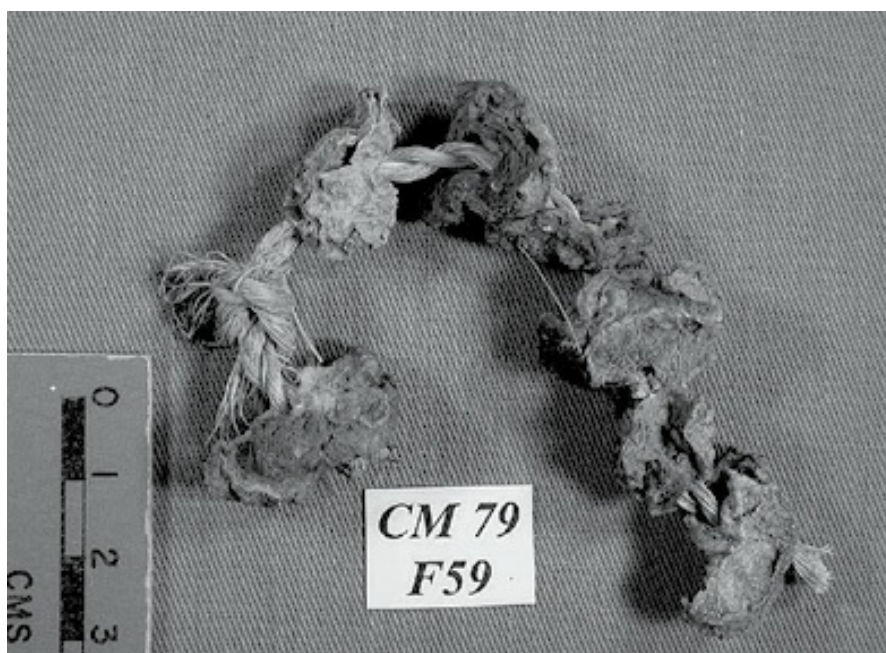


**Image 15** This string of buttons was recovered from a burial site. Photograph by Martin Terry

El-Seedi et al., (2005) suggested that the presence of only mescaline was the result of mescaline’s relative stability, compared to other alkaloids. Bruhn et al. (1978) reported 2.25% total alkaloid content in the almost thousand year old peyote from Cuatro Ciénegas. They observed mescaline and four isoquinolines. Bruhn & Holmstedt (1974) analyzed peyote buttons from Rusby in 1887 and compared them to newer material. They found that the material from 1887 contained slightly more alkaloid content overall than the new peyote contained (8.86% vs 8.41%), but that the mescaline content, specifically, was lower in the eighty-seven year old buttons. Nothing conclusive was determined, but they did comment that “the mescaline content of the ‘old mescal buttons’ was found to be much lower than that of the “new mescal buttons.” Only minor discrepancies could be observed regarding the other alkaloids. It is not possible to say whether the relatively lower amount of mescaline in the old material is due to degradation of mescaline with time, or is just a natural variation.”

**Table 1.** Summary of the archeological evidence discussed in Adovasio & Fry (1976).

|                                          |                                            |                                         |
|------------------------------------------|--------------------------------------------|-----------------------------------------|
| 8440–8120 BC<br>(continuous to –1040 AD) | BONFIRE SHELTER<br>Val Verde County, Texas | ONLY <i>Dermatophyllum</i>              |
| 7500 BC–570 AD                           | FRIGHTFUL CAVE<br>Val Verde County, Texas  | <i>Dermatophyllum</i> & <i>Ungnadia</i> |

|                                         |                                            |                                      |
|-----------------------------------------|--------------------------------------------|--------------------------------------|
| 7000 BC—1000 AD                         | EAGLE CAVE<br>Val Verde County, Texas      | <i>Dermatophyllum &amp; Ungnadia</i> |
| 7000 BC -1000 AD                        | COONTAIL SPIN<br>Val Verde County, Texas   | <i>Dermatophyllum &amp; Ungnadia</i> |
| 4000 BC—1000 AD                         | FAT BURRO CAVE<br>Coahuila, Mexico         | <i>Dermatophyllum &amp; Ungnadia</i> |
| 2500—200 BC                             | ZOPILOTE CAVE<br>Coahuila, Mexico          | <i>Dermatophyllum &amp; Ungnadia</i> |
| 420—1040 AD                             | BONFIRE SHELTER<br>Val Verde County, Texas | ONLY <i>Dermatophyllum</i>           |
| 810—1070 AD<br>(corrected 1070—1280 AD) | CUATRO CIENÉGAS (CM79) Coahuila, Mexico    | ONLY <i>Lophophora</i>               |

Despite their questions, this material and its associated data are highly significant to the claims in Adovasio & Fry as these are by far the oldest known archaeological finds of peyote or peyote objects, falling deep into the same Archaic period and occurring in the very same ‘neighborhood’ as Adovasio & Fry’s Val Verde County archaeological references, a context where Schuetz (1963) mentioned peyote and the red bean co-occur.



**Image 16.** Shumla peyote effigy. Believed to have come from a residential site rather than accompanying a burial. Photograph by Martin Terry

The simple use of the peyote plant itself would surely have preceded processing and reforming it into high potency effigies, so it makes no sense to place peyote consumption at a later date based on a dearth of specimens. A much simpler explanation than a sequential replacement of *Dermatophyllum* by *Lophophora* could be that botanical materials from *Lophophora* does not persist as



well as the red bean or those effigies, or perhaps that peyote buttons are more readily eaten by rodents.

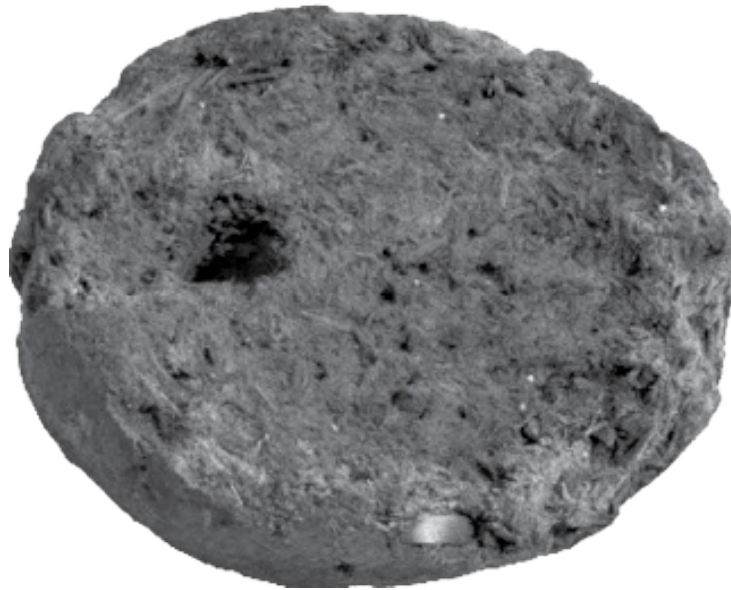


**Image 17** Back of one of the Shumla effigies. Photograph by Geoffrey Brune; courtesy of Martin Terry



**Image 18** Front of the same Shumla effigy. Photograph by Geoffrey Brune; courtesy of Martin Terry

There are three points that are worthy of closer examination.

1. The plaited and twilled basketry in the finds was woven closed. Because it would be necessary to tear them open to access the large quantities of seeds inside, Adovasio & Fry suggested that they were used for drug storage. There were quite a lot of *Ungnadia* seeds inside: Adovasio & Fry report eleven pounds in a single basket, and

Martin similarly reports finding half a bushel stored in one badly deteriorated basket at Shumla. However, Adovasio & Fry closed their paper by saying that “[the] enormous quantities found in some of the sites seems much more than ritual alone would require, particularly given the small amount needed to become crazed. The incidental use of such agents as simple intoxicants is therefore not to be discounted.” In fact, non-drug uses for the seeds can more readily explain the presence of seeds in those large amounts.

Two alternative scenarios come to mind. Martin (1933) speculated that the large quantities may have meant that they were eaten as food. The people at Shumla may have found some method to detoxify them prior to consumption, as the toxicity of *Ungnadia* seems quite likely to involve the high levels of cyanogenic lipids mentioned in Seigler et al. (1971). If so, and if the detoxification process involved prolonged leaching, perhaps the closed baskets were used to enclose the seeds.

They could also have been sound producers. The sound that such a container would produce whether shaken, tilted or rotated would be amazing to a person in a peyote-induced state.

2. A larger problem concerning assertions of relative toxicity enters the picture, as *Ungnadia* and *Dermatophyllum* do not appear to be as toxic as some literature suggests. Neither *Ungnadia* nor *Dermatophyllum* have a locatable report of a human lethality: we have been unable to verify any human death resulting from the ingestion of either type of seed. At least, there is no such report in either medical or morbidity literature: only early anecdotal comments exist for *Dermatophyllum*, and nothing has been located for *Ungnadia*. A direct question voiced to Ronald Siegel in late May 2017 was dodged, casting doubts on his published statement that *Dermatophyllum* had killed a child. It seems that, unlike the red bean, one or two *Ungnadia* seeds can be eaten with impunity.

Curiously, both plants share a reputation of being terribly dangerous; careful reading of those claims’ origins is recommended.

3. Let’s examine more closely why Adovasio & Fry proposed that *Ungnadia speciosa* may be used as an intoxicant. Their original comment: “*Ungnadia speciosa* is a suspected psychotropic agent because it is invariably associated with the red bean” (1976: 94). That is to say, the primary reason they suspected the seed to possess

psychoactivity was its common abundance accompanying the red bean.

Adovasio & Fry had referenced the account of a poisoning event in a child that was described in Havard (1885: 507–508): “These, although pleasant to the taste, are quite poisonous; cooking does not render them innocuous. An adult can eat one or two with impunity; three or four soon produce giddiness and a sensation of heat and discomfort at the pit of the stomach.” Havard then discussed a child who, after eating two or three seeds, “[...] grew very giddy, staggered up to his mother, asked for water and then fell.” The child recovered in a few hours. Havard’s short account of the child’s giddiness and collapse seems to be the only example suggesting human “intoxication” and was the only piece of evidence for *Ungnadia*’s psychotropic use that was offered in support by Adovasio & Fry. There is no indication in either the scientific or drug culture literature that anyone has deliberately experienced, or sought, intoxication from *Ungnadia*. Accordingly nothing that is known of its reported chemistry suggests this plant to possess psychoactivity.

We mentioned that Martin (1933) proposed there may have been archaic food use of *Ungnadia* seeds. That might seem far-fetched considering what we are discussing but humans, such as Havard (1885), Stanford (1981) and Andés (1902), have all mentioned eating limited numbers, sometimes one, of the seeds without adverse effects. The seeds have long been known to be sweet tasting but causing nausea and vomiting if too many are eaten (one or two can be fine according to Havard 1885). The induction of vomiting early in the toxic syndrome may be why a report of a human fatality has remained elusive for *Ungnadia*?

For unclear reasons, a physician named Geoffrey Stanford, and some friends, evaluated the potential of the seeds as a food and reported eating up to twenty without any ill effects. They apparently asserted that an animal study caused them to abandon their evaluation. They claimed that “Rats which had ingested Mexican buckeye seeds soon exhibited numerous signs of both neurological and organ damage and most died within 3 weeks.” Wildflower Center webpage citing Stanford 1981. Clearly Stanford and his associates did not die from eating twenty seeds, however no actual

meaningful details were included about those rats and we are unable to locate any publication of their results, so it is not possible to say much more.

Havard (1885) appears to be the only source to mention any effect beyond nausea and vomiting.

All poisonings may correctly be called intoxications, but it is misleading to refer to all poisons as intoxicants: users most often actively choose intoxicants for their effects, whereas the actions of poisons are commonly experienced only through accident or other mishap.

As for the mountain-laurel, Dayton (1931) may be the source of later claims (e.g., Siegel, 1989) of children dying from the red bean: "Children have been known to die as a result of eating the seeds, one of which is said to be sufficient to kill an adult human being." Dayton here references Havard (1896: 39–40), whose account was actually a misquote of an anecdote in Wood (1877) about a single frijolillo (mescal-bean). Wood's account did not mention children.

According to Merrill (1977), more than 30 tribes and groups were familiar with the red bean, and possibly as many as 47. Less than half (13-15) actually ingested them. Four to six of those groups are believed to have combined the red beans with peyote tea. Two added red beans to their sprouted-corn beer. Six had medicine societies which restricted red bean use to members during ceremony, sometimes limiting ingestion to a single time during their initiation (always men). Other groups allowed free use of the red bean to both men and women.

Reported human employment spans a diverse and contradictory spectrum, including use as an intoxicant (with common names of the "big drunk bean," "whiskey bean" and "mescal bean"), as a stimulant for dancing, as a purgative, as a soporific variously claimed to last for 1-3 days, for unclear purposes by secret societies, and sometimes for magical purposes in which it was not ingested. It is commonly assumed to be a hallucinogen, but this claim has been disputed. It was used topically as a war medicine. It also was employed in horse medicine, including both oral and external use. It has occasionally been used for seeking visions or seeing the future. It has been burned inside of homes for 'good luck,' and been attached to the fringe of clothing to provide protection against

menstrual blood. Beans were often used as beads and for charms. Bandoliers of beans were highly prized, including by peyote leaders (Merrill, 1977).

The first recorded use of “mescal beans” in reference to this plant seems to be in Hugh Lennox Scott’s Ft. Sill ledger notes, from 1889-1897. However, as far as I am aware, these were not published until much later in Meadows, 2015.



**Image 19** *Dermatophyllum secundiflorum*: flowers.



**Image 20** *Dermatophyllum secundiflorum*: pods.

Earlier workers who were familiar with the bean did not refer to it as mescal, instead choosing names such as coral bean, poison bean,

frijolillo, frijolillo, or frijolito.’ This new and unusual name for the ancient red bean seems to have appeared around or during the same time period as Scott’s original notes.

Comments in Garcia’s famous 1760 bilingual confessional include two points that are applicable to our discussion of the red bean’s intoxicant qualities:

Has comido carne de gente? Have you eaten people’s flesh?

Has comido el peyote? Have you eaten the peyote?

Te emborrachaste? Did you get drunk?

Has comido frijolillo? Have you eaten the ‘little bean’?

Te emborrachaste? Did you get drunk?

Has baylado mitote? Have you danced the mitote?

Garcia was 1) familiar with the use both of the red bean and of peyote, and 2) does not refer to either as mescal. He uses the familiar names peyote for the cactus and frijolillo for the bean. Based on the lines subsequent to each, he also clearly regards both as for intoxication.

The ‘vanished’ tribes and groups of south Texas did not actually disappear into oblivion. Instead they ‘melted’ together, their descendants still prominently represented among the people who live there today (Logan, 2001). Coahuiltecan is a catch-all name including many peoples in South Texas. One of Logan’s informants voiced a comment suggesting a continuity of use for both peyote and the red bean. “We come from indigenous people who were hunters and gatherers, and then they build the missions, and then they embrace Catholicism, they become farmers. ... The sun would go down, they would sneak out, they would go do their *mitotes*, and they would have their mescal bean ceremony and the peyote ceremonies, and then they would get caught and they would get beat by the priests or by the Spanish soldiers who went to hunt them down. ... To this day we still do the same type of ceremonies” (Cohen, 2001).

Clearly the red bean had some value to people, but there are many unknowns. It is probable that the red bean and peyote were never considered interchangeable by the cultures using them but instead had separate applications and rituals.

Woods (1877) anecdotally “asserted” that one seed was potentially fatal; this has echoed onward to today and has transformed into

established fact. Schultes (1937) commented “the red bean drink was highly toxic, often resulting in death from overdoses.” (Schultes did not indicate how “often” or include a reference.) Adam Gottlieb (1973) similarly urged caution: “Extremely toxic. Even just a little too much (1/2 bean for some) may cause convulsions and death”. He suggested a quarter bean as a dose.

It is curious that this perception of extreme danger is so common, given the absence of any credible report of a human death. There are only the historical anecdotes mentioned above, or those involving another cytisine source such as *Laburnum* spp. (Cytisine, a partial nicotinic agonist is the primary alkaloid in the red-bean and there is no question that it could potentially be fatal with a large enough dosage.) There are very few published bioassay reports. However, I know two people who have undertaken a bioassay, one of whom ate three beans. It seems reasonable to wonder how many additional unpublished bioassays have occurred, as there is no venue where those type of accounts could find an outlet. The trip reports at Erowid (Anon 1997, Anon 2006) are the closest resource of that type. The largest amount claimed to have been eaten by a human was fourteen seeds, (Howard, 1957).

The published accounts sound overall uninteresting and rather unpleasant. The most intriguing element, in light of those accounts, is that people have historically used it. That alone seems a likely stimulus for new people to try the red bean.

There is one comment that caught my attention: “One fatal case was reported after ingesting 34 to 50 mg of cytisine. One chewed seed of *Sophora secundiflora* has been reported to be lethal to humans, but supporting evidence is unavailable. ... A lethal dose of seed pods of cytisine-containing *Laburnum anagyroides* Medik. for large animals is estimated as 0.5 g/kg.” (ToxNet, 2017)

I have not yet been able to learn anything about the particulars of the “one fatal case,” whose quoted dose falls within a range of what could in fact be obtained from a few beans. This stands at odds with the oral LD50 numbers for mice (50mg/kg in Hatfield et al., 1977, and 100mg/kg in Dale & Laidlaw, 1912) and also with the results of the two failed suicide attempts by a German pharmacist discussed at ToxNet.nlm.nih.gov under cytisine.

Cytisine is available in pure form to help nicotine addicts quit

smoking. *ToxNet* (2017) offers the following adverse reactions: “Pallor, dilated pupils, incoordination, drowsiness, headache, delirium, and hallucinations have been reported. ... Numbness of the hands, muscle weakness, and incoordination can occur. ... Primary effects of toxic doses include: profuse vomiting (which may persist for several hours), abdominal pain, hypotension, tachycardia, confusion, agitation, tremor, and fatigue with an onset time of 15-60 minutes.” Outside of stimulation, intoxication and purging appear to be the most commonly reported applications among the few groups who actually used them. In light of all of that, it is not clear why some people are attracted to the bean.

One reason the beans might still be sought by the occasional bioassayist is the rare account of their visionary use. The Ponca reported receiving visions on occasion, while any visionary use that the Pawnee and the Wichita may have associated with red bean was limited to medicine society novitiates at the time of their initiation. Swanton (1942) suggested there was a visionary or divinatory component for the Hasinai Caddo, who used both the red bean and peyote for “intoxication.”

Merrill (1977) attributed any visions to set, setting, cultural beliefs, and expectations. “[There] is no evidence that any of these alkaloids, ingested either in isolation or in combination with the others, are capable of inducing hallucinations.” The primary use of the red bean, per Merrill, was for “emesis, purging, and perhaps stimulation.”

Delirium, agitation and hallucinations have been mentioned in cytisine overdoses and in some *Laburnum* poisonings (*ToxNet*, 2017). Wiegand (2007) did not mention “hallucinations” in their red bean case but did describe an “agitated delirium” with a “fluctuating consciousness.” Oral or high doses of tobacco can be hallucinogenic albeit physically distressing (Janiger & Dobkin de Rios, 1973 & 1976). Cytisine feels somewhat similar to nicotine but has been more relaxed and less euphoriant in our bioassays.

Perhaps the confounding point in the debate about whether the red bean is a hallucinogen or not involves simply how one chooses to define ‘hallucinogen.’ Is a ‘hallucinogen’ necessarily limited to something that most people are willing to experience or deliberately repeat? Clearly nicotine can be regarded to possess hallucinogenic



properties despite how few people use it for that purpose. The red bean may be prove to be similar if an adequate dosage is employed.

Evaluating the red bean holds some challenges: Hatfield et al. (1977) reported 0.25% cytisine in the beans, while Husemann (1896) found 3.23% and 3.37%. Greshoff (1900) gave 3.5%. Tabex, on the other hand, is derived from *Laburnum anagyroides* seeds, and contains 1.5 mg of pure cytisine per tablet. Furthermore, it has been approved for human use since 1965. For someone who is bent on tasting the bean that seems like a saner starting place than the red bean itself. This is clearly an area in need of much more study, even 140 years after Wood's work.



**Image 21** Tabex from Bulgaria; ordered online in April 2017.

## ENDNOTE

After more than a dozen failures to pass a federal peyote law, often by attempting to sneak a ban into the rewording of an appropriations bill involving liquor traffic, Congress successfully included a provision for admission of peyote addicts when it created the two federal Narcotic Farms in 1929 (US Congress, 1929). It was confirmed by the US Public Health Service in 1945, and again in 1955, that no peyote addicts ever entered either facility (Slotkin, 1975).

As of 2017, it is still possible to find services offering to help break peyote addiction; one need only google “peyote addiction treatment.” One of these services, “ProjectKnow,” comments that “[some] people can use peyote religiously for years, and then one

day stop cold turkey. Others need help and support to break their addiction.” Their material suggests that sedatives, professional supervision and “spiritual support” may be needed to offset the hallucinations and other withdrawal symptoms of peyote addiction. Medical doctors have never been in short supply on the anti-peyote bandwagon.

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# Reflections on the Peyote Road with the Native American Church – Visions & Cosmology

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*Jerry Patchen*

Self-taught ethnobotanist, scholar and author of *Trout's Notes*; active with Cactus Conservation Institute and Shulgin Archives Project

## ABSTRACT

The historical courageous struggle of the Native American Church (NAC) to use their sacrament Peyote is unprecedented in American culture. Without the Native Americans' indomitable spirit and arduous legal battles extending over four centuries, there would be no legal use of Schedule 1 controlled substances in the United States, except for cannabis in various states. As an attorney representing the NAC for four decades, the author was integrally involved in protecting and advancing the religious freedom rights of Indians and the legal status of Peyote. In 2005, he was awarded the distinguished Lifetime Achievement Award by the State Bar of Texas for this service. He chronicles his extensive knowledge of Peyote, its history, some important individuals, legal proceedings, law, and the contributions by ethnologists, ethnobotanists, anthropologists, and academics from related fields, to the victory of the NAC. Having served as an officer in the NAC and participated in many NAC Peyote prayer services, the author shares some of his personal visions and life-shaping experiences with Peyote.

## WHY WOULD AN ATTORNEY ADDRESS AN ETHNOPHARMACOLOGICAL SYMPOSIUM?

It is the case that the law has a dramatic impact on the ethnopharmacological search for and use of psychoactive drugs.

There has been an interplay between law and psychoactive drugs in the Americas since the 1600s. The courageous and historical struggle of Native Americans to use their sacrament Peyote, *Lophophora williamsii*, blazed the trail securing the legal right to use psychoactive Schedule I controlled substances in the United States. The Native American Church (NAC), assisted by ethnologists, ethnobotanists, anthropologists, pharmacologists, and psychiatrists, was the spear point that established the court precedents and legislation that resulted in the legal use of Peyote and *ayahuasca* as sacraments for religious purposes in the U.S.

Serving as an attorney for the NAC over four decades, I provided *pro bono* representation to protect and secure the legal status of Peyote for use by Native Americans in NAC prayer services (Peyote meetings). I also represented the Texas Peyote dealers, who are licensed by the Drug

Enforcement Administration and the Texas Department of Public Safety to harvest and sell Peyote to Indian members of the NAC. I fought many legal battles for Indians arrested for possession of Peyote in courts throughout the U.S., along with advancing Native American religious freedom rights in the U.S. Congress. I will present a survey of historical and contemporary law regarding Peyote. There is extensive literature on Peyote which covers scientific and academic studies. There is a void in the literature describing Peyote visions, which are varied and unique to time, person, place, and events. I discuss visions I experienced in NAC Peyote meetings and some Indian cosmology.

My wife Linda and I participated in Peyote meetings with the fabled, fearless, horse-riding

Indian warriors of the Southern Plains (Fig. 1). With their buffalo food supply purposefully decimated, their numbers annihilated through massacre and disease, conquered and removed from their homelands, the Plains Indians were restricted to reservations by the U.S. Cavalry parading under the banner of God-ordained Manifest Destiny. We were privileged and fortunate to join in Peyote meetings with Indian elders of the NAC whose grandfathers and grandmothers had survived the Indian genocide<sup>42</sup>, and who were removed from the Southern Plains to Oklahoma (Fig. 2). Plains Indian wisdom and traditions were orally passed on from

grandparents to grandchildren. We were in direct contact with the lineage, experiences, and wisdom of the free-spirited Indians, specifically the Apache, Comanche, Kiowa, Cheyenne, and Arapaho, the Southern Plains Indians who pioneered and developed the Peyote ceremony in its present-day form, and who were instrumental in establishing the NAC in Oklahoma in 1918 (Fig. 3).

**42.** Author's comment: The Cherokee Trail of Tears is well known, as is the Wounded Knee Massacre. Every tribe experienced its own genocide, land seizure, displacement, and removal to reservations. By way of example, the Pawnee tribe had a population over 10,000 before the Indian Wars. By the time of their removal, they numbered approximately 1,500. The proud Cheyenne, fierce warriors, victims of the Sand Creek massacre, came near to total extinction. The Wichita tribe, which numbered in the thousands, was reduced to 572 when they were removed to an Oklahoma reservation. Dee Brown's bestselling book *Bury My Heart at Wounded Knee* is an excellent treatise on the American Indian Genocide.

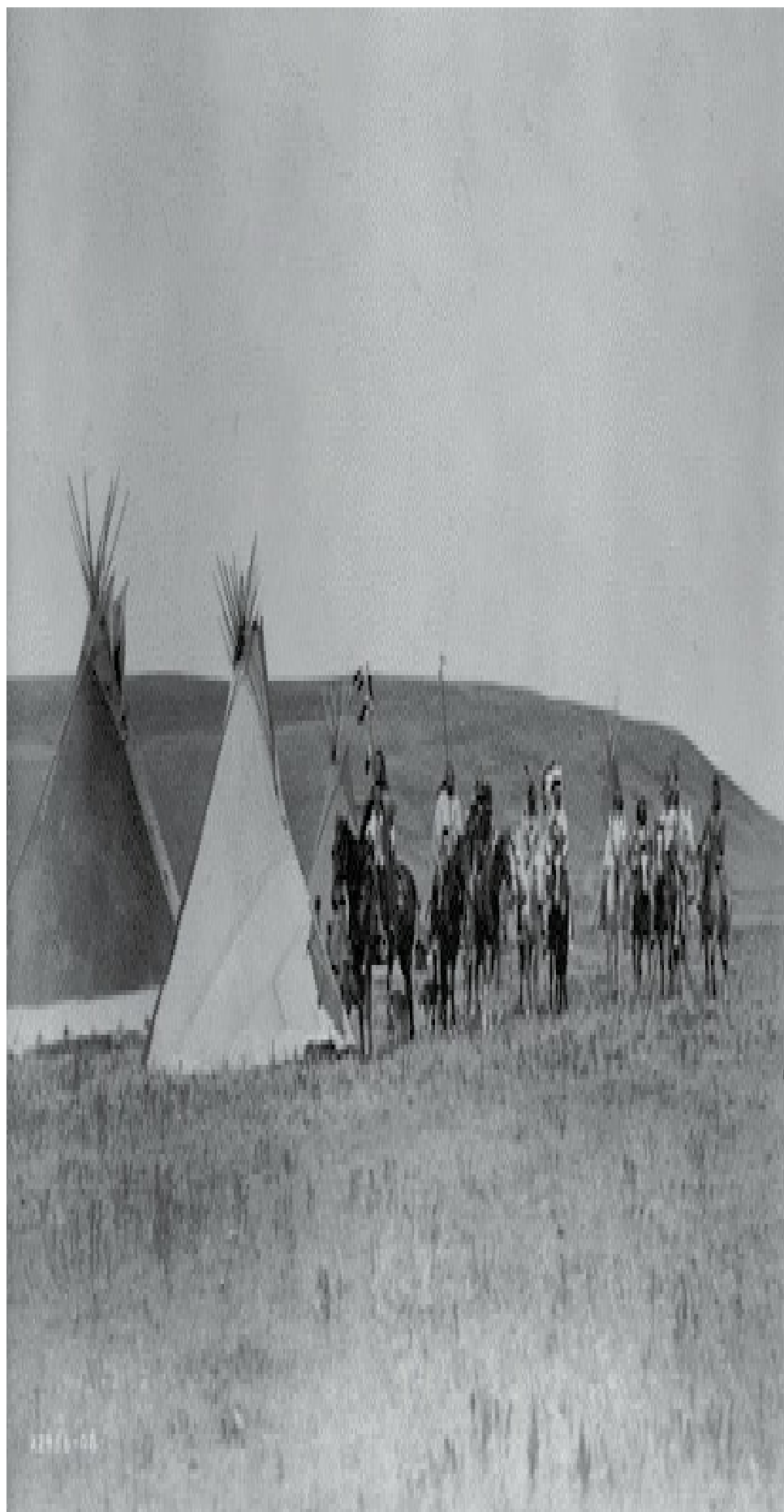


**Fig. 1** Gathering War Party. Courtesy of the Library of Congress, LC-USZ62-103068.



**Fig. 2** The Old Cheyenne – Edward Curtis Courtesy of McCracken Research Library.



**Fig. 3** Peyote cactus in bloom.

## THE ESTABLISHMENT OF THE NATIVE AMERICAN CHURCH IN OKLAHOMA

The Carizzo, Lipan Apache, Mescalero Apache, and Tonkawa ranged south into what is now Texas and Mexico. They were in contact with Mexican Indian Tribes. The Apaches brought Peyote to their Comanche allies. It was then spread to other Southern Plains tribes. Ultimately, Peyote spread to the Northern Plains Indians and later to the Navajo. A number of the elements found in the 19th-century Peyote ritual of the Southern Plains Indians were present in their Mexican precursors, including drums, rattles, tobacco, fire, and ceremonial foods such as corn and meat, and of course Peyote.<sup>43</sup>

**43.** Swan, Daniel C., 1999. *Peyote Religious Art – Symbols of Faith and Belief*. Univ. Press of Mississippi, 3.

The NAC is a syncretic religion. Indians readily adopted Christian concepts and combined them with their own cosmology. Article II of the Charter of Incorporation of the NAC of 1918 states:

The purpose for which this corporation is formed is to foster and promote the religious beliefs of the several tribes of Indians in the state of Oklahoma, in the Christian religion with the practice of the Peyote Sacrament . . . and to teach the Christian religion with morality, sobriety, industry, kindly charity, and right living and to cultivate a spirit of self-respect and brotherly union among the members of the Native race of Indians. . . .<sup>44</sup>

**44.** Stewart, Omer C., 1987. *Peyote Religion: A History*. U of Oklahoma Pr., Norman, Okla., 224. Author's note: Omer Stewart, long-time anthropologist at the University of Colorado, dedicated his life's work to the study of Peyote. Stewart's book *Peyote Religion* is the seminal treatise on Peyote. Stacy Schaefer's definitive study, *Peyotism: Amada's Blessings from the Peyote Gardens of South Texas* (Univ. of New Mexico Press, 2015), is a remarkable contemporary book lovingly focused on Amada Cardenas. See also: La Barre, Weston, 1938. *The Peyote Cult*, Yale Univ. Publications in Anthropology – Number 19. Yale Univ. Press; Aberle, David, 1966, revised 1982. *The Peyote Religion Among the Navaho*. The Univ. of Chicago Press. Omer Stewart's student George Morgan produced an outstanding thesis on Peyote: Morgan, George R., 1976. *Man, Plant and Religion – Peyote Trade on the Mustang Plains of Texas*. PhD Thesis, Univ. of Colorado.

