

MUSHROOMS:

A WEALTH OF NUTRACEUTICALS AND
AN AGENT OF BIOREMEDIATION



Editors:

**Mohan Prasad Singh
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Mushrooms: A Wealth of Nutraceuticals and an Agent of Bioremediation

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FOREWORD

Limited data is available worldwide in the area of mushroom research. There is a strong need to explore the various nutraceuticals in mushrooms. Lifestyle diseases like obesity, diabetes, and atherosclerosis are very common nowadays. Researchers worldwide are working on the edible components of daily diets that can improve the chances to overcome the rate of lifestyle diseases in common people. Polysaccharide like β -glucans, is the very important nutraceuticals in this respect that have been explored recently for their therapeutic potential. Various nutraceuticals having potent medicinal properties have been discussed in this book. In this book, the editor included the chapters in a sequence-wise manner. Initially, the medicinal properties of different edible and non-edible mushrooms have been mentioned. Diabetes is the next area that is explored in this book. The treatment of both type I and type II diabetes by mushrooms and their nutraceuticals has been included in this book. The authors of this book show their hard efforts to accumulate all the information related to the therapeutic potential of mushrooms. Cancer is the next centre of attraction and one of the major portions of this book written by several authors. Anticancer properties are very well fully discussed in a couple of chapters. Figures and tables are well positioned in this book. Antimicrobial properties also have been well written in a single chapter of this book. The last portion of this book emphasizes the bioremediation aspects of various mushrooms. Overall, this book offers a complete package that includes the therapeutic and bioremediation properties of various mushrooms. All these chapters are very vital for the readers and are written in a very comprehensive manner to maintain the interest of the readers. References are recent and well-arranged in a comprehensive manner. The editor has done a fantastic job of editing this book by pinpointing and revising the major areas of this book.

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PREFACE

Mushrooms have been an important source of nutraceuticals from the beginning, containing various nutraceuticals, like β -glucans, lectins, unsaturated fatty acids, phenolic compounds, tocopherols, ascorbic acid, and carotenoids. These nutraceuticals offer significant therapeutic potential for the treatment of a number of lifestyle diseases like obesity, diabetes, heart disease, stroke, etc. In addition, the mushroom also can be utilized as an important agent of bioremediation. Mushroom exhibits strong high metal absorption capacity and can be utilized to improve the fertility of aquatic and land ecosystem.

This book comprises a new efficient treatment strategy for the treatment of various lifestyles and other most common diseases with the help of mushrooms and their nutraceuticals. This book also shows the efficient bioremediation strategy exhibited by most common mushrooms. The starting chapters of this book exhibit the nutritional and medicinal values of various edible and non-edible mushrooms. In addition, the therapeutic activity of various bioactive components of mushrooms also has been explored in these starting chapters. Antidiabetic properties of different mushrooms are also explored in the starting chapters of this book. For both type I and type II, the therapeutic potential of mushrooms have been included in this chapter. In the middle of the chapters, the anticancer properties of various edible and non-edible mushrooms have been thoroughly discussed in this book. Various nutraceuticals present in different edible and non-edible mushrooms offer considerable anticancer properties, which are discussed in these middle chapters. A good number of figures and tables has been included regarding the anticancer properties of different mushroom and their nutraceuticals. In the last section of this book, some *in silico* approaches by utilizing mushrooms to treat various diseases have been included. Some of the last chapters also exhibited the application of fungal xylanase enzymes. One chapter in the last section also shows the antimicrobial properties of various mushrooms. A major portion of the last chapters explores the bioremediation properties of various mushrooms.

Overall, we can say that this book offers a combo pack of the treatment of lifestyle diseases along with an agent for bioremediation that shows a strong capacity to improve the fertility of aquatic and land ecosystems. This book attracts researchers worldwide working on the therapeutic potential of mushrooms and their nutraceuticals. In addition, students are also interested in this book to see the therapeutic activity of mushrooms. Thus, this book will be a complete package for researchers, scientists, and students working in the field of mushroom research.

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CHAPTER 1

Nutritional and Medicinal Values of Mushroom

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Abstract: Humans have ingested both wild and farmed mushrooms for their nutritional and therapeutic properties. Mushrooms are a good source of protein, carbohydrates, and dietary fiber compared to energy and fat. They are rich in vitamins like riboflavin, niacin, and folates, as well as minerals and trace elements like potassium and copper. Due to their distinct flavor, they have been eaten as food for ages. Aside from being a nutrient-dense diet, certain mushrooms are also considered a rich source of physiologically active chemicals with potential therapeutic value in Chinese medicine. Phenolic chemicals, sterols, and triterpenes are examples of bioactive secondary metabolites that occur in mushrooms. Mushrooms are essential in traditional medicine for their healing powers and characteristics, as well as their long history as a food source. It has been shown to have positive benefits on health and the treatment of certain ailments. Mushrooms have a variety of nutraceutical qualities, including the prevention or treatment of Parkinson's disease, Alzheimer's disease, hypertension, and stroke risk. Due to their antitumoral properties, they are also used to lower the likelihood of cancer invasion and metastasis. Mushrooms are antimicrobial, antioxidant, immune system boosters, and cholesterol-lowering agents, and essential bioactive compounds. Mushrooms and mushroom derivatives may have health benefits if included in our daily diet.

Keywords: Bioactive compounds, Food supplements, Medicine, Mushroom .

INTRODUCTION

As the world's population grows, so does interest in the production and subsequent use of mushrooms as a food source. Since 1990, the mushroom industry has gotten a lot of attention, which has resulted in a significant increase in production. In recent years, mushrooms have emerged as one of the most important sources of functional foods and medications [1]. The popularity of edible mushrooms has grown as a result of their taste, flavor, and nutritional value [2, 3]. Mushrooms are superior to animal proteins and other animal products, as evidenced by several previous research [4]. However, distinguishing edible and medicinal mushrooms is difficult since many popular edible species have thera-

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peutic characteristics, and numerous medicinal mushrooms are also edible [1]. *Agaricus bisporus* is the most widely farmed fungus, followed by *Lentinus edodes*, *Pleurotus* spp., and *Flammulina velutipes*. Mushroom output is steadily increasing, with China being the world's largest producer [5, 6]. Wild mushrooms, on the other hand, are gaining popularity due to their nutritional, sensory, and, most importantly, pharmacological properties [7].

Mushrooms are the fruiting structures of specialized fungi that can break down organic matter and recycle nutrients again in the soil. These fungi can turn lignocellulosic waste into lucrative protein-rich biomass that contains all of the needed elements. The use of mushroom fungi to convert leftovers reduces pollutants in the atmosphere while also acting as fertilizer, animal fodder, soil conditioner, and bioremediation [8]. Photosynthesis and agro-industries produce almost 200 billion tonnes of organic matter every year [9]. Firstly, mushroom cultivation began in the caves of France. In 600 AD, the Chinese attempted it again. In 1978, it produced only 60,000 tonnes. Following that, artificial mushroom cultivation began in China and Japan. Over the last 55 years, innovative and simple cultivation technologies have been created, resulting in a large increase in mushroom production from 0.30 million tonnes in 1961 to 18.58 million tonnes in 2016 [10].

China's oyster mushroom (*Pleurotus ostreatus*) is the world's third most extensively grown fungus [11]. In India, it is widely used by women's self-help groups on a small to medium level. It is presently quite popular in practically all of India's states, which have diverse climatic circumstances. The Chinese mushroom (*Volvariella volvacea*) is another tropical mushroom that has taken over Odisha and may be found in every corner of the state. It is the world's sixth most popular mushroom [12]. In India, the button mushroom has a significant market share maximum and makes up roughly 80% of the overall mushroom population manufacture. Tropical mushrooms, such as *Pleurotus* spp., *Volvariella volvacea*, and *Calocybe indica*, showed 20% of total production and are grown virtually all year in different parts of the country. The Indian subcontinent is recognized for its diverse agro-climatic regions and ecosystems that support various mushroom species [13].

Mushrooms may be a new source of antimicrobial chemicals, primarily secondary metabolites as well as primary metabolites. The best-researched species, *Lentinus edodes*, appears to exhibit antibacterial activity against bacterial strains [14]. They have a high nutritional value because they are high in protein, contain a high quantity of vital amino acids and fiber and are low in fat but high in critical fatty acids (Fig. 1).



Fig. (1). Nutritional and medicinal properties of mushrooms (Adapted from- www.mushroom-appreciation.com).

NUTRITIONAL COMPOSITION OF MUSHROOM

Carbohydrates make up the majority of mushroom fruiting bodies, for 50% to 65% of their dry weight (Table 1). Free sugars account for around 11% of total sugars. *Coprinus atramentarius* contains 24 percent carbohydrate by dry weight [15]. Mannitol, commonly known as mushroom sugar, accounts for approximately 80% of free sugars, making it the most prominent. A fresh mushroom contains 0.9 percent mannitol, 0.28 percent reducing sugar, 0.59 percent glycogen, and 0.91 percent hemicellulose [16].

Protein is a significant component of mushroom dry matter. Mushroom protein concentration is affected by substratum composition, pileus size, harvest period, and mushroom species [17]. Mushroom protein level has also been noted to fluctuate from flush to flush. On a dry weight basis, the protein content in the mycelium of *A. bisporus* is 32%-42%. Mushrooms have a higher protein content than most other vegetables and wild plants. Literature survey illustrated the 14.71 to 17.37 percent protein found in the fruiting bodies of *Lactarius deliciosus* and *Lactarius sanguifusus* where as 5.20 to 18.87 percent protein in the fruiting bodies of *L. deliciosus* and *L. sanguifusus*, correspondingly [18] (Table 2).

Table 1. Nutritional composition of fresh mushrooms.

S. No.	Components	Weight (%)
1.	Water	87.5
2.	Carbohydrates	8.5
3.	Proteins	4.6
4.	Crude fibres	0.9
5.	Fat	0.11
6.	Ash	1.3
7.	Lipids	0.21
8.	Minerals	0.79

Table 2. Approximate composition of some edible mushrooms.

S. No.	Species	Carbohydrate (%)	Fat (%)	Moisture (%)	Ash (%)	Protein (%)
1.	<i>Boletus reticulatus</i>	37.17	2.89	8.01	15.29	36.67
2.	<i>Pleurotus ostreatus</i>	62.27	3.21	10.31	7.25	16.96
3.	<i>Tricholoma myomyces</i>	53.83	3.29	9.03	15.46	18.40
4.	<i>Lactarius salmonicolor</i>	67.18	1.00	8.48	5.64	17.70
5.	<i>Russula anthracina</i>	51.93	9.46	7.24	7.71	23.66
6.	<i>Amanita ceciliae</i>	42.81	5.91	9.34	10.75	31.20
7.	<i>Polyporus squamosus</i>	65.24	3.98	10.32	7.14	13.32
8.	<i>Lactarius deliciosus</i>	51.54	7.38	7.93	6.58	26.57

Compared to carbohydrates and proteins, the fat content of mushrooms is low. Unsaturated fatty acids make up the majority of the fats found in mushroom-fruited bodies. *Suillus granulatus* has a fat content of 2.04%, while *Suillus luteus* has a fat content of 3.66 percent, and *A. campestris* has a fat content of 2.32 percent. Linolenic acid, an important fatty acid, is abundant in mushrooms. Mushrooms are an excellent source of lipids and minerals. Unsaturated fatty acids make up the majority of the fat fraction in mushrooms [19].

Mushrooms, in particular, are a good source of vitamins. Wild mushrooms have substantially higher levels of vitamin D2 than dark-produced *A. bisporus*. In mushrooms, minor vitamin B and C levels are also present, but they are deficient in vitamins A, D, and E [20]. Mushrooms are known for having high levels of mineral elements that are necessary for human health [21]. Heavy metals have the propensity to accumulate in mushrooms [22]. The mineral content of a mushroom is determined by the kind, stage, and diameter of the mushroom's fruiting body. It

also depends on the sort of substratum used to cultivate mushrooms. Wild edible mushrooms have a higher mineral content than produced ones.

MEDICINAL ATTRIBUTES OF MUSHROOMS

The United Nations' third essential Sustainable Development Goal is good health and well-being. The foremost diseases, such as malignancies, diabetes, cardiovascular, stroke, and high blood pressure, which are influenced by changes in lifestyles and nutritional consumption, are now freely and publicly discussed. As a result, there is a pressing need to improve our information and expertise to provide an effective worldwide response [23].

Although mushrooms' medical potential has been recognized for millennia, their therapeutic effects are largely unknown and undiscovered. Mushrooms enrich or complement human food, and their particular chemical compositions also benefit some groups of people suffering from physiological illnesses or ailments. Surgery, radiotherapy, and chemotherapy are the most common treatments for cancer, sometimes known as the “captain of death” Mushrooms provide a novel therapeutic option in the form of immunotherapy. Mushrooms offer a great deal of medical benefits [24]. Mushrooms' biologically active chemicals have medical effects on their consumers.

Currently, more than 20 therapeutic mushrooms are being grown and sold. *Ganoderma lucidum*, *Hericium erinaceous*, *Cordyceps sinensis*, *Lentinula edodus*, and *Schizophyllum commune* are the most valuable mushrooms. *Lentinula*, *Hericium*, *Grifola*, *Flammulina*, *Pleurotus*, and *Tremella* are edible mushrooms with medicinal characteristics [25]. *Ganoderma lucidum*, also called a king of mushrooms, and *Coriolus Versicolor*, are two other mushrooms that are only renowned for their therapeutic capabilities. Due to their harsh texture and bitter taste, they are not edible [26].

Mushrooms offer a great deal of medical benefits. Their biologically active chemicals have medical effects on their consumers. Polysaccharides, triterpenoids, Lentinan, Polysaccharide Krestin (PSK), Peptides, and Entadenine Butyric Acid are among the bioactive chemicals. Proteoglycan and -d glucan containing heterosaccharide chains of xylose, mannose, and galactose are the bioactive fractions of polysaccharides [10].

Antitumor activity is the most important therapeutic action of mushrooms and their metabolites. Mushrooms do not have a direct tumor-killing impact. They essentially act as biological response modifiers (BRM). Immunopotential and immunological modulation are how BRM works (NK Cell). Once mushroom bioactive is used with actinotherapy and chemotherapy in cancer patients, the

negative effects of those treatments are reduced. Another significant function of therapeutic mushrooms is their anti-oxidant properties [27, 28].

The discovery of chemical components derived from the mushroom is beneficial for the worldwide pharmaceutical sector. *Cordyceps* spp. illustrates how *Cordyceps* spp. has become popular among global experts, and researchers are now interested in the entire “Cordyceps universe” [29]. The “turkey tail” mushroom *Trametes Versicolor* treats intestinal, lung, and breast malignancies. *Schizophyllum commune* (split-gill polypore mushroom) and *Lentinus edodes* (shiitake mushroom) are used to treat stomach cancer and cervical cancer [30].

CONCLUSION AND FUTURE PROSPECTS

As a result of their potent medical characteristics, including anticancer, antioxidant, anti-diabetic, antibacterial, and anti-obesity action, mushrooms are becoming increasingly popular. This fungus has recently been shown to contain tyrosinase and ergothioneine, making it more valuable for nutritional and therapeutic uses. However, researchers still have room to investigate the mushroom's cosmeceutical qualities. Furthermore, additional data is needed to assess and establish the actual mechanisms underlying the therapy of specific diseases, as well as to develop innovative medications in this area.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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CHAPTER 2

Mushrooms Against Malignancies: from Chemo-sensitization to Immunopotential

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Abstract: Malignancies have been among the diseases which claim most of the lives around the globe. They also impact the socioeconomic level as well as emotional detriments among the near and dear ones. Various strategies and interventions have been devised to combat these life-threatening conditions. The ill effects associated with synthetic drugs comprising most of the anticancer drugs enforce looking for an alternative source for molecules with therapeutic potential. Mushrooms are one of the most prominent sources of bioactive molecules with diverse medicinal properties. Various mushrooms have shown their ability to inhibit the proliferation of neoplastic cells both in *in vitro* and *in vivo* investigations. Mushrooms and their active constituents can affect the various Hallmarks of Cancer. Mushrooms are not only able to inhibit the proliferation of cancer cells, but they also prevent the onset of carcinogenesis. The anti-angiogenic property of various mushrooms is indicated in several research investigations. The immunomodulatory potential and ability to avert metastasis also aid in the anticancer potential of this wonderful food item. Due to the high nutritive values of edible mushrooms, they have been suggested as nutraceuticals and contribute to nutritional management in diseases including cancer. The active constituents are also proven to have chemosensitizing ability. Preventive management of cancer and reverting chemoresistance have been sought as promising achievements in the clinical management of malignant conditions. Moreover, the nutritional values of mushrooms, along with their therapeutic potential at various fronts against cancer, make them a strong candidate for clinical application. This also warrants the careful

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exploration of mushrooms, their nutritive potential, and bioactive constituents against malignant disorders in laboratory and clinical settings.