Indians honored the “Great Spirit” and the “Great Mystery” long

before the voyage of Columbus. Indians steadfastly honored a Spirit greater than themselves. The Indians were not attached to labels. If the dominant culture insisted that the Great Spirit was God, the Indians' attitude was the Great Spirit by any name is just as powerful and mysterious. Likewise, accepting Christ as the Son of God was in rhythm with the Indian experience that we are all God's children. Indian people are very spiritual and traditionally monotheistic. The Catholic Church has archangels, similarly Indians have spirits. Like Christians, Native Americans have earnestly and humbly used prayer for thousands of years. It was easy for Indians to accept prayer since it had always been a part of their spiritual practice.

Indians honor and respect Mother Earth and all of Nature and are free of the Christian hubris of dominating all forms of life. Indians insist that we are not separate and apart from Nature, we are part of Nature. Before Darwin, Indians realized that all birds, animals, plants, trees, insects, wind, water, and elements are our "relations", and they, along with all life forms, are an inseparable part of Nature. A fundamental distinction between Christianity and Indian cosmology was the Christian belief that humans uniquely possess a spirit or soul, while Indians believe that all life forms have a spirit that ultimately transcends the earth.

Native Americans take the cosmology a step further. All birds, animals, and other life have a spirit, and our spirit can communicate with the spirit of all life. They grew up immersed in Nature, communicating with the spirits of birds, animals, and all life. When this life view is embraced, one learns to perceive a language beyond words that is just as real as the spoken word. The sounds, sights, movements, patterns, intuitions, and feelings that are communicated by birds, animals, plants, trees, and all other life provide inspiration, direction, and omens that become important guide posts in our lives.

## THE SUMMER OF LOVE AND THE BIG BANG!

Linda and I met at the University of Houston in 1967, the Summer of Love (Fig. 4). I was in law school and serving as the Student Association's Attorney General. Linda served as the secretary. The counterculture came into public awareness as a mass movement. A

huge shift and transformation of the social paradigm was occurring, which involved creative expression, art, music, dress, grooming, sexual freedom, civil rights, antiwar politics, Eastern spirituality, yoga, meditation, marijuana, psilocybin, LSD, mescaline, and Peyote. We were young, healthy, and curious college students. So what did we do? We tuned into the zeitgeist – the spirit of the times.

**Fig. 4** Summer of Love.



I happenstance secured some mescaline, which I ingested during yoga and breathing exercises. I was totally unprepared for what occurred. It was the classic kundalini experience. Suddenly, a bolt of lightning coursed up my spine and ignited a thermonuclear explosion. The simultaneous ignition of every atomic bomb on the planet would have been a hummingbird's whisper compared to the magnitude of that explosion.

I experienced the Big Bang. I was instantaneously transported to the moment of creation – the center point of all consciousness – which contained peace, radiance, and ecstatic wonder beyond comprehension. My ego was completely annihilated. I experienced eternal boundlessness, unity beyond time and space. I merged with the Divine. I had a profound sense of knowing that my essence always was, always is, and always will be. I am not suggesting that my personality will survive bodily death, but that my essence will reunite with the Divine Life Force.

Forty-five years later, this remains one of the most influential experiences of my lifetime. My understanding of reality was totally and permanently transformed. We are limited human beings on the planet Earth, and yet paradoxically we are the Universe.

As a young attorney, I was determined to stay within the bounds of the law. I was aware that mescaline was the psychoactive compound



in Peyote. Linda and I learned there was a tradition of Indians annually coming to Texas to the home and property of Amada Cardenas, a legendary Peyote dealer (Peyotera) near Laredo, erecting a tipi, and legally conducting a Peyote prayer service (Fig. 5).



**Fig. 5** Amada Cardenas, age 68 Courtesy of Linda Patchen, Nov. 1972.

In the U.S., Peyote is only abundant and indigenous near Laredo. It occurs in a narrow band east of Laredo that extends down into Mexico. Indians consider it a very special privilege to experience a Peyote meeting where it grows, and where their ancestors pilgrimaged to harvest Peyote and to pray.

### MEETING AMADA CARDENAS AND THE INDIANS

Having learned of the annual Peyote meeting with Amada Cardenas, Linda and I traveled to south Texas in 1972 and found Amada's home, which was located a little south of Mirando City. We shyly tapped on the door of Amada's small, humble casa. Amada opened the door and gave us the most wonderful open-hearted welcome that we have ever experienced. She saw us and emphatically said, "Come in! I am so glad you are here! Can I get you some coffee or something to eat?"

Our experience was not unique. Amada was legendary for her open heart, and open hearth. It did not matter who arrived at her door. She was delighted with every visitor that came to her home. It did not matter to her what color you were. It did not matter whether you were poor. Your position in life was not important to her. She was glad to welcome you. She would busy herself scurrying around providing coffee and food, and taking care of her visitors.

Upon meeting Amada Cardenas, she invited us to come visit the Indians when they came to her home for the annual NAC Peyote meeting in February. We were hesitant to do so because, as we told her, "We do not know any Indians." She responded emphatically, "That is okay, you can be my guest." The following February in 1973, we returned to Amada's home. Arriving mid-afternoon, we parked outside the fence, and saw numerous Indians around her property. There was a tipi erected near the back center of the property. Almost hesitantly, we got out of our car and slowly began walking up her driveway. A striking Indian with a big smile walked toward us and greeted us in a most friendly way. His name was Rutherford Loneman. He invited us to briefly go inside the tipi. We then hung around Amada's home and property observing the activities.

As the sun went down, the Indians entered the tipi and had a NAC prayer service. It was a cold and rather windy February night. Linda and I sat outside all night on a railroad tie on the north side of the tipi. We listened to the singing, drumming, and humble, even pleading prayers of the Indians. The next morning after the meeting, Rutherford Loneman approached us. Rutherford said to us, "I could feel you outside all night. You are looking for something good. Come back next year. I want you to go in the tipi with us."

### RUTHERFORD "WHITE STAR" LONEMAN, NAC PEYOTE ROAD CHIEF

After the invitation from Rutherford Loneman to return, Linda and I made our own pilgrimage to the annual meeting place on the property of Amada Cardenas outside of Mirando City, Texas. We attended our first Peyote prayer service accompanied by Rutherford Loneman (Fig. 6 & 7).



**Fig. 6** Rutherford Loneman, Southern Arapaho, NAC Road Chief.  
Courtesy of Linda Patchen.



**Fig. 7** Jerry & Linda Patchen at Peyote Meeting. Courtesy of Linda Patchen.

An amazing Southern Arapaho Indian Road Chief<sup>45</sup>, Rutherford

was the grandson of Old Man Loneman, who escaped the genocide, was removed to Oklahoma, and passed on his Plains Indian wisdom to Rutherford. During Rutherford's birth, Rutherford's mother consumed Peyote in an old frame house near Concho, Oklahoma, in a practice sometimes used by Indian women during labor. Old Man Loneman, Rutherford's grandfather, erected a tipi near the house. Old Arapaho Chiefs gathered with Old Man Loneman in a Peyote meeting. Immediately after Rutherford was born, he was taken inside the tipi and was passed around to the old Chiefs. Rutherford told me, "Each of them put something in me."

**45.** A Road Chief is the NAC functional equivalent of a Catholic Priest, Jewish Rabbi, or Zen Roshi. The term Road Man is used interchangeably with Road Chief.

Linda and I began an annual pilgrimage, returning every February for decades to the annual meeting at Amada's. Pilgrimage, in and of itself, is a powerful process. We had many glorious experiences and developed many close and loving relationships with Indians from many tribes, most especially Rutherford Loneman, who adopted me in the Indian way as his son.

In addition to an annual meeting in Texas, we began traveling and rendezvousing with Rutherford, other Road Chiefs, and Indian friends, going to Peyote meetings on many different reservations and in many different states, including Oklahoma, Arkansas, New Mexico, Arizona, Colorado, Utah, Nevada, Wyoming, California, and South Dakota. Rutherford could create an atmosphere of love in the tipi that was palpable. Love is an important principle in the NAC. Peyote produces a profound connection with and appreciation for those around you, Nature, all life, and the environment. Peyote produces an astonishing mental clarity and elevated conscious awareness. Peyote can produce powerful and clear visions through all our senses. Peyote fosters deep and meaningful self-examination and a sincere motivation for self-correction and improvement. Peyote is a mirror to your soul. Ecstatic experiences reliably occur in Peyote meetings, fostered by the drumming, the gourd, the singing, the colors, the fire, aromatic cedar, and the whole sacred process.

Linda and I attended a beautiful Peyote Meeting outside of Santa Fe that Rutherford led. He doctored a sick elderly Asian lady with his red-tailed hawk fan during the meeting. She was brought in and

laid in the tipi. Rutherford told me that he removed things from people with his feathers. The next morning at early light, Rutherford held the staff and gourd and sat silent. He looked at the fire and held his hand out toward the fire and said, "From where I sit this morning, it is all right there. It is very simple. It is all right there. Those who have gone on and those that are coming. It is all very simple, and it is all right there." It was a profound moment for me. Rutherford transmitted something ineffable about life. Rutherford always told me, "In the tipi we talk about life, this process of life." Peyote meetings must be approached in a serious and reverent way.

Sometimes during Peyote meetings, the old people would solemnly reach out with tears rolling down their faces, as if they were embracing and touching someone wonderful standing before them, though no one was there. I asked Rutherford why that occasionally occurred. He told me, "Sometimes a Friend of mine comes in here at a special time. I sure want you to meet my Friend. I sure want you to meet my Friend." It was fifteen years later that I experienced the phenomenon he was describing, the appearance of a Spirit image.

## ANCIENT USE OF PEYOTE IN THE AMERICAS

The use of Peyote is the oldest religious practice on the North American continent. Its ancient roots are lost in time. The Witte Museum of San Antonio, Texas, possesses three archaeological specimens of Peyote radiocarbon dated between 3660 and 3780 BCE<sup>46</sup>, the Middle Archaic Period. These Peyote specimens were discovered in a hunter-gatherer context in the Shumla Cave in the lower Pecos Region of Texas, near the confluence of the Rio Grande and Pecos Rivers. Rock art petroglyphs with Peyote motifs in the area have been dated to the same period.

56<sup>47</sup>

<sup>46</sup>. Terry, Martin, et al., 2006. "Lower Pecos and Coahuila Peyote: New Radiocarbon Dates." *Journal of Archaeological Science* 33 (7), 1017- 1021.

<sup>47</sup>. Ibid. See also: Boyd, Carolyn, 2003. *Rock Art of the Lower Pecos*. Texas A&M University Press.

Gas chromatography-mass spectrometry identified mescaline in

the Shumla Cave Peyote specimens, which identification establishes that Native Americans recognized the psychopharmacological properties of Peyote 6,000 years ago. it is reasonable to suggest that Native American use of Peyote is even more ancient; perhaps over 10,000 years, from the era of late Pleistocene Paleo-Indian hunters of mastodons to the present day. The Spanish Franciscan missionary and ethnographer Bernardino de Sahagún, who traveled to Mexico in 1529, chronicled the earliest historical reference to Peyote in his *Historia General de las Cosas de Nueva España*, published in Mexico City in 1591<sup>48</sup>. In 1577, Fernando Hernandez studied plants used by the Aztecs which included Peyotl, the Aztec word for Peyote<sup>49</sup>. When the Spanish Conquistadors arrived in Mexico in the 15th and 16th centuries, the Aztec, Huichol, Tarahumara, Zacateco, and other Indian tribes had ceremonies that centered around the use of Peyote.<sup>50</sup>

<sup>48</sup>. Stewart, Omer, 1987. *Peyote Religion*, 18.

<sup>49</sup>. Ibid, 19.

<sup>50</sup>. Swan, Daniel C., 1999. *Peyote Religious Art*, 3.

## THE PROSECUTION OF NATIVE AMERICANS FOR PEYOTE IN NEW SPAIN

Spanish imperialism included supplanting native religions with Catholicism. Mexico and Peyote did not escape the Inquisition. Christianization was forced at the point of the sword under the authority of the Inquisitor General. Plants used in native rituals were condemned. In 1620, the Inquisitors issued an edict declaring Peyote a “heretical perversity . . . opposed to the purity and integrity of our Holy Catholic Faith.” Further, Peyote was characterized as the “[I]ntervention of the Devil, the real author of this vice . . . .” The inquisitors proclaimed, “[O]ur duty imposes on us the obligation to stop this vice and to repair the harm and great offense to our God and Lord resulting from this practice . . . .”<sup>51</sup> Consequently, Peyote was the first ethnobotanical psychoactive substance prohibited by law and punished by imprisonment in the Americas. The Catholic Church enforced this edict for over two

centuries. In historical Church archives, there are records of 90 prosecutions in 45 locations in North America.<sup>52</sup>

**51.** Ramo de inquisicion, tomo 289, Archivo General de la Nacion Mexico City, cited in Leonard, Irving A., 1942. "*Peyote and the Mexican Inquisition, 1620.*" *American Anthropologist* 44(2), 324-26.

**52.** Stewart, Omer, 1987. *Peyote Religion*, 21-22.

## THE PROSECUTION OF NATIVE AMERICANS FOR PEYOTE IN THE UNITED STATES

Indians in the United States were also prosecuted. The Bureau of Indian Affairs (BIA), from its formation in 1824 through the 1930s, was very strongly influenced by missionary societies. For five decades, federal officials on reservations and in Washington D.C. were appointed by Christian missionary groups. Although the Peyote religion has Christian theology combined with Indian spiritual practices, Christian missionaries began to seek legislation to prohibit the use of Peyote. The first such law criminalizing Peyote was enacted in Oklahoma in 1899. Many other states followed suit, including Nevada in 1913, and Utah and Colorado in 1917.<sup>53</sup>

**53.** Stewart, Omer, 1956. "*Peyote and Colorado Inquisition Law.*" *The Colorado Quarterly* 5 (1), 79-90.

The Oklahoma anti-Peyote law was repealed in 1908 after a delegation of Indian Chiefs, including the famous and eloquent Comanche Chief Quanah Parker (Fig. 8), testified before the Medical Committee of the Oklahoma Constitutional Convention in 1907 (Fig. 9).



**Fig. 8** Indian Delegation testifying to Oklahoma Constitutional Convention, 1907 (Quanah Parker, left to right #5). Courtesy of Fort Sill, Oklahoma Museum # P-4868.





**Fig. 9** Quanah Parker. Courtesy of the Library of Congress, LC-USZ62-98166.

Quanah was the most influential and instrumental Indian in the creation, development, and spread of the Peyote ritual and ceremony in Oklahoma. <sup>54</sup>

**54.** Quanah Parker's mother, Cynthia Ann Parker, was an Anglo who was kidnapped as a child by the Comanches and reared as a Comanche.

The era of prohibition was raging through American culture. The suppression of Peyote became closely involved with the prohibition against the Indian use of alcohol. In 1906, Congress passed a law against the sale of intoxicating liquor to Indians, with a special appropriation to prosecute violators. President Theodore Roosevelt commissioned a well-known prohibitionist zealot, William

“Pussyfoot” Johnson, as a special officer to enforce prohibition in Indian country, and armed Johnson with 100 deputies. Johnson considered Peyote “dry whiskey” and fanatically raided Peyote meetings, arrested and caused the prosecution of Indians for Peyote<sup>55</sup>. Some of the prosecutions were unsuccessful because the law was only intended to apply to alcohol intoxicants. Other cases were defeated as a result of the confusion of Peyote with mescal beans<sup>56</sup>. Nevertheless, many Peyotists were prosecuted and punished for their religious devotion.

**55.** Stewart, Omer, 1987. *Peyote Religion* Chapter 6, Early Efforts to Suppress Peyote, 128-147.

**56.** See: Trout, Keeper. “*Mescal, Peyote, and the Red Bean; A Peculiar Conceptual Collision in Early Modern Ethnobotany*”, ESPD 50 Book.

## ROLE OF ETHNOLOGISTS, ETHNOBOTANISTS, AND ANTHROPOLOGISTS IN PROTECTING THE RIGHTS OF NATIVE AMERICANS TO USE PEYOTE

A BIA commission began in 1912 to lobby for a federal law against Peyote. In 1918, the U.S. House of Representatives held extensive committee hearings. James Mooney, an ethnologist with the Bureau of American Ethnology of the Smithsonian Institution, led the defense of Peyote. (Fig. 10) Mooney studied the Kiowa pictorial calendar in the late 1800s. Between 1891 and 1918, Mooney spent many months with Southern Plains Indians on reservations in Oklahoma. He observed and participated in several Peyote meetings. Mooney, Francis La Flesch (also an ethnologist), and William Safford, a botanist, along with many other supporters of Peyote including eloquent Indians, testified that Peyote had done much good and was a sincere and genuine religion. Naturally, there was fierce opposing testimony from prohibitionists. The bill to outlaw Peyote was passed by the House of Representatives, but rejected in the Senate when a senator from Oklahoma, under pressure from his Indian constituency, persuaded his colleagues to vote against it.<sup>57</sup>

**57.** Stewart, Omer, 1987. *Peyote Religion* Chapter 8, Efforts to Pass a Federal Law, 213-





**Fig. 10** James Mooney (1861-1921). U.S. Bureau of Ethnology. Courtesy of Smithsonian Institute – Bureau of American Ethnology Collection

A bitter conflict occurred between the BIA and Bureau of American Ethnology as a result of Mooney supporting Indians during the 1918 hearings. The BIA accused the ethnologists of “encouraging Indians to maintain old, heathenish, unhealthy, uncivilized customs so that scientists could write books, take pictures, and thus exploit the Indians with cheap publicity while doing nothing to help them become civilized.”<sup>58</sup> Mooney defended himself and ethnologists, and denounced the accusation as an “absolute falsehood.” He returned to the Kiowa reservation in Oklahoma.

The commissioner of Indian Affairs requested that the director of the Smithsonian recall Mooney, on the grounds that he was interfering with the administration of the BIA, had participated in Peyote ceremonies, and had assisted the Indians in incorporating their religion as the Native American Church. To the shame of the Bureau of American Ethnology and the Smithsonian, Mooney was recalled and never again allowed to return to Oklahoma to continue

his study of Peyote. He died a few years later of a heart attack.<sup>59</sup>

**58.** Ibid, 221.

**59.** Ibid, 219-222.

The first attempt to pass a federal anti-Peyote law was in 1937, during Franklin D. Roosevelt's administration. Frank Takes Gun, a Crow Indian from Montana and President of the Native American Church, rallied the support of seven anthropologists<sup>60</sup>. The group included Richard Evans Schultes, then a Harvard graduate student with the Harvard Botanical Museum. Schultes presented a bibliography of 383 references regarding research on Peyote, and related his field research in Oklahoma. Schultes and the other anthropologists concluded that Peyote is not a "habit-forming drug" and is used as a "religious sacrament" <sup>61</sup>. The United States Senate Committee accepted their conclusion. By this time, the Christian missionaries had been supplanted in the Bureau of Indian Affairs by administrators more protective of the religious rights of Indians. The efforts to prohibit Peyote on a federal level ended for three decades, until the 1960s.

**60.** Franz Boas, PhD, Columbia, A.L. Kroeber, PhD University of California Berkeley, Ales Hrdlicka, PhD Smithsonian Institution (anthropologist and MD), John P. Harrington Smithsonian Institution, M.R. Harrington, PhD, Curator Southwest Museum, Los Angeles, California, Weston La Barre, PhD Yale, Vince Petrullo, PhD, Works Progress Administration, Washington, D.C.; Personal Archives of author from Frank Takes Gun.

**61.** Personal Archives of author from Frank Takes Gun.

In 1965, the Drug Abuse Control Amendments were proposed. Again, NAC President Frank Takes Gun marshalled evidence from five anthropologists<sup>62</sup> who signed and submitted a joint "Statement on Peyote" to Congress through the Department of Health Education and Welfare. The Statement included in part:

**62.** Weston La Barre, PhD Duke Univ., David McAllester PhD Wesleyan Univ., J.S. Slotkin, PhD Univ. of Chicago, Omer Stewart, PhD Univ. of Colorado, and Sol Tax, PhD Univ. of Chicago - Personal Archives of author from Frank Takes Gun.

"In connection with the current national campaign against narcotics, there has been some propaganda to declare illegal the peyote used by many Indian tribes. We are professional

anthropologists who have made extensive studies of Peyotism in various tribes. We have participated in the rites and partaken of the sacramental peyote. We therefore feel it our duty to protest against a campaign which only reveals the ignorance of the propagandists concerned.

. . . [T]he Native American Church is a legitimate religious organization deserving of the same right to religious freedom as other churches . . . .”<sup>63</sup>

<sup>63</sup>. Personal Archives of author from Frank Takes Gun.

W.B. Rankin, Deputy Commissioner of the Department, wrote Frank Takes Gun in January 1966 that Peyote was to be added to the Drug Abuse Controlled Amendment of 1965. However:

“I am writing to state that on the basis of the evidence you have submitted, we recognize that Peyote has a non-drug use in bona fide religious ceremonies of the Native American Church. It is not our purpose to bring regulatory action based on the shipment, possession, or use of Peyote in connection with such ceremonies.”<sup>64</sup>

<sup>64</sup>. Ibid.

The 1965 Amendment was not enforced against the NAC. Ultimately, in 1971, the Federal Code of Regulations Section 1307.31 incorporated a specific exemption for the NAC, declaring in part, “The listing of peyote as a controlled substance in Schedule I does not apply to the nondrug use of peyote in bona fide religious ceremonies of the Native American Church.”

## THE JURISPRUDENCE OF PEYOTE IN THE UNITED STATES FROM 1970 ONWARD

The First Amendment to the United States Constitution provides, “Congress shall make no law respecting an establishment of religion, or prohibiting the free exercise thereof.” In 1963, in the case of *Sherbert vs. Verner*, 374 U.S. 398, the United States Supreme Court, in an elegantly written opinion by Justice Brennan, declared, “The door of the Free Exercise Clause stands tightly closed

against any governmental regulation of religious beliefs. . . . In this highly sensitive constitutional area, only the gravest abuses, endangering paramount interests, give occasion for permissible limitation.” The Court established the “compelling interest” test, which required the States and the federal government to balance the right of the free exercise of religion against government restriction, while giving great weight to religious freedom. The Court concluded that the regulated conduct must pose “some substantial threat to public safety, peace or order”, even when the religious practice is “abhorrent to the authorities.”<sup>65</sup>

<sup>65</sup>. *Sherbert vs. Verner*, 374 US 398 (1963) , p. 402, 403.

In a shocking decision in 1990, Justice Scalia, speaking for the U.S. Supreme Court, overruled the 30-year compelling interest test of *Sherbert* in the case of *Oregon vs. Smith*, 494 U.S. 872. The U.S. Supreme Court held that the Oregon state criminal law prohibiting the possession of Peyote was paramount to the Free Exercise Clause of the First Amendment of the United States Constitution. The Supreme Court held that police power is superior to freedom of religion. With the stroke of his pen, Justice Scalia transformed the nation’s “first liberty” into a constitutional step-child.

A dark cloud hung over the continued religious use of Peyote by the Native American Church. The NAC had no remedy in the courts and was forced to turn to the United States Congress as the last resort. The use of Peyote is central to the religious practice of the NAC. The existence of the NAC was threatened. To ensure the continued religious use of Peyote by the NAC, I helped create and draft the strategy of petitioning the U.S. Congress to enact the Religious Freedom Restoration Act (RFRA), and to amend the American Indian Religious Freedom Act of 1978 (AIRFA) to specifically include Peyote.

Outstanding and respected Native American leaders, such as Reuben Snake, Jr., a Winnebago, descended on Congress. Native American rights’ attorneys such as James Botsford and attorneys with the Native American Rights Fund went to the halls of Congress and ardently advocated for the passage of RFRA and AIRFA. Botsford was one of the primary authors of AIRFA and his advocacy was vital. The NAC, joined by a large coalition of religious

institutions from many faiths, including Baptist, Methodist, Jewish, Mormon, Unitarian, and other associations, lobbied Congress for the passage of RFRA. The strategy was successful: RFRA<sup>66</sup> was passed in late 1993 and the Amendment to AIRFA<sup>67</sup> was passed in 1994 as a result of the Native American Church initiative.

**66.** Title 42 USC 2000bb-1 RELIGIOUS FREEDOM RESTORATION ACT of 1993

Sec. 3, Free exercise of religion protected

(a) In general - Government shall not substantially burden a person's exercise of religion even if the burden results from a rule of general applicability, except as provided in subsection (b).

(b) Exception - Government may substantially burden a person's exercise of religion only if it demonstrates that application of the burden to the person— (1) is in furtherance of a compelling governmental interest; and (2) is the least restrictive means of furthering that compelling governmental interest.

**67.** American Indian Religious Freedom Act (AIRFA) Amendment, 42 USC § 1996a

Sec. 2 - Traditional Indian Religious Use of Peyote (b)(1) Notwithstanding any other provision of law, the use, possession, or transportation or peyote by an Indian for bona fide traditional ceremonial purposes in connection with the practice of a traditional Indian religious practice is lawful, and shall not be prohibited by the United States or any State. No Indian shall be penalized or discriminated against on the basis of such use, possession or transportation, including, but not limited to, denial of otherwise applicable benefits under public assistance programs.

(2) This section does not prohibit such reasonable regulation and registration by the Drug Enforcement Administration of those persons who cultivate, harvest, or distribute peyote as may be consistent with the purposes of this section and section 1996 of this title.

This legislation, fostered by the arduous efforts of the NAC, was foundational in the favorable decision involving *ayahuasca* by the U.S. Supreme Court, *Gonzales v. UDV*<sup>68</sup>, which relied on RFRA & AIRFA. The same is true for the *Santo Daime* decision in a U.S. District Court in *Holy Light of the Queen v. Mukasey*<sup>69</sup>. Without the tenacious commitment of the NAC, there would be no legal use of Peyote or *ayahuasca* in the U.S. today.

**68.** *Gonzales v. O Centro Espirita Beneficiente Uniao do Vegetal (UDV)* 546 U.S. 418 (2006). Author's comment: Working with Jeffrey Brofman, as an attorney representing the UDV, I found Jeffrey to be courageous, caring, and unyieldingly dedicated to his stewardship of the UDV. Brofman is the Quannah Parker of the UDV.

**69.** Oregon Church of the Holy Light of the Queen v. Mukasey 615 F.Supp.2d 1210 (D. Or., 2009).

Richard Glen Boire, attorney and editor of the 1990s Entheogen Law Review, and I determined that 17 states provide various levels of protection for religious use of Peyote, in addition to protection by the federal government. If the state does not appear below, there were no explicit legislative exemptions found concerning Peyote.

|                       | Religious intent, good faith practice or ceremony | With a bonafide religious organization | Within NAC ceremony | NAC membership required | Native American descent or tribal enrollment required | On reservation only |
|-----------------------|---------------------------------------------------|----------------------------------------|---------------------|-------------------------|-------------------------------------------------------|---------------------|
| FEDERAL <sup>29</sup> |                                                   | X                                      | X                   | X                       |                                                       |                     |
| AK <sup>30</sup>      |                                                   | X                                      | X                   | X                       |                                                       |                     |
| AZ <sup>31</sup>      | X                                                 |                                        |                     |                         |                                                       |                     |
| CA <sup>32</sup>      | X                                                 | X                                      |                     |                         |                                                       |                     |
| CO <sup>33</sup>      |                                                   | X                                      |                     |                         |                                                       |                     |
| ID <sup>34</sup>      | X                                                 | X                                      |                     |                         | X                                                     | X                   |
| IA <sup>35</sup>      | X                                                 |                                        | X                   |                         |                                                       |                     |
| KS <sup>36</sup>      |                                                   |                                        | X                   | X                       |                                                       |                     |
| MN <sup>37</sup>      | X                                                 |                                        | X                   | X                       |                                                       |                     |
| NV <sup>38</sup>      | X                                                 | X                                      |                     |                         |                                                       |                     |
| NM <sup>39</sup>      | X                                                 | X                                      |                     |                         |                                                       |                     |
| OK <sup>40</sup>      |                                                   |                                        |                     | X                       |                                                       |                     |
| OR <sup>41</sup>      | X                                                 |                                        |                     |                         |                                                       |                     |
| SD <sup>42</sup>      |                                                   |                                        | X                   |                         |                                                       |                     |
| TX <sup>43</sup>      |                                                   | X                                      | X                   | X                       | X                                                     |                     |
| UT <sup>44</sup>      | X                                                 |                                        |                     |                         | X                                                     |                     |
| WI <sup>45</sup>      | X                                                 |                                        | X                   |                         |                                                       |                     |
| WY <sup>46</sup>      | X                                                 |                                        |                     | X                       |                                                       |                     |

**70.** 21 C.F.R. § 1307.31 (1985)

**71.** Alaska Stat. § 11.71.195 (2017)

**72.** A.R.S. § 13-3402 (2017)

**73.** People v. Woody (1964) 394 P2d 813 (1964)

**74.** C.R.S. 27-80-209 (2016)



- 75.** Idaho Code § 37-2732A (2017)
- 76.** Iowa Code § 124.204 (2016)
- 77.** K.S.A. § 65-4116 (2017)
- 78.** Minn. Stat. § 152.02 (2017)
- 79.** Nev. Rev. Stat. Ann. § 453.541 (2017)
- 80.** N.M. Stat. Ann. § 30-31-6 (2017)
- 81.** Whitehorn v. State, 561 P.2d 539 (1977)
- 82.** ORS § 475.752 (4) (2017)
- 83.** S.D. Codified Laws § 34-20B-14 (2016)
- 84.** Tex. Health & Safety Code § 481.111 (2017)
- 85.** Utah Code Ann. § 58-37-8 (12)(b) (2016)
- 86.** Wis. Stat. § 961.115 (2017)
- 87.** Wyo. Stat. § 35-7-1044 (2017)

## THE RITUAL FORM OF THE PEYOTE MEETING

Many authors have detailed the ritual form of the Peyote meeting. Omer Stewart provides very detailed descriptors of the Peyote ritual.<sup>**88**</sup> As there is abundant literature easily available on the form of the Peyote meeting, I will only briefly describe the Peyote meeting ritual in general terms.