Keywords: Angiogenesis, Cancer, Chemoresistance, Immunity, Metastasis, Mushrooms.

INTRODUCTION

The majority of therapeutic interventions against malignant disorders attempt to impact the rapid cell division of transformed cells. The chemotherapeutic agents used in the treatment of cancer are mostly compounds synthesized or derivatized from natural compounds. Shortcomings of most of the agents used in cancer treatment include the dampening of the immunity of the host. The chemicals striking the high rate of cell division also affect the rapidly dividing cells of the immune system. Moreover, there are many other undesired consequences associated with the use of chemical anticancer drugs of synthetic nature. These undesired effects include proneness to infection, anatomical damage, physiological disorders, and discomfort to the patients [1, 2]. Therefore, natural products having medicinal properties have been explored by mankind for ages to prevent and cure human health disorders. These natural compounds mostly impose no or minimal unwanted consequences or harm to human health. Nevertheless, traditional lifestyle practices promote a connection with nature for food, medicine, and other supplements, including materials for shelter and safety. These traditional medicinal practices integrate food and medicine, and prescribe and restrict the food items or ingredients based on their nature [3, 4]. The nature of these food items is a product of their biochemical composition. Among many food items having the dual benefits of nutrient richness and medicinal properties, the mushroom is the prime [4 - 6]. Mushrooms are the nutritious fruiting body of fungi of a specific group and have been reported in human consumption for ages during human development in various parts of the world [4, 7, 8].

The mushroom itself is preventive for many human disorders by fulfilling the essential nutrient requirement, maintaining physiological and immunological homeostasis, and supplementing vitamins and minerals [4, 8 - 11]. Moreover, the medicinal benefits associated with mushrooms not only include healing potential in many human anomalies but can also boost immunity and tough to counter the contract or onset of disease conditions [9, 11, 12]. Many forms of mushrooms belong to a variety of genera and species and may have distinctive bioactive compounds. This diversity in their bioactive compounds allows them to provide several advantages to humankind [5, 6, 13, 14]. The mushrooms with medicinal and rich nutritional values include *Agaricus bisporus*, *Grifola frondosa*, *Coriolus*

versicolor, *Osmoporus odoratus*, *Pleurotu spp.*, *Hypsizygus marmoreus*, *Amauroderma*, *Lentinula spp.*, *Trametes versicolor*, *Cordyceps*, *Phellinus*, *Polyozellus*, and *Antrodiac innamomea* which are relatively common for their utilization as compared to many other mushroom forms [4]. The advantages of mushrooms for humans are not limited to their nutritional values and medicinal benefits; they also aid in environmental management and the production of value-added substances [4 - 6, 13 - 16].

The benefits of mushrooms for human health also encompass activity against malignant disorders [4, 17 - 23]. The anticancer properties of mushrooms are well known and depicted in many traditional medicinal practices. *Ganoderma*, *Pleurotus*, *Hericium cirrhatum*, *Inonotus obliquus*, *Fomitopsis pinicola*, *Agaricus*, *Phellinus*, *Sparassis crispa*, *Grifola frondosa*, *Cordyceps*, *Coriolus*, and *Hericium erinaceus*, etc. are few among common mushrooms being exploited for their antineoplastic abilities [4, 17 - 23]. The consumption of mushrooms has been reported to prevent the occurrence of malignant disorders of a variety of origins [18, 24, 25]. The direct action of mushrooms and their bioactive against critical molecules involved in the initiation and progression of neoplasm pave the path for therapeutic benefits [4, 17 - 23]. The 'Hallmarks of cancer', including neovascularization and metastasis, is also resisted by mushroom and their bioactive components [4, 23, 26 - 34]. Mushrooms, such as *Ganoderma*, *Pleurotus*, etc., and many secondary metabolites of peptide and polysaccharide nature derived from mushrooms can prevent the molecular players from triggering angiogenic events [31, 35, 36]. Reports also indicate that mushrooms can diminish the potential of endothelial cells to form vessels [23, 27, 37]. Nevertheless, the anti-metastatic potential of mushroom consumption and their bioactive compounds have been recorded [33, 38, 39]. Various mushrooms, including *Agaricus blazei*, *Cordyceps sinensis*, *Pleurotus*, *Ganoderma lucidum*, *Grifola frondosa*, *Poria cocos*, and *Lentinula edodes*, have shown their anti-metastatic potential against a variety of cancer cells, including those of breast, prostate, pancreatic, skin, colon, and lung origin. The antimetastatic potentials of mushrooms are not only confirmed in *in vitro* settings, but they have been proven in experimental models and cohort studies [4, 9, 40].

One of the major reasons for exploring natural products to identify the effective therapeutic agent is the onset of chemoresistance against chemicals classically used in clinical settings [1, 2, 4, 41 - 43]. Malignant cells often reprogram their cell physiology to prevent the anticancer effect of drugs [2, 41 - 43]. However, it is very uncommon for cancer cells to show resistance against natural metabolites derived from various living forms. Mushrooms, through their bioactive metabolites, not only directly cause cytotoxicity against cancer cells but also elicit the sensitivity of cancer cells against standard anticancer drugs [44 - 47].

Through their bioactive compounds, the mushroom can prevent the occurrence of neoplastic disorders [4, 18, 24]. The enriched presence of nutrients and essential components, such as amino acids, polysaccharides, fibers, minerals, and vitamins, make mushrooms very promising candidates for nutritional management in weak patients, either suffering from infectious or malignant disorders [7, 48, 49]. The generous presence of trace elements and antioxidants beneficial for human health aids in the advantages of mushrooms along with their nutritive values. Although the information supporting uses of mushrooms in food, medicine, environmental management, and production of value-added products has been substantially accumulated in recent years with experimental data support, its optimal utilization is yet to be achieved. Despite being a key component prescribed in many traditional medicinal practices to cure human ailments, it is believed that this wonderful group of fungi can provide several unknown advantages in the preventive and clinical management of malignant disorders.

MUSHROOMS AS A PROMISING SOURCE OF THERAPEUTIC AGENTS

Mushroom is characterized as one of the most robustly consumed functional food. From the classical era to modern days, mushrooms have been widely valued as a conventional medicinal remedy in respect of human benefits. Although the lack of enough clinical data and research evidence is a major obstacle to establishing mushrooms as a therapeutic candidate for clinically correlated diseases, recent years have witnessed an expansion in research interest and investigations to explore its medicinal benefits. Therefore, more expanding evidence-based research is recommended to correlate their significance in health and biomedical sciences. In the current scenario, the major attribute of mushrooms is their medicinal properties, which have been elaborated worldwide. In the recent few decades, the key medicinal properties of mushrooms have been broadly identified and distributed as their antioxidant, anti-microbial, anti-diabetic, anticancer antiallergic, neuroprotective, and immune modulator [29, 50, 51].

Medicinal mushroom products of *Osmoporus odoratus* in petroleum ether, acetone, chloroform, and water extract are known for their antimicrobial action against pathogenic strains, such as *Streptococcus pyogenes*, *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli*, and *Pseudomonas aeruginosa*. The water extract of *Osmoporus odoratus* showed antibacterial activity against pathogenic microorganisms, and it is comparable with that of standard antibiotics ampicillin rather than chloramphenicol [52]. Medicinal mushroom, such as *Grifola frondosa*, is enriched with vanadium and are known for their hypoglycemic activity [53]. Likewise, an *in vivo* study with the bioactive

compound of *Agaricus bisporus* showed a significant decline in blood glucose levels in diabetic rats showing their antidiabetic potential [54]. An individual with cardiovascular disease has more susceptible to heart attack/stroke. The cardioprotective role of medicinal mushrooms has been recently reported [55]. Bioactive ingredients of mushrooms like *Grifola frondosa* (Maitake), *Pleurotus eryngii* (Eringi), and *Hypsizygus marmoreus* (Bunashimeji) can be used as protective agents in atherosclerosis. In the atherosclerosis-susceptible C57BL/6J mouse model, these bioactive compounds decrease total cholesterol concentration and are expected to show similar effects in the human body. Furthermore, the consumption of 30% dried mushroom by atherosclerotic mice resulted in reduced total cholesterol levels in atherosclerosis-susceptible mice in comparison to control mice [55]. Some bioactive mushroom, such as A lectin from *A. bisporus* and a protein from *A. polytricha* is dedicated to enhancing immune fitness [5, 40]. *Pleurotus* species contains efficacious compounds such as 1,6-branched 1,3- β -glucans, which can promote NK cells, macrophages, and T cells activation as well as their cytokine production [9]. The liver is a factory of metabolic processes where the detoxification process takes place to mitigate the side effect of drugs. *Ganoderma lucidum* shows hepatoprotective activity against Bacillus Calmette-Guerin (BCG) vaccine-induced liver cancer injury in mice [56]. Previous studies suggested that mushrooms such as *Agaricus*, *Amauroderma*, *Coprinus*, *Ganoderma*, *Grifola*, *Lentinula*, *Phellinus*, *Pleurotus*, and *Polyozellus* genera may aid some advantages to support immune health and inflammatory responses. Natural metabolites, such as β -glucans, β -proteoglycans, lectins, triterpenes, ergosterol, glutamine, and arginine, are major bioactive components of mushrooms [8, 57]. Mushrooms also exhibit a key role in the management of neurological complications. Deficiencies of amino acids can attract various neuropsychological distorts [58, 59]. Mushrooms are enriched with protein content and essential amino acids. The consumption can replenish the nutrient pool which are needed for the precursors of neurotransmitters and regulators of physical as well as mental health [4]. Moreover, the components of mushrooms can elevate the pool of regenerative biomolecules supporting nerve growth. Phenol analogous compounds (hericenons C, D, E, F, G, H) are one such compounds from *H. Erinaceus* that induce the synthesis of nerve growth factors and have an ameliorative effect in Alzheimer's disease [48].

Biologically active components of mushrooms with medicinal properties have been distinguished and approved as promising anticancer agent and are extensively used as a clinically safe remedy in combination with chemotherapeutic interventions [60]. Recently, an *in vitro* clinical investigation with *Antrodia innamomea* showed strong inhibitory action against breast cancer cell line MCF7. It also plays a vital role in radio/chemotherapy sensitization of cancer stem cells by altering mRNA expression [61, 62]. Studies revealed that

complex polysaccharides extracted from mushrooms had been identified as a better and more effective antitumor solution. This complex sugar derived from mushrooms can potentially induce apoptosis in cancer cells leading to tumor suppression through elevated immune function and efficacy of cancer therapy such as chemotherapy [63 - 66]. β -glucans are active metabolites of mushrooms well known for their biological activity, specifically related to the immune system. Hence, activating and reinforcing the host immune system seems to be the best strategy for inhibiting the growth of cancer cells [67]. The crude extract of *Pleurotus pulmonaris* promotes liver cancer cell death by inhibiting PI3K/AKT signaling pathway. The further findings suggested that extracted proteoglycans from *Ganoderma lucidum* have a protective effect against liver injury [12]. Recently, Zheng and co-workers' findings demonstrated that hepatic cancer cell line H22 was susceptible to the triple-helical β -glucan (THG), isolated from *Lentinus edodes*, indicating their antitumor potential [14]. Due to their high nutrient value and chemical constituents, mushrooms have been strongly recommended as a functional food and warrant more evidence-based studies to explore their diverse application against various abnormal health conditions.

ANTICANCER POTENTIAL OF MUSHROOMS

Mushroom comprises many bioactive compounds showing many health benefits without exerting any adverse effects. Moreover, mushrooms have several therapeutic potencies that can be exploited against all types of cancer. There are more than 100 different species of mushrooms, such as *Ganoderma lucidum* (reishi), *Trametes versicolor* or *Coriolus versicolor* (turkey tail), *Lentinus edodes* (shiitake), and *Grifola frondosa* (maitake), etc. that are proven to bear the ability of antineoplastic activity against the diverse forms of malignancies. The anticancer potential of mushroom is illustrated in Fig. (1).

Mushrooms in the Prevention of Malignancies

Mushrooms have different types of bioactive compounds, utilized in the prevention of malignancies due to their high nutritional and medicinal values. A number of clinical trials have been conducted to cure cancer *via* extracts of the edible mushroom. Many of the bioactive components, such as polysaccharides, proteins, lentinan, hispolon, krestin, lectin, cordycepin, calcaelin, laccase, illudin S, psilocybin, *Hericium* polysaccharide A and B (HPA and HPB), ganoderic acid, schizophyllan, etc. are found in the mushroom which actively participated in the cancer cure [40].

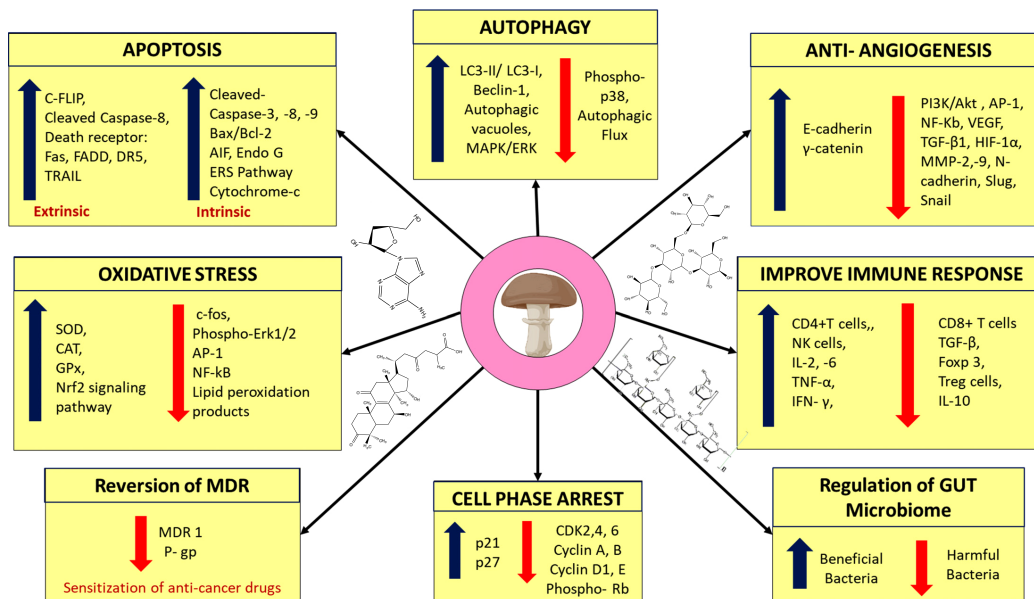


Fig. (1). The anticancer potential of mushroom.

In the cancer prevention strategy, the polysaccharides critically work. Among these polysaccharides, β -glucan is one of the main bioactive compounds of mushrooms for their medicinal value. β -glucan is a polymer of glucose, mainly originating from the cell wall of the fungus, bacteria, *etc.*, so it has been shown to have antineoplastic activity by stimulating innate and adaptive immunity [18, 40]. Moreover, these can be used for targeted therapy as drug carrier molecules [18, 40].

Lentinan is an isolated active polysaccharide biomolecule derived from the *Lentinula edodes* mushroom. Lentinan showed its anti-malignancy effect by its immunostimulatory action *via* modulating different signaling pathways. Lentinan exerts its anti-proliferative activity by activating immunocytes. Many of the signaling pathways, such as TLR4/Dectin1-MAPK and Syk- PKC - $\text{NF}\kappa\text{B}$, work in cancer proliferation, and have been modulated by lentinan. In parts of the world, including Japan and China, lentinan was approved as adjuvant drug therapy for malignancy prevention. It is reported that lentinan is clinically used as a therapeutic medicine to treat about 9474 cases of malignancy, including lung cancer (3469 cases), gastric cancer (3039 cases), colorectal cancer (1646 cases), ovarian cancer (183 cases), cervical cancer (130 cases), non-Hodgkin lymphoma (70 cases), pancreatic cancer (15 cases), cardiac cancer (15 cases), nasopharyngeal cancer (14 cases), duodenal cancer (1 case) and 110 cancer cases [68].