**88.** Stewart, Omer, 1987. Peyote Religion, 339-375.

The exquisite beauty and ambience of the NAC Peyote ceremony is beyond words. This ineffable experience cannot be adequately described in language. A tipi is erected immediately before the meeting. The door of the tipi always faces east. The participants enter the meeting at sundown, single file and clockwise, and sit in a circle on blankets and small cushions on the ground. There is something very special about sitting together with a group in a

circle. Even more so, there is something extraordinary about sitting on the ground and connecting with the earth. A small meeting might have only 10 to 15; an average meeting has 20 to 30 participants; a large meeting perhaps as many as 40 (Fig. 11).

**Fig.11** Peyote Meeting at Mirando City, Texas. Courtesy of Robert Black, [Mirandocity.com](http://Mirandocity.com).



An altar is constructed from sand and clay in the shape of a crescent moon immediately before the meeting. The Road Chief sits on the west side of the tipi facing east, the Drummer sits to the right, and the Cedar Chief to the left of the Road Chief. The Fire Chief sits next to the door and feeds the fire with hand-split links of wood throughout the night. A Chief Peyote, which is a large dried Peyote, often passed down through a family lineage, is placed at the center of the crescent moon. There are many purposes for meetings, such as a birthday, appreciation, wedding, healing, education, departing soldier, honoring someone, or memorial for a deceased. The focus of all minds and prayers is on the purpose of the meeting. This is a powerful process.

The Road Chief Frank Takes Gun is holding the instruments used in the meeting – staff, feather fan, and gourd rattler. He is standing in front of the crescent moon altar on which sits the small Chief Peyote (Fig. 12). The Drummer is sitting behind the drum, and the Cedar Chief sits to the left. As the Road Chief sings, Peyote is passed around the circle clockwise. After the Road Chief sings four songs, the instruments, including the drum, are passed around the circle; each individual sings Peyote songs if they wish to do so, or they may simply pass the instruments on. The instruments circulate around the tipi for various rounds. At midnight, the Fire Chief brings in water. After several more rounds, in the morning a woman brings a water bucket into the meeting, and prays over the water. The water is then circulated to all the participants. Ultimately, there is a conclusion song sung by the Road Chief.



**Fig. 12** Frank Takes Gun, 1956. Original photo. Author's archives from Frank Takes Gun.

During the conclusion, a small ceremonial breakfast consisting of corn, dried meat, fruit, and water is passed around the tipi circle, clockwise, after someone prays blessings on the food. This is a glorious time. There is conversation, laughter, and expressions of love and gratitude. Stories are exchanged. With their oral tradition, Indians are gifted and spellbinding storytellers. Traditionally, everyone stays at the meeting place and visits until the noon meal. This is a time of visiting, meeting new friends, exchanging information, and experiencing satisfaction and conviviality prior to leaving for home. Many participants have driven long distances. I have found the Peyote meeting form that was established by the Comanches and Kiowas to be inspirational and brilliant.

## THE ORIGIN OF THE PEYOTE TRADE IN TEXAS AT LOS OJUELOS

The tradition of Indians making long pilgrimages to Texas to harvest and trade for Peyote with Hispanics occurred as early as 1870 in the small Rancheria Settlement of Los Ojuelos,<sup>89</sup> the birthplace in 1904 of Amada Cardenas and her husband Claudio Cardenas. The Peyote traders were known as Peyoteros. Indians would come to Los Ojuelos by horseback or wagon, and later in Model T's, to secure dried Peyote. Dry Peyote is ideal for transport. It is lightweight, small in volume, and can be preserved indefinitely. Green Peyote is bulky and subject to spoiling on the long trip back to Indian country.

**89.** Morgan, George R., 1976. *Man Plan and Religion*, iv.

Hispanics living in Los Ojuelos began to harvest and dry Peyote for Indians that traveled there. Esiquio Sanchez, Amada Cardenas's father, was a Peyotero. She related that her brothers would go out with her father and harvest Peyote to take back to their home in Los Ojuelos. At age four, Amada and her sisters would turn each Peyote button over on caliche beds daily as part of the drying process.

In 1932, Amada married Claudio Cardenas, Sr., who was also from Los Ojuelos (Fig. 13). They worked together and carried on the

Amada family's tradition of harvesting, drying and trading Peyote with the Indians at Los Ojuelos. In 1942, they moved five miles north of Los Ojuelos to the outskirts of Mirando City, a small town with a population of around 300, and continued their Peyote trade. It was said of Claudio, Sr. that he would give up his bed for Indians that had traveled a long, exhausting distance, and sleep in his truck. Claudio, Sr. passed away in 1967, and Amada continued in the Peyote trade.





**Fig. 13** Claudio, Sr. and Amada Cardenas. Courtesy of Linda Patchen, gift from Amada. (Note: Chief Peyote in Claudio's hand).

The annual NAC Peyote meeting at Amada's home in Mirando City has continued through 2018. Amada was the Mother Teresa of the Native American Church. She was love in action. Her home became the national home for all Native American Churches. Amada was loved and is still revered throughout Indian country as a saint. Tens of thousands of Indians and individuals of all races have visited Amada. Amada passed away in 2005, one month prior to her 101st birthday. I was honored to deliver the eulogy at Amada's funeral (Fig. 14).



**Fig. 14** Rare Snake Peyote in bucket on Amada Cardenas' porch; Courtesy of Linda Patchen.

## FRANK TAKES GUN

### — THE JOHNNY APPLESEED OF THE NAC

No single individual achieved as much for the NAC as Frank Takes Gun (1908-1988), a Crow Indian from the Crow Reservation in Montana. His skill in creating organizational structure, chartering NAC chapters in many states, bringing court cases, and leading the passage of legislation in Indian states and the U.S. Congress, was amazing and unmatched.

The long odyssey of Frank Takes Gun fighting for the rights of Indians to use Peyote began when he was sixteen years old. In 1924, he was with his family on the Crow reservation at a Peyote meeting. After the meeting, U.S. Marshals arrived and arrested the Road Chief, Big Sheep. The women were crying, "Holy Creator, we prayed all night to you for something good in our lives. Then these men came and took Big Sheep away. We do not understand. What can we do?" The old men gathered. Frank Takes Gun was the only person there who could speak English. They instructed him to get in a horse-drawn buckboard with Big Sheep's wife, go where they had taken Big Sheep, and bring him back home. As if by miracle, when the teenager Takes Gun talked to the Marshals, they released Big Sheep. Takes Gun and Big Sheep's wife brought him home.<sup>90</sup> Big Sheep was ultimately charged with possessing Peyote.<sup>91</sup>

<sup>90</sup>. Oral history told by Frank Takes Gun to author.

<sup>91</sup>. *Montana v. Big Sheep*, 243.P.1.1067, 75 Mont. p. 219 (1926).

I was privileged to know Frank Takes Gun in his later years. In the 1980s, I arranged for him to fly from Montana to Laredo so he and Amada could have a reunion after many years of being apart. I picked him up at the airport. As we drove 45 miles east to Amada's, Takes Gun related to me that the two-lane asphalt highway we traveled on had been an old single-lane dirt wagon and vehicle trail when he was first on the roadway. He explained that some fifty years earlier, Big Sheep had taken him down to the Peyote area

around Los Ojuelos as a reward for Takes Gun having secured Big Sheep's release from jail.

I asked Takes Gun if they had put up a tipi and had a Peyote meeting on the trip with Big Sheep. He told me they had brought some tarps, cleared an area of the chaparral and simply strung some tarps in a circle as a wind break. They gathered mesquite wood and had a Peyote meeting with a fire in the center of the open-air tarps. As he related this story, I was suddenly at that Peyote meeting he was describing, even though it had occurred fifty years earlier. My visual, aural, somatic, tactile, and olfactory senses were all keenly experiencing the Peyote meeting, the same as if I was present. I seemingly was not driving the vehicle on the highway. After being present at the meeting for several minutes, I came back from this impactful vision in perplexed amazement. I told Takes Gun what had occurred, that I was there observing the meeting and totally unaware of driving the vehicle. Takes Gun simply looked at me, pointed to his temple with his right index finger, and said, "This mind is a powerful thing."

Takes Gun was a truly great man. In 1944, at age 36 (Fig. 15 – back row, third from left) he was elected Vice President of the Native American Church of the United States (NAC U.S.). Mack Haag (Fig. 15 - front left). Haag was the first signatory on the NAC Oklahoma 1918 Charter, and served as Vice President and later President.



**Fig. 15** First Officers of the NAC of the U.S.. Front row: Mack Haag (Southern Cheyenne), Alfred Wilson (Southern Cheyenne). Back row, left-right: Joe Kaulity (Kiowa), Truman Dailey (Oto), Frank Takes Gun (Crow). Courtesy of Author, gift from Takes Gun.

Though he was not an attorney and had no legal training, Takes Gun was a brilliant legal strategist. Very few attorneys in any area of law achieved in their careers the success with state and federal legislation, and the court victories, of Frank Takes Gun. During the decades that he served the NAC, he defeated attempted federal anti-Peyote legislation in 1937, and convinced the Federal Bureau of Indian Affairs (BIA) to recognize the NAC in 1945. His successful advocacy resulted in the following state legislatures legalizing Peyote in Colorado, New Mexico, Utah, North Dakota, Montana, Nevada, and Wyoming<sup>92</sup> (Fig. 16) Various other Indian country states, such as Texas, had no anti-Peyote law in this time period.

**92.** Personal archives of author from Frank Takes Gun.



**Fig. 16** Frank Takes Gun, Sam Captain, Dela Oliver, James Oliver with Utah NAC Charter – The Olivers were placed in jail several times and fined heavily. Courtesy of Author, gift from Frank Takes Gun.

Takes Gun organized, chartered, and served as an officer in Native American Churches throughout Indian country, including Colorado, Texas, California, Nevada, Wyoming, and New Mexico. The term NAC is a generic term for all of the churches that operated in various states. Schisms occurred and in some cases the names of specific churches were changed. The NAC U.S. remains only in Texas<sup>93</sup>. I was honored to serve as an officer in the NAC U.S. with Frank Takes Gun and Amada Cardenas in the 1980s and 1990s (Fig. 17). In 1965, his advocacy caused the exemption of Peyote from the Drug Abuse Control Amendment. In 1967 he was instrumental in the Navajo Tribal Council repealing their anti-Peyote ordinance.<sup>94</sup>

**93.** The Native American Church is not a monolith. Since the formation of the Native American Church in Oklahoma in 1918, the NAC divided into various official organizations. The original NAC in Oklahoma was the mother church. It advised and aided the incorporation of NAC churches in other states, and in 1934 amended its charter accepting NAC churches from many states as legal affiliates. In 1944 the NAC of Oklahoma nationalized its name and amended its charter to the name of the Native American Church of the United States. A few years later, because some Oklahoma leaders preferred the old traditional state organization without national focus the NAC of Oklahoma reinstated its original name, the Native American Church. In 1950, a new charter was obtained for the NAC US without replacing the Oklahoma State Church. In 1955, the NAC US changed its name to the NAC of North America as a result of expansion into Canada. In 1946, because Texas was vital to the Peyote supply, a NAC US was also established in Texas of which Frank Takes Gun and four prominent NAC leaders from Oklahoma were the Trustees. Claudio Cardenas and Amada Cardenas were added as Trustees to the Texas NAC US in 1957. The only remaining NAC US is in Texas. Today, three primary National Native American Churches are the NAC of Oklahoma, the NAC of North America and the NAC of Navajoland. There are many small independent NAC churches without any national organizational affiliation.

**94.** Stewart, Omer, 1987. Peyote Religion, 310-311.





**Fig. 17** Officers of NAC U.S. - Feb. 1988. Front left to right: Frank Takes Gun, age 80, Amada Cardenas, age 84; back left to right: Jerry Ettcity, Jerry Patchen, Rutherford Loneman) Courtesy of Linda Patchen.

ARIZONA - A master of litigation, Frank Takes Gun directed significant precedent-setting Peyote cases in several courts. His first major success was in *Arizona v. Mary Attakai*<sup>95</sup>. In July 1960, Judge Yale McFate ruled that the state of Arizona has police power to prohibit the use of substances, even in religious rites, if necessary to protect public health and safety. Holding that liberty of conscience secured by the Constitution may not be construed to justify practices within the peace and safety of the public, Judge McFate ruled:

**95.** Decision of the Honorable Yale McFate.

The use of Peyote is essential to the existence of the Peyote religion. Without it, the practice of the religion would be effectively prevented. From the foregoing, it follows:

First, the only significant use made of Peyote is in connection with Indian rites of a bona fide religious nature, or for medicinal purposes.

Second, there are no harmful after-effects from the use of peyote.

Third, it is not a narcotic, nor is it habit-forming.

Fourth, the practical effect of the statute outlawing its use is to prevent worship by members of the Native American Church, who believe the Peyote plant to be of divine origin and to bear a similar relation to the Indians –most of whom cannot read – as does the Holy Bible to the white man.<sup>96</sup>

**96.** State of Arizona vs. Mary Attakai, Superior Court, Coconino County, Flagstaff, Arizona, No. 4098 July 26, 1960.

california - In April 1962, three Navajo men, Jack Woody, Leon Anderson and Dan D. Nez, were arrested and charged in San Bernardino County with illegal possession of Peyote (Fig. 18). Frank Takes Gun masterminded the defense. Working with attorneys, he marshalled evidence from anthropologists and psychiatrists, and ensured that the attorneys raised Constitutional objections.

Nonetheless, Judge Hillard of the Superior Court convicted all three defendants. Takes Gun mobilized an appeal to the California Supreme Court, maintaining that California could not constitutionally apply a statute proscribing the use of Peyote so as to prevent Indians from using Peyote as a sacrament similar to the bread and wine used in Christian churches. Justice Tobriner's opinion held that an examination of the evidence compelled the conclusion that the statutory prohibition most seriously interfered upon the observation of the religion:

Although Peyote serves as a sacramental symbol similar to bread and wine in certain Christian churches, it is more than a sacrament. Peyote constitutes in itself an object of worship; prayers are directed to it much as prayers are devoted to the Holy Ghost. On the other hand, to use Peyote for nonreligious purposes is sacrilegious. Members of the church regard Peyote also as a 'teacher' because it induces a feeling of brotherhood with other members; indeed, it enables the participant to experience the Deity. Finally, devotees treat Peyote as a 'protector'. Much as a Catholic carries his medallion, an Indian G.I. often wears around his neck a beautifully beaded pouch containing one large Peyote button.<sup>97</sup>

**97.** The People v. Jack Woody, et al. 394 P. 2d. 831 (1964).

# Three Arrested For Possession Of Peyote Drug



**NO PEACE PIPE** — Ready for battle are Navajo Indians charged with possession of peyote. Two of the defendants, Jack Woody and Leon Anderson (from left) discuss the case with Frank Takes Gun, president of

Native American Church, and their interpreter, Mrs. Howard Yazzie, outside the county courthouse yesterday. A third defendant, Dan Dee Nez, is not shown. (Sun-Telegram photo)

**Fig. 18** The San Bernardino Daily Sun Article – Author's personal archives from Frank Takes Gun.

The California Supreme Court accepted the opinion of scientists, including anthropologist Omer Stewart and pharmacologist Gordon Alles,<sup>98</sup> that Peyote has no deleterious effect on the Native Americans and that the moral standards of members of the NAC were higher than those outside of the church. The court rejected the Attorney General's argument that "Peyote . . . obstructs enlightenment and shackles the Indian to primitive conditions." In

persuasive language reversing the convictions of the three defendants, the court concluded:

**98.** Stewart, Omer, 1987. Peyote Religion, 308.

[T]he right to free religious expression embodies a precious heritage of our history. In a mass society, which presses at every point toward conformity, the protection of a self-expression, however unique, of the individual and the group becomes important. The varying currents of the subcultures that flow into the mainstream of our national life give it depth and beauty. We preserve a greater value than an ancient tradition when we protect the rights of the Indians who honestly practiced an old religion in using Peyote one night at a meeting in a desert Hogan near Needles, California.<sup>99</sup>

**99.** The People v. Jack Woody, et al. Ibid.

TEXAS - In August of 1967, Texas passed a total ban on Peyote. The new Texas law placed severe criminal penalties on the growing or distribution of Peyote, mescaline, and other hallucinogens. There was no exemption for the use of Peyote for Indians or religious purposes. Texas was the only source of Peyote for the Native American Church. The NAC was in a state of deep distress over the loss of their sole source of Peyote.

Takes Gun swung into action. He arranged for a test case. Sam Houston Clinton, Jr., an attorney in Austin, Texas who worked with the ACLU, agreed to assist. Takes Gun enlisted the aid of David Clark, a brave Navajo. <sup>100</sup> There were five male Peyote dealers in south Texas. One by one Takes Gun requested each of them to provide Peyote. They all refused, fearing arrest. He then went to Amada Cardenas. Amada was courageous and readily agreed to provide Peyote. She and her husband, Claudio, Sr., had previously been arrested in 1953 for Peyote and prevailed in the case.

**100.** David Clark became the first president of the Native American Church of Navajoland.

David Clark drove out of Amada Cardenas' driveway in Takes Gun's Ford with Peyote. The Texas Highway Patrol had been alerted by Takes Gun of his intention. The vehicle was stopped and David

Clark was arrested, placed in jail, and charged with possession of Peyote. In April of 1968, David Clark's case went to trial before Judge E. James Kazen in the Webb County, 49th District Court in Laredo. Judge Kazen, citing the *Mary Attakai* case and the *Jack Woody* case, found the Texas law unconstitutional (Fig. 19).



**Fig. 19** Judge E. J. Kazen (center) Reunion Peyote Meeting at Amada's in late 1990's Drusilla Kazen, Wife (right); Lisl Kazen Friday grand-daughter (left) – note eagle feather and Peyote robe presented to Judge Kazen at Amada's in 1969 – Courtesy of Linda Patchen.

After the decision, the Native American Church conducted a Peyote meeting in honor of Judge Kazen at Amada Cardenas' home in October 1969. Judge Kazen attended the Peyote meeting. He was presented with an eagle feather and given the name "Eagle Feather, symbolizing wisdom and justice." He ate some Peyote and "found it bitter and unpalatable." <sup>101</sup>

**101.** The Laredo Times, October 13, 1969. "Judge Kazen Honored by Indian Tribes In All Night Ceremony." No. 103.

Upon learning of Takes Gun's victory in the David Clark case, the area director of the BIA, Graham Holmes, wrote a congratulatory letter to Takes Gun, stating:

Your management of the Native American Church has been amazingly successful. The winning of the recent case in Texas is the last step in the long battle for the right of the members of the Church. Many years ago when you first started this crusade, no one could have predicted that you would win every battle, and that the Native American Church would finally reach its rightful place and receive its rightful recognition in this country. <sup>102</sup>

**102.** Personal Archives of author from Frank Takes Gun.

Humphrey Osmond of New Jersey's Bureau of Research of Neurology and Psychology likewise wrote a congratulatory letter stating:

Congratulations on once again steering your church through the rapids. You have undoubtedly been a fine pilot for them. I still think of that remarkable time, or perhaps one should call it out of time, that we enjoyed together almost twelve years ago in the tepee on the bluffs of North Battleford. It remains one of the most vivid and remarkable experiences of my life <sup>103</sup> (Fig. 20).

**103.** Ibid.





**Fig. 20** (left to right) William Russell - President NAC Montana, Frank Takes Gun and Humphry Osmond, M.D. (psychiatrist) who coined the word psychedelic - Original photo. Author's archives from Frank Takes Gun.

Until he drew his last breath, Frank Takes Gun remained an ardent advocate for the religious freedom of Native Americans. On September 18, 1988, I delivered the eulogy at his funeral in Lodge Grass, Montana overlooking the Little Bighorn River, near the site where U.S. Cavalry Commander George Custer met his fate.

### RUTHERFORD LONEMAN'S FUNERAL MEETING

On August 8, 1988, while coincidentally visiting Amada, I received a phone call that Rutherford Loneman had passed away early that morning. I was heartbroken. I remember crying. Rutherford had led a Peyote meeting for our oldest child, Maya, when she was fourteen, and gave her the name "Morning Star." I had always envisioned that Rutherford would lead a meeting for all three of our children. Ultimately, Anthony "White Thunder" Davis, a Pawnee, led a meeting for our daughter, Michelle, whom he named "White Star", and for our son, Justin, whom he named "White Wolf." After receiving the call, I was sitting beside Amada and mourning

Rutherford's passing. I began to see and feel an energy field radiating soft purple light from Amada's left side into my right side. I felt a tremendous amount of strength and energy being directly transmitted to me by Amada, who just sat silently beside me. I said gently, "Amada, I am sure getting a lot of strength from you." She continued to look straight ahead and nodded her head, acknowledging the process that was occurring.

Funeral arrangements were immediately undertaken for a service and burial of Rutherford on the Arapaho reservation at Concho, Oklahoma. Rutherford's wife, Wanada Loneman, a who belonged to the Sac and Fox Tribe, planned a NAC funeral Peyote meeting. I knew what that meant and somewhat felt a sense of dread, although I knew I must be there. The Sac and Fox bring the body of the deceased in the tipi and lay the body on the ground inside the tipi throughout the Peyote funeral meeting.

Linda and I traveled to Oklahoma for the funeral. The Peyote funeral meeting was led by a Sac and Fox Road Chief. Rutherford was laid out on the ground along the north side, with blankets around his body up to his shoulders. Wanada sat next to Rutherford. Linda sat next to Wanada with me sitting on Linda's right. I was sad and having a difficult time throughout the beginning hours of the meeting. My Indian father, closest friend, and teacher lay deceased a few feet from me. I had a container of small, strong, specially dried Peyote buttons. I ate a lot of Peyote. I would eat two or three Peyote buttons often. Rutherford always told me, "If you are in a meeting, eat Peyote. If you cannot sit comfortable, eat Peyote. If your mind is spinning and agitated, eat Peyote. If something is bothering you, eat Peyote. You are in the tipi to eat Peyote."

Suddenly, Rutherford appeared bigger than life. His physical body was laid out a few feet to my left, yet he simultaneously appeared in the center of the tipi above the fire before me. He had a big smile on his face. Rutherford said to me, "Son, don't be upset. Don't be sad. This is just another lesson that I am teaching you about life, this process of life." As he completed this communication, a ray of tremendously powerful energy about 8 inches in diameter streamed down from his chest into my chest. It was the most joyful and exhilarating moment of my life. I completely understood the process

of life. This life wisdom was radiated into every dimension of my being. I experienced a sure knowing that we are all an interconnected, inseparable, and eternal unity of all that is, was, or ever will be. We are all part of an inseparable whole. I was elated. I was at the funeral of my dearest and closest friend, and I was experiencing ecstatic joy and appreciation for life. It was an unimaginable divine paradox.

The next morning, we came out of the tipi and proceeded to the grave site at the Arapaho cemetery for a traditional burial. I was filled with an afterglow and still in contact with the incredible Divine Universal Life Force transmitted to me from Rutherford's image. The next day, the essence experience was still with me, but beginning to fade. As the days and weeks passed, it gradually became fainter and fainter. Ultimately, it vanished. The memory of the experience was still intellectually there, but not the direct connection with it.

### ANTHONY "WHITE THUNDER" DAVIS, PAWNEE

My close friend Denny Sandoval, a Navajo, sensed that with Rutherford Loneman's passing, I had lost my mooring, my anchor with the NAC. Denny committed to sponsor a meeting for Linda and me at Dzit Na Ooditii, on the Navajo reservation. Denny selected his close friend, Marcellus "Bear Heart" Williams, a Creek Indian Road Chief from Oklahoma, to lead the meeting for us. Marcellus requested Anthony "White Thunder" Davis (1911-2003) (Fig. 21), a Pawnee Road Chief, to be the Cedar Chief at our Peyote meeting. A wise elder is generally designated to be the Cedar Chief. The Peyote meeting went well. I keenly paid attention to everything that was occurring during the meeting. At midnight, Anthony Davis gave the traditional Cedar Chief prayer with cedar. The meeting continued for several hours, then Marcellus called for his wife Edna to bring in morning water an hour before dawn. Again, it was Anthony's duty as Cedar Chief to give a prayer with cedar. He said words and then gave a short prayer in the Pawnee language. Linda and I were sitting on the northwest side very close to where Marcellus and Anthony were sitting. As Anthony began the cedar prayer, I took special notice. Somehow, there was a time warp. There was no time between Anthony's midnight prayer and his morning prayer. It was

as if he had reversed time from his midnight prayer, and somehow linked it with his morning prayer. That caught my attention. I had experienced Rutherford seemingly reversing time in a meeting on a prior occasion.



**Fig. 21** Anthony “White Thunder” Davis holding anHINGA fan he made. Courtesy of John Running.

Anthony completed his prayer. He then stood erect with the cedar and an eagle feather in his hand, stepped close to the altar, and cast the cedar on the coals. Bending forward and reaching down, he touched the Chief Peyote on the crescent moon altar with the tip of the eagle feather. Anthony then raised the eagle feather up in an arc, ending with his arm fully extended with the eagle feather pointing straight up. He opened another dimension with the eagle feather. Christ was standing in the arc. I was astonished. Simultaneously with the appearance of this Christ image, I heard Marcellus softly cry, “weihai” acknowledging that he saw the Spirit. The image of

Christ vanished after a few timeless seconds. I looked toward Marcellus, who had formerly been a Presbyterian ordained Minister. Marcellus, looking directly at me, softly quoted Biblical scripture: "At first we see through a glass darkly, then face to face" (1 Corinthians 13:12). I knew that Marcellus had seen what I had seen. Linda saw a bright transcendent light that filled the entire tipi. She recognized the light as the divine. I am convinced that the three of us, Marcellus, Linda, and I, were the only individuals that had seen the vision.

I am not asserting that Jesus Christ was actually standing in the arc, although I did view a clear vision of Christ standing before me. I have a Christian heritage. I was reared in the Southern Baptist Church as a child. I received an eight-year pin for not missing a Sunday. My three sisters and I were marched to the Baptist Church every time the doors opened. As a young teenager, I developed serious questions about Christianity concerning the proposition that a wonderfully good and helpful person, reared in a foreign culture, who had never heard the name of Jesus Christ, was damned to eternal hellfire. I resisted worshiping such a cruel and punishing God. Yet, because of my long cultural history with Christianity and years of Bible study, the image of the divine necessarily appeared to me in Christian form. I had no other model for Divinity. As Richard Schultes suggested, had I been Jewish, the image of Divinity would appear as Abraham; to a Buddhist as the Buddha; to a Hindu as Lord Krishna; to a physicist as patterns of energy; and to an Amazonian Indian as an image of a Jaguar. In fact, while visiting in South America our daughter Michelle had a profound vision of Divinity as a female Jaguar embracing around her and melding into her with protection and Divine love (Fig. 22). Interestingly, an image of Divinity appeared to Dennis McKenna as the process of photosynthesis. Anthony Davis had an experience where he saw a bright light that he referred to as Christ. He also had two different visions where a white wolf appeared to him as Divinity, and on another occasion a scissor-tailed fly catcher. I once asked Anthony why I experienced seeing Jesus Christ. He told me, "I don't know. Sometimes things like that just happen around me." It was clear to me that it was not something that he consciously caused or willed. One must understand the role of the imagination - the imaginal. My

simple way of expressing the imaginal is, “Spirit communicates with image, but spirit is not the image.” The 5th-century Neoplatonist, Proclus, writing on Plato, penned:

Self-realization of the Gods necessarily happens in such a way that the formless take form, and the shapeless take shape, with each soul receiving a firm and simple vision of the Gods according to that soul’s particular nature, with imagination providing shape and form to these visions.<sup>104</sup>

**104.** Proclus, On the Republic of Plato, Vol I.39.5-11. Author’s note: The 3rd-century Neoplatonist philosopher Iamblichus advances the same idea.



**Fig.22** Michelle Mackey oil painting of jaguar vision Courtesy of Michelle Mackey.

In this respect, I depart from the fundamentalist view that understands psychedelic visions literally. Our beliefs are limitations. The Tao that can be spoken is not the Tao.

Naturally, after the vision I had in the tipi with Anthony, I pursued a relationship with him. A few months later in a Peyote meeting, Anthony accepted me as his son. Not long after making that relationship with me, Anthony became very ill, and was admitted to the Indian hospital in Santa Fe with sepsis. He almost died. He was very weak, thin, and frail. It was very cold in Santa Fe, so my son Justin, aged five, who adored Anthony, and I went to Santa Fe, bundled Anthony up, and brought him to our home in the



temperate Houston climate. Linda lovingly nursed Anthony back to health. It was a long and slow process, but he gradually regained his health. He was determined. He struggled to move around, saying, “I want to walk good on this Mother Earth.” (Fig. 23, 24 & 25).