Hispolon is one of the major bioactive compounds of the medicinal mushroom *Phellinus linteus*. Its polyphenolic nature makes it a potential candidate to attenuate the growth and proliferation of malignancy. Many of the investigations reported that its treatment strongly inhibited the cell growth of different origins of cancer, including MCF-7, MDA-MB-231 (breast carcinoma) [69], NPC-39, HeLa, SiHa (cervical cancer) [30], HONE-1, NPC-BM, NPC-039 (nasopharyngeal cancer) [70], A549, H661 (lung cancer) [71], U87MG (glioblastoma) [72], DU145, LNCaP, PC3 (prostate cancer) (49318940), MV4-11, SK-Hep1 (hepatocellular carcinoma) [73], HL-60, U937, THP-1 (leukemia) [74], SGC-7901, MKN-45, MGC-803 (gastric cancer) [75], T24, J82 (bladder cancer) [76], Hep3B, TCMK-1 (renal cancer) [25] and KB (human epidermoid) [77] cancer cells. Hispolon works against the cell survival of cancer by triggering the cascade of apoptosis, arresting the cell cycle progression, and preventing the metastasis by modulating different cancer progressive signaling events and their regulators, including PI3K/Akt, MAPK, and NF- κ B [78].

Lectin is a carbohydrate-binding specific type of protein that interacts with glycoprotein and glycolipids [79]. Lectins are considered a novel anticancer therapeutic to cure any type and different origin of malignancies. Many of the literature surveys reported that lectin exerts its anti-neoplastic activity *via* accelerated apoptosis and autophagic nature [80]. Leukemia T cell [81], CT-26 cells [82], A253 cells [83], HeLa cells [84], U87 cells [85], A549, MCF-7, PC-3, A-2780 [86] and many more different origin of cancer *In-vitro* as well as *In-Vivo* have been significantly getting down cell survivability when treated with a different form of lectin *via* activating apoptotic cascade and other cell survival signaling pathways, including MAPK, PI3K, Akt and so on [87].

Cordycepin is one of the major bioactive compounds isolated from mushroom *Cordyceps* and has potent anticancer activity [88]. Another name of cordycepin is a 3-deoxyadenosine because it is a similar structure to adenosine but lacks a hydroxyl group in 3' of ribose [54]. Cordycepin exerts cytotoxicity and induces cell death in the various origin of cancer *In-vitro* as well as *In-Vivo*, but their mechanism of action on the cancer cell is not fully understood. Recently some research evidence explained the mechanism action of cordycepin. In liver cancer, it induces apoptosis *via* the induction of an apoptotic action cascade [89]. In the colon and bladder cancer, cordycepin arrests the cell cycle in the G2/M phase and elevates the expression of cJNK and p21WAF-1 [90, 91]. In lung and breast cancer, it induces apoptosis *via* increasing the expression of proapoptotic regulators, including caspase 3, caspase 9, MMP-9, JNK, *etc.*, and attenuating the expression of antiapoptotic regulators, such as NF- κ B, Bcl-2, p65, ERK, *etc* [92 - 96]. It has also been reported that cordycepin exerts cytotoxicity and induces cell

death *via* the apoptotic manner in different cancer cells, such as prostate cancer, leukemia, glioblastoma, neuroblastoma, prostate cancer, *etc* [97].

Hericium polysaccharides A and B is a polysaccharide isolated from the fruiting body of the *Hericiumerinaceus* species of mushroom. *Hericium* polysaccharide A and B have the potency to cure cancer by exerting their cytotoxicity and inducing apoptosis. *Hericium* polysaccharide A and B have shown anti-proliferative activity in human colorectal cancer cells (HCT-116 and DLD1) *via* inducing apoptosis by the modulation of Bax and Bcl-2 expression and inducing caspase 3 and 9 expressions. It also modulates the mitochondrial membrane potential and generates ROS [98].

Mushroom for Nutritional Management During/after Malignancies

Mushroom is rich in sources of key nutrients and bioactive materials, which have multiple health benefits. They are enriched with many essential amino acids, polysaccharides, proteins, fibers, minerals, and vitamins (thiamine, riboflavin, ascorbic acid, ergosterol, and niacin). Mushroom protein contains all the nine essential amino acids required by the human body [7, 49]. Certain types of mushrooms are used as energy-restricted diets due to their low-fat content and energy, followed by high protein content and dietary fibers [48]. Mushroom is also rich in many essential unsaturated fatty acids, such as linoleic and oleic acids. The bio-processing and cultivation of mushrooms are very economical in terms of biochemical properties, low resources, and area for growth. Therefore, the nutritional, medicinal, bioremediation and biodegradation values of mushrooms are increasing day by day and have gained acceleration in recent years [10, 99]. Medicinal mushrooms may have nutritional properties for cancer patients during and after exiting oncological care with respect to the quality of life, mitigation of adverse side effects of conventional therapy, and modulation of immune function. Of note, the most conventionally used treatment options are chemotherapy, radiotherapy, and surgery. However, the application of treatment options is dependent on many factors such as type of cancer and staging. Existing anticancer remedies are very complex having various clinical manifestations and off-target effects resulting in reduced dietary intake, decreased absorption of minerals and nutrients, modulated metabolic efficiency, and immune function that affects the survival and quality of life of cancer patients [57, 100].

Selenium (Se) is an essential nutrient and has multiple benefits for humans at trace levels. This biomaterial is utilized for the biosynthesis of selenoenzymes and selenoproteins such as thioredoxin reductase, glutathione peroxidase, iodothyronine deiodinase, and selenoprotein W and P, respectively. These enzymes and proteins are essential for antioxidant defense, detoxification, anti-

inflammation, immunomodulation, carcinogenesis prevention, thyroid functioning, and sperm motility and maturation. Therefore, Se has considered an important micronutrient for humans [101, 102]. The Se-containing mushrooms vary according to the form of cultivation, soil selenium content, and latitude. Studies demonstrated that Se participates in the cell cycle and apoptosis process. Deficiency in Se may contribute to the disruption of immune function in some types of cancer. Therefore, the mushroom can be added as a nutritional supplement for the management of cancer [11, 103, 104]. Recently, a random-effect meta-analysis study was done to elaborate on the nutritional value of mushrooms in multiple cancers. According to this finding, the higher consumption of mushrooms was significantly associated with a lower risk of cancer, particularly breast cancer [17]. Likewise, medicinal mushrooms, such as *Agaricus sylvaticus*, *Agaricus blazeimurill*, *Antrodia cinnamomea*, *Coriolus versicolor*, and *Ganoderma lucidum*, may have therapeutic potential for cancer patients during and after conventional treatment with regards to the quality of life, reduction of adverse effects of conventional care, and immune fitness. This study indicated that mushroom consumption may greatly benefit cancer patients' management [105]. However, the mechanisms of the various health benefits of mushrooms in cancer are still unexplored and require intensive investigation, especially in terms of their exceptional role as a dietary supplement and anticancer agent. Further, advanced clinical research is required to clarify the role of medicinal mushrooms in cancer care.

Mushrooms as Anti-angiogenic Agents

Angiogenesis induction mainly depends on the ratio between blood vessels and tissue, which decides the tumor size [106]. Different angiogenic factors contribute to getting an adaptive environment for tumor growth and proliferation [107]. The different bioactive compound of mushroom has also posed a potent antiangiogenic property which counteracts the proliferation migration and nascent tube formation activity of the endothelial cell. Protein, polysaccharides, and secondary metabolites of the *Ganoderma* group of mushrooms potentially express IFN- γ and IL-12 in lung cancer cell A549 [35], inhibits NF- κ B and uPA mediated protein degradation, VEGF and TGF expression in PG lung carcinoma cells [26], inhibits angiotensin-II and VEGF in MDA-MB-231 and PC-3 cell [108], attenuates tube formation in Chorio-allantoic membrane (CAM) [36] and inhibits the EGFR and VEGF in human colorectal adenocarcinoma Colo205 cell [31].

Grifola frondosa inhibits ROS-mediated ERK (1/2) phosphorylation and VEGF in HUVEC cells [36]. Groups of *Pleurotus* mushrooms inhibit the ROS, and MMPs and induce Caspase 3 and 9 in the Breast cancer cell line (MCF-7), inhibiting

VEGF and Akt activation in HUVEC and Human mesothelioma (NCI-H28) [109]. Group *Agaricus* reduced the expression of VEGF, FGF-2, and TGF- β in the mice model and inhibited vWF expression in Lewis lung carcinoma (LLC) [110].

The Group of *Antrodia* showed anti-angiogenic activity by inducing (IFN- γ) and IL-12 and inhibiting VEGF in CAM cells [111], attenuating tube formation in human microvascular endothelial cells (HMEC-1) [37], and inhibiting endothelial cell tube formation in Bovine aortic endothelial cells [27] The polysaccharide of *Fomitopsis pinicola* mushroom also inhibits tube formation in matrigel tubes [112]. Species *Trametes robiniophila* downregulates the expression of HIF, JNK, STAT3, and ERK and regulates p53 expression in HUVEC and mouse mammary tumor cells (4T1) [113, 114].

The Anti-metastatic Potential of Mushroom

Cancer metastasis is one of the major issues to cure most cancer cases, responsible for high morbidity and mortality of cancer patients. In the metastatic phase, cancer spreads from where it originated and moved by the bloodstream and infected another tissue. This is also called the 4th stage of cancer. The bioactive compound derived from mushrooms has the potency to work in the metastatic phase. Loganathan *et al.* reported that well-characterized extract isolated from the medicinal mushroom *Ganoderma lucidum* (GLE) has the potency to reduce the MDA-MB-231 tumor growth and breast to lung cancer metastasis [33].

Many scientific investigations have revealed the antimetastatic activity of mushrooms in the different origins of cancer, such as medicinal mushroom extract mixture Agarikon.1 extracted from Mushrooms Co, Croatia declines the survival of metastatic colon cancer in CT26. WT cell line and tumor-bearing mice [39], mushroom beta-glucans (MBGS) derived from *Ganoderma lucidum* species prevent primary metastasis in Lewis lung carcinoma (LLC) bearing mice (C57BL/6) [28], the mushroom mixture of five mushroom species: *Agaricus blazei*, *Cordyceps sinensis*, *Ganoderma lucidum*, *Grifola frondosa*, and *Lentinula edodes* prevent metastasis of triple-negative 4T1 cell line and 4T1 bearing mice (4T1 M. U-care mice) [34], Hot water (HWE) and microwaved 50% ethanol (MWE) extract of *Hericium erinaceus* edible mushroom potentially inhibit metastasis of CT-26 colon cancer transplanted mice and prevent cancer migration from the colon to lungs [32], purified fraction-III (PEF-III) of *Pleurotus highking* mushrooms potentiate to reduce the migratory ability of triple-negative breast cancer lines MDA-MB-231 and HCC-1937 *via* inhibition of Akt signaling pathways [38]. Huaier, bioactive isolates of mushroom *Trametes robiniophila Murr* significantly pause the survival and migration in the liver in both human melanoma A375 cancer cells and tumor tissue. Huaier significantly reduces the

expression of hypoxia-inducible factor-1 α (HIF-1 α), vascular endothelial growth factor (VEGF), astrocyte-elevated gene-1 (AEG-1), and N-cadherin along with upregulation of the expression of E-cadherin [23]. Cheng and colleagues reported that a triterpene mixture extracted from the mushroom *Poria cocos* can attenuate the survival and metastasis of chemoresistant PANC-1 pancreatic cancer cells, breast cancer lines MDA-MB-231, and MCF-7. Triterpene mixture downregulates the expression of CDC20 in cancer cells [115].

MUSHROOM AND IMMUNO-POTENTIATION AGAINST CANCER

Mushroom ingredients have been shown to alter both the nonspecific innate and adaptive-specific immune systems, making them effective in the battle against cancer. The interplay between host pattern recognition receptors (PRRs) and pathogen-associated molecular patterns (PAMPs) is crucial to an immune system's response to antigen invasion [20]. Toll-like receptors (TLRs) establish signaling networks that synchronize innate immunity & induce adaptive response against numerous invaders, whereas PRRs activate innate immunity *via* pathogen identification [116].

Mushroom metabolites influence the immune system *via* several molecular processes. Substances present in mushroom cell walls, particularly β -glucans, are likely to be a significant PAMP engaged in triggering an immunological response. The PRR identifies toadstool constituents *via* employing leukocyte factor antigen-1 (LFA-1) [also called complement receptor 3 (CR3)], toll-like receptor 2 (TLR-2), and Dectin-1 [20]. Macrophages, dendritic cells, monocytes, and neutrophils all express Dectin-1, the β -glucan receptor [117]. The interaction of the β -glucan receptor with Dectin-1 initiates the signaling cascade stimulating MAPK, NF- κ B, and T cells to release interferon (IFN- γ), interleukin (IL-2), tumor necrosis factor (TNF- α) [118]. Such cytokines may then induce adaptive immunity by driving T cells to differentiate into T helper (Th) cells, which moderate humoral immune response [20, 118].

Radioactive emission has been proven to cause altered expression of cytokine profile [119]. TNF- α is regarded as a crucial facilitator in the pathophysiology of radiation exposure; consequently, its level is elevated due to radiation-induced tissue trauma and erythrocytopenia. PG101, a protein-bound polysaccharides fraction obtained from *Lentinus lepideus* mycelial cultivation revealed remarkable potential as a principal or booster treatment option in immunocompromised patients with bone marrow dysfunction [119, 120]. Throughout 24 days, PG101 boosted the concentrations of IL-1, IL-6, GM-CSF and reduced the level of TNF- α significantly. Likewise, *Sparassis crispa* derived branched β -D-glucan, SCG

raised the proportion of $\gamma\delta$ T cells to Natural Killer cells in the peritoneal cavity, liver, and spleen [120].

On being detected by pathogen recognition receptors, mushroom chemicals that are administered directly into cancer cells or consumed orally trigger immune cells to commence cell-mediated or immediate cytotoxicity on cancerous cells [6]. Lentinan elicits generic immunological responses while enhancing the generation of macrophages & CTLs (cytotoxic T Lymphocytes) cells. The water-soluble extracts of *Pleurotus rhinoceros* and *P. tuber-regium* encourage the maturation of NK cells and lymphocytes, thus inferring anti-neoplastic activity. It also promotes the propagation of Th cells, CD4/CD8 ratio population, and macrophage, preceded by a spike in spleen weight and size, therefore, accrediting to elevating the proportion of monocyte and granulocytes among the population [121, 122].

Treg (Regulatory T cells), which constitute a subpopulation of CD4+ T cells, balance immune system homeostasis and moderate autoimmune reactions. They play a significant role in tumorigenesis by producing secretory cytokines (like TGF β , *etc.*). Research findings showed that the *Lentinula mycelia* extracts (LEM) stimulate anti-cancer properties by might suppressing Treg-mediated immunosuppression as the frequency of CD4+ Foxp3+ cells (Treg) in the spleen, plasma TGF- β levels and Foxp3 in melanoma tissues reduces significantly after the treatment [19 - 22].

MUSHROOM AND CHEMOSENSITIZATION

A variety of cytotoxic drugs available, such as cisplatin, 5-fluorouracil (5FU), cisplatin (CPL), doxorubicin (DOX), gemcitabine, mitomycin C, cyclophosphamide, methotrexate, vinblastine, estramustine, *etc.*, are a standard anti-cancerous drug which is alone or with combination used in the chemotherapy for the prevention of different origin of cancer. But the side effect, high cost, and their limitations, and multi-drug resistance have been major drawbacks associated with these drugs [123]. Therefore, to minimize the side-effect, overcome the multidrug-resistance phenomena, and increase the therapeutic efficacy of the standard anti-cancer drug, used some natural bioactive compounds, which work as an adjuvant and reduce the cons of standard drugs [2, 41, 43]. Hilelsohn and his colleague reported that they isolated a bioactive component (PDF), a beta-glucan types molecule, from maitake mushroom, which has anti-cancer properties and treated gall bladder cancer T24 cells with certain standard anticancer drugs, such as carmustine (BCNU), 5FU, CPL, and DOX. They found that PDF increases the efficacy of standard anticancer drugs from 50% to 90%. Moreover, in the clinical trial, it was also found that PDF reduced the side effect and pain when it was administrated to the patient [45].