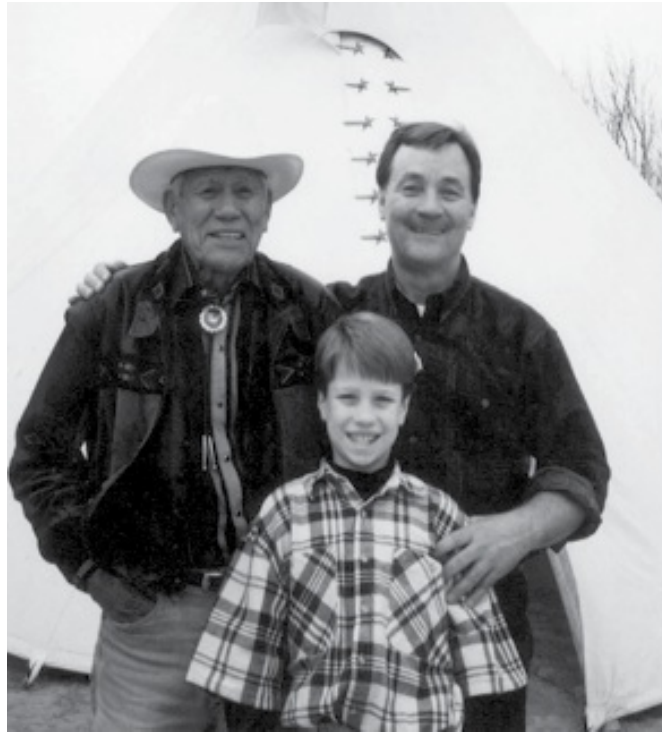


**Fig.23** Anthony “White Thunder” Davis, Justin Patchen and Jerry Patchen. Courtesy of Linda Patchen.



**Fig. 24** White Star – Mother of Anthony “White Thunder” Davis.





**Fig. 25** Anthony "White Thunder" Davis holding Mexican eagle "Totachi" – cara cara Peyote Fan that he made for Michelle Mackey and presented at her Peyote meeting. Courtesy of Linda Patchen.

By late spring, Anthony had regained his health and strength. He wanted to take me to Oklahoma for a special annual Mother's Day meeting. Anthony and I traveled from Houston to Kiowa country at Hog Creek, Oklahoma. We were well greeted and the meeting started in a nice way. It was a stormy night in May. It was raining, thundering, and lightning some during the meeting, but that was of no concern. Everyone had a good feeling. After midnight water, the staff and gourd reached Anthony around 2:00 am. We were sitting together on the south side of the tipi, with me on his right. Anthony handed me the gourd that was being passed with the staff, and opened his Peyote box, which was sitting between us. He took out a gourd that his wife Julia, an Arapaho, had beaded for him. She had passed away two years before, after 49 years of marriage. He said to me, "Son, I do not get this gourd out often anymore, but I am going to use it tonight."

Anthony began singing old Comanche songs he favored. As he was singing, a phenomenon occurred that was awe-inspiring. Simultaneously with his songs, continuous lightning began to occur

all around. There was constant thunder. It was not rolling thunder, but continuous thunder and lightning. It was a very dark night, but suddenly the sky was as bright as the noonday sun. It was "White Thunder." Anthony sang two songs, then stopped and spoke a few words. When he stopped singing and spoke, the lightning and thunder ceased. When he began singing again, the same constant thunder and lightning occurred again. I sat there astounded. Witnessing this phenomenon, I understood the origin of his name, "White Thunder." Anthony completed his turn singing, and the thunder and lightning again stopped. He passed the instruments to his left. I opened his Peyote box so that he could place his gourd back into the box. I looked at Anthony and our eyes locked. I said, "Damn! That's powerful." With an austere gaze at me, he momentarily shook the gourd in his hand. Simultaneously, there was a quick burst of thunder and lightning. Anthony then placed his gourd back in his Peyote box. I treasure the experience of Anthony introducing me to "White Thunder."

Anthony lived with Linda and me for several months a year for the next twelve years. We had marvelous experiences together until he passed on. The three of us went down to Amada's every year for the annual meeting. He was in high demand to lead Peyote meetings throughout Indian country. I traveled with him to many Peyote meetings. We sure enjoyed ourselves together.

Like all Indians, he was a great storyteller, but Anthony's presence communicated something beyond words. Anthony always taught me, "Whatever happens, take it in a good way. It's all good." Anthony "White Thunder" Davis was a blessing in our lives.

We can experience the Mystery, yet ultimately we are confronted with a Great Mystery that our small minds can never grasp.

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# Phylogenetic Analysis of Traditional Medicinal Plants: Discovering New Drug Sources from Patterns of Cultural Convergence

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Jeanmaire Molina, PhD

Long Island University Brooklyn, New York

## ABSTRACT

Medicinal and psychoactive plants have long been used by different cultures worldwide, inspiring the development of modern pharmaceutical drugs. Phylogenetic investigation of these traditional plants may shed light on which plant groups are used similarly by various cultures (cultural convergence), and which may be evolutionarily important pharmacologically. New York City (NYC) is a microcosm of global cultural diversity, which makes it convenient as a location to survey and phylogenetically analyze traditionally important medicinal plants. In a separate study, culturally diverse psychoactive plant genera and their effects were also phylogenetically analyzed. In both studies, medicinal and psychoactive plants were found to be phylogenetically clustered within certain groups or clades, suggesting evolutionarily conserved bioactivity independently discovered by different cultures through generations of trial and error. The phylogenetic scaffold also allows us to make predictions about unstudied taxa within a clade, to prioritize assays that test for bioactivity known to exist in other members of that clade. Phylogenetic ethnopharmacology, as evidenced in these studies, offers a refreshing perspective to the process of drug discovery, and facilitates scientific validation of traditional therapies through patterns of cultural convergence.

## INTRODUCTION

Traditional medicine encompasses culturally transmitted forms of medicine, including the use of plants and other natural products, outside conventional medicine (World Health Organization, 2013). Traditional medicine is the primary form of health care system for 80% of the world's population (Alves and Rosa, 2005). Given its long history of use, safety and efficacy (Gu et al., 2014), the demand for this alternative form of medicine has been growing even in developed nations where conventional medicine is well established. More than 80% of plant-derived pharmaceuticals have been developed from plants used traditionally, including common analgesics such as aspirin and morphine, antimalarials like quinine and artemisinin, and even the anticancer drug irinotecan (Farnsworth, 1988; Fabricant and Farnsworth, 2001). Thus, it is not surprising that the US National Cancer Institute's strategy of random collection and evaluation of 12,000 plant species in the 1960s only resulted in the development of two pharmaceutical drugs, taxol & camptothecin (Atanasov et al., 2015). This suggests that the process of drug discovery could greatly benefit from ethnobotanical leads and would allow us to prioritize screening among the >300,000 species of plants, of which only 15% have been systematically investigated phytochemically (Atanasov et al., 2015). Furthermore, analysis of traditionally important medicinal plants and their medicinal uses within a phylogenetic framework would allow us to determine plant groups that have evolved medicinal attributes based on their ubiquitous use for similar applications by diverse cultures.

Previous studies (Saslis-Lagoudakis et al., 2012; Xavier and Molina, 2016; Alrashedy and Molina, 2016) have shown that traditional medicinal plants across different cultures are phylogenetically clustered, with different cultures using related but geographically disjunct plants for similar therapeutic applications, a pattern of cultural convergence (Xavier and Molina, 2016; Alrashedy and Molina, 2016). The traditional uses can be viewed as traits; common occurrence of these traits within a group may be assumed to be a conserved character purportedly inherited by all members of that group. This signifies that these plant groups, or clades, possess evolutionarily conserved phytochemicals and

bioactivity that have been independently discovered by different cultures through repeated trial and error over time (Gupta et al., 2005), and their record of safety and efficacy has allowed these plants to persist through generations of use. Though previous studies (Xavier and Molina, 2016; Alrashedy and Molina, 2016) were limited in the plant taxa included in the phylogeny, and may have missed other pertinent phylogenetic patterns, this is easily rectified through the addition of more plants and their traditional uses. This could corroborate the therapeutic importance of previously identified plant clades (Xavier and Molina, 2016; Alrashedy and Molina, 2016) and highlight other plant groups and taxa that may be pharmacologically important.

Xavier and Molina (2016) presented a phylogeny of 95 medicinal plant species used by various immigrant cultures in New York City (NYC). NYC is a microcosm of global cultural diversity, which makes it convenient to study cross-cultural ethnobotanical patterns. In their study, Xavier and Molina (2016) found that certain families showed disproportionate importance as traditional therapies for gastrointestinal (e.g., Lauraceae, Zingiberaceae), respiratory (e.g., Lamiaceae) and musculoskeletal ailments (Burseraceae), and even as antibiotics (e.g., Meliaceae). Surveyed immigrant cultures included Indian (Ayurvedic), African, Latin/Caribbean, Islamic/Middle Eastern and Chinese. Here, I add plants used by Native Americans and immigrant Europeans to uncover additional phylogenetic patterns. In a separate study, psychoactive plants were also analyzed phylogenetically by Alrashedy and Molina (2016). Similarly, certain plant families emerged as cross-culturally important, as hallucinogens (e.g., Myristicaceae, Convolvulaceae, Solanaceae), anxiolytics (Lamiaceae), antidepressants (Apocynaceae), analgesics (Papaveraceae), and as aphrodisiacs (asterids). Within these families, similar phytochemicals mediate similar psychoactive effects via the same neurological mechanisms, yet interestingly, unrelated families promoting the same psychoactive effect were also found to sometimes modulate similar neurological pathways. This mechanistic convergence is exemplified in the unrelated Myristicaceae and Convolvulaceae, whose members are often used as hallucinogens by different cultures, yet which have evolved distinct phytochemicals similarly acting as serotonin

agonists. To highlight other psychoactive groups that may be cross-culturally important, additional psychoactive plants from Australia and Africa were added to the phylogeny. In both cases, new phylogenetic patterns emerged in the updated phylogenies. This emphasizes the utility of phylogenies in finding pharmacologically important medicinal plant sources from patterns of cultural convergence.

## MATERIALS & METHODS

To update the medicinal plant phylogeny in Xavier and Molina (2016), 21 genera used in Native American traditional medicine and 43 genera used in Western/European herbalism were added (for a total of 139 genera), with their medicinal uses mapped on the phylogeny (Table 1). Plant names were obtained from online catalogs of NYC herbal stores, and scientific names, if unavailable on the product label, were retrieved from Internet searches based on the common name on the label. rbcL sequences for respective genera were downloaded from Genbank (<https://www.ncbi.nlm.nih.gov/genbank/>), aligned and phylogenetically analyzed to reconstruct a genus-level phylogeny following methods in Alrashedy and Molina (2016). If the majority (>60%) of the genera within a clade is used for the same medicinal application by different cultures, then presumably this is a conserved “trait” for members of that clade, and this medicinal application is indicated on the ancestral node (e.g., in Lamiaceae, 6 were used for gastrointestinal concerns out of 9 genera, so  $6/9=67\%$ , and the “gastrointestinal trait” is placed by the node in Figure 1). Medicinal applications were categorized as follows: gastrointestinal, cardiovascular, respiratory/immunostimulant, nervous, musculoskeletal and antiparasitic/antibiotic, and were primarily obtained from Moerman (2003), Alshamrani (2016) and UMMC (2017).

To update the psychoactive plant phylogeny (Alrashedy and Molina, 2016), a total of 25 psychoactive genera – 10 used multiculturally, 5 from Australia, and 10 from Africa – (Table 2; Sobiecki, 2008; Voogelbreinder, 2009) were added to the psychoactive phylogeny published in Alrashedy & Molina (2016) for a total of 151 genera. rbcL sequences were downloaded from

Genbank, aligned and phylogenetically analyzed. Psychoactive effects (hallucinogen, stimulant, sedative, anxiolytic, antidepressant, aphrodisiac, analgesic) from the said references were also superimposed on the phylogeny.

## RESULTS & DISCUSSION

### PHYLOGENY OF PLANTS USED IN NYC HERBAL MEDICINE

Figure 1 presents the genus-level phylogeny of traditional medicinal plants used by immigrants in NYC (Xavier and Molina, 2016), updated with plants and their uses from Native American and Western/European herbalism (Moerman, 2003; Alshamrani, 2016; UMMC, 2017). In this phylogeny that conforms to expected relationships from the Angiosperm Phylogeny Group (2016), 3 new clades were identified to be cross-culturally important (i.e., 3 or more genera were used cross-culturally): the family Asteraceae and orders Dipsacales and Fagales, in addition to the 10 families that were previously identified (Xavier and Molina, 2016)—Lauraceae, Zingiberaceae, Malvaceae, Meliaceae, Combretaceae, Burseraceae, Fabaceae, Apiaceae, Rubiaceae, Lamiaceae). However, some of these clades are inherently diverse, and their identification here may be an artifact of this diversity. For example, Asteraceae has >1600 genera, while Burseraceae only has 19. To account for this disparity, Figure 2 shows the relative proportion of medicinally important genera within the family, obtained by dividing the number of traditional medicinal genera included here by the overall generic diversity within the family (from Christenhusz and Byng, 2016). Though Fagales and Dipsacales are ordinal classifications, they only have 19 and 33 genera, respectively. Plant groups with the highest relative medicinal importance, in ascending order, include Lamiaceae (used for gastrointestinal and respiratory ailments, represented at c. 5%), Zingiberaceae (8%, gastrointestinal), Lauraceae (9%, gastrointestinal/antibiotic), Meliaceae (10%, antibiotic), Dipsacales (16%, nervous system applications), Fagales (20%, gastrointestinal/antibiotic), and Burseraceae (27%, musculoskeletal ailments). These plant families are disproportionately used medicinally by various cultures in NYC.



**Gastrointestinal, respiratory and antibiotic plants.** As discussed in Xavier and Molina (2016), the presence of essential oils rich in terpenes, terpenoids and phenolics in members of Lamiaceae (Kumari et al., 2014), Zingiberaceae (Kumari et al., 2014), and Lauraceae (Ahmad et al., 2013) contribute to their therapeutic applications for gastrointestinal ailments. These phytochemicals exhibit carminative, antispasmodic and anti-inflammatory effects (Lewis and Elvin-Lewis, 2003; Heinrich et al., 2012). They also possess antimicrobial properties, explaining the use of Lauraceae members as antibiotics (Joshi et al., 2010). In Lamiaceae, the volatile oils also exert respiratory activity as an expectorant and antitussive, and for mitigating bronchial infections (Mamadaliyeva et al., 2017).

In the order Fagales, which overall only has 19 genera, phenolics (e.g., ellagic acid) as well as tannins are described to be gastroprotective (Polya, 2003; European Medicines Agency, 2011). Flavonols that characterize Fagales (Giannasi, 1986) like galangin (Polya, 2003), kaempferol (Calderon-Montano et al., 2011), and quercetin (Cushnie and Lamb, 2005) are also antibacterial. However, in the unrelated Meliaceae, limonoids are the primary antimicrobial constituents (Roy and Saraf, 2006).

**Nervous system plants.** The order Dipsacales, with only 33 genera, has been highlighted as a medicinally important group for nervous system complaints, particularly for the sedative action of its members. The popular herbal valerian (*Valeriana officinalis*), widely used to alleviate insomnia and anxiety in folk medicine (Shi et al., 2014), contains the sesquiterpene valerenic acid which stimulates the GABAergic system, the main inhibitory neurotransmitter system, resulting in its sedative and muscle-relaxing effects (Yuan et al., 2004). Iridoids and related valepotriates in valerian may also contribute to its tranquilizing effects (Polya, 2003). GABA-stimulating sesquiterpenes were also identified in *Nardostachys* spp. (Takemoto et al., 2009) used as a sedative in Ayurvedic/Indian culture (Chaudhary et al., 2015), as well as in *Viburnum* spp. used in Native American (Moerman, 2003) and traditional Chinese medicine (Wang and Wang, 2013). There was no ethnobotanical use for the Dipsacales member *Sambucus nigra* as a sedative, but experimental evidence was found

that suggest extracts of the plant have anticonvulsant activity by increasing the inhibitory neurotransmitter GABA (Ataee et al., 2016). These studies suggest that Dipsacales may be an important evolutionary group to explore for tranquilizing/sedating drugs.

**Plants for musculoskeletal applications.** Relative to its diversity, many members of Burseraceae have been employed in various cultures as treatments for musculoskeletal problems such as pain and arthritis (Xavier and Molina, 2016), making up 27% of the medicinal plant genera (Figure 2). Triterpene acids such as boswellic acids and mansumbinoic acid have been found to promote its anti-inflammatory effects (Duwiejua et al., 1993). The sesquiterpenoid furanoedesma-1,3-diene has also been found to bind to opioid receptors, promoting analgesia, similar to morphine (Spinella, 2001). Thus, newly discovered species within this family should first be explored for such antinociceptive molecules.

## PHYLOGENY OF CULTURALLY IMPORTANT PSYCHOACTIVE PLANTS

Psychoactive plant taxa were also phylogenetically clustered (Figure 3) in certain families. The families Aizoaceae, Ranunculaceae, Malpighiaceae, Apiaceae and Caprifoliaceae were not in Alrashedy & Molina (2016) and emerged as cross-culturally important in the updated phylogeny (Figure 3) after addition of new genera. However, after correcting again for the disparities in generic diversity, as in Figure 2, plant families that remain disproportionately important include, in ascending order, Malpighiaceae (4%, hallucinogen, Figure 4), Ranunculaceae (7%, analgesic), Convolvulaceae (11%, hallucinogen), Papaveraceae (10%, sedative/analgesic), Caprifoliaceae (11%, sedative), Solanaceae (16%, hallucinogen/sedative) and Myristicaceae (19%, hallucinogen). These families are discussed here and the reader is referred to Alrashedy and Molina (2016) for a discussion of the phytochemistry and pharmacology of the other families.

**Hallucinogenic plants.** The presence of serotonin-mimicking alkaloids, e.g., harmaline, harmine, beta-carboline and dimethyltryptamine (DMT) in members of Malpighiaceae (Callaway et al., 1999) may mediate their hallucinogenic effects by acting as 5HT receptor agonists (Aghajanian and Marek, 1999). This is true

for *Banisteriopsis caapi* and *Diplopterys cabrerana* (Ratsch, 2005). The confamilial *Sphedamnocarpus* is used in African divination practices (Sobiecki, 2008), and phytochemical and pharmacological studies would likely confirm the presence of 5HT ligands. The same serotonergic mechanism is exerted by hallucinogenic members of the unrelated families Myristicaceae and Convolvulaceae (Polya, 2003; Schiff, 2006), each possessing serotonin-mimicking compounds such as DMT and ergot alkaloids, respectively. Though phylogenetically related to Convolvulaceae, Solanaceae surprisingly modulates its psychoactive effects through tropane alkaloids (e.g., atropine, scopolamine) that work via anticholinergic mechanisms, resulting in sedation and deliriant hallucinations characterized by confusion and stupor (Duncan and Gold, 1982), in contrast to the higher-level cognitive and perceptual changes in serotonergic hallucinogens (Aghajanian and Marek, 1999).

**Plants for sedation and analgesia.** The closely related Papaveraceae and Ranunculaceae, of the order Ranunculales, both promote analgesia, but current experimental studies seem to suggest different mechanisms. Morphine and codeine are benzyloisoquinoline alkaloids (BIAs) characteristic of Ranunculales (Hagel and Facchini, 2013), and they bind to opioid receptors to relieve pain (Spinella, 2001; Polya, 2003). Phylogenetically, it is expected that BIAs would also mediate analgesia in Ranunculaceae. The BIA berberine in *Hydrastis canadensis* does work this way (Chen et al., 2015; Mikołajczak et al., 2015). However, in *Aconitum* ssp., anesthesia is mediated by the diterpenoid alkaloid aconitine, which targets Na<sup>+</sup> channels (Polya, 2003), while in *Clematis*, flavonoids seem to be antinociceptive (Mostafa et al., 2010). It is possible that other pain-relieving BIAs exist in Ranunculaceae. Apart from analgesia, sedation in Papaveraceae is also mediated via the opioid pathway (Spinella, 2001). In contrast, sedative members of the unrelated Caprifoliaceae mediate their effects via the GABAergic pathway, as discussed previously (see Dipsacales above).

Caprifoliaceae (Dipsacales) is highlighted in both phylogenies (Figs. 1 and 3), which underscores the neuropharmacological importance of this clade. The families Apiaceae, Apocynaceae, Asteraceae, Fabaceae, Malvaceae and Rubiaceae were also

redundant in both phylogenies, but this is perhaps a function of their generic diversity that made them easily accessible, hence their ubiquitous ethnobotanical uses. Nonetheless, pharmacological studies of these families would still be interesting to understand certain trends, such as the prominent use of Apiaceae members as stimulants, or the use of Apocynaceae members as antidepressants.

## CONCLUSION

Traditionally important medicinal and psychoactive plants are phylogenetically clustered within certain groups or clades, whose members have been independently discovered by different cultures through generations of trial and error. This implies an evolutionarily conserved phytochemistry that should be pharmacologically investigated. Though the identification of certain commonly used plant groups may be a function of their innate diversity, investigation of their phytochemistry is still worthwhile. The phylogenetic scaffold allows us to make predictions about unexplored taxa within a plant family and prioritize assays that test for bioactivity known to exist in other members. For instance, anti-inflammatory assays could be explored for newly discovered species in Burseraceae, which was highlighted here as a plant family cross-culturally important in alleviating musculoskeletal pain and inflammation. Phylogenetic ethnopharmacology, as evidenced in these studies, offers a refreshing perspective to the process of drug discovery and facilitates scientific validation of traditional therapies through patterns of cultural convergence.

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**Table 1** List of medicinal plants used in Native American and European/Western traditional medicine and added to the NYC herbal phylogeny published in Xavier and Molina (2016). Medicinal uses were obtained primarily from Moerman (2003), Alshamrani (2016) and University of Maryland Medical Center (2017).

| FAMILY           | SCIENTIFIC NAME                  | COMMON NAME            | PREDOMINANT CULTURE | TRADITIONAL MEDICINAL USES                                                                                     |
|------------------|----------------------------------|------------------------|---------------------|----------------------------------------------------------------------------------------------------------------|
| Adoxaceae        | <i>Sambucus nigra</i>            | elderberry             | European/Western    | Respiratory/immune support, antibiotic                                                                         |
| Adoxaceae        | <i>Viburnum prunifolium</i>      | stagberry              | Native American     | Nervous; female reproductive                                                                                   |
| Apocynaceae      | <i>Apocynum androsaemifolium</i> | bitterroot             | Native American     | Gastrointestinal, respiratory/immune support, cardiovascular, antibiotic, nervous, urinary                     |
| Aristolochiaceae | <i>Asarum canadense</i>          | snake root             | Native American     | Gastrointestinal, respiratory/immune support, cardiovascular, female reproductive, urinary, stimulant          |
| Asteraceae       | <i>Arctium lappa</i>             | great burdock          | European/Western    | Gastrointestinal, respiratory/immune support, cardiovascular                                                   |
| Asteraceae       | <i>Arnica montana</i>            | arnica                 | European/Western    | Musculoskeletal                                                                                                |
| Asteraceae       | <i>Calendula officinalis</i>     | pot marigold           | European/Western    | Gastrointestinal                                                                                               |
| Asteraceae       | <i>Echinacea spp.</i>            | coneflower             | Native American     | Gastrointestinal, respiratory/immune support, cardiovascular, musculoskeletal                                  |
| Asteraceae       | <i>Lactuca serriola</i>          | prickly lettuce        | European/Western    | Gastrointestinal, respiratory/immune support, cardiovascular                                                   |
| Asteraceae       | <i>Silybum marianum</i>          | milk thistle           | European/Western    | Gastrointestinal                                                                                               |
| Asteraceae       | <i>Tussilago farfara</i>         | coltsfoot              | European/Western    | Respiratory/immune support                                                                                     |
| Asteraceae       | <i>Rudbeckia hirta</i>           | coneflower             | Native American     | Respiratory/immune support, antibiotic                                                                         |
| Berberidaceae    | <i>Berberis vulgaris</i>         | European barberry      | European/Western    | Gastrointestinal, musculoskeletal, antibiotic                                                                  |
| Betulaceae       | <i>Alnus rubra</i>               | red alder              | Native American     | Gastrointestinal, respiratory/immune support, musculoskeletal, antibiotic                                      |
| Betulaceae       | <i>Betula papyrifera</i>         | paper birch            | Native American     | Gastrointestinal, respiratory/immune support, cardiovascular, female reproductive, musculoskeletal, antibiotic |
| Caprifoliaceae   | <i>Valeriana officinalis</i>     | valerian               | European/Western    | Nervous                                                                                                        |
| Caryophyllaceae  | <i>Stellaria media</i>           | chickweed              | European/Western    | Musculoskeletal                                                                                                |
| Cupressaceae     | <i>Juniperus scopulorum</i>      | rocky mountain juniper | Native American     | Gastrointestinal, respiratory/immune support, cardiovascular, musculoskeletal, antibiotic, urinary, cosmetic   |
| Fabaceae         | <i>Trifolium pratense</i>        | red clover             | European/Western    | Gastrointestinal, respiratory/immune support, cardiovascular, female reproductive                              |
| Fagaceae         | <i>Quercus robur</i>             | oak                    | European/Western    | Gastrointestinal, antibiotic                                                                                   |
| Gentianaceae     | <i>Gentiana lutea</i>            | yellow gentian         | European/Western    | Gastrointestinal                                                                                               |
| Hamamelidaceae   | <i>Hamamelis virginiana</i>      | witch hazel            | Native American     | Gastrointestinal, respiratory/immune support, cardiovascular, musculoskeletal, urinary                         |
| Hypericaceae     | <i>Hypericum perforatum</i>      | St. John's wort        | European/Western    | Gastrointestinal, nervous                                                                                      |
| Iridaceae        | <i>Iris missouriensis</i>        | rocky mountain iris    | Native American     | Gastrointestinal, musculoskeletal, urinary                                                                     |
| Juglandaceae     | <i>Juglans cinerea</i>           | walnut                 | Native American     | Gastrointestinal, cardiovascular, female reproductive, antibiotic                                              |
| Lamiaceae        | <i>Glechoma hederacea</i>        | ground ivy             | European/Western    | Gastrointestinal, respiratory/immune support, urinary                                                          |
| Lamiaceae        | <i>Marrubium vulgare</i>         | white horehound        | European/Western    | Gastrointestinal, respiratory/immune support                                                                   |
| Lamiaceae        | <i>Melissa officinalis</i>       | lemon balm             | European/Western    | Gastrointestinal, nervous                                                                                      |
| Lamiaceae        | <i>Thymus vulgaris</i>           | common thyme           | European/Western    | Gastrointestinal, respiratory/immune support, antibiotic                                                       |

|                  |                                 |                  |                  |                                                                                                         |
|------------------|---------------------------------|------------------|------------------|---------------------------------------------------------------------------------------------------------|
| Lamiaceae        | <i>Vitex agnus-castus</i>       | chaste berry     | European/Western | Female reproductive                                                                                     |
| Lauraceae        | <i>Sassafras albidum</i>        | sassafras        | Native American  | Gastrointestinal, respiratory/immune support, cardiovascular, antibiotic, urinary                       |
| Loganiaceae      | <i>Spigelia marilandica</i>     | pink root        | Native American  | Gastrointestinal                                                                                        |
| Melanthiaceae    | <i>Trillium erectum</i>         | red trillium     | Native American  | Gastrointestinal, respiratory/immune support                                                            |
| Myricaceae       | <i>Myrica cerifera</i>          | wax myrtle       | Native American  | Gastrointestinal, musculoskeletal, antibiotic                                                           |
| Onagraceae       | <i>Oenothera biennis</i>        | evening primrose | Native American  | Gastrointestinal, musculoskeletal                                                                       |
| Papaveraceae     | <i>Sanguinaria canadensis</i>   | blood root       | Native American  | Gastrointestinal, respiratory/immune support, cardiovascular, female reproductive, urinary, stimulant   |
| Polygonaceae     | <i>Polygonum pennsylvanicum</i> | pinkweed         | Native American  | Gastrointestinal, cardiovascular, female reproductive                                                   |
| Polygonaceae     | <i>Rumex crispus</i>            | curled dock      | European/Western | Gastrointestinal, cardiovascular, antibiotic                                                            |
| Portulacaceae    | <i>Portulaca oleracea</i>       | purslane         | European/Western | Gastrointestinal, respiratory/immune support, cardiovascular, musculoskeletal, urinary                  |
| Ranunculaceae    | <i>Actaea racemosa</i>          | black cohosh     | Native American  | Respiratory/immune support, female reproductive, musculoskeletal                                        |
| Rosaceae         | <i>Agrimonia eupatoria</i>      | agrimony         | European/Western | Gastrointestinal                                                                                        |
| Salicaceae       | <i>Populus tremuloides</i>      | quaking aspen    | Native American  | Gastrointestinal, respiratory/immune support, nervous, female reproductive, musculoskeletal, antibiotic |
| Scrophulariaceae | <i>Verbascum thapsus</i>        | great mullein    | European/Western | Respiratory/immune support                                                                              |
| Vitaceae         | <i>Vitis aestivalis</i>         | summer grape     | Native American  | Gastrointestinal, respiratory/immune support, cardiovascular, musculoskeletal                           |

**Table 2** List of psychoactive plants added to the phylogeny published in Alrashedy and Molina (2016). Psychoactive effects were obtained primarily from Sobiecki (2008) and Voogelbreinder (2009).