In-vitro and *In-Vivo* study conducted by Xu *et al.* reported that the hot water extract (Pp) from *Pleurotus pulmonarius* mushroom possesses an anti-malignancy property. The administration of Pp in the liver cancer cell line Huh-7 and mice, possesses significantly reduces the expression pattern of p-Akt and iNOS, whereas increased the expression of cleaved caspase-3 which accelerates the induction of cancer cell death. They also observed that when liver cancer cells Huh-7 and mice were treated with standard anticancer drug cisplatin along with Pp, Pp significantly improved cisplatin's efficacy even in very low concentrations [124].

A bioactive compound isolated from the *Ganoderma* species of mushroom also possesses antineoplastic activity. Phenolic extract from *Ganoderma* species significantly elevates the growth and proliferation retardation ability of Taxol and cisplatin in the HER2+ BC cell line MBA-MD-435 cell line [46]. Another study revealed that the extract from *Ganoderma* species also reduced multi-drug resistance, confirmed by miR-378 in MDA-MB-231 cells [47]. Hesperidin, which has been shown to have therapeutic potential against malignant cells, is a polyphenolic compound, derived from *Phellinus linteus* mushroom. It is reported that Hesperidin also has a potent chemo-sensitization ability with conjugation of gemcitabine drugs, which potentially decreases the survivability of BxPC-3 and AsPC-1 pancreatic cancer cells [44].

ANTICANCER COMPOUNDS OF MUSHROOMS AND THEIR MOLECULAR TARGETS

Pre-historically, cancer fungo-therapy has been a vital aspect of contemporary traditional ethnomedicine. It has become a potential scientific discipline involving the utilization of anti-cancer agents obtained from toadstools/mushrooms [24]. Being a maker of dozens of metabolites, the uniqueness of medicinal toadstools is that they exert a synergistic effect on diverse tumor-related events when employed as therapy. As a result, not only are investigations of particular fungal-derived chemicals vital, but so is a study into the complex cytotoxic effect generated by the permutations of compounds in their extracts [13].

Fomitopsis pinicola, a non-poisonous European mushroom, is said to have homeostatic and anti-inflammatory potential with a history of usage in Korean citizenry [125]. The mushroom's chloroform preparations showed ROS-mediated apoptotic effect nearly twice as specific to colorectal cancer cells (SW-480) as to HEK293 cells. Furthermore, the lysates were capable of preventing SW-480 cells from migrating in the scratch wound and trans-well assays by downregulating matrix metalloproteinase (MMPs) [96].

Agaricomycetes saprotroph, *Hericium erinaceus* has received quite a bit of scientific interest, and its primary and secondary biometabolites, as well as their potential medical applications, have been extensively researched [126]. Specific isolated chemicals, such as erinacines obtained from the fungal mycelium or hericenones extracted from the fruiting bodies, are identified [127]. Erinacine A, a mycelial cyanthine diterpenoid derivative, has been shown to suppress the development of tumor cell lines and cancers of the gastrointestinal system. It was likely to induce the potentiation of the p70S6K, JNK1/2 MAPKs, and mTOR networks in DLD-1, human colorectal adenocarcinoma cell line by arresting the cell cycle through ROS-mediated stimulation of the oxidative stress mitochondrial function [128]. Cofilin-1 and profilin-1 are actin-binding proteins that are triggered by the Erinacine A-induced ROS reaction and mediate the anti-invasive impact, according to proteome analysis [129].

Cerebrosides are yet another family of metabolites found in fungi, and cerebroside E extracted from *H. erinaceus* has demonstrated a marginal reduction in tube formation in HUVEC cell lines, making it a versatile angiogenesis antagonist. This chemical also showed anti-toxic capabilities, lowering the harm inflicted by cisplatin in LLC-PK1 renal cells in culture — qualities that might lead to its usage in complicated cancer chemotherapeutics [130]. *In vivo* studies employing mouse skin [131] and human leukemia-derived mice xenograft tumors [132] indicated anti-tumorigenic efficacy of the lanostan-type triterpenoids inonotodiol and inonotsuoxides are isolated from Agaricomycetes class, *Inonotus obliquus*. Modest molecular weight polyphenolic compounds inhibited topoisomerase II activity, resulting in growth retardation in cultured human colon HCT116 carcinoma cells, indicating that they might be used as anticancer chemotherapeutics [133]. Few of the bioactive compound derived from mushrooms are depicted in Fig. (2).

FUTURE PROSPECTIVE

Many types of medicinal mushrooms exist on the earth, and their bioactive compound has diverse medicinal properties, including anti-neoplastic activity, anti-angiogenic activity, anti-oxidant activity, *etc.*, *via* either activating or modulating the immune system regulator, which controls the growth, proliferation, and invasion of cancer. These bioactive isolates regulate immunity by immune cell development, maturation and activation. Mushroom polysaccharides are known to stimulate latent natural killer cells, T cells, B cells, and macrophage-dependent immune system responses [134]. Many studies on mushroom have proved that mushroom effectively cures cancer patient by reducing the survival, proliferation, and metastasis of cancer, work as an adjuvant

in chemo-sensitization, and have a deleterious effect on multi-drug resistant activity and potent immunomodulatory activity. Jin *et al.* reported that *Ganoderma lucidum* mushroom administrated cancer patients live a better life than control [135]. 30 to 40% of Cancer patients are affected by sleeping disorders so much, which generate fatigue, augmented depression, higher pain, and lower survivability. Some journals reported that some species of mushroom intake reduce the sleeping associated disorder along with work as a pain killer and anti-fatigue agent [136 - 138].

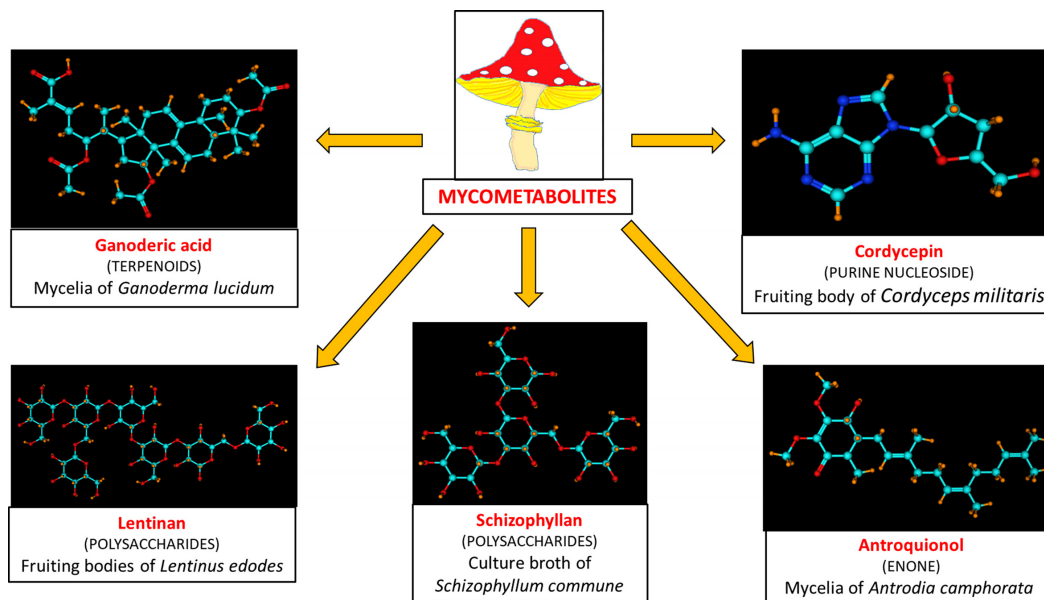


Fig. (2). Bioactive compound derived from mushrooms.

Chemo and radiotherapy induce bone marrow suppression in the cancer patient, which could be counteracted by medicinal mushrooms [139]. Most mushrooms have the bioactive compound beta-glucan, which have also the ability of hemopoietic activity [140]. Jin *et al.* reported that mushroom *Ganoderma lucidum* with anticancer drugs had been shown to have a positive effect on cancer patients (especially lung cancer, colon cancer, and breast cancer) as compared to being treated with a placebo and chemo/radiotherapy alone [135].

A meta-analysis conducted on 1,094 patients suffering from respective colorectal cancer treated with the main bioactive compound polysaccharide K isolated from mushroom *Coriolus versicolor*, showed an OS risk ratio of 0.71 (95% CI: 0.55–0.90; $p = 0.006$). The disease-free survival risk ratio was 0.72 (95% CI: 0.58–0.90; $p = 0.003$) [141]. Another meta-analysis was conducted on 3117

patients associated with lung carcinoma, administered Lentinan IV (1-1.5gm/day, 2-8 weeks), derived from mushroom *Lentinula edodes*. Bioactive compound lentinan with chemotherapy drugs showed more efficacy in treating lung cancer as compared to chemotherapy alone (pooled RR 0.79, 95% CI: 0.74–0.85) [68].

The benefits of mushrooms have been considered for ages, however, the experimental pieces of evidence to support these claims came in recent years. Due to substantial exploration of the medicinal benefits of mushrooms, evidence supports the clinical advantages of these wonderful natural assets. Although mushroom and their bioactive components have demonstrated promise in treatment as well as prevention of malignancies of a variety of origins, further exploration is still needed to uncover the true potential of mushrooms. Further, the identification of bioactive compounds, their molecular characterization, and mechanistic investigations will also help in improving the benefits of mushrooms. With the advances in techniques related to *in silico* predictions, the bioactive compounds and their derivatives must be predicted for their efficacy in binding with their molecular targets. Many natural metabolites have limited utilization due to low bioavailability, solubility, and weak target interaction. The pharmaceutical chemistry methods along with computational tools, can eliminate these shortcomings associated with any drug candidate, including those derived from mushrooms, through predictive assistance. Mushrooms are very rich in nutrients and are enriched with vitamins, minerals, fibers, and essential amino acids. However, due to diet preferences, religious beliefs, and some myths, its utilization is not very common in many parts of the world. Awareness about the health benefits of mushrooms, and promoting the mushroom production, and processing sector will aid in utilizing its benefits.

CONCLUSION

Mushrooms have many advantages in the management of malignant disorders. The benefits of mushroom consumption are not only limited to its nutritional value, but it also contains numerous bioactive components. These mushroom bioactive compounds have preventive and curative potential against neoplastic disorders. Mushrooms are not only enriched in nutrients like proteins, carbohydrate but they also contain a substantial amount of essential amino acids, vitamins, minerals, and fibers that promote the homeostasis of well-being. The compounds having medicinal values also provide aid in the maintenance of health by potentiating the immunity of the host. Moreover, malignant disorders cause suppression of immunity in patients, which can also be countered by mushrooms and their bioactive components. The immunity-boosting ability of mushrooms has the potential for their use as an adjunct in the clinical management of malignant

disorders. The neoplastic disease conditions led to malnourishment due to loss of appetite, poor gastrointestinal absorption, enhanced energy demand, and other associated factors. The inclusion of mushrooms in the diet plan of cancer patients has an aiding role in replenishing the nutrient requirement and providing essential substances to keep immunity tidy.

The chemosensitizing ability of various mushrooms is recorded in preclinical settings. This ability of mushrooms has multiple uses in anticancer therapy. The sensitization of cancer cells by mushrooms can reduce the required amount of anticancer drugs to achieve the target effect. Moreover, reducing the required dose will prevent the high dose-associated side effects of chemotherapeutic agents. Nevertheless, the inclusion of mushrooms in the diet will not be taken as a therapeutic intervention by the patient. This will prevent psychological derailment in cancer patients by eliminating the perceived fear of drug intake. Moreover, mushrooms have neuropsychological benefits. Although mushrooms have many promises against a variety of human health disorders, including cancer, optimal clinical use is still not achieved. An obstacle like diet preferences, lack of experimental pieces of evidence supporting assertions claimed in traditional medicinal practices, scientific awareness, and low popularity must be addressed to make mushrooms and their components more commonly used. Recent years witnessed the identification of bioactive compounds, their molecular targets, and mechanisms for the anticancer activity of different mushrooms. With advances in technology, interactions of these compounds with molecular moieties are being determined. Attempts are being made to eliminate the limitations like low bioavailability, weak molecular interactions, and non-specific binding through tools of pharmaceutical chemistry and computational strategies. Although research work to explore the medicinal benefits of mushrooms gained its pace in the last decade, the large portions of advantages associated with mushrooms are still to be revealed. Owing to variety, diversity, and medicinal benefits, mushrooms have a key role to play in preventive measures and clinical treatment of cancer. Further investigation will contribute to the known benefits of mushrooms for their optimal utilization for human health maintenance.

AUTHOR CONTRIBUTIONS

NKV, SCS, SKP, NC, and DS did the conceptualization and designing of the manuscript; VKS, AM, YKR, DS and NKV performed the literature survey; All authors contributed to writing the manuscript. All authors read and approved the final version.

CONSENT OF PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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CHAPTER 3

Anti-proliferative, Anti-angiogenic, Anti-apoptotic, and Anti-metastatic Effects of Mushroom**Vartika Mishra¹, Priyanka Yadav¹, Aprajita Tiwari Pandey¹ and Mohan Prasad Singh^{1,*}**¹ Centre of Biotechnology, University of Allahabad, Prayagraj 211002, India

Abstract: Cancer is the second leading cause of mortality globally after cardiovascular diseases. It is attributed to various genetic and epigenetic changes in the genome, while lifestyle and environmental factors have a say in its rate of progression. Conventional agents like chemotherapy, radiotherapy, and surgical interventions though successful to some extent, are always associated with toxic side effects. A promising alternative could be herbs that form a part of our daily consumption. Mushrooms consumed worldwide have been found to be a treasure of macromolecules like β -glucan, α -glucan, resveratrol, concanavalin A, cibacron blue affinity protein, p-hydroxybenzoic acid, ergosterol, linoleic acid, *etc.* that are responsible for mediating anti-tumor, immunomodulatory, antioxidant and anti-diabetic roles. Various experiments have demonstrated the potential of mushrooms as an anti-cancer agent. This chapter summarizes the effect of mushroom extracts and bioactive constituents against various hallmarks of cancer like sustained proliferation, evading apoptosis, angiogenesis, immune evasion and metastasis, along with underlying mechanisms. At the end of the chapter, we also talked about what still can be done and where we need to focus so that future studies can add to the already existing knowledge about this natural reservoir of anti-cancer compounds.

Keywords: Anti-angiogenic, Anti-apoptotic, Antimetastatic, Antiproliferative, Mushroom.

INTRODUCTION

Since the dawn of the 20th century, finding an answer to the dilemma posed by cancer has been most challenging for man. The disease, which took a toll on millions of lives, has remained an unanswered mystery. Researches throughout the world have been going on, but a real breakthrough still evades us. The disease took in its ambit not less than 1.3 million people in 2020 [1], and is second to only cardiovascular diseases when accounting for mortality. What is really worrisome

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is the sync between the incidence of cancer, the changing lifestyle of man, and the nature of his surroundings. Who among us is not being subjected to an environment full of automobile fumes, polluted water, edibles treated with a variety of chemicals and land overwhelmed with herbicides and pesticides. Alcohol abuse, tobacco consumption, and cannabinoids are finding their presence very common among youth nowadays. And to this, what is more, intriguing is people are being alienated from meditation, exercise, a nutrient-rich diet, and many more things which can help the body to find a way from stresses developing inside it. It is worth acknowledging that an increased incidence of cancer is attributed to all the above-mentioned reasons. The picture will be more gruesome if we don't find an alternative that is more sustainable for us in the long term. But what we have discussed so far are controllable factors and should be worked upon on an individual and collective basis but Cancer isn't this simple; it is manifested even with aging, exposure to biological entities like bacteria and viruses and *via* mutations in genetic material either by exposure to carcinogens and radiations [2]. Biologically, genetic, epigenetic and metabolic alterations taking place inside the cells when they accumulate over a considerable period of time for successive cell divisions result in Cancer. These changes trigger a plethora of genes to express themselves constitutively; thus, normal cells lose their capability to regulate homeostatic mechanisms [3]. This is manifested in uncontrolled cell cycle events leading to hyperproliferation, evasion of apoptosis and immune response, angiogenesis, epithelial to Mesenchymal transition and metastasis [4]. Additionally, malignant cells also exhibit the Warburg effect, whereby tumors display high levels of glucose uptake and lactate production even in the presence of adequate oxygen, and this increased aerobic glycolysis could contribute to the immortalization of cells [5]. These genetic and metabolic reprogramming in cancer cells support their growth, survival, proliferation and maintenance in the hostile environment [3].

Notwithstanding challenges, it has been inherent to the human mind to ponder over the problem nature poses to us. Cancer is no exception, and we found some tangible results in our basket in the form of chemotherapy, radiotherapy, hormonal therapy, immunotherapy, nanomedicines and surgical interventions [6]. These therapies, when used individually or in combination, have checked the growth of cancer cells and caused the shrinkage of tumor size to a significant level though none of them have proved to be an exclusive remedy for cancer treatment so far. What is of concern with this repertoire is the side effect they have on our bodies [7]. Chemotherapy is the main approach for the treatment of metastatic tumors. However, it is associated with serious side effects, such as bone marrow suppression, neurotoxicity, gastrointestinal reaction and liver and kidney damage. In addition, currently used chemotherapeutic agents, such as alkylating agents, mustards, anti-metabolites, spindle poisons, and DNA binders

and cutters, target a specific pathway, which ultimately shrinks tumor size but often fails to eradicate tumors or prevent their recurrence. Repeated treatment with these agents eventually results in tumors that become resistant to the chemotherapies [8]. During radiotherapy, patients receive a high total dose of ionizing radiation fractionated over a period of weeks. These radiations are themselves known to possess cancerous effects that can lead to secondary tumors, thus adding to already existing criticality [9]. While surgical interventions can remove primary tumors, they may stimulate the hematogenic distribution of tumor cells, leading to increased metastases growth [10].

In the quest to resolve the shortcoming of conventional therapeutics, an option of choice was natural herbs which have been known to have several biological properties of advantages. Among many such herbs, we will discuss mushrooms' effect in treating cancer. Mushrooms have been used since the dawn of human civilization as an important constituent of our diet [11]. Not only are mushrooms rich in nutrients required by our body for normal maintenance, but in addition to that, they are also reported to have numerous biologically active compounds, *e.g.*, α - glucans, β - glucans, lentinan, lipopolysaccharides, resveratrol, cibacron blue affinity purified protein, concanavalin A which together induce pharmacological actions such as antimicrobial, anti-inflammatory, immunomodulatory, antidiabetic, cytotoxic, antioxidant, hepatoprotective, anticancer, antioxidant, antiallergic, antihyperlipidemic, and prebiotic properties [12]. All these attributes have attracted scientists to study in detail the effect of mushroom on cancer. Here we will discuss this one by one in relation to how mushroom may target hallmarks of cancer and thereby inhibit it.

ANTI-PROLIFERATIVE EFFECT

Normal cells require mitogenic growth signals in order to move from a quiescent state to an active proliferative state. However, these factors are limited in supply, and thus, cell proliferation is restricted. Additionally, the progression of the cell cycle in somatic cells is controlled by a balance between proliferative and antiproliferative signals as well as *via* cyclin-cdk complexes [13]. Cancer cells defy the above limitation of trophic factors by a mechanism of autocrine signalling whereby they actively produce growth-inducing mitogens, and the balance is tilted in favour of proliferative signals *via* loss of function mutation in tumor suppressor gene and gain of function mutation in proto-oncogenes as listed in Table 1 [16]. Constitutive expression of Ras-ERK, PI3K-Akt and mTOR signalling pathways, nuclear factor-kappa B [NF- κ B], mitogen activated protein kinase pathway [MAPK], Akt, Wnt, Notch pathways, as well as universal disruption of Rb mediated control of G1/S transition enables cancer cells to undergo sustained proliferation [14, 15]. This is further supported *via* the

amplification of cyclin D, cyclin E, CDK4, G₁/S cyclins, CDKs, and the E2F-family transcription factors and epigenetic inactivation of INK4 and posttranslational reduction in levels of CIPs and KIPs [17]. All these changes manifest themselves in the disorganisation of cell cycle control mechanisms prolonging the survival of cancer cells.

Table 1. Loss of function mutation in tumor suppressor gene and gain of function mutation in proto-oncogenes.

Proto-Oncogenes	Tumor Suppressor genes
<i>ras</i>	PTEN
<i>c-src</i>	Rb
EGFR	p ₅₃
VEGF	INK4A
HER2	Bcl2
BCR/ABL	nm23
C-KIT	BRCA2
Cyclin E	APC
Cyclin D1	p ₁₆
MITF	NF1
Beta Catenin	NF2
K-ras	RBI

Studies have shown a prominent anti-proliferative effect of mushrooms. When pancreatic cancer cells were treated with hot water extract of *Agaricus blazei*, it inhibited the proliferation of cells *via* induction of cell cycle arrest at the G₀/G₁ stage [18]. Similarly, *Agaricus blazei* also inhibited the proliferation of prostate cancer cells in both androgen-dependent and androgen-independent manner [19]. The suppression of aromatase activity in breast cancer cells diminishes its ability to proliferate, which is mediated by *Agaricus bisporous* [20]. In addition to this, a protein-bound polysaccharide from *P. linteus* mushroom induces G₂/M phase arrest in SW480 human colon cancer cells [21]. Mushrooms of the genus *Ganoderma* are another source that can potentially retard the rate of proliferation in malignant cells. *In-vitro* experiments have revealed that when colorectal adenocarcinoma cells are subjected to *Ganoderma tsugae* extracts proliferation was inhibited by induction of G₂/M cell cycle arrest. The underlying mechanism involved the downregulation of cyclin A while simultaneously upregulating p21 and p27 [22]. Similar to this, polysaccharide and terpenes derived from *Ganoderma lucidum* suppresses the proliferation of mouse melanoma cells [B16F10], rat adrenal medulla pheochromocytoma cells [PC12], and human

bladder cancer cells [HUC-PC and MTC-11]. This is mediated *via* the down-regulation of cyclin D1, reduced expression of molecules involved in PI3K/AKT/mTOR and MAPK pathways and inhibition of protein synthesis [23]. Oyster mushrooms which form a good part of our consumption, can serve as an alternative to target cancer cells. This has been shown experimentally when Methanol extract derived from *Pleurotus ostreatus* induced upregulation of p21, p53, p27 and p19 genes and downregulated expression of E2f transcription factor 1, PCNA, CDK4, CDK6 and Transcription factor DP-1 in breast cancer cells leading to an inhibition of cell proliferation and corresponding cell growth. Additionally, incubation of HT-29 cells with the same extract [1mg/ml] for 48 hours resulted in an increase in cell cycle arrest from 26% to 66% at G0/G1 phase. Further, an ethanolic extract derived from *Pleurotus ostreatus* [0.8mg/ml] inhibited the proliferation of HL60 human promyelocytic leukemia cells by 78.2% in a dose-dependent manner while Ethanol and water extract of *Pleurotus tuberregium* inhibited proliferation of HCT116 cells, however, ethanol extract was seen to be more promising when compared with water extract. Moreover, polypeptide isolated from the mycelium of *Pleurotus eryngii* suppressed the proliferation of Hela 229 cells by 61.40%. Many more experiments have revealed that extracts derived from various mushroom species have been shown to upregulate p15, p19, p21, p53 and p27 genes while also downregulating E2F1, TFDP1, CDK4, Ki-67 and PCNA gene expression. The resultant outcome was that the proportion of malignant cells in the G0/G1 phase increased while that in the G2/M phase decreased, thereby leading to cell cycle arrest and inhibition of proliferation [12]. From above, we can conclude that mushrooms have a repertoire of bioactive compounds which can inhibit the proliferation of malignant cells and thus may save us from the malignancy which takes a toll on millions (Table 2).

Table 2. Anti-proliferative effects of mushroom.

S.no.	Mushroom species	Cancer cell line	Mechanism of action	References
1	<i>Phellinus linteus</i>	T24 cells of Bladder cancer	Ethanol extract inhibits the growth of cancer cells by induction of oxidative stress and its cytotoxic effect.	[24]
2	<i>Agaricus blazei</i>	MCF7 cells of Breast cancer	The water extract induced the proliferation of cells by enhanced expression of c-Jun/AP1 genes.	[25]
3.	<i>Agaricus brasiliensis</i>	W256 cells of Breast cancer	The extract reduced patients' loss of weight and tumor growth induced by cachexia.	[26]

(Table 2) cont....

S.no.	Mushroom species	Cancer cell line	Mechanism of action	References
4.	<i>Ganoderma lucidum</i>	MDA-MB-231 cells and 4T1 cells of Breast cancer	The fraction showed an inhibitory effect against Akt phosphorylation on Ser473 and downregulation of Akt expression, which triggered inhibition of NF-kappaB, cyclin D1, and subsequently cdk4. Extract inhibited tumor growth and migration <i>via</i> inhibition of Wnt/ β -catenin signalling on other cell line.	[27]
5.	<i>Lignosus rhinocerus</i>	MCF-7 cells of Breast cancer	An antiproliferative property of the extract found.	[28]
6.	<i>Phellinus linteus</i>	MCF-7 cells of Breast cancer	Ethanol extract inhibited the growth of cancer cells by induction of oxidative stress and its cytotoxic effect. Water extract Inhibited proliferation <i>via</i> increasing p27Kip1 expression and arrest cell cycle at the S phase.	[24 29]
7.	<i>Pleurotus highking</i>	MCF-7 cells of Breast cancer	Purified fraction-III decreased the size and number of tumor spheres.	[30]
8.	<i>Cordyceps sinensis</i>	<i>In vivo</i> – mice model Cervical cancer	Administration of the extract to mice resulted in a reduction of tumor incidence, enhancement of the immune system, and restoration of the content of glutathione, glutathione reductase activity, glutathione S transferase activity, peroxidation of lipid, glutathione peroxidase activity, catalase activity, and activity of Na ⁺ /K ⁺ -ATPase.	[31]
9	<i>Pleurotus nebrodensis</i>	HCT116 cells of Colon cancer	Cold water extract significantly inhibited the proliferation of cells.	[32]
10	<i>Cordyceps militaris</i>	<i>In vitro</i> and mice model RKO cells of Colorectal cancer	The extract inhibited cell proliferation and tumor growth in the mice model.	[33]
11.	<i>Coriolus versicolor</i>	<i>In vivo</i> – a meta-analysis of trials on Colorectal cancer and Gastric cancer	The fraction exhibited antiproliferative activity against cancer.	[34]
12	<i>Hericiium erinaceum</i>	<i>In vivo</i> – mice model and <i>in vitro</i> on Gastric cancer	Ethanol extract caused tumor growth arrest.	[35]
13	<i>Phellinus igniarius</i>	SGC-7901 cells of Gastric cancer	Ethanol extract arrested the cell cycle at G0/G1 phase	[36]

APOPTOSIS

Apoptosis or programmed cell death is a homeostatic mechanism to maintain cell population. Additionally, it is required to eliminate the cells which are under stress due to immune action, DNA damage and disease. The process involves an interplay of multiple signalling pathways and is regulated by multiple complicated extrinsic and intrinsic ligands. Morphologically the cells undergoing apoptosis are characterised by cell shrinkage, pyknosis, blebbing of the plasma membrane, karyorrhexis, DNA fragmentation, chromatin condensation and compaction of cytoplasm. Programmed cell death is an energy-dependent molecular cascade that can choose one among the two alternative pathways, *i.e.*, the extrinsic or death receptor pathway and the intrinsic or mitochondrial pathway [37, 38]. Malignant cells, *via* successive changes in their genetic makeup, evade this process of apoptosis. This is achieved *via* a favoured tilt in an expression of anti-apoptotic genes, *e.g.*, Bcl-2, Bcl-xL, Mcl-1, Bcl-w, A1/Bfl-1, and Bcl-B/Bcl2L10 as against pro-apoptotic genes, *e.g.*, Bid, Bim, Puma, Noxa, Bad, Bmf, Hrk, and Bik. Additionally, defective p53 genes, dysregulated inhibitors of apoptosis proteins [IAPs], reduced caspase activity and impaired death receptor signalling also aid cancer cells in defying apoptotic pathways [39, 40].

The task of any anti-cancer agent is to reprogram the gene expression so that the balance in malignant cells in favour of anti-apoptotic genes shifts in favour of proapoptotic proteins [40]. Experiments have suggested that mushrooms can serve this role efficiently. *In-vitro* studies had revealed that when human leukemic THP-1 cells were treated with *A. blazei* extract, there was depolarization of the mitochondrial membrane potential, release of cytochrome c from mitochondria to cytosol, increased generation of reactive oxygen species and upregulation in activity of caspase-9. Additionally, the treatment led to an increased level of proapoptotic proteins Bax and Bad [41]. Furthermore, ethanol crude extract and hot water extract of *Agaricus brasiliensis* Murill induced apoptosis in CAL 27 cells *via* release of Ca^{2+} ions, decrease in $\Delta\Psi_m$, translocation of apoptosis-inducing factor [AIF] to the nucleus, induction of DNA fragmentation, activation of caspase 3 and PARP degradation [42]. Similar to this, treatment of mcf-7 cell lines with *Pleurotus ostreatus* polysaccharides resulted in increased caspase-9, caspase-3, Bax and phospho-JNK expression and reduced mitochondrial membrane potential leading to apoptosis [12]. Moreover, n-hexane extract prepared from *Pleurotus sajor-cazu*, when applied to HCT116 cells, upregulated expression of several proapoptotic proteins such as Fas, HSP 60, Bid, Bax, p53, caspase 3, SMAC, survivin, *etc.* and simultaneously downregulated level of Bcl2 proteins resulting in enhanced Bax/Bcl2 ratio and apoptosis induction *via* the intrinsic pathway. Mushrooms are as effective against Leukemias as they are found to be against solid tumors. Water soluble non-starch polysaccharide derived

from *Pleurotus tuberregium* promoted apoptosis in HL60 cells *via* enhancing Bax/Bcl2 ratio [12]. When human chronic myeloid leukemia cells were subjected to ethanol extract of *Ganoderma tsugae*, there was corresponding induction of mitochondrial and death receptor-mediated apoptosis. This was accompanied by DNA fragmentation, followed by cytochrome c release, caspase-3/8/9 activation, PARP cleavage, Fas activation, Bid cleavage, and Bax/Bcl-2 dysregulation [43]. There is no dearth of data, and even *in-vivo* models have demonstrated the efficacy of mushrooms in combating cancer *via* the promotion of apoptosis. Anti-tumor protein isolated from *Pholiota nameko* has successfully activated the death receptor pathway and mitochondrial apoptotic pathway in the BALB/c mouse model of MCF-7 tumor xenografts leading to a subsequent withering of tumor in the mouse model [44]. Conjugated linoleic acids present in white button mushrooms have been demonstrated to be effective in inducing apoptosis of tumor cells in nude mice when compared with unfed controls [45]. All these studies suggest the potential of mushrooms in re-establishing the homeostatic pathway of programmed cell death in cancer, thereby enhancing the chances of its elimination from the body (Table 3).

Table 3. Mushroom species and apoptosis.

S.No.	Mushroom species	Cancer cell line	Mechanism of action	References
1.	<i>Phellinus linteus</i>	T24 cells of Bladder cancer	The Ethanol extract induced apoptotic cell death due to increased expression of caspase-3 and -9.	[24]
2.	<i>Antrodia cinnamomea</i>	MDA-MB-453 and BT-474 cells of Breast cancer	The treatment-induced apoptosis mediated by cell cycle arrest at sub-G1, DNA fragmentation, dysfunction of mitochondrial caspase-3/-9 activation, cytochrome c release, and degradation of PARP and BCL2/ BAX dysregulation.	[46]
3.	<i>Cordyceps militaris</i>	MDA-MB-231 cells of Breast cancer	Apoptosis related to inhibition of AKT activation and PI3K/Akt inhibitor played a key role in the anticancer activity of the extract. Moreover, apoptosis was associated with caspase-3 activation and inactivation of AKT, causing mitochondrial dysfunction.	[47]
4.	<i>Lignosus tigris</i>	<i>In vivo</i> – mice model and MCF-7 cells of Breast cancer	Apoptosis related to inhibition of AKT activation and PI3K/Akt inhibitor played a key role in the anticancer activity of the extract. Moreover, apoptosis was associated with caspase-3 activation and inactivation of AKT, causing mitochondrial dysfunction.	[48]
5.	<i>Phellinus linteus</i>	MCF-7 cells of Breast cancer	The ethanol extract induced apoptotic cell death due to increased expression of caspase-3 and -9.	[24]

(Table 3) cont....