| Family         | Scientific Name              | Common Name     | Predominant Culture | Traditional Medicinal Uses             |
|----------------|------------------------------|-----------------|---------------------|----------------------------------------|
| Aizoaceae      | <i>Aptenia cordifolia</i>    | ibohlololo      | African             | analgesic                              |
| Aizoaceae      | <i>Carpobrotus spp.</i>      | pigface         | Australian          | analgesic                              |
| Apiaceae       | <i>Anethum graveolens</i>    | dill            | Multicultural       | sedative, aphrodisiac                  |
| Apiaceae       | <i>Conium maculatum</i>      | hemlock         | Multicultural       | sedative, aphrodisiac                  |
| Apiaceae       | <i>Daucus carota</i>         | wild carrot     | Multicultural       | stimulant, aphrodisiac                 |
| Apiaceae       | <i>Ferula spp.</i>           | giant fennel    | Multicultural       | stimulant, aphrodisiac                 |
| Apiaceae       | <i>Foeniculum vulgare</i>    | fennel          | Multicultural       | stimulant                              |
| Apiaceae       | <i>Heracleum spp.</i>        | cow parsnip     | Multicultural       | sedative, aphrodisiac                  |
| Apocynaceae    | <i>Vinca spp.</i>            | periwinkle      | Multicultural       | anxiolytic, sedative                   |
| Apocynaceae    | <i>Xysmalobium undulatum</i> | leshokhoa       | African             | anxiolytic/sedative? (= anti-hysteria) |
| Caprifoliaceae | <i>Centranthus spp.</i>      | centranthes     | African             | sedative                               |
| Convolvulaceae | <i>Cuscuta spp.</i>          | dodder          | Multicultural       | stimulant, aphrodisiac                 |
| Convolvulaceae | <i>Evolvulus alsinoides</i>  | sky convolvulus | Multicultural       | sedative                               |
| Fabaceae       | <i>Albizia adianthifolia</i> | muvhadangoma    | African             | hallucinogen (= induces dreams)        |



|               |                                   |                   |               |                                 |
|---------------|-----------------------------------|-------------------|---------------|---------------------------------|
| Fabaceae      | <i>Bauhinia bowkeri</i>           | umlandlovu        | African       | hallucinogen                    |
| Fabaceae      | <i>Canavalia maritima</i>         | coastal jack bean | Australian    | sedative, analgesic             |
| Fabaceae      | <i>Chamaecrista mimosoides</i>    | umbonisela        | African       | sedative                        |
| Fabaceae      | <i>Erythrophleum lasianthum</i>   | umkhwangu         | African       | analgesic                       |
| Fabaceae      | <i>Indigofera flavicans</i>       | naiego            | African       | hallucinogen (= induces trance) |
| Lamiaceae     | <i>Clerodendrum floribundum</i>   | buwatanganing     | Australian    | stimulant, analgesic            |
| Lamiaceae     | <i>Stachys aethiopica</i>         | bolao ba litaolla | African       | anxiolytic (= soothing)         |
| Malpighiaceae | <i>Sphedamnocarpus pruriens</i>   | pupuma            | African       | hallucinogen?                   |
| Malvaceae     | <i>Brachychiton diversifolius</i> | nanungguwa        | Australian    | stimulant                       |
| Ranunculaceae | <i>Clematis glycinoides</i>       | headache vine     | Australian    | analgesic                       |
| Rubiaceae     | <i>Galium spp.</i>                | bedstraw          | Multicultural | stimulant                       |

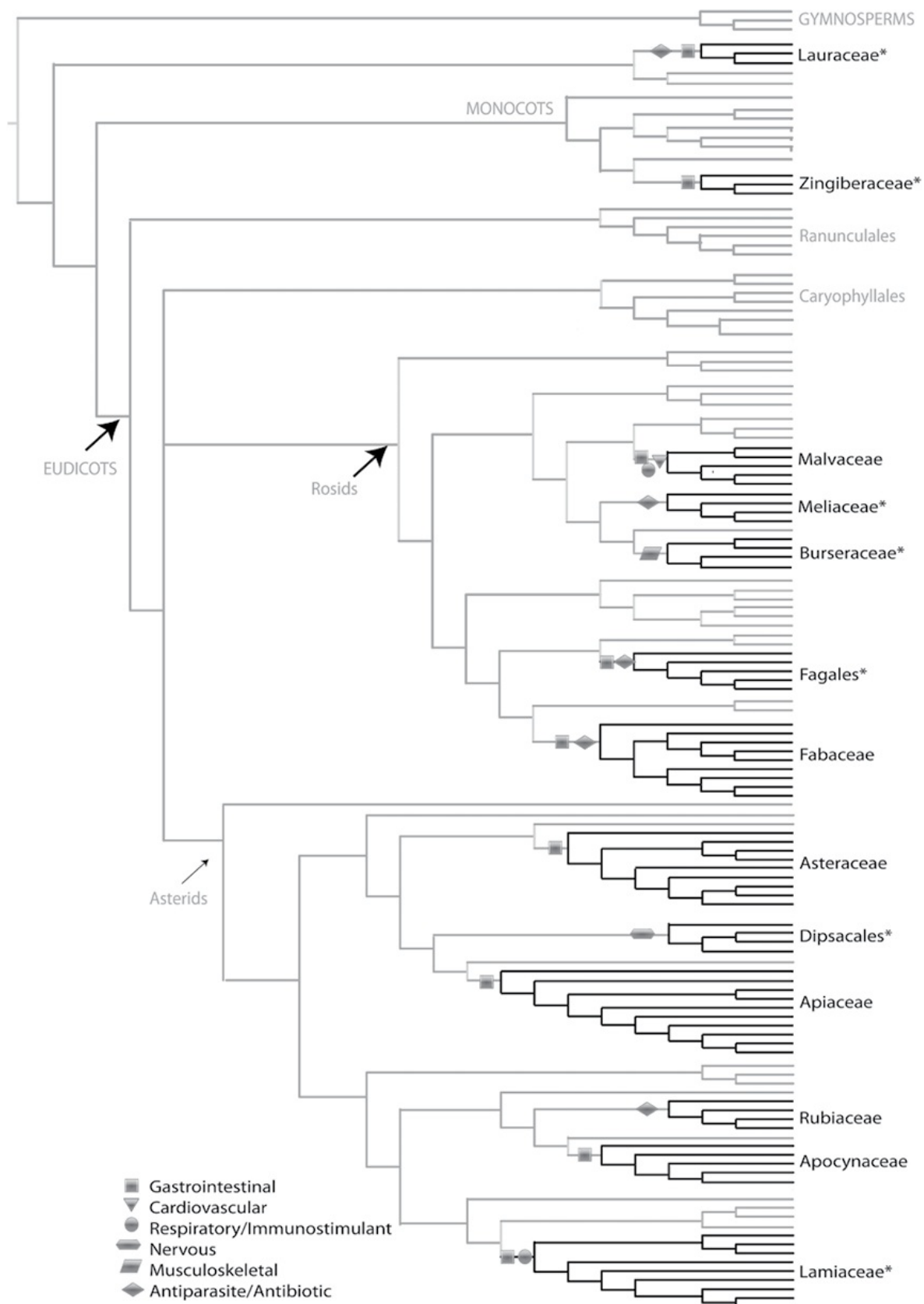


**Fig. 1** Phylogeny of traditionally important medicinal plants (139 genera) used by various immigrant cultures in NYC. Branches in black (bold) represent genera of ethnopharmacologically important plant groups/clades with their corresponding taxon names (family/order). Symbols on nodes represent the primary therapeutic application of that clade. “\*” indicates clades that are disproportionately important even after correcting for generic diversity (cf. Fig. 2).

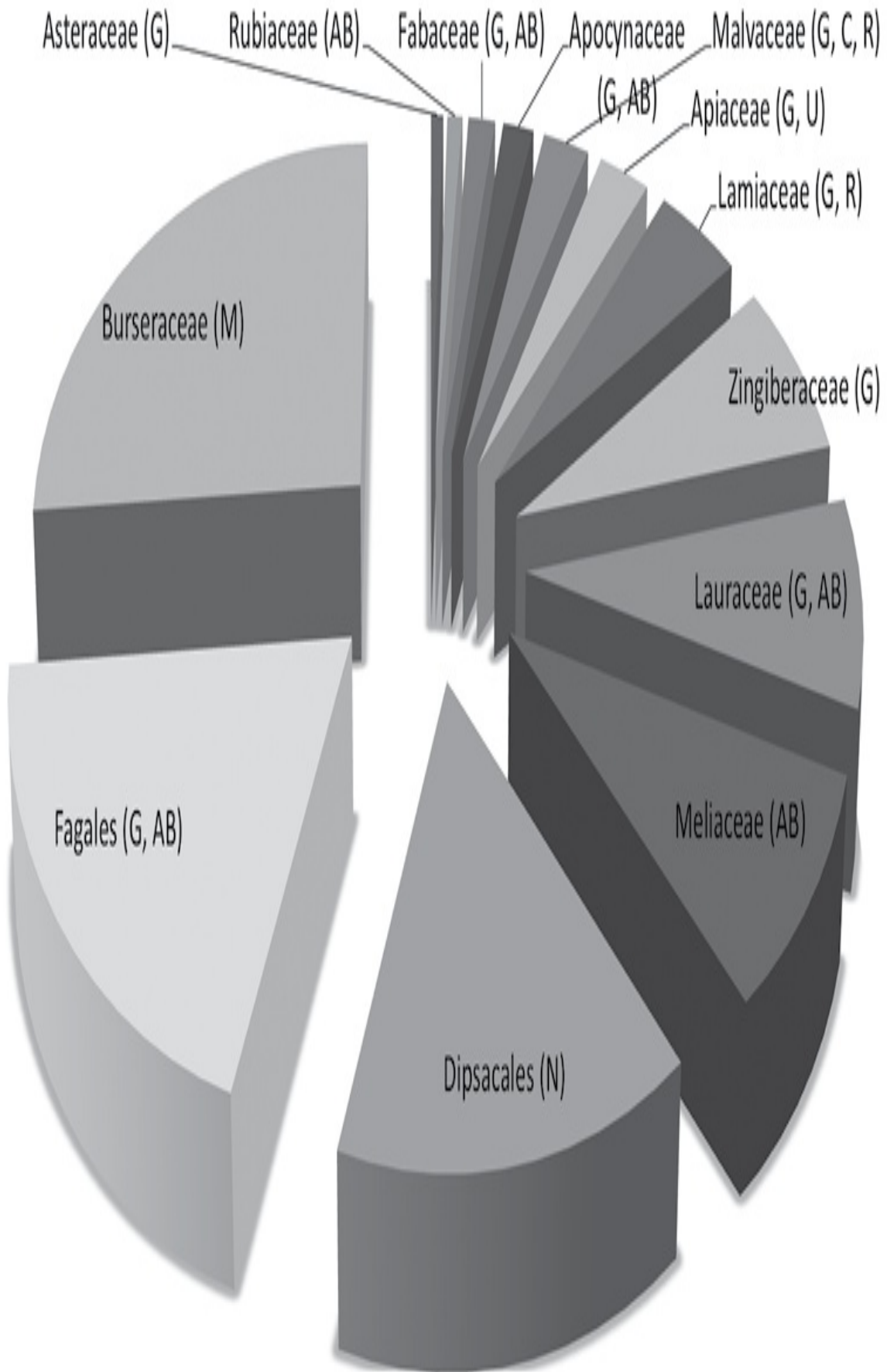


**Fig. 2** Relative medicinal importance of each clade identified in the NYC herbal phylogeny (Fig. 1). Proportions were standardized according to generic diversity within the clade, e.g., Asteraceae is represented by 9 medicinal genera here but has 1623 genera total, so its medicinal importance here is relatively nil ( $9/1623=0.0055$ ). Cross-culturally important medicinal clades include Lamiaceae, Zingiberaceae, Lauraceae, Meliaceae, Dipsacales, Fagales and Burseraceae in ascending sequence and are discussed in text. AB: antibiotic; C: cardiovascular; G: gastrointestinal; M: musculoskeletal; N: nervous; R: respiratory; U: urinary.

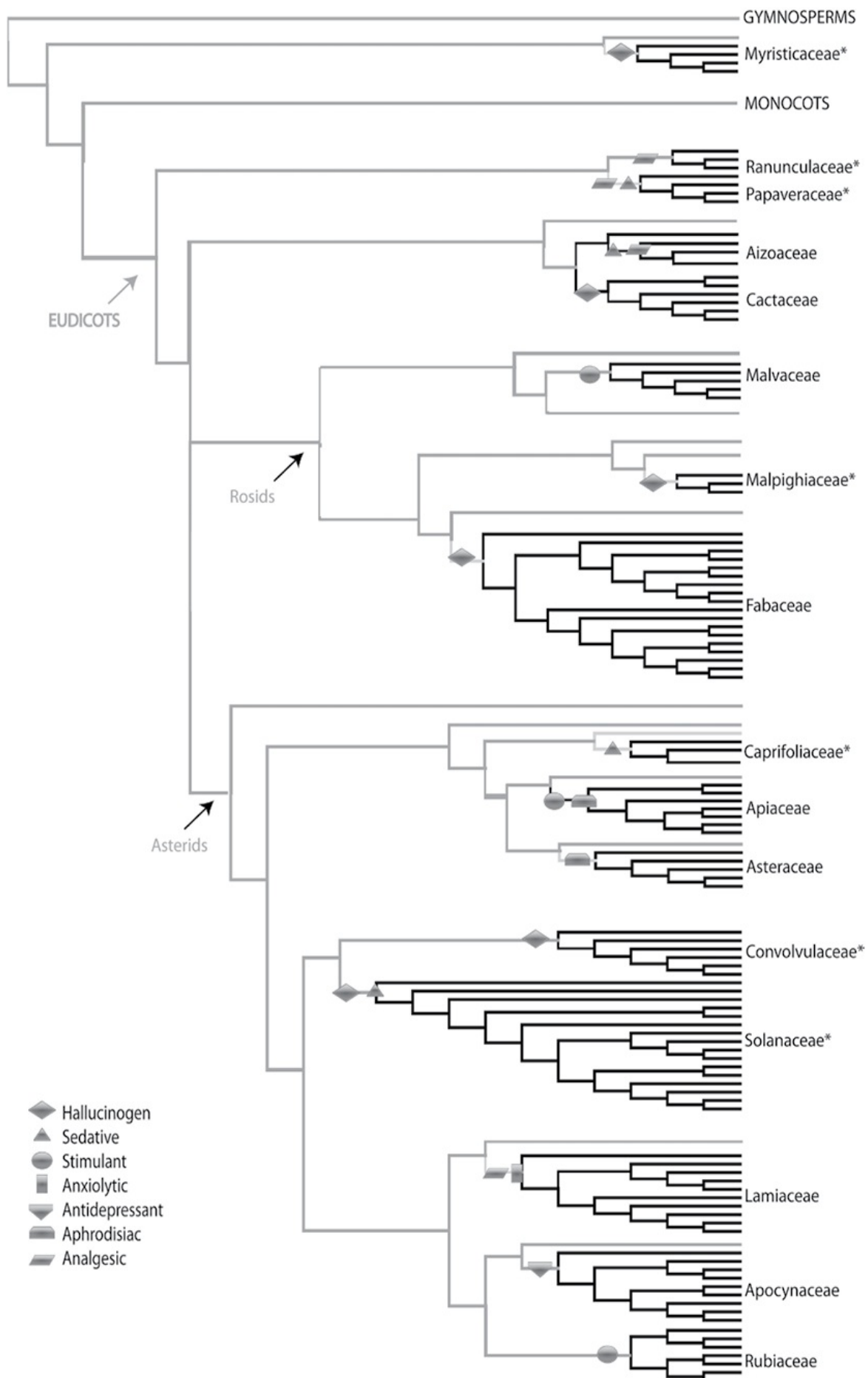


**Fig. 3** Phylogeny of culturally important psychoactive plants (151 genera). Branches in black (bold) represent genera of ethnopharmacologically important plant groups/clades with their corresponding taxon names (family). Symbols on nodes represent the primary psychoactive effect of that clade. “\*” indicates clades that are disproportionately important even after correcting for generic diversity (cf. Fig. 4).

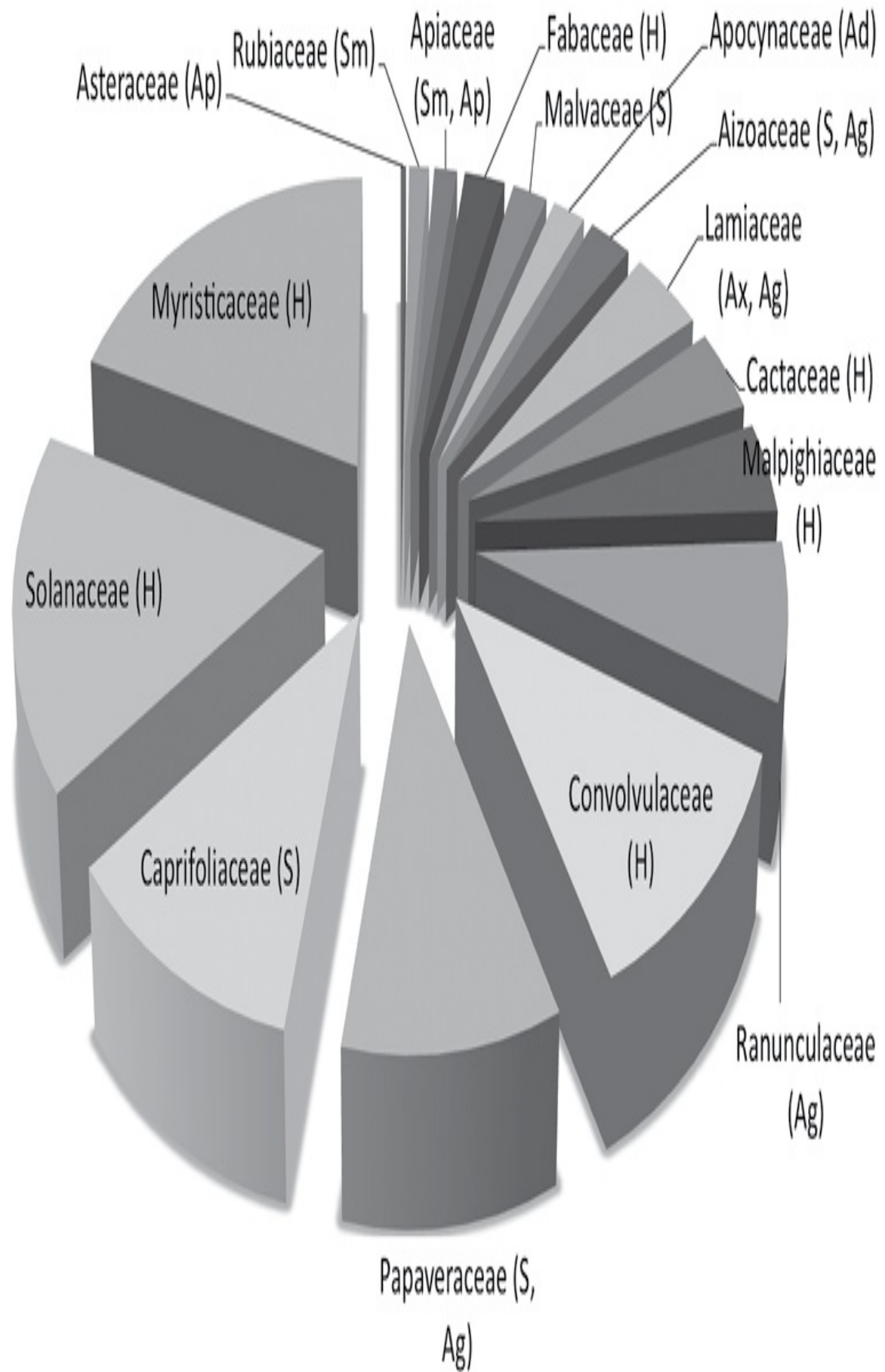




**Fig. 4** Relative psychoactive importance of each clade in the psychoactive plant phylogeny (Fig. 3). Proportions were standardized according to generic diversity within the clade. Cross-culturally important psychoactive clades include Malpighiaceae, Ranunculaceae, Convolvulaceae, Papaveraceae, Caprifoliaceae (Dipsacales), Solanaceae and Myristicaceae in ascending order. Ag: analgesic; Ad: antidepressant; Ap: aphrodisiac; Ax: anxiolytic; H: hallucinogen; S: sedative; Sm: stimulant.

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# Ethnopharmacology Meets the Receptorome: Bioprospecting for Psychotherapeutic Medicines in the Amazon Rainforest

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*Dennis J. McKenna, PhD*

Director, Ethnopharmacology,  
Heffter Research Institute;  
Assistant Professor, Center for Spirituality and Healing,  
University of Minnesota,  
Minneapolis, MN

Note: This paper consists of a subset of the data presented in the multi-author publication in the *Journal of Ethnopharmacology*:

McKenna, D.J., Ruiz, J.M., Hoyer, T.R., Roth, B.R., Shoemaker, A.P., 2011.

Receptor screening technologies in the evaluation of Amazonian ethnomedicines with potential applications to cognitive deficits. *Journal of Ethnopharmacology* 134, 475-492. I am grateful to my co-authors for their contributions to this work, and thank them for permission to present sections of it in this paper.

## ABSTRACT

Ethnopharmacological relevance: Amazonian peoples utilize a variety of psychoactive plants that may contain novel biologically active compounds. Efforts to investigate such remedies in terms of neuropharmacology have been limited. Aim of this study: This study identified Amazonian ethnomedicines with potential for the treatment of cognitive deficits in schizophrenia and dementias, and characterized their interactions with CNS neurotransmitter receptors *in vitro*. Materials and Methods: Approximately 300 Amazonian species with folk uses or constituents indicative of central nervous system activity were incorporated into a database constructed from literature searches, herbarium surveys, and interviews with traditional practitioners. Approximately 130 of these targeted species were collected in Loreto province, Peru, and 228 fractions derived from them were screened in 31 radioligand receptor assays via the resources of the NIMH Psychoactive Drug Screening Program (PDSP). Results: 91 samples displayed  $\geq 60\%$

inhibition of radioligand-binding activity in receptor assays. Conclusions: Potential CNS activity was detected in about 40% of the samples screened, with some correlations to both folk uses and phytochemical constituents. These results may point to novel and potentially therapeutic CNS-active compounds.

## INTRODUCTION

Advances in psychopharmacology have resulted in the development of medications that are effective for the treatment of overt psychotic symptoms of schizophrenia, sometimes characterized as positive symptoms of the disease. By contrast, the negative symptoms of schizophrenia are associated with neurocognitive deficits in functions such as attention, executive functions, short- and long-term memory, and verbal ability (Lysaker and Buck, 2007; Peuskens et al., 2005). Treatment of the neurocognitive deficits in schizophrenia is likely key to eventual long-term recovery and productive reintegration of individuals with schizophrenia into social, educational, and employment contexts. While “atypical” antipsychotics such as clozapine have shown some promise for the treatment of neurocognitive deficits in schizophrenia, there remains a continued need for the identification of structurally novel compounds that are more effective, and have more acceptable side-effect profiles (Hill et al., 2010). Similar considerations also inform the search for effective medications to treat neurocognitive deficits in Alzheimer’s disease and other dementias (Mangialasche et al., 2010).

Ethnopharmacology – the interdisciplinary investigation of biologically active substances used by indigenous cultures – has repeatedly demonstrated utility for the discovery of natural compounds that eventually find medical applications. In the field of psychopharmacology, ethnopharmacological research has uncovered a wide spectrum of CNS-active compounds, ranging from sedatives to anxiolytics to analgesics to hallucinogens. Receptor-binding methodologies – in which isotopically labeled compounds are employed to selectively label neurotransmitters or other receptors – have been widely utilized in drug discovery. The technique enables rapid screening of compound “libraries” or crude extracts derived from plants or other natural sources. The

application of ethnopharmacology to identify potentially therapeutic psychotropic medicines with a history of human use, combined with receptor-binding and functional receptor assays to identify activity in crude extracts, is a productive approach to the discovery and evaluation of psychotropic ethnomedicines that may be suitable for development into clinically applicable psychotherapeutic agents.

## ETHNOPHARMACOLOGY APPLIED TO CNS DRUG DISCOVERY

The search for new psychotropic medications for the treatment of diseases of the nervous system and mental illnesses has benefited enormously from ethnopharmacology. The history of CNS drug discovery is inextricably intertwined with ethnopharmacology, due to the considerable ingenuity displayed by human societies in identifying and utilizing diverse psychotropic plants. A plethora of psychotropic plant-derived natural substances has resulted. The alkaloid reserpine, for example, from the plant *Rauvolfia serpentina* L. Benth ex Kurz (Apocynaceae), was used in treating psychosis in Ayurvedic medicine, and provided the prototype of modern antipsychotics (Curzon, 1990); the hallucinogens LSD and psilocybin were regarded as possible pharmacological models of psychosis, and basic research with these compounds led to insights into the function of serotonin in the central nervous system (Geyer and Vollenweider, 2008). Some have been a mixed blessing, as their pharmacological properties render them prone to abuse; others, even though abused, also have therapeutic properties that have been a boon to modern medicine; almost all, abused or not, have proven to be valuable tools for basic researchers investigating the neuropharmacology of brain functions and dysfunctions (Duke, 1995; Vortherms and Roth, 2006).

## NATURAL PRODUCTS IN THE TREATMENT OF SCHIZOPHRENIA AND NEUROCOGNITIVE DEFICITS

Ethnopharmacology has led to the discovery of botanical medicines or natural products useful in psychiatric disorders such

as anxiety and depression, sleep disorders, and dementias. The identification of natural products effective for the treatment of psychosis has met with less success. The alkaloid reserpine, from the Ayurvedic medicine *Rauvolfia serpentina*, is the prototype antipsychotic; its discovery resulted from ethnopharmacology, but it was quickly supplanted by synthetic neuroleptics such as chlorpromazine (Marder et al., 1993), although it still finds occasional use in the treatment of tardive syndromes (Fernandez and Friedman, 2003). Recent research has resulted in the identification of traditional medicines with promise for the treatment of a range of psychiatric/neurological disorders including seizures, anxiety, substance abuse, depression, psychosis, and dementias; with few exceptions, most of these studies are in the early stages (Lake, 2000). In a few instances, e.g., *Ginkgo biloba* L. (Ginkgoaceae) for dementia and memory deficits, and St. John's Wort (*Hypericum perforatum* L. (Hypericaceae) for depression, these natural medicines have been commercialized as popular dietary supplements (Fugh-Berman and Cott, 1999). There has been considerable interest in recent years in the investigation of botanical remedies for dementia and cognitive disorders (Howes et al., 2003; Kidd, 1999; Ott and Owens, 1998), but almost all of the interest has been focused on cognitive deficits of dementias rather than those associated with schizophrenia. The influence of botanical medicines on schizophrenia, either on the exacerbation of symptoms by patients self-medicating with St. John's Wort in combination with antidepressants (Lal and Iskandar, 2000; Parker et al., 2001), exacerbation of extrapyramidal symptoms by betel nut (*Areca catechu* L. (Arecaceae) (Deahl, 1989), or the incidental amelioration of symptoms by betel nut (Wilson, 1979; Sullivan et al., 2000), or in adjunct treatment with *Ginkgo biloba* (Zhang et al., 2001), has been noted, but systematic clinical studies are rare. Many of these reports are case studies related to one or at most a few patients (Hanes, 2001). Most published clinical studies have been conducted by Chinese researchers, and are often published in Chinese in journals not readily accessible to Western investigators; moreover, many of these studies have focused on herbal adjunct treatments to conventional antipsychotic therapies, and not on the positive or negative symptoms of schizophrenia (Zhu et al., 1996; Yamada et

al., 1997; Zhang et al., 1987; Wang, 1986; Hu, 1984; Yuan, 1979). Thus the clinical literature on botanical therapies for schizophrenia is both disappointing and tantalizing; there are promising leads, but the information is sketchy, clinical studies are lacking, and those that do exist are almost all within the context of Chinese Traditional Medicine. Other than the sparse reports on betel nut, there is little published on cognition-enhancing ethnomedicines in schizophrenia. The Amazon basin represents another geographic area with a high biodiversity index and numerous indigenous ethnomedical traditions (Schultes and Raffauf, 1990). Ethnomedical practices in the region incorporate shamanic elements in which the use of psychotropic plants, such as the hallucinogen *ayahuasca* (Coe and McKenna, 2017) is the rule rather than the exception. Amazonian traditional healers are often familiar with the psychotropic properties of many botanical remedies, but ethnopharmacologists have paid disproportionate attention to hallucinogens; those with nootropic, or cognition-enhancing, properties are poorly investigated. Nonetheless, intriguing leads to cognition enhancers have been noted (Schultes, 1993, 1994; McKenna et al., 1995).

## RADIOLIGAND-BINDING METHODOLOGIES IN DRUG DISCOVERY

The development of radioligand receptor-binding methodologies, pioneered by Solomon Snyder and colleagues in the early 1970s, was a significant breakthrough that has been particularly important for the neurosciences (Pert and Snyder, 1973). The technique gave molecular pharmacologists the means to selectively label specific receptors, enzymes, or other cellular targets using isotope-labeled compounds. Such methodologies have been invaluable for the elucidation of the sites and mechanisms of action of a vast array of drugs and other bioactive substances. Receptor-binding methodologies have also been an important tool in drug discovery, enabling the rapid, cost-effective screening of compound libraries for activity against a variety of molecular targets, including neurotransmitter receptors (Phillipson, 1999). The application of these methodologies to the detection and bioassay-directed

isolation of psychotropic or neuroactive compounds in plant extracts has been successful in the identification of constituents with analgesic activity (Phillipson, 1999; Sampson et al., 2000), anti-epileptic activity (Jäger et al., 2004), serotonin-reuptake inhibition activity (Nielsen et al., 2004), and Ayurvedic medicines with memory-enhancing activities (Misra, 1998). More recently, functional assays have emerged as high-throughput approaches to screen for the activities of compounds at CNS targets (Armbruster and Roth, 2005).

## OBJECTIVES OF THE PRESENT STUDY

In the present study, we utilized a combination of screening approaches to evaluate a selected sample of Amazonian ethnomedicines for indications of CNS activities that may have therapeutic applications for the treatment of cognitive deficits. We used literature reviews, databases, surveys of herbarium collections, and field interviews with traditional healers to compile a database of approximately 311 candidate species. Approximately 130 species from this original list were collected, and crude extracts and fractions were screened in a broad spectrum of *in vitro* radioligand receptor-binding assays.

## METHODS AND MATERIALS

### IDENTIFICATION AND PRE-SELECTION OF TARGETED SPECIES

We relied on a variety of resources to partially pre-select candidate species for collection and follow-up investigation. Because of the lack of extensive published data on the use of Amazonian ethnomedicines specifically for schizophrenia or cognitive deficits, and due to the lack of exact correspondence between Western diagnostic categories and cultural conceptualizations of mental disease, we elected to develop a list of species targeted for collection that conformed to a broad set of inclusion criteria. The rationale for this approach was that initial, broadly defined inclusion criteria would be less likely to overlook candidates of potential interest compared to inclusion criteria that were more narrowly defined.

Our reasoning was that fractionation and *in vitro* screening of a set defined using broad criteria would rapidly result in the identification of a subset of collections inviting more extensive evaluation.

### LITERATURE SURVEY

We initially relied on literature searches in PubMed, supplemented by published ethnobotanical references on Amazonian ethnomedical species and on searches in the NAPRALERT<sup>sm</sup> database to identify targeted species. Four published volumes were key to our literature survey, viz. Duke and Vasquez, 1994; Schultes and Raffauf, 1990; Von Reis and Lipp, 1982; Von Reis, 1973.

In addition to published volumes, targeted species were selected based on peer-reviewed journal articles accessed through Pubmed. Three of these were key references for the identification of promising leads (Schultes, 1993; Schultes, 1981; Russo, 1992).

### NAPRALERT<sup>SM</sup> SURVEYS

NAPRALERT<sup>sm</sup> and Pubmed were primary online resources used in conducting the literature survey. The NAPRALERT<sup>sm</sup> database (<http://www.napralert.org>) is a natural products database maintained and administered by the Program for Collaborative Research in the Pharmaceutical Sciences in the College of Pharmacy, University of Illinois at Chicago (Loub et al., 1985; Farnsworth, 1993). It contains information on the ethnomedical uses, chemical constituents, and pharmacological and biological activities of natural products from plant, animal, microbial, and marine sources. The information is compiled from a variety of sources including published abstracts, journals, government reports, newsletters, patents, and books. Approximately 50% of the data is derived from a systematic survey of the literature from 1975 to the present, but includes some data from older sources, some as old as 1650. NAPRALERT<sup>sm</sup> is the most comprehensive collection of data on natural products and ethnomedicine in existence. Of particular relevance to this project, NAPRALERT<sup>sm</sup> contains over 3600 biological/pharmacological activity codes related to compounds and extracts. For example, there are approximately 98



codes related to central nervous system activity; more than 50 codes related to autonomic nervous system activity; over 126 codes related to receptor-binding or receptor-mediated activity. Initially, NAPRALERT<sup>sm</sup> was searched for references to plants or extracts having one or more pharmacological codes related to CNS activity, with the additional constraint that the plants were native to South America (Table 1). Plants indigenous to South America that were identified in searches of the NAPRALERT<sup>sm</sup> pharmacological activity codes were parsed for occurrence in Peru, then the genus and species (or the genus if the species was not listed) was searched again in NAPRALERT<sup>sm</sup> using its “3-part” search protocol, which retrieves information on ethnomedical uses, biological activities detected in extracts evaluated *in vitro* and in animal models (including humans), lists secondary compounds isolated, and presents a consolidated citation summary. Genera and species retrieved from the NAPRALERT<sup>sm</sup> searches were further parsed to omit well-known and well-studied species (e.g., *Nicotiana tabacum* L. (Solanaceae), *Banisteriopsis caapi* Spruce ex. Griseb Morton (Malpighiaceae). Additionally, species with relatively well-studied secondary chemistry (as evidenced by the existence of extensive phytochemical studies in published literature) were not included as candidates, or were assigned a lower priority than species with relatively unstudied phytochemistry, on the rationale that species with limited phytochemical data were more likely to yield novel compounds.

## COLLECTIONS DATABASE

The information acquired through NAPRALERT<sup>sm</sup>, PubMed, published books, and later through herbarium surveys and field interviews with local informants, was incorporated into a database using the program Filemaker Pro<sup>TM</sup> (Filemaker, Inc., Santa Clara, CA). Filemaker is a relational database that accommodates the incorporation of large text blocks into data fields, and that permits simultaneous searches on numerous text and numerical parameters. It is easily customized for specific uses, is cross-platform compatible (Macintosh<sup>TM</sup> and Microsoft Windows<sup>TM</sup> PCs) and can be published on the World Wide Web using HTML formats. Filemaker Pro<sup>TM</sup> was thus ideal for the purposes of this project, as it

enables data to be shared among all investigators and is suitable for eventual publication of the data on the Internet. The initial database was constructed using Filemaker Pro 5<sup>TM</sup>, but the software was periodically upgraded over the course of the project, and the current version now runs under Filemaker Pro 9<sup>TM</sup>. The Filemaker database was initially constructed as a repository for the data collected on targeted species in the literature surveys, but over the course of the project lifetime, this database was expanded to include the collection data on the acquired specimens (including herbarium voucher labels), digitized scans of targeted species and associated herbarium labels from the Herbarium Amazonense at UNAP, and records of the fractions generated by chemical-fractionation protocols and the summarized results of radioligand binding.

Based on the data extracted from NAPRALERT<sup>sm</sup>, PubMed, and other data sources, searchable database fields were defined for probable CNS activities (including all of the searched NAPRALERT<sup>sm</sup> activity codes, plus additional activity definitions based on folk uses). Additional fields included information on the plant parts used, modes of preparation, routes of administration, presence/absence of classes of secondary compounds, and results of radioligand receptor assays (Table 2).

## HERBARIUM SURVEY

Species that were targeted for collection based on the data collected from NAPRALERT<sup>sm</sup> and the other literature searches specified were cross-referenced with the genera on file in the Herbarium Amazonense at the Universidad Nacional de la Amazonía Peruana (UNAP) in Iquitos. In some cases, the identical species were found in the herbarium, while in others only related species were found, and in still others, there were no specimens on deposit. If the genus and species of interest was found in the herbarium, or if related species belonging to the same genus were found, the specimens were digitally photographed, and these images, along with the data recorded on the herbarium labels, were incorporated into the database. The herbarium labels in most cases contained information on the location of the collection, the collector(s), date of collection, and, rarely, information on ethnobotanical and/or ethnomedical uses. All of this information

was also incorporated into the database.

**Table 1** Selected NAPRALERTsm Activity codes relevant to Neuropsychiatry (Modified from Lake, 2000)

| CNS activity (NAPRALERT code)        | Number of Cumulative Citations as of 2009 |
|--------------------------------------|-------------------------------------------|
| Anticonvulsant activity (11006)      | 783                                       |
| Narcotic antagonist activity (11020) | 45                                        |
| Antipsychotic activity (11081)       | 24                                        |
| Tranquilizing effect (11041)         | 225                                       |
| Memory-enhancing effect (11044)      | 263                                       |
| Antiaggressive effect (11052)        | 24                                        |
| Antidepressant activity (11062)      | 254                                       |
| Antianxiety activity (11094)         | 29                                        |
| Psychotropic activity (11032)        | 45                                        |
| Hallucinogenic activity (11012)      | 162                                       |
| Monoamine oxidase inhibition (16005) | 127                                       |

**Table 2** Searchable categories defined in the Filemaker™ Collections Database.

|                               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|-------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| CNS Activities                | analgesic; anxiolytic; stimulant; sedative; sudorific; antipyretic; tranquilizer; smoked <sup>a</sup> ; snuffa; epilepsy; tremorogenic; paralytic; memory; geriatric; dementia; depressant; intoxicant; hallucinogen; anticonvulsant; convulsant; headache; narcotic; antitussive; hysteria; insomnia; insanity; nervousness; “susto” <sup>b</sup> ; tremors; vertigo; depression; magical <sup>c</sup> ; tonic; spasmolytic; aphrodisiac; nervous disorders.                                                       |
| Preparation methods           | Decoction; Infusion; Poultice; Topical Application; Baths; <i>Ayahuasca</i> Admixture; Not Specified; Not Processed; Squeezed Juice; Macerate; Powder; Alcoholic Extract.                                                                                                                                                                                                                                                                                                                                           |
| Plant parts utilized          | Wp – whole plant; Ap – aerial parts; Lv – leaves; Bk – bark; Rt – roots; Br – branches; St – stems; Wd – wood; Sd – seeds; Fl – flowers; Ft – fruits; Sp – sap; Lx – latex; Rz – rhizomes; Co – corms; Eo – essential oil; Ns – not specified.                                                                                                                                                                                                                                                                      |
| Secondary compound occurrence | acetogenins; acyclics; alkaloids (any type); benzenoids; betaines; cardenolide glycosides; chromones; coumarins; diterpenes; essential oil; flavonoids; glycosides; indole alkaloids; iridoids; isoflavonoids; isoquinoline alkaloids; lactones; lignans; lipids; monoterpenes; nitrogen heterocycles; non-protein amino acids; phenylpropanoids; polyacetylenes; pyrrolizidine alkaloids; quinoids; quinoline alkaloids; saponins; sesquiterpenes; $\beta$ -carbolines; steroids; triterpenes; unknown; xanthones. |
| Binding profiles <sup>d</sup> | 5HT1A; 5HT1B; 5HT1D; 5HT1E; 5HT2A; 5HT2C; 5HT3; 5HT5A; 5HT6; 5HT7; $\alpha$ 1A; $\alpha$ 1B; $\alpha$ 2A; $\alpha$ 2B; $\alpha$ 2C; D1; D2; D3; D4; D5; DOR; MOR; H2; M1; M2; M3; M4; M5; DAT; NET; SERT.                                                                                                                                                                                                                                                                                                           |

**a** Preparations that were commonly smoked or snuffed were interpreted as likely to display psychoactive effects.

**b** “Susto” is a folk disease commonly recognized in Amazonian ethnomedicine that is similar to generalized anxiety disorder (cf. Logan, 1993).

**c** “Magical” indicates the plant is used in the context of ritual, witchcraft, or sorcery rather than for a specific pharmacological action. It is included here because plants used in this context are often psychoactive or have other CNS activities.

**d** 5HT – 5-hydroxytryptamine, (serotonin) receptor subtypes;  $\alpha$  – alpha adrenergic receptor subtypes; D – dopamine receptor subtypes; DOR, MOR – delta-opiate and mu-opiate receptors; H<sub>2</sub> – histamine-2 receptor; M – muscarinic acetylcholine receptor subtypes; DAT – dopamine reuptake transporter; NET – norepinephrine reuptake transporter; SERT- serotonin reuptake transporter.

## SPECIMEN COLLECTIONS

Specimen collections were carried out in the Loreto province of Peru on several different expeditions between November 2004 and July 2006. The initial focus of the collections was on the acquisition of targeted species that had been identified in the literature surveys and for which location data was available. In addition, other species, not originally on the target-acquisition list, came to our attention in the course of fieldwork, usually as a result of information shared by local informants, and these were also collected when possible. Other targeted species were not collected either because no location data was available, the location of the populations was inaccessible, or the species were not known from the area of collections. Herbarium voucher specimens for each collection were prepared and assigned a unique collection number. Duplicate vouchers were deposited in the Herbarium Amazonense and in the Herbarium of the Bell Museum of Natural History, University of Minnesota. In addition to the vouchers, small samples (~100 – 500 g) of plant materials were also collected for each specimen to provide material for chemical analysis and bioassay. The bulk collections were ground in a ball mill, dried at ~60° C in a forced-convection plant drying room at Gracia Ethnobotanicals, and stored in heat-sealed polyethylene-lined storage pouches (4.5 mil, 10 x 12” or 9.5 x 16”, Fisher Scientific catalog # 01-812F series) until shipment.

## COLLECTION DATA AND HERBARIUM LABELS

The Filemaker™ database program was used to design collection labels, and each collection was assigned a unique collection number. Collection data included the family, genus, species, and taxonomic authority of the collected specimen, the GPS coordinates and other location data, the date of collection, the name of the collectors, the

elevation in meters (where known), common names, the plant parts collected, any pertinent data on the specimen derived from the literature and NAPRALERT<sup>sm</sup> searches (and incorporated from the targeted species in the database), and a cross-reference to NAPRALERT<sup>sm</sup> profiles, if they existed. By designing the labels as a layout in the Filemaker<sup>™</sup> database, it enabled collection data to be easily revised, updated, and selectively searched and sorted. A complete list of all collected specimens is available as supplementary data, posted online at: <http://www.sciencedirect.com/science/article/pii/S0378874110009>

### COLLECTION AND EXPORT AUTHORIZATIONS

Collections in the Loreto region and the export of dried plant biomass and herbarium voucher specimens were carried out under joint authorization from UNAP, Department of Biosciences, and INRENA (Instituto Nacional Recursos Naturales), the Peruvian Department of Natural Resources that has jurisdiction over bioprospecting, export of plant specimens, and scientific investigations of Peruvian biota. Bulk dried samples were shipped to the Department of Chemistry at the University of Minnesota and stored at room temperature until extractions could be carried out. Herbarium voucher specimens were hand-carried to the University of Minnesota and released into the care of Dr. George Weiblen, vascular plant curator of the Herbarium at the Bell Museum of Natural History. A full set of duplicate voucher specimens was deposited in the Herbarium Amazonense at UNAP in Iquitos.

### SCREENING OF EXTRACTS AND FRACTIONS IN RADIOLIGAND ASSAYS

Bulk dried plant specimens were processed into crude extracts in preparation for screening. 20 to 50 grams of the powdered, dried plant material were placed in a 250 mL screw-capped rotary shaker flask, and covered with ca. 150 mL of 1:1 CH<sub>2</sub>Cl<sub>2</sub>:MeOH. The flask was gently agitated on a rotary shaker table for 24 hours. The solvent was decanted, additional solvent was added, and the extraction procedure was repeated for an additional 24 hours. The extracts were combined, and the solvent was removed under vacuum by rotary evaporation. Other investigators have reported

yields ranging from 2 to 16% of the dry weight using a similar strategy (Zhu et al., 1996), so extraction of 50 grams of plant material yields between 1 and 8 g of crude extract. The combined extracts were reduced in volume to ca. 5% of the original volume by rotary evaporation. The concentrated extracts from each collection were transferred to 30 mL screw-capped Nalgene™ vials for storage. Vials were labeled with a collection number keyed to the collection data in the project database, plant part, weight of plant material extracted, and final volume of the concentrated extract. In instances where multiple plant parts were collected (e.g., bark and leaves), each part was extracted and processed separately. Excess dried plant material was resealed in the heat-sealable plastic pouches, labeled, and stored until needed for further extractions.

#### PREPARATION OF CRUDE EXTRACTS FOR SCREENING

Samples were screened using the resources of the NIMH Psychoactive Drug Screening Program (PDSP), first at Case Western University Medical School and, later, after the program relocated, at the Department of Pharmacology in the School of Medicine at the University of North Carolina at Chapel Hill. Samples were submitted to the program in two batches, and preparation procedures were modified for the second batch to address some of the difficulties encountered in screening of the initial batch, in order to improve the reliability of the results. Full details of the sample preparation can be found in the original reference, online at: <http://www.sciencedirect.com/science/article/pii/S0378874110009> via%3Dihub

#### RADIOLIGAND RECEPTOR-BINDING AND FUNCTIONAL ASSAYS

The NIMH Psychoactive Drug Screening Program (PDSP) has published standardized methods for radioligand-binding assays and functional assays (for example see Roth et al., 2002; Shapiro et al., 2003; Keiser et al., 2009). Assays are conducted according to standardized methods, but the details of each assay vary according to the receptor being analyzed. Full details of the methods used in the radioligand receptor assays and the functional assays are described in the PDSP Assay Protocol Book

(<https://pdspdb.unc.edu/pdspWeb/?site=assays> ).

## RESULTS

### ETHNOBOTANICAL CHARACTERISTICS TARGETED VS. ACQUIRED COLLECTIONS

Initial literature and database surveys resulted in the compilation of 258 species targeted for acquisition. Subsequent herbarium surveys and interviews with traditional practitioners resulted in an expanded list of 311 species. 80 species and 62 genera on the original list were collected, and a total of 121 species and 90 genera were collected. The family distribution of the targeted and acquired collections is shown in Figure 1. In general, the most represented families in the targeted list were also the most represented in the acquired collections, with the Apocynaceae, Fabaceae, Rubiaceae, and Solanaceae being the most frequently represented families on both lists.

### FOLK USE CATEGORIES

36 categories of folk use deemed to be indicative of CNS activity were defined in the Filemaker database (Table 2). Of these, the five most frequently represented categories in both the targeted collections and the acquired collections were intoxicants, hallucinogens, analgesics, stimulants, and those used for geriatric purposes (Table 3).

### PHYTOCHEMICAL DISTRIBUTION

Based on published literature, the phytochemical distribution of targeted and acquired collections (Figure 2), show a parallel distribution, with the most frequently represented phytochemical categories being 1. Unknown constituents; 2. Alkaloids of any type; 3. Triterpenes; 4. Sesquiterpenes; 5. Flavonoids; 6. Isoquinoline alkaloids; and 7. Indole alkaloids. The distribution of collections in these categories show approximately the same frequencies with some discrepancies (Figure 2). For example, flavonoids were more frequent in the acquired species than in the targeted species (16.5% vs 12.9%), while species reported to have isoquinoline alkaloids and indole alkaloids were somewhat more frequent in the acquired

species than in the targeted collections (12.4% of acquired species contained isoquinolines vs. 9% of targeted species; 9.9% of acquired species were reported to contain indole alkaloids, vs. 7.4% of targeted species).

### RECEPTOR-BINDING ASSAYS

A total of 228 crude extracts and fractions were screened in the radioligand receptor assays. Of these, 91 samples displayed “hits” in one or more receptor assays, with a “hit” being defined as  $\geq 60\%$  inhibition of the radioactive ligand (Table 4). Table 5<sup>105</sup> presents the data according to the receptor subtypes screened. A total of 39 genera displayed “hits”; Table 6 displays the genera displaying “hits” ranked by the number of active fractions for each genus.

**105.** Table 5 has been omitted for brevity, but can be accessed online in the full paper at: <http://www.sciencedirect.com/science/article/pii/S037887411000913X?via%3Dihub>

Fig. 1 Family distribution of targeted genera, compared to family distribution of collected genera.



## Distribution of secondary compounds in collections

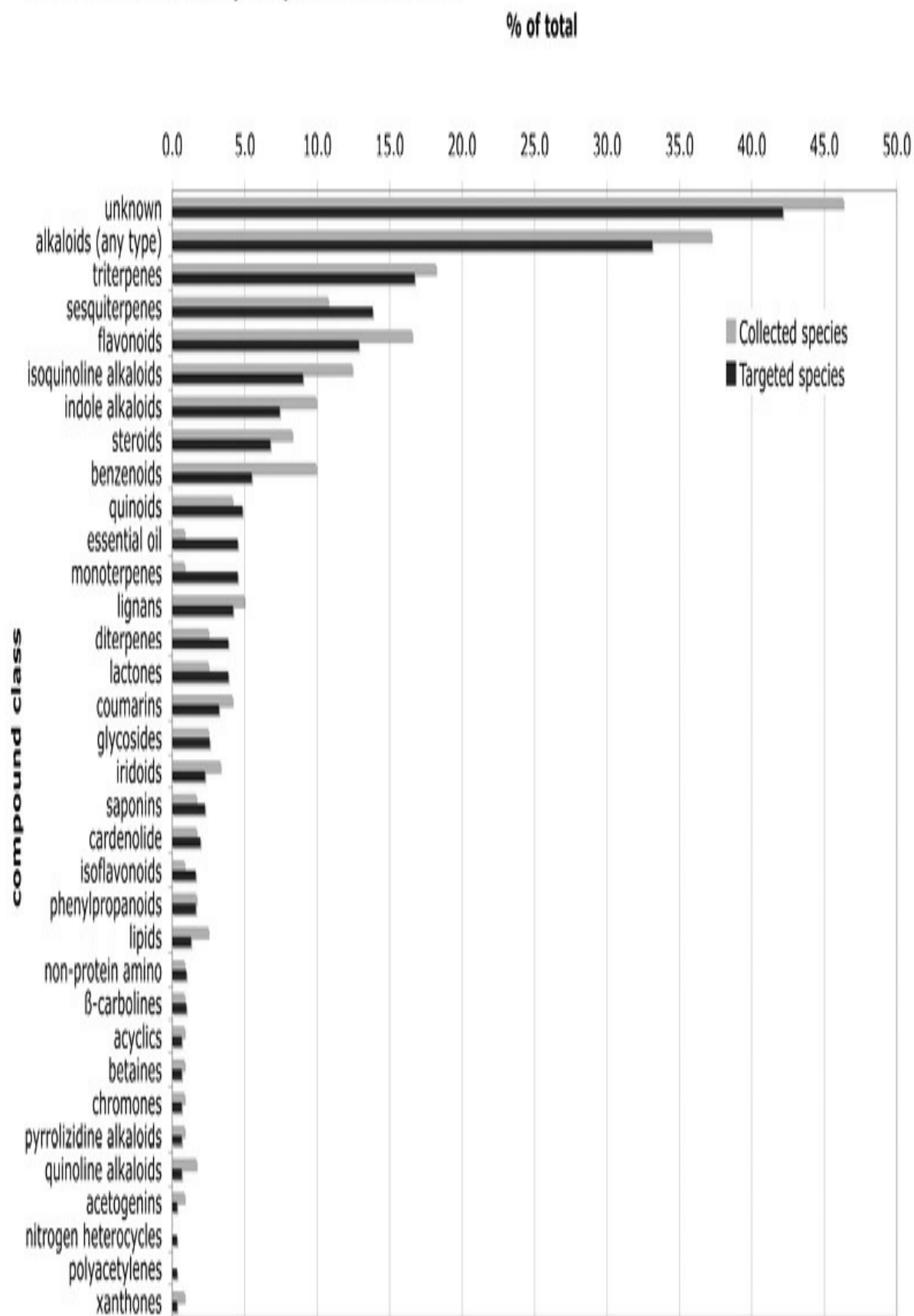
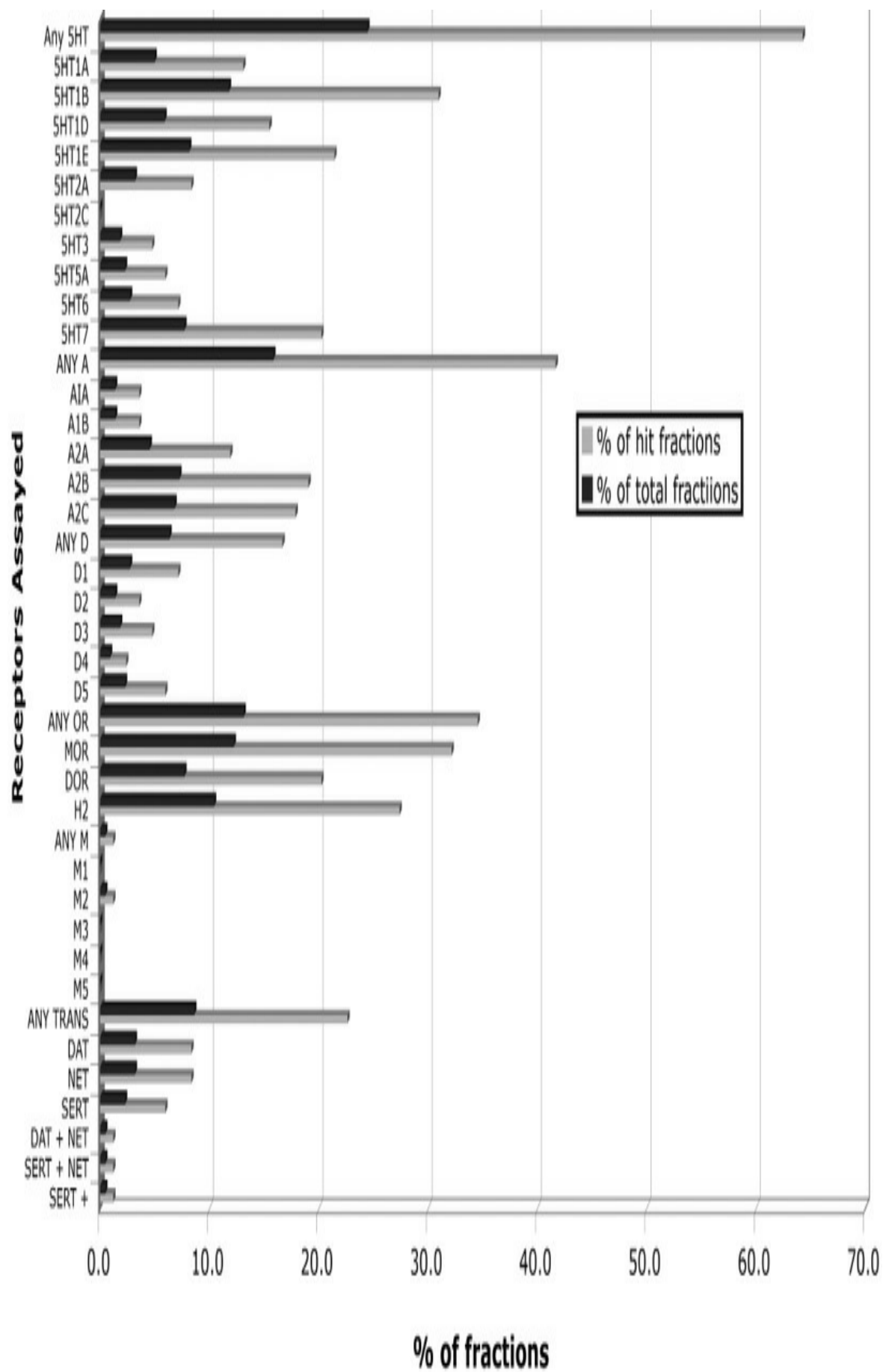


Fig. 2 Distribution of secondary compound classes in targeted and acquired species.

**Table 3** Frequency of folk use categories in targeted and acquired collections

| Folk Use        | Targeted<br>(number) | Targeted<br>(%) | Collected<br>(number) | Collected<br>(%) |
|-----------------|----------------------|-----------------|-----------------------|------------------|
| intoxicant      | 84                   | 27.0            | 29                    | 24.0             |
| hallucinogen    | 76                   | 24.4            | 31                    | 25.6             |
| analgesic       | 61                   | 19.6            | 35                    | 28.9             |
| stimulant       | 51                   | 16.4            | 21                    | 17.4             |
| geriatric       | 47                   | 15.1            | 16                    | 13.2             |
| nervousness     | 41                   | 13.2            | 10                    | 8.3              |
| magical         | 40                   | 12.9            | 20                    | 16.5             |
| antipyretic     | 38                   | 12.2            | 22                    | 18.2             |
| tranquilizer    | 35                   | 11.3            | 9                     | 7.4              |
| insanity        | 35                   | 11.3            | 19                    | 15.7             |
| anxiolytic      | 34                   | 10.9            | 9                     | 7.4              |
| sedative        | 34                   | 10.9            | 9                     | 7.4              |
| headache        | 33                   | 10.6            | 16                    | 13.2             |
| spasmolytic     | 28                   | 9.0             | 8                     | 6.6              |
| dementia        | 26                   | 8.4             | 7                     | 5.8              |
| narcotic        | 23                   | 7.4             | 5                     | 4.1              |
| tonic           | 23                   | 7.4             | 8                     | 6.6              |
| anticonvulsant  | 22                   | 7.1             | 9                     | 7.4              |
| insomnia        | 21                   | 6.8             | 4                     | 3.3              |
| susto           | 20                   | 6.4             | 5                     | 4.1              |
| memory          | 18                   | 5.8             | 6                     | 5.0              |
| depressant      | 16                   | 5.1             | 4                     | 3.3              |
| hysteria        | 16                   | 5.1             | 3                     | 2.5              |
| paralytic       | 15                   | 4.8             | 3                     | 2.5              |
| depression      | 15                   | 4.8             | 9                     | 7.4              |
| snuff           | 12                   | 3.9             | 12                    | 9.9              |
| aphrodisiac     | 12                   | 3.9             | 6                     | 5.0              |
| nerv. disorders | 11                   | 3.5             | 5                     | 4.1              |
| tremors         | 10                   | 3.2             | 5                     | 4.1              |
| sudorific       | 9                    | 2.9             | 5                     | 4.1              |
| epilepsy        | 9                    | 2.9             | 9                     | 7.4              |
| smoked          | 8                    | 2.6             | 8                     | 6.6              |
| vertigo         | 6                    | 1.9             | 1                     | 0.8              |
| tremorogenic    | 5                    | 1.6             | 2                     | 1.7              |

|             |   |     |   |     |
|-------------|---|-----|---|-----|
| antitussive | 4 | 1.3 | 2 | 1.7 |
| convulsant  | 2 | 0.6 | 1 | 0.8 |





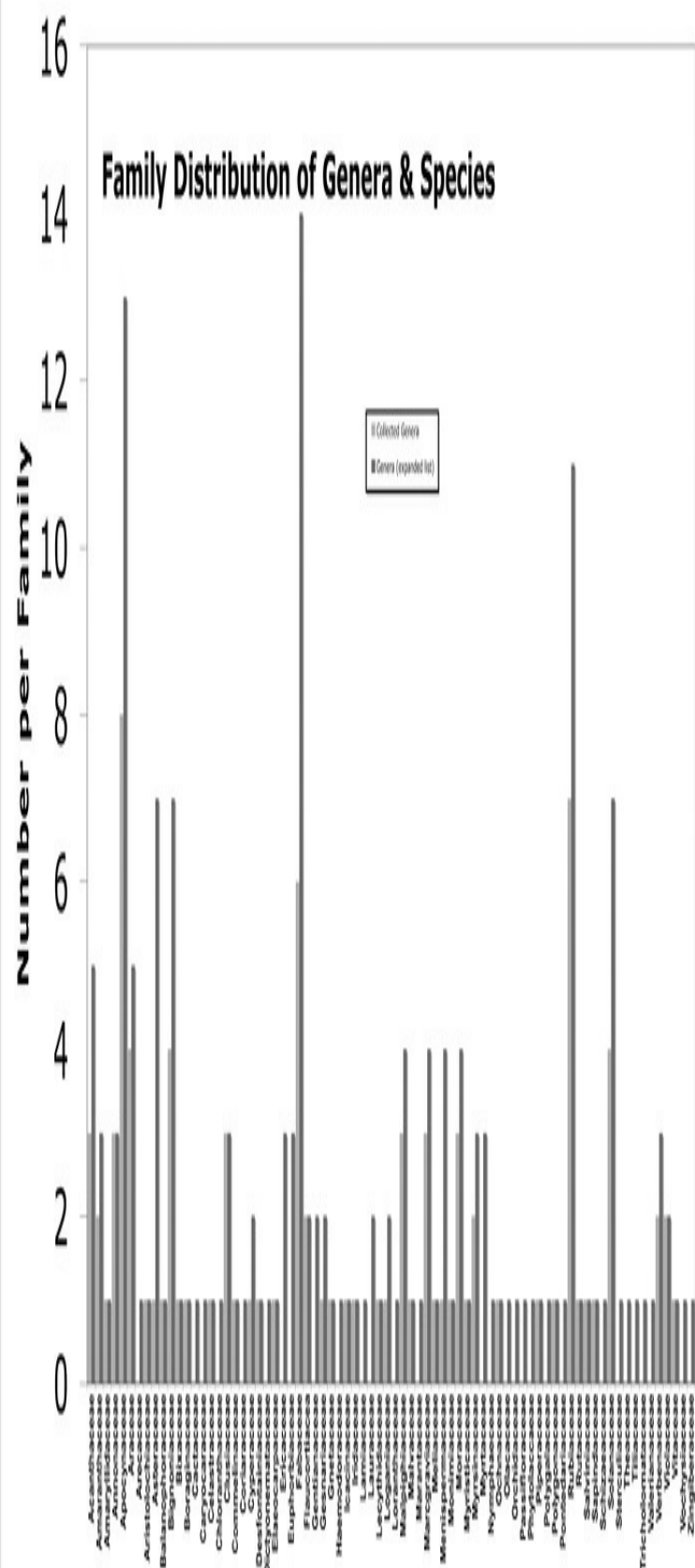


**Fig. 3** Receptor-binding profiles of extracts and fractions.

## DISCUSSION

A major finding of this study is that the largest number of receptor “hits” were concentrated in those genera that characteristically contain indole alkaloids (Table 6); secondarily, the greatest number of “hits” overall were with one or more 5HT receptors (Figure 3). The taxonomic distribution of the collected species corresponded in most respects to that of the species on the expanded list of targeted species. From an expanded list of 311 species and 172 genera, we were able to acquire 121 species in 90 genera. 80 species in 62 genera were on the original list of targeted collections, while 38 species and 34 genera collected were on the expanded target list, but not on the original list. 116 genera, representing 178 species, were on the original list but were not collected. 40 genera and 70 species were collected that were related, but not identical, to species on the original or expanded target list.