S.No.	Mushroom species	Cancer cell line	Mechanism of action	References
6.	<i>Pleurotus highking</i>	MCF-7 cells of Breast cancer	The fraction decreased the size and number of tumor spheres and promoted apoptosis by changes in the ratio of the expression of proapoptotic [p53 and BAX] and antiapoptotic [BCL2] genes.	[30]
7.	<i>Pleurotus eryngii</i>	HCT116 cells of Colon cancer	Cold water extract promoted apoptosis due to the increased ratio of BAX/BCL2. Moreover, it had the potential to inhibit the migration of cells and heterotypic cell-cell adhesion.	[32]
8.	<i>Pleurotus nebrodensis</i>	HCT116 cells of Colon cancer	Cold water extract promoted apoptosis, due to the increased ratio of BAX/ BCL2. Moreover, it had the potential to inhibit the migration of cells and heterotypic cell-cell adhesion.	[32]
9.	<i>Pleurotus ostreatus</i>	COLO-205 cells of Colon cancer	Water extract induction of apoptosis due to increased expression of proapoptotic genes [caspase-3, caspase-9, BAX, cyclindependent kinases [CKIs], p16, and p21] and decreased expression of anti-apoptotic genes [BCL2].	[49]
10.	<i>Pleurotus ostreatus</i>	HT-29 and HCT-116 cells Colon cancer	it induced p53-independent apoptosis <i>via</i> an increased level of p21 [cyclin-dependent kinase inhibitor] and p53 [tumor suppressor] with decreased activity of Rb phosphorylation.	[50]
11.	<i>Ganoderma applanatum</i>	Caco-2 cells of Colorectal cancer	The extract induced cell apoptosis <i>via</i> a p53-independent pathway, which was proved by an increased ratio of mRNA BAX/BCL2 with the regulation of p53 and caspase-3.	[51]
12.	<i>Ganoderma lucidum</i>	<i>In vivo</i> – mice model and <i>in vitro</i> HCT116 cells of Colorectal cancer	Ethanol extracts of sporoderm-broken spores stimulated apoptosis and arrested the cell cycle at the G0/G1 <i>via</i> deregulation of the expression of cyclins D1, p21, p16, PARP, BCL2, BAX, NAG-1, and caspase-3 protein, as well as the genes relevant in regulation of apoptosis.	[52]
13.	<i>Grifola frondosa</i>	<i>In vitro</i> TMK-1, MKN28, MKN45 and MKN74 cells of Gastric cancer	Water-soluble extract showed that the extract induced cancer cell apoptosis <i>via</i> caspase-3 pathways.	[53]
14.	<i>Phellinus igniarius</i>	<i>In vitro</i> SGC-7901 cells of Gastric cancer	Ethanol extract promoted apoptosis by an imbalance of mitochondrial membrane potential, activation of caspase-9, -3, PARP cleavage, and increased proportion of BAX/ BCL2.	[36]

ANGIOGENESIS

The growth of malignant cells relies on an adequate supply of oxygen, nutrients and the removal of waste products. Hence vascular support is critical to the development of tumor. In the absence of adequate oxygen, tumor cells may undergo apoptosis or necrosis. However, this is avoided beforehand by cancer cells [54]. The hypoxia induced by uncontrolled proliferation stimulates the activation of pro-angiogenic factors leading to neovascularization. In simple terms, the process of forming new blood vessels from existing ones by cancer cells to cope with oxygen tension in tumor microenvironment is referred to as angiogenesis [55]. The mechanistic principle underlying this neovascularization involves sprouting angiogenesis, Intussusceptive angiogenesis, Vasculogenesis, Recruitment of endothelial progenitor cells, as well as Vascular mimicry [56]. The proangiogenic factors like vascular endothelial growth factor [VEGF], basic fibroblast growth factor [bFGF], angiogenin, transforming growth factor [TGF]- α , TGF- β , etc. aid in the process of vascularization while factors like angiostatin, endostatin, interferon, platelet factor 4, thrombospondin, prolactin 16 kd fragment, and tissue inhibitor of metalloproteinase-1, -2, and -3 act as antiangiogenic factor thereby inhibiting the formation of new blood vessels in tumor microenvironment [57]. The balance in expression of both activators and inhibitory angiogenic factors reflects the aggressiveness of tumor cells [54].

What aids in tumorigenesis can serve as a target to inhibit the growth and further survival of cancer cells. Mushrooms, as a repertoire of bioactive compounds, can interfere with the neovascularization process. Experiments have demonstrated that *Ganoderma lucidum* inhibited early events of angiogenesis in prostate cancer cell lines [PC-3] [58]. The bioactive constituents of *G. lucidum* modulate the phosphorylation of Erk1/2 and Akt kinases in PC-3 cells, thereby inhibiting constitutively active AP-1 leading to a downregulation in the expression of VEGF factor and TGF-beta 1. Both these are proactively involved in the promotion of neovascularization, thus, a downturn in their level leads to the suppression of angiogenesis [56]. Additionally, triterpenoids isolated from various species of mushrooms have been seen to inhibit VEGF, PDGF, EGF and other factors are known to promote angiogenesis [59]. Similarly, when breast cancer cell lines MDA-MB-231 were treated with *Phellinus linteus*, significant inhibition of neovascularization and capillary morphogenesis of human aortic endothelial cells were observed *via* a downturn in the expression of VEGF factor, which itself is a result of inhibition of serine-threonine kinase AKT signalling through suppression of phosphorylation of AKT at Thr308 and Ser473 in breast cancer cells [29]. Furthermore, extract of freeze-dried *Hericium erinaceus* mushrooms, when given intracutaneously to Balb/c mice, resulted in reduced mRNA and protein expression of COX-2, 5-LOX and VEGF factor resulting in the inhibition of the

process of neoangiogenesis in the tumor cells [60]. *Grifola frondosa*, more commonly known as maitake mushroom, has been known for its anti-cancer activity. This edible mushroom has dose-dependently inhibited VEGF-induced proliferation, chemotactic migration, and capillary-like tube formation suppression of angiogenic factor [e.g., VEGF] and extracellular digestive enzyme [e.g., MMP-2 and -9] production, and elevation of enzyme inhibitor [tissue inhibitor of metalloproteinases [TIMP]-1 and TIMP-2] inhibition of angiogenic factor [e.g., VEGF, PDGF, etc.] and extracellular digestive enzyme [e.g., MMP-2 and -9] as well as simultaneous production, and elevation of enzyme inhibitor [tissue inhibitor of metalloproteinases [TIMP]-1 and TIMP-2] [61]. Many more studies have been done on how different species of mushrooms can be used to prevent the process of neovascularization, thereby inhibiting malignant cells. This has been elucidated in Table 4.

Table 4. Mushrooms and angiogenesis.

S.No.	Mushroom species	Cancer cell line	Mechanism of action	References
1.	<i>Grifola frondosa</i>	Chick chorioallantoic membrane [CAM] model of angiogenesis	Water extract effectively inhibited angiogenesis by blocking VEGF signalling.	[61]
2.	<i>Lentinula edodes</i>	PC3 cells of Prostate cancer	Ethanol extracts decreased the level of VEGF.	[62]
3.	<i>Agaricus bisporus</i>	PC3 cells of Prostate cancer	Ethanol extract decreased the level of VEGF.	[63]
4.	<i>Ganoderma lucidum</i>	HO 8910 cells of Ovarian cancer	The treatment caused downregulation of the VEGF expression	[63]
5.	<i>Phellinus linteus</i>	MDA-MB-231 and MCF-7 cells of Breast cancer	Water extract caused downregulation of VEGF related to inhibition of capillary morphogenesis and suppression of serine-threonine kinase AKT signaling were also observed.	[29]
6.	<i>Pleurotus tuber-regium</i>	Wild-type and transgenic zebrafish embryos and HUVECs	ethyl acetate fraction significantly inhibited blood vessel development.	[79]
7.	<i>Ganoderma tsugai</i>	Human colorectal adenocarcinoma Colo205	Inhibits EGFR and VEGF	[64]
8.	<i>Grifola frondosa</i>	HUVEC	Inhibits ROS-mediated ERK [1/2] phosphorylation and VEGF	[61]
9.	<i>Pleuretus eous</i>	Breast cancer cell line [MCF-7]	Inhibits ROS, MMPs Induce Caspase 3 and 9	[65]

(Table 4) cont....

S.No.	Mushroom species	Cancer cell line	Mechanism of action	References
10.	<i>Agaricus brasiliensis</i>	Tumor model in mice	Inhibits VEGF, FGF-2 and TGF- β	[66]
11.	<i>Antrodia cinnamomea</i>	Chorio-allantoic membrane [CAM]	Inhibits VEGF Induce [IFN- γ] and IL-12	[67,68]
12.	<i>Trametes robiniophila</i>	HUVEC, mouse mammary tumor cells [4T1]	Inhibits HIF, JNK, STAT3 and ERK Regulates p53 expression	[69-71]
13.	<i>Poria cocos</i>	Human pancreatic adenocarcinoma cell line [BxPC-3 cell line]	Inhibits NF- κ B, MMP-7	[72,73]
14.	<i>Cordyceps taii</i>	Human lung cancer cell line [A549], Gastric cancer cell line [SGC-7901]	Inhibits VEGF expression	[74]
15.	<i>Cordyceps bassiana</i>	Proliferation of vascular smooth muscle cells [VSMC]	Down-regulates JNK-MAPK pathway	[75]

IMMUNOMODULATION

Cancer cells survive *via* defiance of normal immune machinery [77]. This is attributed to weaker expression of MHC antigens, adhesion molecules and secretion of immune suppressive molecules such as IL-10, and PGE-2 by malignant cells. Immunotherapy has gained ground as the fifth pillar of cancer treatment owing to its ability to remodel immune cells so that they are able to act against cancer cells. The main drivers of immunotherapy are checkpoint inhibitors [CPIs] and chimeric antigen receptor [CAR] T cells. However, these therapies have their own shortcomings in the form of immune-related adverse events and inflammatory responses against healthy tissue. A promising alternative to this can be herbs like mushrooms which are known to possess immunomodulating properties owing to the presence of certain bioactive compounds. Beta-glucans which form the major structural component of the mushroom cell wall, are a potent active ingredient recognized in several immunological activations [immunostimulatory] and immunomodulatory effects. It has been found to activate both innate and adaptive arms of the immune system against cancer cells. The interaction between beta-glucan and DC cells is facilitated by the expression of various pattern recognition receptors like dectin-1, dectin-2, TLR2, TLR6 and CR-3 on the DC cell surface. This binding of beta-glucan with complementary receptors activates downstream signalling pathway, *e.g.*, activation of Nf- κ B, which then induces maturation of DC cells and subsequent release of cytokines and chemokines. The secretion of cytokines like TNF- α , IL-10, IL-6 and IL-23 by DC cells further stimulates T and B cell maturation and proliferation and respiratory burst. Similar to DC cells, binding of beta-glucan to the dectin-1 receptor on macrophages stimulates them for the secretion of several cytokines

such as TNF- α , IL-12, IL-1 β , IL-10, CXCL2, IL-6 as well as enhances their phagocytic ability against cancer cells. These polysaccharides also significantly increased NK cell cytotoxicity by stimulating interferon [IFN] and perforin secretion and increasing the expression of the activating receptor NKp30, with CR3 as a key receptor [76]. All these innate components together act against cancer, alongside the cytokines produced by these cells also activate the adaptive arm, *i.e.*, T and B cells, to target malignant cells. Additionally, The association of beta-glucan to PRRs on DCs and Macrophages upturns their ability to present antigens to T cells leading to the activation of CD8 cytotoxic T lymphocytes. Interaction of glucans with corresponding receptors induces apoptosis of PMN-MDSCs while simultaneously leading to differentiation of M-MDSCs into potent antigen-presenting cells. Thus it reverses M-MDSCs mediated T cell suppression in the cancer microenvironment. Furthermore, Beta-glucan decreases the number of Treg cells at tumor site and subdues their immune suppression activity [12, 78, 79]. All the above factors reactivate the immune cells to target malignant cells, thereby removing them from circulation. Thus mushrooms can act as a potent immunotherapeutic alternative to treat cancer without having any side effects that other conventional immunotherapies are posing before us.

METASTASIS

The dissemination of cancer cells from the site of primary tumor to distinct tissue sites leading to the formation of new colonies, is known as metastasis. It is one of the hallmarks of cancer and accounts for more than 90 percent of cancer-related deaths. However, less than 0.1 percent of tumor cells participate in this process. This complex and interdependent mechanism involves 5 distinct steps - invasion, intravasation, circulation, extravasation, and colonization. Activation of invasion is brought about by various epigenetic modifications triggered by environmental stimuli like aging, circadian disruptions, tumor microbiota, *etc.* Epithelial cells, which are non-motile under normal conditions, are transformed to develop the ability of invasion, dissemination and resist stress. This process is known as Epithelial to Mesenchymal transition and is the sine qua non for metastatic progression and drug resistance. Invasion is followed by intravasation, which is marked by the entry of malignant cells into vasculature *via* disruption of endothelial cells lining the blood vessels. This stage is characterised by over-expression in the integrins. Inside the vasculature, the circulating tumor cells are exposed to physical stresses of circulation like compression and deformation and various kind of immune cells. Cancer cells are smart enough to undo the effect of cytotoxic CD8⁺ T lymphocytes, NK cells, and macrophages *via* the production of IL-6, IL-8, and IL-1 β , thereby stimulating other immune mediators to suppress the anti-cancer activity of immunological agents. When these tumor cells pass through small capillaries, they become entrapped and extravasate. Sinusoidal

capillaries aid in this process; hence, it is easier for malignant cells to extravasate at the site of the liver and bones. After successful extravasation, the cancer cells interact with the surrounding tissue microenvironment and start to colonize at new site, thereby forming secondary tumor. The entire process has multiple target sites, which, if suppressed or induced, can lead to the inhibition of metastasis [80].

Mushrooms, as studied under previous headings, have been a reservoir of bioactive compounds which are known to target different hallmarks of cancer. Together these hallmarks induce the process of metastasis, as described in the above paragraph. Hence, it was not a big deal to hypothesize that mushrooms will be able to suppress the process of invasion and metastasis in cancer cells. The scientific findings are in congruence with this hypothesis. A significant inhibition in metastatic potential is reported when cancer cell lines were treated with mushroom extracts either *in-vitro* or *in-vivo* models. One of the most common medicinal mushrooms *Ganoderma lucidum*, when fed to nude mice, inhibited the number of breast-to-lung cancer metastases *via* down-regulating expression of genes associated with invasive behaviour [HRAS, VIL2, S100A4, MCAM, I2PP2A and FN1] in MDA-MB-231 cells [80]. *Pleurotus ostreatus*, which is the second most consumed mushroom worldwide, is known to possess levostatin, which has inhibited metastasis *via* inhibition of MMP-2 and MMP-9 [12, 81]. Additionally, polysaccharides like beta-glucan, which form a major component of the mushroom cell wall as described above, activate the immune cells to target the malignant cells more efficiently. Thus reducing the chance of cancer cells to settle and adapt in the new environment for metastatic spread. Here we have summarised some of the experiments which demonstrate the antimetastatic potential of mushrooms. To conclude, we can say that metastasis is the end result of the summation of all hallmarks of cancer, and mushroom inhibits metastasis by suppressing the characteristic hallmarks significantly.