Examination of the family distribution of collected and targeted species and genera indicates a fairly good correspondence in both categories, i.e., those families that were most represented in the target list were also most frequent in the acquired collections (Figure 1). The Apocynaceae, Araceae, Bignoniaceae, Fabaceae, Rubiaceae, and Solanaceae were among the most frequently represented families in both the target list and the acquired list. The distribution of the genera and species on the lists appears to be determined by the criteria for folk use (CNS activity) more than the natural distribution of genera and species in the Amazonian biome. Although the families cited above contain some of the largest numbers of species and genera in Amazonian flora, other families are underrepresented in the sample compared to their abundance in the Amazonian flora (Ayala, 2003). Underrepresented families in the target and collection lists include the Asteraceae, Cucurbitaceae, Cyperaceae, Euphorbiaceae, Melastomataceae, Orchidaceae, and Poaceae.

The most frequently encountered categories of folk use based on published reports were similar in both the targeted collections and the acquired collections (Table 3). The most frequent categories in both were intoxicants or hallucinogens, followed by analgesics,

stimulants, and those used in geriatrics. The acquired collections contained a greater percentage of analgesics than the targeted collections (28.9% vs. 19.6% in the targeted collections). The acquired collections also contained relatively greater proportions of “magical” plants, antipyretics, plants used for insanity, and headache remedies than the targeted species, and a smaller proportion of plants used for nervousness, tranquilizers, anxiolytics, or dementia than the proportions represented in the targeted collections. Some folk categories do not have any correspondence to Western diagnostic criteria, for example “susto”, which resembles chronic depression but is not classified as such (Logan, 1993).

**Table 4** Distribution of samples showing “hits” in receptor assays

| Receptors assayed | Number of Samples Displaying “Hits” in Binding Assays |                 |
|-------------------|-------------------------------------------------------|-----------------|
|                   | ≥ 60% inhibition                                      | ≥ 75%inhibition |
| 5HT1A             | 11                                                    | 7               |
| 5HT1B             | 25                                                    | 10              |
| 5HT1D             | 13                                                    | 12              |
| 5HT1E             | 18                                                    | 9               |
| 5HT2A             | 7                                                     | 1               |
| 5HT2C             | 0                                                     | 0               |
| 5HT3              | 4                                                     | 3               |
| 5HT5A             | 5                                                     | 4               |
| 5HT6              | 6                                                     | 2               |
| 5HT7              | 18                                                    | 10              |
| D1                | 6                                                     | 4               |
| D2                | 3                                                     | 2               |
| D3                | 4                                                     | 1               |
| D4                | 2                                                     | 1               |
| D5                | 5                                                     | 2               |
| α1A               | 3                                                     | 2               |
| α 1B              | 3                                                     | 2               |
| α 2A              | 8                                                     | 7               |
| α 2B              | 16                                                    | 4               |
| α 2C              | 15                                                    | 10              |
| DOR               | 17                                                    | 12              |
| MOR               | 29                                                    | 17              |
| H2                | 24                                                    | 17              |
| M2                | 1                                                     | 0               |
| DAT               | 8                                                     | 7               |



|      |   |   |
|------|---|---|
| NET  | 6 | 0 |
| SERT | 2 | 1 |

a Abbreviations for binding sites assayed are listed in Table 2.

The phytochemical distribution of secondary compounds, based on published literature, in the targeted and acquired collections shows approximately the same frequencies, with the most frequent phytochemical categories being 1. Unknown constituents; 2. Alkaloids of any type; 3. Triterpenes; 4. Sesquiterpenes; 5. Flavonoids; 6. Isoquinoline alkaloids; 7. Indole alkaloids (Figure 2). These similarities are probably a reflection of our limited knowledge of the overall abundance of secondary compounds in the Amazonian flora, and are an indication of what has been reported in published literature rather than the actual distribution. There are some discrepancies; for example, flavonoids were more frequent in the acquired species than in the targeted species (16.5% vs 12.9%), while species reported to have isoquinoline alkaloids and indole alkaloids were somewhat more frequent in the acquired species than in the targeted collections (12.4% of acquired species contained isoquinolines vs. 9% of targeted species; 9.9% of acquired species were reported to contain indole alkaloids, vs. 7.4% of targeted species). It is noteworthy that the largest category of secondary compounds in both the acquired and targeted collections is “unknown”, which is a reflection of the paucity of phytochemical investigations in this subset of Amazonian flora, and of the Amazonian flora as a whole. There are some indications of clustering with respect to the phytochemical profiles, in that the largest numbers of overall receptor interactions were samples from characteristically alkaloidal families (Table 6). However, these results should not be over interpreted, since alkaloids were the second most abundant category of secondary constituents in this sample, after “unknown” constituents (2). Since the sample contains such a large proportion for which the phytochemical profiles are “unknown”, it is difficult to gain an accurate picture of the correlations that may exist between phytochemical profiles and receptor interactions.

A total of 228 crude extracts and fractions were generated from the acquired collections, and of these, 91 generated “hits” in one or more receptor-binding assays, with a “hit” being defined as  $\geq 60\%$

inhibition of radioligand binding. This data is summarized and presented in various ways in Tables 4-6<sup>106</sup>. Perhaps unsurprisingly, the greatest number of active fractions (“hits”) was clustered in genera in families that are known to be rich in alkaloids, since these secondary products frequently affect the central nervous system. The 6 top-ranked genera in Table 6 are from alkaloid-rich families, and of these, 3 of the 6 belong to the Apocynaceae, a family that is well known for its abundance of indole alkaloids.

**106** Note that Table 5 is omitted from this paper but available online (vide supra).

**Table 6** Genera displaying “hits” in receptor assays, ranked by the number of active fractions

| Genera                 | Family         | Fractions displaying “hits” | No. of species collected |
|------------------------|----------------|-----------------------------|--------------------------|
| <i>Tabernaemontana</i> | Apocynaceae    | 8                           | 2                        |
| <i>Hamelia</i>         | Rubiaceae      | 7                           | 1                        |
| <i>Potalia</i>         | Gentianaceae   | 7                           | 1                        |
| <i>Ambelania</i>       | Apocynaceae    | 6                           | 1                        |
| <i>Aspidosperma</i>    | Apocynaceae    | 5                           | 1                        |
| <i>Erythrina</i>       | Fabaceae       | 4                           | 1                        |
| <i>Gloeospermum</i>    | Violaceae      | 3                           | 1                        |
| <i>Gnetum</i>          | Gnetaceae      | 3                           | 1                        |
| <i>Sloanea</i>         | Elaeocarpaceae | 3                           | 2                        |
| <i>Byrsonima</i>       | Malpighiaceae  | 2                           | 1                        |
| <i>Cybianthus</i>      | Myrsinaceae    | 2                           | 1                        |
| <i>Eucharis</i>        | Amaryllidaceae | 2                           | 1                        |
| <i>Lantana</i>         | Verbenaceae    | 2                           | 1                        |
| <i>Mimosa</i>          | Fabaceae       | 2                           | 1                        |
| <i>Siparuna</i>        | Monimiaceae    | 2                           | 2                        |
| <i>Teliostachya</i>    | Acanthaceae    | 2                           | 1                        |
| <i>Xylopia</i>         | Annonaceae     | 2                           | 2                        |
| <i>Abuta</i>           | Menispermaceae | 1                           | 1                        |
| <i>Alternanthera</i>   | Amaranthaceae  | 1                           | 1                        |
| <i>Annona</i>          | Annonaceae     | 1                           | 1                        |
| <i>Bixa</i>            | Bixaceae       | 1                           | 1                        |
| <i>Duroia</i>          | Rubiaceae      | 1                           | 1                        |
| <i>Guarea</i>          | Meliaceae      | 1                           | 1                        |
| <i>Indigofera</i>      | Fabaceae       | 1                           | 1                        |
| <i>Justicia</i>        | Acanthaceae    | 1                           | 1                        |
| <i>Lippia</i>          | Verbenaceae    | 1                           | 1                        |
| <i>Mansoa</i>          | Bignoniaceae   | 1                           | 1                        |
|                        |                |                             |                          |

|                     |                |   |   |
|---------------------|----------------|---|---|
| <i>Mayna</i>        | Flaucortiaceae | 1 | 1 |
| <i>Memora</i>       | Bignoniaceae   | 1 | 1 |
| <i>Norantea</i>     | Marcgraviaceae | 1 | 1 |
| <i>Philodendron</i> | Araceae        | 1 | 1 |
| <i>Psychotria</i>   | Rubiaceae      | 1 | 1 |
| <i>Remijia</i>      | Rubiaceae      | 1 | 1 |
| <i>Schlegelia</i>   | Bignoniaceae   | 1 | 1 |
| <i>Sida</i>         | Malvaceae      | 1 | 1 |
| <i>Tovomita</i>     | Clusiaceae     | 1 | 1 |
| <i>Triplaris</i>    | Polygonaceae   | 1 | 1 |
| <i>Witheringia</i>  | Solanaceae     | 1 | 1 |
| <i>Zanthoxylum</i>  | Rutaceae       | 1 | 1 |

The overall distribution of “hits” at all receptors screened is graphed in Figure 3. 91 active fractions displayed inhibition in receptor-binding assays of  $\geq 60\%$ ; over 60% of “hit” fractions (vs. approximately 25% of total fractions) were at one or more 5HT receptor subtypes. Of the 5HT subtypes screened, none of the samples displayed  $\geq 60\%$  inhibition at 5HT<sub>2C</sub> receptors. The most frequent 5HT receptors displaying “hits” were 5HT<sub>1B</sub>, 5HT<sub>1D</sub>, 5HT<sub>1E</sub>, 5HT<sub>7</sub>, and 5HT<sub>1A</sub>, respectively, with all other 5HT receptors screened showing less than 10 “hits” out of the 91 samples screened (Table 4, Figure. 3). More than 10% of samples displayed “hits” at  $\alpha_2A$ ,  $\alpha_2B$  and  $\alpha_2C$  receptors, while less than 5% showed activity at  $\alpha_1A$  and  $\alpha_1B$ -adrenergic receptors. Only about 5% of the sample showed activity at any dopamine (D) receptors; the most frequent dopaminergic receptor showing activity was D<sub>1</sub>, at which 6 out of 91 samples displayed more than 60% inhibition. Over 30% of samples displayed “hits” at  $\mu$ -opiate receptors, and about 20% inhibited binding at  $\delta$ -opioid receptors; altogether, 46 samples gave “hits” at one or both opiate receptors. Histamine H<sub>2</sub> receptors also gave relatively large percentages of “hits” (28%). Surprisingly, only one sample yielded a “hit” on any muscarinic cholinergic receptor (M<sub>2</sub>) (Table 4).

Table 7 shows the distribution of receptor activities with respect to folk classification of the CNS activities of the collections. Analgesia was the most frequent folk use of the collections indicative of probable CNS activity, followed by antipyretics and headache remedies. There does not appear to be any clear correlation between receptor binding and folk uses. The receptor “hits” are distributed in

about the same proportions in all folk categories, with 5HT,  $\alpha$ -adrenergic, and opiate-receptor inhibition the most common, with lower levels of activity at the remaining receptors assayed.

**Table 7** Summary of receptor-binding profiles vs. categories of folk use

| Folk Uses         | 5HT | ALPHA | DA | DOR/MOR | H <sub>2</sub> | M <sub>2</sub> | TRANS | Total |
|-------------------|-----|-------|----|---------|----------------|----------------|-------|-------|
| analgesic         | 25  | 17    | 5  | 13      | 9              | 1              | 4     | 74    |
| antipyretic       | 15  | 13    | 5  | 6       | 10             | 1              | 4     | 54    |
| headache          | 11  | 10    | 5  | 6       | 6              | 0              | 1     | 39    |
| stimulant         | 13  | 5     | 3  | 7       | 4              | 0              | 3     | 35    |
| hallucinogen      | 11  | 5     | 2  | 9       | 4              | 0              | 1     | 32    |
| intoxicant        | 11  | 5     | 1  | 9       | 4              | 0              | 1     | 31    |
| geriatric         | 9   | 5     | 0  | 6       | 4              | 0              | 2     | 26    |
| magical           | 11  | 4     | 1  | 5       | 4              | 0              | 0     | 25    |
| sedative          | 6   | 6     | 2  | 3       | 1              | 0              | 3     | 21    |
| anxiolytic        | 6   | 5     | 2  | 3       | 1              | 0              | 1     | 18    |
| nervousness       | 7   | 5     | 1  | 3       | 1              | 0              | 1     | 18    |
| insanity          | 7   | 2     | 2  | 2       | 2              | 0              | 0     | 15    |
| tonic             | 5   | 2     | 1  | 4       | 3              | 0              | 0     | 15    |
| tremors           | 2   | 3     | 1  | 4       | 2              | 0              | 2     | 14    |
| narcotic          | 2   | 3     | 1  | 4       | 2              | 0              | 1     | 13    |
| memory            | 5   | 3     | 0  | 2       | 1              | 0              | 1     | 12    |
| depression        | 3   | 1     | 1  | 3       | 2              | 0              | 0     | 10    |
| spasmolytic       | 6   | 1     | 1  | 1       | 0              | 0              | 1     | 10    |
| aphrodisiac       | 3   | 1     | 2  | 1       | 0              | 0              | 2     | 9     |
| anticonvulsant    | 2   | 1     | 2  | 2       | 0              | 0              | 1     | 8     |
| sudorific         | 3   | 1     | 0  | 1       | 1              | 0              | 1     | 7     |
| epilepsy          | 1   | 1     | 0  | 1       | 0              | 0              | 1     | 4     |
| tranquilizer      | 2   | 2     | 0  | 0       | 0              | 0              | 0     | 4     |
| dementia          | 2   | 0     | 1  | 0       | 0              | 0              | 0     | 3     |
| insomnia          | 1   | 0     | 1  | 1       | 0              | 0              | 0     | 3     |
| nervous disorders | 0   | 1     | 0  | 0       | 0              | 0              | 2     | 3     |
| antitussive       | 1   | 0     | 0  | 1       | 0              | 0              | 0     | 2     |
| paralytic         | 1   | 1     | 0  | 0       | 0              | 0              | 0     | 2     |
| susto             | 1   | 0     | 1  | 0       | 0              | 0              | 0     | 2     |
| convulsant        | 0   | 0     | 0  | 1       | 0              | 0              | 0     | 1     |
| hysteria          | 1   | 0     | 0  | 0       | 0              | 0              | 0     | 1     |
| depressant        | 0   | 0     | 0  | 0       | 0              | 0              | 0     | 0     |

**Table 8** Receptor profiles of anti-dementia plants reported by Schultes (1993)

| Collection # | Genus & species | Receptor “hits” |
|--------------|-----------------|-----------------|
|              |                 |                 |

|     |                                     |                                                                                                  |
|-----|-------------------------------------|--------------------------------------------------------------------------------------------------|
| 106 | <i>Abuta rufescens</i>              | 5HT1B, 5HT1E, 5HT7, D3, D4, D5                                                                   |
| 067 | <i>Gnetum leyboldii</i>             | 5HT7, MOR, DOR, H2, $\alpha$ 2C                                                                  |
| 105 | <i>Schlegelia macrophylla</i>       | 5HT1B, 5HT1E                                                                                     |
| 087 | <i>Tabernaemontana heterophylla</i> | 5HT1A, 5HT1B, 5HT1D, 5HT2A, 5HT6, 5HT7, $\alpha$ 2A, $\alpha$ 2B, $\alpha$ 2C, DOR, MOR, H2, NET |
| 097 | <i>Tabernaemontana sananho</i>      | 5HT1A, 5HT1B, 5HT1D, 5HT1E, 5HT7                                                                 |

## CONCLUSIONS

The study has shown that interactions with serotonin receptor subtypes were the most common activity detected, followed by  $\alpha$ -adrenergic receptors, opiate receptors, and histamine H2 receptors. In contrast, fewer than 10% of samples showed any interaction with dopamine receptors or monoamine transporters, and only one sample displayed any inhibition of muscarinic receptors (Figure 3 and Table 4). Although inhibition of 5HT receptors was the most common, there were anomalies in this data as well; at the criteria level defined as a “hit” ( $\geq 60\%$  inhibition), none of the samples yielded “hits” at 5HT2C receptors, while 7 samples yielded “hits” at the homologous 5HT2A receptor, although only one of these (*Potalia resinifera* Mart. (syn. *Potalia amara* var. *resinifera* (Mart.) Progel) (Loganiaceae) had an inhibitory value greater than 70%. The factors contributing to this distribution of receptor interactions in this sample may be both co-evolutionary (in the sense that plants evolve biologically active constituents to mediate their interactions with other organisms) and ethnobotanical (in the sense that indigenous populations will introduce an unconscious bias into their selection of plants with CNS activity). Since all of the plants screened have one or more folk uses related to CNS activity, it is unsurprising that there is a spectrum of receptor interactions; what is perhaps more surprising is that there appears to be little correlation between folk uses and receptor interactions; the relative proportions of receptor inhibitions is about the same regardless of the folk use. Analgesics, for example, are not overrepresented by opiate receptor interactions; this category contains nearly twice as many 5HT receptor interactions, although this may be misleading because serotonin is also involved in analgesia. There are also indications of correlations in some cases; nearly 50% of the plants used for “insanity” show inhibition at 5HT receptors; similarly, 41%

of plants used for “memory” and 35% used for “geriatric” show 5HT interactions. Plants used as “hallucinogens” or “intoxicants” have a high proportion of 5HT interactions (~35%), as might be expected since the actions of hallucinogens are known to be mediated through 5HT receptors (Nichols, 2004).

Roth (Roth et al., 2000, 2004a; Gray and Roth, 2007a, 2007b) reviewed serotonin receptor subtypes that show promise for the development of medications to treat cognitive deficits in schizophrenia. These investigators highlight 5HT<sub>1A</sub> partial agonists, 5HT<sub>2A</sub> antagonists, 5HT<sub>4</sub> partial agonists, and 5HT<sub>6</sub> antagonists as likely targets for improving cognition in schizophrenia. On these criteria, 6 species in our collections displayed 5HT<sub>1A</sub> receptor interactions, 5 species displayed 5HT<sub>2A</sub> interactions, and 3 species displayed interactions at 5HT<sub>6</sub> receptors. 5HT<sub>4</sub> receptors were not included among the receptors assayed in this study. The species that displayed inhibition of binding at the receptors mentioned may represent candidates for further investigation.

A review by Gray and Roth (2007b) discusses other receptors that bear investigation as potential targets for cognition enhancers, in addition to the 5HT receptors mentioned above. These include D<sub>1</sub> agonists, D<sub>4</sub> agonists and antagonists, nicotinic  $\alpha 7$  and nicotinic  $\alpha 4\beta 2$  agonists, M<sub>1</sub> and M<sub>4</sub> agonists, M<sub>5</sub> antagonists, NMDA enhancers, glycine transport inhibitors, AMPA/kainite receptors, mGluR<sub>2/3</sub> and mGluR<sub>5</sub> agonists,  $\alpha$ -adrenergic agonists, sigma agonists, and GABA-A agonists and antagonists. Of the receptors mentioned, our collections included 6 fractions that showed inhibition at D<sub>1</sub> sites, and 2 at D<sub>4</sub> sites. 35 samples showed inhibition at one or more A<sub>2</sub> subtypes in binding assays. Only 1 sample was active at any muscarinic site (M<sub>2</sub>) in binding assays; no other samples inhibited binding at other muscarinic sites.

Schultes (1993) reported on 28 species that are used in the Northwest Amazon to treat dementia-like disorders in the elderly. Of the species cited by Schultes, 18 were represented in our collections and 4 displayed inhibition at various receptors, including 5HT, dopamine subtypes, opiate subtypes, and adrenergic subtypes (Table 8). Of the samples screened, various fractions from *Tabernaemontana heterophylla* Vahl (Apocynaceae) (collection # 87) displayed activity at 6 5HT subtypes, 3 adrenergic subtypes,

both opiate subtypes, the histamine H<sub>2</sub> receptor, and the norepinephrine transporter (NET). *Tabernaemontana* is a chemically well-studied genus, known to contain indole alkaloids and with numerous folk uses in Amazonian ethnomedicine (Van Beek et al., 1984). 6 of 8 fractions derived from this species were active in the receptor assays. Another species, *Tabernaemontana* sananho Ruiz & Pavon (Apocynaceae) is not mentioned by Schultes, but fractions showed an inhibition profile similar to *T. heterophylla* at several 5HT receptor subtypes. These results suggest that future investigations should focus on a more complete characterization of *Tabernaemontana* alkaloids at receptor subtypes relevant to cognitive functions.

Other investigators have applied radioligand receptor-binding assays as tools to detect potentially therapeutic activity in medicinal plant extracts (Phillipson, 1999; Sampson et al., 2000; Jäger et al., 2004; Nielsen et al., 2004; Misra, 1998; Zhu et al., 1996), but none have been applied to the investigation of Amazonian ethnomedicines. Moreover, most previous studies have utilized a restricted battery of receptor screens applied to a relatively small number of extracts. The present study is the first to apply an extended battery of receptor assays to a large number (>228) of extracts and fractions derived from 121 species in 90 genera. The data reported here must be considered incomplete, or at least as a work in progress. The results reported highlight both the promise and the limitations of such an approach. It has provided, for example, a picture of the distribution of CNS activity (to the extent that this is reflected in receptor interactions) in a subset of Amazonian flora, sampled according to both ethnobotanical and phytochemical criteria. It has not succeeded in definitively identifying one or more Amazonian species that are certain to lead to the development of medications that will find clinical use for the treatment of cognitive deficits in schizophrenia or dementias. It has, however, identified a subset of species that are promising candidates for further investigation.

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# A Preliminary Report on Two Novel Psychoactive Medicines from Northern Mozambique

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*Dale Millard*

Wasiwaska, Research Center for the Study of Psychointegrator Plants, Visionary Art and Consciousness,  
Florianópolis, Brazil

## ABSTRACT

This communication seeks to report, for the first time on the use of a medicinal plant *Aeschynomene cristata* Vlake for psychoactive purposes. Although several species of *Aeschynomene* are used medicinally in various parts of the world, this is the first report of a member of this genus being used for psychoactive or visionary purposes.

## INTRODUCTION

In February of 2017, the author was asked to join a team of scientists on an exploration trip to Mount Mabu which only became known to the scientific community as recently as twelve years ago. Mount Mabu is the largest of several granitic inselbergs, extending east of Lake Malawi, and north of the Zambezi River into Northern Mozambique. The mountain itself consists of a relatively rare type of wet forest, surrounded by vast *Brachystegia* woodlands. This means that the species of the wet forest have been in isolation for long evolutionary periods [ Bayliss et al, 2014]. This forest has been described as possibly the largest tract of unbroken medium altitude forest in Southern Africa, and is situated at 900 -1400 meters. In the recent past this forest type used to be more common, though due to deforestation largely to support a highly destructive charcoal industry, much has been cleared. The region has received little

scientific investigation, probably due to its remoteness and fact that Mozambique endured civil war from 1977 - 1992. Then in 2013, after 20 years of peace, fighting resumed and is ongoing, making the area potentially unsafe for travel. Since the first trip in December 2005, there have only been ten trips to the region which have revealed both high levels of biodiversity and well as numerous new endemic species of plants and animals. Due to the war, it is believed that many people withdrew into this forest seeking safety. Currently, the people living in villages around the forest are mostly Makua, from the larger Lomwe group. Lomwe, which is also the name of the spoken language, is believed to have originated out of the Congo basin about a thousand years ago. Virtually all inhabitants of this region rely on subsistence farming. The Lomwe are Mozambique's largest matriarchal tribe and are still strongly animist to this day, maintaining their ancestral belief system. Many of the Lomwe believe they originated from a cave on nearby sacred Mount Namuli from where all animals and humans were born. A female foot is said to be imprinted outside the cave. Hence the matriarchal family structure.

## MATERIALS AND METHOD

The author's role in the expedition was to perform the first preliminary ethnobotanical survey of the region, and particularly the wet forest, as virtually nothing is known about the use of the plants from this biome. The study was conducted over a period of 9 days and consisted of formal interviews with healers from the surrounding communities. In addition walks were conducted into the forest where the healers were asked to point out medicines and explain how they are used. Both Lomwe and Portuguese interpreters were present. In total six healers were interviewed regarding approximately 60 plant species used as medicine. It was during these interviews that psychoactive properties of *Aeschynomene cristata* were mentioned by one of the informants. It was decided to devote a two day period specifically to explore the knowledge of this healer, who is the main focus of this communication. Of all the plant medicines observed in the survey, about 25% are ascribed to having magico-medicinal properties, that is, plants that are used in conjunction with a particular ritual or

belief system. Due to this, extra care was taken to exclude other phenomena such as dreams, when questioning healers specifically about possible psychoactive roles of medicines. Plant specimens were collected and positively identified by Hassam Patel of the Zomba Herbarium, Malawi. Samples of *Aeschynomene cristata* root bark were collected and are awaiting chemical analysis.

## RESULTS AND DISCUSSION

The history of this particular healer is worth mentioning. He is an African male, currently 42 years old. At age 20 he began developing psychological problems, which in a western model may be associated with schizophrenia. He described hearing voices and seeing visions. Unable to face his community he escaped to live in the forest. It was here where his deceased grandfather appeared to him, and proceeded to show him which plants to use to heal himself. This kind of initiation whereby a healer receives knowledge or training directly from their ancestral spirits is not a rare phenomenon in Africa. This is significant as it often involves the use of new or different species of plants, as well as unique ways in which the plants are employed.

This healer described the use of two plants species used for visionary or psychoactive purposes. The first being a well known medicinal plant, *Myrothamnus flabellifolius* Welw. also known as the Resurrection plant. This plant is capable of virtual total desiccation, returning to a green vegetative state within an hour of receiving water. This common name is derived from this habit. Locally the plant is known as Thriabe. The young leaves of this plant are smoked by several African tribes for asthma and other chest complaints [Gechev et al, 2014]. Smoking the leaves is reported to have a mild sedative effect which this healer described as being similar to smoking cannabis. This plant has a wide distribution and its use in this way is known to the author to be widespread throughout Southern Africa.

The second plant reported as being used to induce visionary phenomena is known locally as Mwecheche and botanically as *Aeschynomene cristata*. Not much is known of the chemistry of this genus, though several species of *Aeschynomene* are used medicinally throughout the tropics. *Aeschynomene abyssinica* Vatke is a well

known anti-cancer plant in Kenya [ Ochwang'i et al, 2014 ] *Aeschynomene fascicularis* Schltdl. & Cham is used in Mayan traditional medicine to treat cancer [Caamal-Fuentes et al, 2011]. The Buddha Pea *Aeschynomene indica* is a famous herb both in Chinese and Ayurvedic medicine used to treat kidney stones and urinary tract infections. This plant has demonstrated potent antimicrobial activity [Aruna et al, 2012]. The seeds of this plant are known to contain Rotenoids, neurotoxic to pigs and rodents [Haraguchi et al, 2003]. However the benzene and alcoholic extracts of roots of the Asian *Aeschynomene aspera* L. were found to have significant hepatoprotective properties similar to silymarin in a study using carbon tetrachloride to induce hepatotoxicity in rats [Thirupathy Kumaresan and Pandae,2011].

The plant is vetch-like in its growth habits and reaches from 1 – 3 meters in height. The specimens observed were growing in rich, black loam soils on the border between the two vegetations types. The *Aeschynomene* genus consists of about 60 species occurring throughout the world in tropical and sub tropical regions. *A cristata* is found in Africa and Madagascar. Original distribution of this and several species of *Aeschynomene* is difficult to determine as they are believed to be introduced so widely.

The roots are first washed in water to remove soil. Then the root bark is scraped from the roots, dried and pounded to a fine powder. Small quantities (an estimated ¼ teaspoon) of this powder are insufflated into the nose, causing immediate burning and sneezing. The onset is said to begin within 2 minutes, characterised by a buzzing in the ears and difference in visual and colour perception, resolving in approximately ten minutes. When questioned about dosage and safety of this plant, the informant stipulated that it was not dangerous, and if one did this several times the effects would last longer, and if one increased the dosage, it was relayed by direct translation “that one sees small people”, and specifically “not the tall ones!” These little people were described as being at about knee height. Though when questioned further about these little people, it was also stated that “one can see anything according to his own spirit.”

The informant said he did not use this medicine in patients, unless they specifically requested it. He explained that he took this

medicine personally in order to receive answers, to diagnose illness, and to learn which medicine to use for a particular patient. He also mentioned that sometimes he would take it before praying, or before ritual dancing which amongst the Makua is often associated with trance states. It was later confirmed with the hunters who together with the healers are the only people who venture deep into the forest, that they use the powdered root bark blown into the noses of their hunting dogs in order to sharpen their senses. A similar practice has been reported in the Amazon amongst the Ecuadorian Shuar [Bennett and Alarcon, 2015].

Unfortunately due to limited time and bad weather, the author was unable to confirm these psychoactive effects with any other healers of the area. To the author's knowledge, this the first time a member of this genus has been reported to elicit psychoactive effects.

At present the samples collected are awaiting analysis to see if perhaps they contain known or new psychoactive chemistry.

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# Ethnopharmacology – From Mexican Hallucinogens to a Global Transdisciplinary Science

## [Keynote]

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*Michael Heinrich* <sup>I,III\*</sup> & *Ivan Casselman* <sup>II,III</sup>

I. Research Cluster ‘Biodiversity and Medicines’ / Research Group ‘Pharmacognosy and Phytotherapy’, UCL School of Pharmacy, University of London, England

II. Rubia Solutions Inc. Vancouver, Canada

III. Environmental Sciences, Southern Cross University, Lismore, Australia

### ABSTRACT

Psychoactive natural substances have been reported from practically all regions of the world, but Mexican indigenous cultures have played a crucial role having influenced medical, toxicological, biological, chemical, pharmaceutical, and, of course, anthropological research.

Especially in the 1950’s and 1960’s peyotl, teonanacatl and other psychoactives came to the attention of researchers and revelers alike. In this overview we highlight the developments of ethnopharmacology from the initial development of the term until today using one psychoactive species as an example - *Salvia divinorum*. In 1962 “ethnopharmacologists”, Albert Hofmann and R. Gordon Wasson, documented and collected a flowering specimen of *Ska María Pastora* allowing the species botanical description as *Salvia divinorum* Epling & Játiva. Five years later Efron et al. (1967) organised a symposium “Ethnopharmacologic search for psychoactive drugs” which over the next decades would give its name to a discipline which today is much more broadly defined, dealing with local and traditional medicines, their biological activities and chemistry. Globalisation has resulted in a world-wide

commodification of many traditional medicines and psychoactives, as exemplified by *S. divinorum*. This fascinating Lamiaceae has become globally recognized for its best known active constituent salvinorin A, a kappa-opioid antagonist which has a unique effect on human physiology.

While today ethnopharmacology is a thriving discipline, the interest in psychoactive substances is no longer central to the discipline. The search for anti-cancer agents (which also started in earnest in the 1960's) had been of particular relevance and today includes among its many foci:

- The scientific study of local and traditional knowledge not only in remote regions, but for example, also in urban immigrant communities
- Research linking ethnopharmacology to biodiversity research both in terms of a sustainable use of natural resources (ecosystems)
- Pharmacological studies with the aim of understanding the effects of complex mixtures on specific diseases or disease targets
- The safety of herbal medicines
- Anthropological and historical approaches on the use of medicinal and food plants and the link between food and medical uses of plants and fungi.

50 years on ethnopharmacology is very different from what D. Efron and colleagues had envisioned.

## INTRODUCTION

To the best of our knowledge, the term “ethnopharmacology” was first published in 1967 by Efron and colleagues who used it in the title of a book on hallucinogens: *Ethnopharmacological Search for Psychoactive Drugs* (Efron, et al., 1970; Holmstedt, 1967). Thus with this book, we celebrate both 50 years of a ground-breaking symposium and the introduction of a new term. This introduction is much later than, for example, the term ethnobotany which in 1896 was coined by the US-American botanists William Harshberger

describing the study of human's plant use. Both ethnopharmacology and ethnobotany investigate the relationship between humans and plants in all its complexity. "Ethnopharmacology" also replaced the many other terms which had been used previously like "Pharmakoëthnologie" used already by Tschirch (1910) in his classic *Handbuch der Pharmakognosie* or pharmacoetnologia or Aboriginal botany. (cf. Heinrich, 2014).

However, there is considerable variation in terms for what constitutes ethnopharmacology. In a book edited in 2015 by the first author and Prof. Anna Jaeger (Heinrich and Jaeger, 2015), we compiled definitions of ethnopharmacology as they were given by the contributors to this book. The range from definitions which are very much embedded in the:

- Sociocultural sciences [e.g. Dan Moerman (USA): Ethnopharmacology is the study of the way people use plants, informing us about the varying ways people create meaning about these living objects.];

- Biomedical research [eg. Pravit Akarasereenont (Thailand): "A science dealing with the study of the pharmacology of traditional medicine and focusing on the active substances and their pharmacological action." or Thomas Efferth (Germany): "Ethnopharmacology focuses on research on efficacy, safety, and modes of actions of traditional medicines with pharmacological methods."]

In general the multidisciplinary of the field is highlighted very well clearly recognized by [e.g. Tony Booker (UK): The study of the historical and modern interactions between humans and flora, fauna and minerals and how these substances, their extracts and the chemical compounds derived from them, may be utilised to prevent and treat ill-health in people and their dependent animals]. Others stress the link between local and traditional knowledge with research conducted by academically trained investigators, with – in our view – Graham Jones (Australia) expressing it most eloquently and clearly: "Ethnopharmacology constituting a respectful marriage between modern science and ancient wisdom with much to be gained in both directions."<sup>107</sup>

<sup>107</sup>. Note added by Editor, Dennis McKenna. My personal favourite definition is that

proposed by Holmstedt and Bruhn (1983): “The interdisciplinary scientific exploration of biologically active agents traditionally employed or observed by humans.” In my opinion this definition is succinct, specific and sufficient, in that it notes that ethnopharmacology is not restricted to medicines, nor to plants, or to substances ingested, but also correctly restricts the discussion to “traditional use.”

Consequently, ethnopharmacology is not a very sharply circumscribed field of research and is heavily influenced by the academic, cultural and political background of a researcher.

In the beginning, the discipline of ethnopharmacology was focused primarily on the study of the traditional use psychoactive substances. However, the trajectory of this discipline has expanded in to an array of studies. We explore one of the early ethnopharmacological studies, the discovery, description and chemical elucidation of the Mexican Lamiacea *Salvia divinorum*. While this species is not as famous as other Mexican psychoactives such as *Psilocybe* mushrooms, it does demonstrates one of the earliest ethnopharmacological studies, as well as a 50 year trajectory of discovery, from the description of the plant to its genetic profiling.

There can be no doubt that in 2018 ethnopharmacology is a thriving discipline, embedded in a range of larger disciplinary contexts like botany, pharmacy, anthropology, and medicine. Established journals now publish thousands of articles in this field of research and while there are not many institutes that have the term in their name, many groups based in the pharmaceutical, biological, chemical and other schools publish in the field. This is impressive for a field that has had a surprisingly short history.

## THE EARLY YEARS

While research on local and traditional plants dates back many centuries and includes, for example, the many explorers “discovering” exotic treatments, the modern history is a post-World-War II development. The 1950’s and 1960’s saw a dramatic socio-cultural change in “Western” societies. As part of the opening up of the rigid post-WW2 societies, numerous new developments in the cultures including music, the performing, and visual arts, but also tremendous socio-cultural conflicts formed new societal perspective. A key element of this was a fast developing interest in

psychedelic substances, most importantly hallucinogenic plants. For example, in the 1960's and 1970's the psychologist and prolific writer Timothy Leary (1920 - 1996) impacted on the political and societal thinking on mind-altering drugs including most notably LSD and those which were derived from traditional and local knowledge (especially *Psilocybe* spp.). With the group's experiments on psychedelic substances during his "Harvard Years" (1960 – 1963), Timothy Leary may have had more impact on what later one was called ethnopharmacology, than we are aware of.

Cannabis and products derived from it became an important element of this (counter-)culture. A key role in this context played research on and experiences with hallucinogenic plants and fungi from modern day Mexico, The highly toxic *Toloatzin* or Jimson weed *Datura stramonium* L. (Solanaceae) is one of the main and widely distributed hallucinogenic plants and fungi of Mesoamerica (together with peyotl - *Lophophora williamsii* (Lem. ex Salm-Dyck) J.M. Coult., ololiuhqui – *Turbina corymbosa* (L.) Raf. and the mushrooms teonanacatl – *Psilocybe* spp.); all have long traditions of use as hallucinogens. The following example, however, was only discovered by Western societies in 1962 - *Salvia divinorum*. It sparked great interest both in scientific terms and by those interested in its use. While no detailed historical information is available, it is clear that this discovery also contributed to the interest in holding the symposium at the University of California, San Francisco Medical Center (January 28-30 1967) and, therefore, to the book by Efron et al (1967, republished 1970)

## Salvia Divinorum

In 1962, ethnopharmacologists, Albert Hofmann and R. Gordon Wasson, undertook an expedition to Oaxaca, México (Hofmann, 1980; Wasson, 1962). Their main informants in the region became a curandera – Maria Sabina – who later became first persecuted and then famous. She provided the essential link between Mazatec traditional culture and the 'explorers'. On this trip, they recorded several different plants and their use by Mazatec healers. As well as recording the cultural uses, they attended ceremonies, which incorporated the use of *S. divinorum* Epling & Jativa, a member of the Lamiaceae (Labiatae). This expedition contributed much to the

early understanding of the cultural role and use of this species. Wasson and Hofmann were also able to obtain a flowering specimen of this plant, making the scientific description of *S. divinorum* possible (Epling and Jativa 1962; Casselman et al 2014). This “discovery” was met with great excitement and led to a flurry of research in ethnopharmacology, phytochemistry, neuropharmacology and other disciplines.

Many years later, in 1982, Ortega and his team (Ortega, Blount, and Manchand, 1982) isolated and identified the main active compound in *S. divinorum*, salvinorin A. In the early 1990s, the psychoactive properties of salvinorin A were elucidated (Siebert, 1994). With the confirmation of its psychoactivity, the cultural adoption of *S. divinorum* as a “new” psychoactive, outside of Mexico, gained considerable momentum.

## THE BOTANY OF *SALVIA DIVINORUM*

All recorded native populations of *S. divinorum* are in Oaxaca, southern Mexico. This state is bordered by the Pacific Ocean to the west and, in the north, the Sierra Mazateca mountain range. Much of this mountain range is covered by tropical montane cloud forest (Ott, 1995, 1996; Reisfield, 1993), an ecosystem typified by high humidity and persistent cloud cover. Growing in the understory of the forest, *S. divinorum* has been found in several locations between 500 and 1500 meters altitude (Ott, 1995, 1996). Populations of this plant are mostly found near water courses in partial or full shade and grow in moist, nutrient-rich soil. In these conditions, *S. divinorum* grows and reproduces primarily vegetatively, flowering sporadically when enough sun penetrates the forest canopy (Reisfield, 1993).

*S. divinorum* grows up to 1.5 m in height and has a hollow, quadrangular stem, which is green, translucent and crisp (Ott, 1996; Reisfield, 1993). The leaves are 10–25 cm long, 5–10 cm wide, and are opposite on the stem, elliptic in shape and have serrated margins (Epling and Jativa 1962; Ott 1996; Reisfield 1993). Numerous glandular and non-glandular trichomes are present on the leaf surface (Kowalczyk, et al., 2013; Siebert, 2004). The flowers have white corollas with purple calices. The flowers are three to four centimeters in length and grow on panicles of 20 to 30 flowers.

According to reports on wild populations, as well as laboratory experiments, *S. divinorum* does not produce flowers on a regular, seasonal basis (Reisfield, 1993; Valdés, et al., 1987). In Oaxaca, this plant is observed to flower between October and June (Reisfield, 1993). Flowering is initiated by set durations of uninterrupted darkness greater than 12 hours (Reisfield, 1993). In laboratory experiments, it has been found that if plants are exposed to light during a dark period, flowering is aborted and the plant returns to vegetative growth (Reisfield, 1993).

There is limited information on the sexual reproduction of *S. divinorum*, however, it is very adept at clonal propagation both naturally and anthropogenically. On the basis of the reported reproductive behaviour of *S. divinorum*, it has been suggested that the more recent evolutionary trajectory of this plant may have been influenced by humans (Reisfield, 1993). It is hypothesized that *S. divinorum* may have been translocated from its original environment at some point in history, however, this has not been confirmed nor have other populations of *S. divinorum* been discovered in the Americas (Reisfield, 1993). The pollination vector for *S. divinorum* is also uncertain. It has been suggested that the pollination may be ornithophilous (Reisfield, 1993). This is corroborated by the dimensions of the corolla as well as the sugar content and the volume of nectar produced (Reisfield, 1993).

## HISTORY OF *SALVIA DIVINORUM*

Until 1964, the use of *S. divinorum* appears to have been confined to the Mazatecs, an indigenous Mexican group located in northeast Oaxaca. The name Mazatec or Mazateca is said to mean “Lords of the Deer,” and was the name given to this group by the Aztec (Mooney, 1911). After Spanish colonization in the 1500s, the Dominicans and Jesuits began to convert indigenous peoples to Catholicism (Mooney, 1911). Although Spanish attempts at conversion were largely successful, the Mazatec also maintained their traditional beliefs, which are still practiced today (Hofmann, 1990, 1980; Mooney, 1911; Ott, 1996). The Mazatec employ three main plants with psychoactive properties as part of their spiritual practices. These include *Psilocybe* spp. mushrooms, the seeds from *Ipomoea violacea* L. (morning glory) and the leaves of *S. divinorum*

(Allen, 1994, 1997; Foster, 1984; Schultes, 1969). Mazatec use of *S. divinorum* takes place primarily during healing and divination ceremonies, as well as in the training of medical practitioners (Giovannini and Heinrich, 2009).

There are four illnesses for which Mazatecs are known to have used *S. divinorum* (Johnson, 1939; Ott, 1996; Prisinzano, 2005; Valdés, Diaz, and Paul, 1983). First, this plant is often employed to cure eliminatory dysfunction such as diarrhoea. Secondly, people who are near death can be given an infusion of the plant's juices as a palliative, after which it is reported that the patient often recuperates for a short time. Thirdly, *S. divinorum*, in small doses, is used to cure headaches and rheumatism. Finally, it is given to cure a Mazatec illness known as *panzón de arrego* or a swollen belly. This Mazatec illness is believed to be caused by a curse from a brujo, (male witch) someone who practices black or evil magic (Prisinzano, 2005; Ott, 1996; Valdés, Diaz, and Paul, 1983; Johnson, 1939).

*S. divinorum* is tended in secret groves, deep within the forest, by medicinal practitioners known as a *curandero* (male) or *curandera* (female) (Reisfield, 1993). It is planted in rich, black soil at the bottom of a gully, usually in close proximity to a stream (Diaz, 2013). Cuttings can be taken from the mother plant and planted directly into the moist soil, however, this plant will also root itself, if a branch breaks off and falls on the ground (Beifuss, 1997). Although these *S. divinorum* groves may be natural, it is difficult to determine the extent of human influence (Ott, 1996; Reisfield, 1993). The locations are well-protected by each individual *curandero* or *curandera* to avoid theft, and more importantly, contamination by malicious magic (Johnson, 1939). The large, mature leaves of *S. divinorum* are harvested by pinching the petiole of the leaves close to the main stem of the plant. The leaves are either eaten or crushed into a fine pulp using a mortar and pestle, and then infused in water (Campbell, 1997; Valdés, 2001).

Mazatec *curanderos* and *curanderas* are trained through an informal apprenticeship, during which they are led through a series of progressive visions by an experienced teacher (Valdés, Diaz, and Paul, 1983; Diaz 1979). These visions are initiated by the three psychoactive plants mentioned previously and are an integral part



of training. Over a period of two years, *curanderos* and *curanderas* ingest these plants at regular intervals to integrate the knowledge from their experiences into their practice (Valdés, Diaz, and Paul, 1983). Initially, trainees ingest increasingly larger doses of *S. divinorum* leaves, which show them the way to heaven, where the initiated learn from the tree of knowledge (Valdés, Diaz, and Paul, 1983).

During consumption of *S. divinorum*, either the leaves are chewed or the juice from crushed leaves is infused in water and ingested as a liquid (Diaz, 2013, 1979; Valdés, 2001). These ceremonies are led by a *curandero* or *curandera*, and last approximately two to three hours, during which time the participants, who ingested the plant, are guided through different states of consciousness (Schultes, Hofmann, and Rätsch, 2001; Ott, 1996; Valdés, Diaz, and Paul, 1983; Hofmann, 1980, 1990; Estrada, 1977; Schultes, 1976). These ceremonies take place at night in a dark and remote location to prevent disruptions (Valdés, 2001; Valdés, Diaz, and Paul, 1983; Diaz, 1979), as absolute quiet is considered essential to the success of the ceremony. Several leaves are rolled into cigar-shaped tubes, chewed and swallowed. If the participant is unable to chew the leaves or manage the bitter taste, he or she is permitted to drink juice-infused water instead (Estrada, 1977). During each ceremony, there is one person present who does not ingest *S. divinorum*. It is the role of this person to watch over the ceremony and prevent any harm to participants (Diaz, 1979; Valdés, Diaz, and Paul, 1983). After the effects of *S. divinorum* have worn off, the *curandero* or *curandera* will often bathe the participant in the juice of the leaves (Valdés, 2001), which is said to end the effects of the experience (Valdés, Diaz, and Paul, 1983). After the ceremony, participants are “debriefed”; this dialogue helps to explain the meaning of their visions and ensure the success of the ceremony (Diaz, 1979; Estrada, 1977; Hofmann, 1990; Valdés, Diaz, and Paul, 1983).

The Spanish chronicled many of the rituals, which employed psychoactive plants, but very little about *S. divinorum* was recorded. One reason for this could be that the Mazatecs have several names for *S. divinorum*. In their native language it is referred to as Ska Maria Pastora, Ska Maria, Ska Pastora, and in Spanish it is called Hojas de Maria Pastora, Hojas de la Pastora,

Hoja de adivinación, Hierba Maria or La Maria (Valdés, 2001; Valdés, Diaz, and Paul, 1983; Schultes, 1972; Wasson, 1962). The Mazatecs associate this plant with the Christian saint, Mary (Valdés, Diaz, and Paul, 1983), however, the reference to her as a shepherdess is not consistent with Christian mythology (Wasson, 1962). This name may reflect an interpretation of a pre-contact description of the plant that was later incorporated into Christian beliefs (Ott, 1995).

In the scientific literature, *S. divinorum* has not received as much attention as the other plants used by the Mexican indigenous peoples including the Mazatec; the seeds of the morning glory *Ipomoea violacea* and hallucinogenic mushrooms *Psilocybe* spp. (Valdés, 2001; Valdés, Diaz, and Paul, 1983; Schultes, 1970). *S. divinorum* was first mentioned in western academic literature in 1939 by anthropologist J. Johnson (Johnson, 1939). In 1945, B. Reko reported a “magic plant” used by the Mazatecs called “hoja de adivinación” or “the leaf of the prophecy”, indicating that the indigenous people used this plant to produce visions (Valdés, Diaz, and Paul, 1983; Diaz, 1979; Schultes, 1967). Seven years later in 1952, R. Weitlander reported “yerba de Maria” used by *curanderos* in Oaxaca (Weitlander, 1952). The first botanical specimen of *S. divinorum* was collected by A. Pompa, a Mexican botanist. He described this plant as “xka [sic] Pastora” however, he was unable to collect a flowering specimen at the time leaving his collection only identified to the genus level (Pompa, 1957).

R. Gordon Wasson was a very important ethnopharmacologist and chronicler of psychoactive plants, especially those used by the Mazatec people. Wasson is best known for his research on the traditional Mexican use of *Psilocybe* spp. mushrooms. In July 1961, during his second expedition to Mexico, Wasson participated in an *S. divinorum* ceremony along with Albert Hoffman, known for his discovery of lysergic acid diethylamide or LSD (Reisfield, 1993; Hofmann, 1980; Wasson, 1962). In doing so, Wasson and Hoffman were the first western academics to participate in, and record, this ceremony. In December 1962, Wasson and Hoffman successfully collected a flowering sample of *S. divinorum*, which was classified by Carl Epling as a new species (Epling and Jativa, 1962). Contrary to popular belief, the first living *S. divinorum* specimen to be

propagated outside Mexico was not collected by Wasson and Hoffman, but by psychiatrist and ecologist, Sterling Bunnell, who, in 1962, brought back a living *S. divinorum* specimen to UCLA Davis from an expedition to Oaxaca (Siebert, 2003).

Research on the effects of salvinorin A on its molecular target, the kappa-opioid receptor, has been extensive since it represents the only known non-nitrogenous kappa-opioid receptor selective agonist (Casselman, et al., 2014).

In conclusion, *S. divinorum* was “discovered” just five years prior to the symposium on ethnopharmacology. We have no information on the links between these “discoveries” and the developing plans for such a symposium. It may well be timely, to start a historical project on academic and social developments in the USA and beyond driven by the ethnopharmacologic search for psychoactive substances .

## ETHNOPHARMACOLOGY 50 YEARS ON

Returning to the ethnopharmacology at the end of the 2nd decade of the third millennium, ethnopharmacology today has a very different focus and interest. In the years after the symposium, it seems that only limited research was going on, aside from studies on psychoactive plants and fungi as exemplified by *S. divinorum*.

The next key event was the launch of the *Journal of Ethnopharmacology* in 1979, which was founded by Laurent Rivier and Jan G. Bruhn. Here the scope shifted to “a multidisciplinary area of research concerned with the observation, description, and experimental investigation of indigenous drugs and their biological activity” (Rivier and Bruhn, 1979). Eleven years later the 1st International Congress on Ethnopharmacology was held in Strasbourg, France (5-9 June 1990) and since then 18 conferences have been held on four continents, all organized by the International Society for Ethnopharmacology (ISE - <http://www.ethnopharmacology.org/>), which was originally founded in 1990 in Strasbourg. In 2013 the Society for Ethnopharmacology, India was founded affiliated to the ISE.

Research is conducted in numerous institutions and most active are many of the fast emerging economies especially in Asia (most notably China, but also India, South Korea, Thailand, and other

ASEAN countries, some African (South Africa) and American countries (esp. Brazil). Clearly, the *Journal of Ethnopharmacology* is the leading journal in the field today. In its first year (1979) 29 articles were published, ten years later (1989) this had risen to 85, in 1999 to 205, and in 2009 to 465, with 2016 seeing 649 published articles. Overall, at the time of writing (August 2017) just over 9600 articles have been published in the *Journal of Ethnopharmacology* alone.

The main areas of research today are on antioxidant, anti-inflammatory and anticancer agents (Table 1). The vast majority of these are *in vitro* or *in vivo* studies. In recent years more clinical studies on traditional preparations (often small and not well designed) have also been conducted. Studies describing the use of medicinal and other useful plants are another element of research in the field of ethnopharmacology, and these are often conducted with the goal that they lead to an experimental study of some of these botanical drugs (cf. Heinrich, et al., 2017). At the same time, it is noteworthy that psychoactive and other effects on the CNS have not been of that much importance (Yeung et al 2018). However, one must also acknowledge that this measure (i.e. keywords used in Medline) is a relatively crude one, most importantly, because research which later on focuses on pure compounds or well-defined extracts may not be coded in such a way that it is visible in this comparison.

|                  |      |                        |     |
|------------------|------|------------------------|-----|
| Antioxidant      | 2057 | Malaria                | 588 |
| Inflammation     | 2054 | Urinary                | 411 |
| Cancer           | 2026 | Central nervous system | 310 |
| Infecti\$        | 1971 | CNS                    | 165 |
| Food             | 1600 | psychoactive           | 62  |
| Diabetes         | 1546 | hallucinogen\$         | 64  |
| Skin             | 1089 | Cosmetic\$             | 188 |
| Gastrointestinal | 826  | Fertility              | 156 |
| Respiratory      | 638  | aphrodisia\$           | 111 |

**Table 1** Main topics covered in ethnopharmacological research (number of hits): Medline database search (13/05/2017) combining “Ethnopharmacology or traditional medicine” with specific therapeutic areas as specified.

(Ethnopharmacology or traditional medicine): 21,697 [Ethnopharmacology only: 11,607] and .....

## CORE CHALLENGES

Plants (and animal) based medicines are an integral part of indigenous medical systems in many regions of the world, and form a part of the traditional knowledge of a culture. While the focus of the symposium which gave ethnopharmacology its “modern” name and the current areas of research differ, it is the conviction of the authors of this paper, that the commonality is in the hope that this research will not only provide scientific evidence both in socio-cultural as well as in biomedical terms but that it will help in empowering people, recognising their autochthonous traditions and enabling them to make the best use of such knowledge.

A key criticism the field had to engage with is the accusation of exploiting local and traditional knowledge without fair and appropriate benefits to the regions of origin and the original keepers of this knowledge and practice. However, scientists have been the first to highlight the inextricable link between cultural and biological diversity. In 1988 a group of dedicated scientists involved in research on local and traditional uses of plants and biodiversity conservation and with strong interest in supporting indigenous and local peoples called for the recognition of indigenous rights and for increased support for research on ethnobiological inventories, on conservation and management programmes – resulting in the *Declaration of Belem* (Posey and Dutfield, 1996). Four years later, in 1992, the Convention on Biological Diversity (Rio Convention) was signed and has since been amended in numerous treaties and protocols, most recently (2010) the Nagoya Protocol (*Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from their Utilization (ABS) to the Convention on Biological Diversity*). This development is both driven by the historical experience of many countries, and as importantly, indigenous peoples in exploitative extractions of biodiversity. Ethnopharmacology was one of the disciplines both involved the debate and affected by the resulting legal changes. 25 years after the Convention on Biological Diversity and 50 years after San Francisco conference that led to a named new field of research, there are still no examples where research and the requirements for benefit sharing have resulted in concrete and long term benefits to the regions or countries of origin.

In the last 25 years, numerous efforts have focused on translating the principles of this treatise into best practice. However, examples of problematic or poor practice also abound. We continue to have a very complex and critical debate about who benefits from this research and on how we best follow the ethical guidelines which in this field are most prominently, based on the Convention on Biological Diversity (the Rio Convention, 1992) and subsequent agreements. An understanding of these efforts needs to be based on the fast changing framework, and for example, the Sustainable Development Goals directly impact on the research and development needs globally. Consequently, modern ethnopharmacological research provides new evidence for old preparations and contributes to primary health care (Heinrich 2010). How to best achieve this is still in its infancy and we – as scientists – have still not achieved large scale contributions to improving healthcare globally.

In this regard ethnopharmacology is embedded in a wider debate about the historical and future role of traditional medicines and medical systems globally. In 2016 some systems of traditional medicine (TM) were included in the 11th edition of the International Classification of Diseases (ICD-11), providing a strong impetus both for closer links between traditional medicines and biomedicine, but also adding new responsibilities to practitioners of TM and to those who investigate such medical systems

Ongoing debates relate to best practice in the field (e.g. Cos, et al., 2006, Heinrich, et al., 2017). Here concerns about what constitutes best practice in terms of concepts and methods are addressed and clearly, there is a need to improve the methods we use in data acquisition and analysis. These debates are shared with many other fields of research, and, for example, best practice in pharmacological research is an important concern in many areas of the discipline. Biomedical research that cannot be reproduced or which is of poor quality or which is poorly reported will ultimately undermine the credibility, relevance, and sustainability of the research process in general (e.g. Mullane, et al., 2015).

## CONCLUSION

This volume celebrates the fiftieth anniversary of a very important

conference, and in this paper, we have looked beyond the scope “ethnopharmacology” covered at its start. While one must acknowledge that psychoactive natural substances are no longer at the center, the detailed look at the history of the discovery of *Salvia divinorum* by Western science and society has been an important driving force not only leading the conference (Schultes, 1967), but has continued with a flurry of neuropharmacological research on the species and its active metabolites. As such it exemplifies how ethnopharmacology links the study of local knowledge and practices and bio-scientific and biomedical investigations. Today’s research is thriving but also the conflict exemplified in the history of “discovering” and researching *Salvia divinorum* are a part of the current scenario. Research in ethnopharmacology must, by definition be interdisciplinary, or preferably transdisciplinary, and applying these findings in prevention and treatment should be an element of such research.

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# AFTERWORD

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An oft-quoted aphorism attributed to the anthropologist Margaret Mead proposes that “one should never hesitate to follow a small group of individuals committed to change as that is the only way in which most change actually happens.”

The scientists who attended and spoke at the first “Ethnopharmacological Search for Psychoactive Drugs” (ESPD) symposium at the UC Medical Center were one such group. They had all been inspired and enlightened by sacred plant potions and other magical chemicals they had imbibed over the years. These researchers knew that there were other ways of knowing; they knew that indigenous peoples understood plants in ways they themselves did not. These scientists knew that there were enchanted plants and animals and fungi still waiting to be discovered; and they knew that hallucinogenic plants, in particular, were vegetal scalpels that shamans employed to dissect, analyze, diagnose, treat, and often cure the ailing human mind and spirit.

These beliefs were well outside the mainstream of western science and medicine in 1967, but have stood the test of time. Psychedelic plants are increasingly accepted as legitimate objects of study and wonder, with the understanding that some of these “new” mind-altering compounds may well soon take a position of honor alongside Mother Nature’s other greatest healing gifts such as ACE inhibitors, antibiotics, aspirin, beta blockers, and statins.

The 2017 ESPD 50 Symposium marked the 50th anniversary of this historic gathering — scientists and researchers traveled from the far corners of the earth to historic Tyringham Hall, Buckinghamshire, to compare notes, discuss results and honor our predecessors. As in the first meeting, the primacy of indigenous wisdom regarding plants and their potential healing benefits were featured or mentioned in almost every presentation. Of particular note this time were rich and detailed accounts of “new” bioactive compounds that were little known or appreciated outside traditional societies in 1967: iboga, kratom, hallucinogenic frog peptides, and ayahuasca admixtures.

Much of the discussion at the recent conference centered not only on the historical use of plants like ayahuasca and peyote, but how the entheogenic compounds they produce are now being employed in clinical settings to treat intractable or even “incurable” afflictions like depression, drug addiction, end of life anxiety, infertility, PTSD, and others – sometimes with promising results.

We discussed the great irony that, at the same time that the world awakens to these biological wonders, the forests and the cultures that know them best are being obliterated at an ever-increasing pace. Speakers at ESPD50 and other attendees departed Tyingham with a redoubled sense of purpose: to further spread the “ethnopharmacological gospel” about the healing power of these plants, animals and fungi; to encourage further scientific research and documentation of these therapeutic experiments and successes; and to fight against the destruction of these species and the forced homogenization of these tribal cultures just as we come to appreciate this healing wizardry as never before.

*Mark J. Plotkin*

Amazon Conservation Team, Kwamalasamutu, Suriname