CONCLUSION

Thus far, we have seen how constituents of mushrooms in various forms have been effective against the characteristic hallmarks of cancer. We have observed what mechanism underlies when cancer cells are treated with mushrooms in inhibition of proliferation, promotion of apoptosis, suppression of angiogenesis and modulation of an immune response. All these synergistically inhibited the process of metastasis which is the most important reason behind cancer-related death. However, still there remain areas that need to be deciphered precisely, like cross-talks between signalling pathways involved in different processes. The effect of mushrooms in combination with other herbs and conventional drugs needs to be carried out against cancer cells to understand whether they will coordinate and complement their activity. Mushroom-based nanoparticles can be

a new paradigm shift in targeting cancer cells at a specific tissue site. While, more scientific studies need to be carried out to check the response of mushrooms bioactive compounds against cancer stem cells. Though these areas need to be focussed upon, what we have is enough to conclude that mushrooms not only enrich the taste of our diet but are also a potential alternative as an anti-cancer therapeutics.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Antidiabetic Attributes of Mushrooms

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Abstract: Mushrooms are macrofungi, with distinct mycelia structure, and fruiting bodies, divided into stalk and cap that contains spores in most of the species. These mushrooms are edible with diverse therapeutic applications. Old civilizations from India, China, and Korea used these mushrooms to cure diseases, especially diabetes. Diabetes is now a newly emerging pandemic, affecting people worldwide, with special reference to developing countries. There are several medications available for the management of diabetes, but their permanent treatment is still to be explored. Due to synthetic medicines and their adverse effect, people are searching for natural therapeutic agents. Many mushroom species have shown their potential to control diabetes and its related complications, such as weight loss, lipidemia, hypertension, etc. In this chapter, we have discussed five different mushroom species, i.e., *Auricularia auricula-judae*, *Agaricus bisporus*, *Ophiocordyceps sinensis*, *Ganoderma lucidum*, and *Pleurotus* species with their potential therapeutic application against diabetes and its related complications.

Keywords: Anti-diabetic properties of mushroom, Diabetes, Diabetes type 1, Diabetes type 2, Edible mushroom, Medicinal mushrooms.

INTRODUCTION

Mushrooms are macrofungi, having mycelia and fruiting bodies with spores, showing a variety of therapeutic activities which is beneficial to human health. Mushrooms are a good nutraceutical agent due to their medicinal and nutritional value. Recent research studies have promoted mushrooms as a biotherapeutic for new generations [1]. Besides, mushrooms are adding value to economic growth because they can be grown worldwide with fewer investments and requirements [2, 3]. Malnutrition is one of the serious concerns in the 21st century. It can be caused due to over intake of food or lack of nutritional aspects in food (vitamins,

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carbohydrates, minerals, saturated fats, fibers, salts) may also be called hidden hunger that may further develop many clinical symptoms, *i.e.*, obesity, loss of weight, and non-communicable diseases (diabetes, cardiovascular diseases, *etc.*). Mushrooms are a rich source of minerals (Ca, P, K, Fe, and Cu), carbohydrates, and vitamins (A, B-complex, C, D, K) [4] which can be found only in meat and animal-based food. Many secondary metabolites (*i.e.*, phenolic compounds, lectines, terpenoids, lactones, sterols, and alkaloids) have shown their potential against cancer, drug-resistant bacteria, diabetes, hypertension, and high blood pressure [5 - 10].

Due to all their nutritional values and culinary effects of secondary metabolites, mushrooms are a potential therapeutic agent against diabetes. It contains a few insulin-like enzymes that can facilitate the break-down of complex carbohydrate molecules into simple sugars and improve the resistance of insulin [11 - 13]. It smoothens the liver, pancreatic endocrine gland, and metabolic functions by stimulating the secretions of insulin and hormones. Many studies have revealed that mushrooms, if supplemented in the diet, may lower the low-density lipoprotein, triglycerides, and total cholesterol and help to increase the level of high-density lipoprotein [14 - 18]. The bioactive compounds, *i.e.*, α , and β -glucans, with other dietary fibers, aid in regenerating the pancreatic β -cells that further increase the flow of insulin in the bloodstream to regulate the glucose level in the blood. Due to their low fat and carbohydrate content, mushrooms are the best food for diabetic patients [19 - 22]. There are many hypoglycemic agents, such as gliclazide, exenatide, insulin, metformin, phenformin, rosiglitazone, tolbutamide, and troglitazone, that are mainly used in treating diabetic patients and are found to be much effective in controlling it. But the major problem is that synthetic drugs may have adverse side effects that might alter the course of diabetes into chronic diabetes complications that may associate with a high rate of morbidity and mortality. Thus, as an alternative, mushrooms can be used as an effective hypoglycemic and anti-diabetic agent in preventing and controlling diabetes because of their nutritional and medicinal values [23] control diabetes to which mushrooms can be a good candidate in terms of medicament agent.

Diabetes mellitus (DM) is one of the most rapidly growing pandemics that needs to be controlled. Developing countries are the most affected by diabetes, and these numbers are increasing day by day. DM can be considered a metabolic disorder that is caused due to the self-destruction of pancreatic β -cells by the antibodies, also called an autoimmune disorder. It is under the heterogeneous and genetic disorder groups [24]. With the destruction of β -cells, less/no insulin secretion occurs, leading to the rise of glucose levels [25]. If the high glucose level persists for a long time, then it may cause several health-related complications, such as cardiovascular disorder, cancer, hypertension, glaucoma, nephropathy,

neuropathy, etc [26 - 38]. The most common DM is diabetes type 1, and diabetes type 2.

Diabetes type 1 is developed due to the autoimmune destruction of pancreatic β -cells, and it is a rare disorder, also called insulin-dependent diabetes mellitus (IDDM), with 5-10% of cases reported, according to Diabetes Care, 2008 report. Type 2 diabetes is caused because of insulin deficiency and resistance of the peripheral tissues, also called non-insulin-dependent diabetes mellitus (NIDM). This type of diabetes is the most common disorder, with a 90-95% occurrence rate [39].

In this chapter, we describe the anti-diabetic attributes of various mushroom species.

DIABETES MELLITUS (DM)

DM is one of the oldest lifestyle-related metabolic disorders, developed due to less insulin secretion or absence of insulin because of β -cells self-destruction by antibodies. Insulin is a hormone that regulates the blood glucose level, secreted by the β -cells of the pancreas, and utilizes the sugars and carbohydrates to form the energy that participates in metabolic actions. The glucose metamorphosis into glycogen is hampered in the liver if the insulin level is not in the normal range which is 4.0-6.0 mmol/L in pre-prandial conditions and up to 7.8 mmol/L in post-prandial conditions [40]. If sugar levels cross the mark of more than 15 mmol/L, then it can cause some serious health-related issues, especially in terms of nerves, kidneys, and cardiovascular [41]. Generally, diabetes can be categorized into two common groups, *i.e.*, type 1 and type 2 diabetes mellitus.

Diabetes Mellitus Type 1 (DMT-1) or Insulin-dependent Diabetes Mellitus (IDDM)

DMT-1 can be diagnosed in the early stages of age with symptoms of ketonuria, and loss of weight due to less insulin secretion/no secretion of insulin by the body of the patients, whose required daily doses of insulin. DMT-1 is an autoimmune disorder caused by the cellular-mediated obliteration of pancreatic β -cells found in Islets of Langerhans [42]. As this disease is diagnosed early, children are the victims, but adults are also affected. As it is a catabolic disorder, glucagon and insulin are not secreted in the bloodstream. In diabetes conditions, the β -cells cannot react to the stimuli received by the cellular signaling pathways [43]. Environmental toxins and other external factors such as viruses (coxsackievirus B4, and mumps virus), and chemotoxins are also contributed to developing the DMT-1. Genetic factors are also a serious concern that increases the risk of developing DMT-1. Human leukocyte antigen (HLA), a complex of genes

(DQA1, DQB1, and DRB1), found on chromosome 6, expresses the essential protein that participates in the immunological process and can facilitate the diabetogenic viruses, to activate the immune response against the pancreatic β -cells.

Diabetes Mellitus Type 2 (DMT-2) or Non-insulin-dependent Diabetes Mellitus (NIDDM)

DMT-2 patients do not need insulin from external sources to stop ketonuria and do not suffer from ketoacidosis. If high glucose levels and ketosis are not in control by oral medications and diet supplements, then an insulin injection is needed to overcome the situation [44]. DMT-2 is caused due to the non-responsiveness of peripheral tissues against insulin action. In the cellular signaling mechanism, the receptors for insulin and other related protein molecules show irresponsive action against insulin. The tissue-specific for insulin actions do not respond and gets resistant, causing an increasing level of glucose in the patient's body [45]. DMT-2 is associated with genetic factors and has a 50% frequency rate of transmission of this disease to their offspring. DMT-2 is also categorized into non-obes, and obes-subtypes. To control this disease, a balanced diet, regular exercise, and oral medication is necessary for a healthy life.

ROLE OF MUSHROOMS IN DIABETES

Edible mushrooms have the potential to control and prevent the onset of diabetes in humans and animals. Mushrooms are rich in bioactive molecules, such as dietary fiber, polysaccharides, proteins, phenolic, alkaloids, terpenoids, steroids, vitamins, minerals, and other compounds that promote various health benefits functions. Such bioactive molecules are known to produce antidiabetic, antioxidant, anticholesterolemic, and antihyperlipidemic molecules that have shown to be promising in the control and prevention of diabetes, cardiovascular disease, inflammation, and cancer [46]. The consumption of mushrooms can neutralize the concentration of reactive species because of the presence of bioactive molecules, which are also very much helpful in the flourishing of gut microflora acting as prebiotics which would in the breakdown of the fats and glucose molecules in food. Thus, edible mushrooms have the potential to promote the normal function of the pancreas and the liver by enhancing insulin sensitivity, production, and release, which would ultimately improve healthy metabolic function [24, 46]. Mushrooms, as a prebiotic, are known to be useful for the growth and development of health-promoting bacteria in the gastrointestinal tract. Many studies have reported that the consumption of mushrooms reduces gut inflammation, obesity, lipid accumulation, insulin resistance, and inflammation in Type II diabetes. It is stated that a higher concentration of blood cholesterol or

hypercholesterolemia contributed to the progression and development of diabetes and its chronic diabetes complications, β -cells dysfunction, and reduced insulin sensitivity. The epidemiological and physiological studies revealed that dietary fiber (mostly carbohydrates including oligosaccharides and polysaccharides that are indigestible by human digestive enzymes) intake can lead to a reduction in the risk of coronary heart disease, stroke, hypertension, diabetes, obesity, overweight, dyslipidemia, hypercholesterolemia, and gastrointestinal disorder. The high levels of dietary fiber intake are also found to be beneficial in improving the homeostasis environment of the glycemic control system by decreasing postprandial glycemia, and insulinemia, enhancing insulin sensitivity, and liver function, and reducing the use of oral medication and insulin doses in Type-I and Type-II diabetes [24, 47]. Mushroom is a good source of dietary fiber [2, 3, 24, 46, 47]. According to studies on the higher amount of dietary fiber intake in Type-I and Type-II diabetes, the non-diabetes subject performed under Randomized Controlled Trials (RCT) to check the effectiveness of new emerging treatments in diabetes prevention and management shows promising efforts in reducing fasting blood glucose and fasting blood insulin levels by enhancing insulin sensitivity in both diabetes and non-diabetes subjects. It is also suggested that the use of fiber supplements is more efficacious in improving diabetes, weight loss, cardiovascular disease, laxation, gastrointestinal infection, and immune activity [24, 46, 47]. According to many studies and report, various mushrooms species are considered potent anti-diabetic agents that are actively participating in controlling diabetes in humans and animals, such as *Auricularia auricula-judae*, *Agaricus blazei*, *Agaricus bisporus*, *Agaricu brasiliensis*, *Agaricus campestris*, *Agaricus sylvaticus*, *Coprinus comatus*, *Cordyceps takaomantana*, *Cordyceps militaris*, *Cordyceps sinensis*, *Grifola frondosa*, *Ganoderma lucidium*, *Hericium erinaceus*, *Inonotus obliquus*, *Lentinula edodes*, *Phellinus baumii*, *Phellinus merrillii*, *Pleurotus eryngii*, *Pleurotus fossulatus*, *Pleurotus ostreatus*, *Pleurotus pulmonarius*, *Sparassis crispa*, *Tremella aurantia*, *Tremella fuciformis* and *Wolfiporia extensa* [2, 24, 48]. The experiment tested on diabetic mice reported that the extracted polysaccharide and α -glucans from the fruiting bodies of *Grifola frondosa* were quite effective in decreasing the concentration of fasting blood glucose, triglycerides, cholesterol, and were reported to increase blood insulin and insulin sensitivity. Another study suggested that mushrooms decrease the hyperglycemia concentration in streptozotocin-induced rats with gestational diabetes. This act of lowering the total blood glucose concentration was mainly attributed to the presence of vanadium and alpha glucose inhibitors in the mushroom. Mushrooms were reported to improve blood glucose, serum lipid profile, liver glycogen, and liver function by enhancing antioxidant activity in the pancreas, liver, and kidney in streptozotocin-induced diabetic rats. Mushrooms were proven to improve innate immunity by modulating

the level of inflammatory cytokines such as tumor necrosis factor- α , interferon- γ , interleukin 4, and interleukin 6 in Type II diabetes rats. Mushrooms have the potential to protect DNA, liver, and pancreas injury by increasing the activity of radical scavenging antioxidants, high-density lipoprotein cholesterol, enhanced catalase, superoxide dismutase, glutathione peroxidase function, suppressed α -amylase, and α -glucosidase activity that result in lowering body fats, free fatty acid concentration, triglycerides, low-density lipoprotein cholesterol, fasting blood glucose levels in diabetic rats [2, 24, 46, 48]. The aqueous extracted polysaccharide of *Ganoderma lucidum*, when administered into diabetic mice, significantly reduces blood glucose levels by suppressing the activity of phosphoenol pyruvate carboxykinase (PEPCK) that is involved in gluconeogenesis, reduced blood glucose levels, lipid peroxidation, low-density lipoprotein cholesterol and enhance high-density lipoprotein cholesterol. Polysaccharides from many different species of mushrooms were reported to reduce insulin resistance and fat deposition by activating autophagy. Furthermore, ergosterol extracted from the *Pleurotus ostreatus* was shown to enhance glucose uptake, GLUT 4 translocation, and phosphorylation of protein kinase B and C in L6 rat's myoblast cell line [46]. Edible mushrooms have the potential to develop into novel therapeutic agents. However, inadequate data regarding the efficacy of mushroom species on diabetes and its molecular mechanism of tackling diabetes as an antidiabetic potential is still unknown. But there was evidence concerning the efficiency of mushrooms as a therapeutic agent that came from animal studies. Hence, future research, investigation, and development should focus on utilizing mushrooms and their products as possible drugs for the treatment of diabetes. One should find a way to convert the extracted mushrooms into suitable pharmaceutical products such as tablets, capsules, and pellets. This major finding may be a boon for those patients who have diabetes and other metabolic syndromes [46].

Mushrooms have been used for their culinary effects since ancient times by the civilizations of India, China, and Korea. There are numbers of mushroom species, that have been tested for their anti-diabetic attributes. Some of them are discussed below in detail.

Auricularia Auricula-judae

Auricularia auricula-judae (*A. auricula-judae*), an edible-medicinal mushroom, exhibits health-beneficial properties found in almost all parts of the world, including India and China. Its medicinal attributes include anti-diabetic, anti-cancer, anti-oxidant, anti-hyperlipidemic, and immunomodulator [49 - 51]. Its water-soluble polysaccharide and dried powder (500 mg/kg; 1000 mg/kg of body weight) have shown promising results to reduce the urinary glucose level, blood

glucose level (35%, and 39%), total cholesterol (18%, and 22%), and triglyceride (12%, and 13%) respectively [51, 52].

Agaricus Bisporus

An *Agaricus bisporus* (*A. bisporus*), also known as the white button mushroom, is an edible mushroom with many medicinal benefits. It has shown a diverse pharmacological potential against many diseases. It contains various nutritional values such as carbohydrates (39.9%), protein (17.5%), fats (2.9%), vitamins (B2, B12, C, D), and dietary fibre. Secondary metabolites and biomolecules, such as polyphenols, terpenoids, and ergothioneine, have shown culinary effects against certain diseases [53, 54]. Dietary supplements with fruiting bodies can increase the glycogen content in hepatocytes and upregulate the expression of glucokinase (GK) in the STZ-diabetic mice model. The fruiting of *A. bisporus* showed significant effects of anti-diabetic, and hypocholesterolemic in diabetic mice [17]. High cholesterol level is considered to show direct effects on the functioning of β -cells and related metabolic activities, which results in the loss of functions of pancreatic β -cells, and the onset of diabetes [55]. *A. bisporus* is rich in dietary fibers that play a crucial role to protect the organs from the adverse effects of diabetes by lowering high glucose and cholesterol levels [47].

Cordycep Sinensis

It is also known as *Ophiocordycep sinensis* (*C. sinensis*), a fungus that grows in the caterpillar. People from Tibet and China have used herbs from ancient times to cure diseases. *C. sinensis* have anti-oxidant, anti-tumor, anti-osteoporosis, anti-inflammatory, anti-arteriosclerosis, and anti-depression attributes. *C. sinensis* considered “soft gold” because of its high value, *i.e.*, \$20,000 - 40,000/kg in the international market. Capsules prepared by the extract from fruiting of *C. sinensis*, were subjected to clinical trial by giving the dose of capsules (3g/day), which showed the potential to reduce the blood glucose level [56]. The administration of the fruiting body of *C. sinensis* to diabetes patients improved their body weight, and polydipsia, which proved it an ideal food for diabetic people [57]. The polysaccharide of *C. sinensis*, accelerates the catabolism of glucose by improving insulin sensitivity and reducing the plasma glucose level in genetically developed animals [58, 59]. Extract prepared from the fermented mycelium of *C. sinensis*, protect the β -cell from damage, reduces the deposition of collagen in the liver, and promotes the activity of renal Na-K-ATPase (NKA) [60].

Ganoderma Lucidum

Ganoderma lucidum (*G. lucidum*), also known as “Reishi/Lingzhi”, has been used by the Chinese civilization since ancient times for good health benefits and long

life. Many secondary biomolecules, β -glucans, ganoderic acid, and their derivatives, glycoproteins, and terpenoids, have been isolated from this mushroom that can be beneficial for health improvement and also very helpful for the prevention of diseases. In many studies, researchers have reported the therapeutic effects of *G. lucidum* in cancer, diabetes, hypertension, hepatitis, and others [61]. *G. lucidum* have excellent activities against high glucose level and low cholesterol level in plasma [62, 63]. Polysaccharide isolated from *G. lucidum* helps to facilitate the flux of Ca_2^+ in β -cells of the pancreas [64]. In a clinical trial, a polysaccharide isolated was administered to 71 DMT-1 patients, showing its potential to lower the high plasma glucose level to a safer concentration level [65]. Another study on polysaccharides of *G. lucidum*, in streptozotocin (STZ)-induced diabetic rats, can increase the expression of antioxidant levels, and serum insulin, and decrease the level of plasma glucose, and lipid peroxidation [66, 67]. *G. lucidum* isolated lanostane triterpenoid having potential inhibitory activity against the α -glucosidase enzyme, generates glucose by the break-down of complex carbohydrate molecules such as sucrose, and starch [68]. Fudan-Yueyang-*G. lucidum* (FYGL), an inhibitor, isolated from the *G. lucidum*, has the potential to inhibit the activity of protein tyrosine phosphatase 1B (PTP 1B), and also showed antidiabetic activity in the diabetic rat model [69].

Pleurotus Species

Pleurotus mushrooms are also known as Oyster mushrooms. This mushroom species have a variety of therapeutic applications, such as anti-hyperglycemic, anti-hyperlipidemic, anti-cancer, anti-aging, anti-microbial, anti-hypercholesterolemic, anti-oxidant, etc. Crude aqueous extract of *Pleurotus pulmonarius*, showed anti-diabetic effects in alloxan-induced diabetic mice, however, it did not show any cytotoxic effects even up to 5 g/kg of body weight in mice [70]. Polysaccharides reduced the 44% blood glucose level administered to diabetic rats, whereas *Pleurotus ostreatus* powder (4%) improved the postprandial glycemia and reduced the total cholesterol by 40%, after two months of dosing to STZ-induced diabetic rat groups [71]. *Pleurotus eryngii* was evaluated for its anti-diabetic, and hypolipidemic activities, and found significantly lower levels of both factors. Its polysaccharide may also reduce cholesterol, triglyceride, and low-density lipoprotein, but increase the level of high-density lipoprotein and enhance insulin sensitivity [72].

SUMMARY AND CONCLUSION

Diabetes mellitus is a metabolic disorder it can be mainly categorized into two types. Type 1 is caused by cellular-mediated autoimmune destruction of the β -cell of the pancreas. Type 2 is caused by the resistance of insulin. Many antidiabetic

agents are available in the market, but they have many adverse effects. Due to synthetic medicine's adverse effects, people are searching for natural therapeutic agents. Due to their nutritional values and culinary effects of secondary metabolites, and other biomolecules, mushrooms are a potential therapeutic agent against diabetes. The bioactive compounds such as α , and β -glucans with other dietary fibers, aid to regenerate the pancreatic β -cells that further increase the flow of insulin in the bloodstream to regulate the glucose level in the blood. The epidemiological and physiological studies revealed that dietary fiber intake can lead to a reduction in the risk of coronary heart disease, stroke, hypertension, diabetes, obesity, overweight, dyslipidemia, hypercholesterolemia, and gastrointestinal disorder. *Auricularia auricula-judae* water-soluble polysaccharide and dried powder (500 mg/kg; 1000 mg/kg of body weight) have shown promising results to reduce the urinary glucose level, and blood glucose level (35%, and 39%), total cholesterol (18%, and 22%), and triglyceride (12%, and 13%) respectively. Dietary supplements of *Agaricus bisporus* fruiting bodies can increase the glycogen content in hepatocytes and upregulate the expression of glucokinase (GK) in the STZ-diabetic mice model. The administration of the fruiting body of *Ophiocordyceps sinensis* to diabetes patients improved their body weight, and polydipsia, which proved it an ideal food for diabetic people. Polysaccharide isolated from *Ganoderma lucidum* helps to facilitate the flux of Ca_2^+ in β -cells of the pancreas. *Pleurotus* mushroom species have a variety of therapeutic applications such as anti-hyperglycemic, anti-hyperlipidemic, anti-cancer, anti-aging, anti-microbial, anti-hypercholesterolemic, anti-oxidant, etc. All these culinary effects of mushrooms are opening the path to controlling diabetes in a natural and much safer way.

FUTURE PERSPECTIVE

The potential of controlling diabetes by the biomolecules found in mushrooms can be increased by enhancing the expression of these molecules, which will further benefit diabetic patients. With the discovery of these therapeutic applications, if people use mushrooms in their daily diet, it could be more beneficial because of their nutritional value.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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CHAPTER 5

Antimicrobial Potential of Mushrooms: Emergence of Mycotherapy

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Abstract: The 21st century enters a “post-antibiotic world,” with just a few alternatives for combating antibiotic-resistant microbial strains. The search for new antimicrobials which could overcome the situation of antimicrobial resistance is of prime importance and the need of hour. Herbal antimicrobials pose a plethora of new antimicrobial drug discoveries. Mushrooms give rise to a number of bioactive chemicals that are known to have anti-pathogenic qualities as well as safer and more effective therapeutic effects in the treatment of human diseases. As a result, this chapter emphasises that mycoconstituents might be an alternate treatment regimen and could play a role in novel drug discovery against various infections. This chapter contains information about the potential use of mycoconstituents in the management and treatment of infectious diseases. The approaches illustrate the importance of primary screening of bioactive molecules from mushrooms as a potential step by offering new possibilities for clinical and pharmacological research and development. Traditional antibiotics can now be substituted with newer and more effective natural antimicrobials derived from mushroom extracts to treat a variety of fatal and multi-drug resistant infectious diseases. As a result, this functional food extract might play a significant role in naturally combating infections and offering a comprehensive approach to treatments. Finally, we will go through the mechanics of mushroom antimicrobial potentials and presents an insight into “Mycotherapy”.

Keywords: Antibiotics, Mushrooms, Mycoconstituents, Pathogenic, Resistance.

INTRODUCTION

Infectious diseases caused by drug-resistant germs can lead to high mortality and hospitalization, placing a huge financial burden on patients and healthcare sys-

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tems while hindering long-term growth goals [1, 2]. The WHO has reported that AMR is one of the top ten public health challenges facing humanity. The cost of AMR in the economy is high. In addition to death and injury, chronic illness leads to long-term hospital visits, the need for more expensive medications, and financial hardship for those affected [3]. Antimicrobial Resistance (AMR) poses a major global challenge to human, animal and environmental health. This is due to the emergence, distribution and spread of multidrug-resistant pathogens (MDR) or 'superbugs'. MDR bacteria live around a triangle or niche between animals, humans and the environment, and these viruses are linked to this triangle. Potential causes of "global resistance" or AMR include overuse of antibiotics in animals (food, livestock and water) and humans, inadequate sanitation/hygiene and removal of weakened antibiotics or residues from the environment through manure/surface. These factors contribute to the suppression of genetic selection in the emergence of MDR bacterial infections in society [4, 5]. Currently, antibiotic resistance is a growing health threat worldwide and is the cause of nosocomial and often fatal infections [6]. The 21st century enters a "post-antibiotic world," with just a few alternatives for combating antibiotic-resistant microbial strains. The European Union (EU) expects that by 2050, this outcome will be responsible for 10 million fatalities per year. One of the primary drivers of the development of novel medicines derived from natural antimicrobial sources is the global increase of AMR versus current treatments [7]. As a result, it is vital that a new class of medication should be developed to fight this resistance. The demand for alternative therapies for epidemics is growing. This, in fact, prompted the emergence of new mycopharmaceuticals with no side effects focused on mushroom bioprospecting. Globally, mushrooms are one of the most important weapons in dietary medicine and can be seen as an effective tool in combating malnutrition as well as numerous ailments and conditions [8, 9]. Many countries use these traditional foods as a nutraceutical or their derivatives have been developed as drug molecules. Several antimicrobial agents are found within mushrooms, making them an excellent source of "green" antimicrobials. Fruit and mycelium bodies contain substances that have different antibodies. In the treatment of human diseases, certain mushrooms have been shown to possess antibacterial properties. In the decades to come, mushrooms can be considered a magic plant that can create a positive reaction because of their soothing properties [2].

CLASSIFICATION OF ANTIMICROBIAL AGENTS

The term antibiotics refer to any substance, natural or synthetic, that inhibits or kills microorganisms, when used therapeutically, antibiotics are referred to as antimicrobial drugs. Antibiotics are broadly classified into five categories on the

basis of their source of origin, mode of action, spectrum or range of susceptible/resistant microbes, function and chemical structure [10].

Classification According to the Type of Action

The activity shown by antibacterials can be either bactericidal or bacteriostatic. The bactericidal effect is demonstrated by attacking bacteria's cell wall or cell membrane and ultimately destroying it completely, while bacteriostatic acts to inhibit or suppress the growth of bacteria by acting on their metabolic pathways or pathways for protein synthesis [11].

Classification based on the Source of Antibacterial Agents

On the basis of their origin, antimicrobial drugs can be divided into three categories: natural and synthetic. Natural antimicrobials are those found in natural organisms which possess life, such as plants, animals, or microorganisms. They comparatively have high toxicity than synthetic antibacterials. Cephalosporins, benzylpenicillin, cefamycins, and gentamicin are natural antibiotics or antibacterials that are well-known examples. In terms of effectiveness, synthetic antimicrobials are comparatively more effective as they are not present in nature, and the microorganism is not exposed to them until they are released. Moxifloxacin and norfloxacin are promising synthetic antibiotics [12]. Aside from natural antimicrobials and synthetics, semisynthetic are those antibiotic drugs found in nature that have little change in their chemical structure and function to benefit from natural ones, *e.g.*, Ampicillin which is based on penicillin.

Classification based on Activity Spectrum

On the basis of their effectiveness, the easy-to-resistant / resistant pesticides can be divided into two groups: narrow-spectrum antibiotics are effective only against either Gram-positive or Gram-negative bacteria, *e.g.*, vancomycin. While broad-spectrum antibiotics are those effective against a wide range of Gram-positive as well as Gram-negative bacteria, *e.g.*, tetracycline [10, 11].

Classification based on Chemical Structure

The unique composition and chemical composition of antibiotics give them unique therapeutic properties. Therefore, basically and in the formulation of antimicrobials, it is divided into two groups: group A and group B, *i.e.*, β - lactams and aminoglycosides, respectively.

β-lactams

These are antibiotics with a four-limbed ring (β -lactam ring), which may have additional side effects or further cycles. This class includes penicillin derivatives, cephalosporins, monobactams, and carbapenems, among others. The structure of β -lactams prevents cross-linking of carbohydrate & peptide components of peptidoglycan and hence is more effective against gram-negative bacteria.

Aminoglycosides

Drugs with two amino sugars joined to an aminocyclitol by a glycosidic bond. Streptomycin, tobramycin, gentamicin, sisomicin, neomycin, netilmicin, kanamycin and other aminoglycosides are commonly used. It generally binds to the phospholipids and lipopolysaccharide of the membrane structure hence permeabilizing the membrane. It can also bind to the 30S ribosomal subunit, thereby preventing the movement along the mRNA, so that the triplet code cannot be read [10, 13].

SOME OTHER WELL-KNOWN ANTIMICROBIAL AGENTS

Tetracycline

It is one of the most commonly used bacteriostatic drugs. It has a sulphonamide group, imparting the effectiveness of gram-positive and gram-negative bacteria. It binds to the 30s ribosomal subunit of ribosomes, allowing it to function by preventing the formation of aminoacyl tRNA reaction. Tetracyclines can be naturally obtained from streptomyces and can be modified and produced in a synthetic form [14].

Macrolides

Macrolides are antibiotics with a macrocyclic lactone ring, with deoxy sugars, (cladinose and desosamine) attached to it. Macrolides bind to the 50S subunit of the ribosome, thus preventing transmission *e.g.*, Roxithromycin and Erythromycin.

Quinolone

Synthetic antibiotic quinolones are found in quinine. It works with topoisomerase, thus inhibiting its function and preventing the transcription and replication of bacterial DNA, *e.g.*, Nalidixic acid.

Streptogramin

Streptogramin is divided into two groups: group A are polyunsaturated macrolactones that inhibit aminoacyl tRNA binding to the ribosome, and group B are cyclic hexadepsipeptides which prevent the action of peptidyl tRNA [15, 16], *e.g.*, Dalfopristin and quinopristin.

FUNCTION-BASED CLASSIFICATION OF ANTIBACTERIAL DRUGS

Antimicrobials target processes like protein synthesis, cell wall synthesis, nucleic acid synthesis, and cell membrane function, which are responsible for the growth of bacteria. Thus based on their mechanism of action, the antimicrobial agents can be divided into the following [11]:

Inhibitors of Membrane Function

The cytoplasmic membrane acts as a selective barrier to the cell. Whenever these active cytoplasmic membranes are disrupted, macromolecules and ions will emerge; this will lead to cell destruction or death. Polymyxins are considered to be the preferred toxins of Gram bacteria as they change the structure of the membrane due to their specification of polysaccharides, creating osmotic imbalances. Ionophores like Valinomycin, Monensin A, Nigericin and Lasalocid form complex ions and transport them in the same way and unregulated manner through the membrane, disturbing its ion concentrations.

Protein Synthesis Inhibitor

These antimicrobials work in the starting and stretching stages of protein synthesis, thus completing the process. As bacterial and eukaryotic ribosomes are very different in structure so they can be targeted selectively with these antibiotics. For example, some antibiotics aminoglycosides bind to the rRNA (16S) helix and produce the same flip-out of A1493 and A1492, which led to the incorporation of negative amino acids in the newly formed series.

Nucleic Acid Synthesis Inhibitor

Prokaryotes and eukaryotes differ in structure and function and contain a variety of DNA and RNA synthesis mechanisms that make them selectively toxic to antibiotics. Antibacterials that fall into this category can be classified as DNA inhibitors and RNA inhibitors. Rifampin, for example, binds to DNA-based RNA

polymerase, forming a wall that prevents RNA expansion. Thus, the normal functioning of the virus works by inhibiting the genetic process. Similarly, Quinolones damage a viral cell by inhibiting DNA duplication (binding to DNA gyrase, inhibiting its activation) [11, 17]. Different modes of classification of antimicrobial agents are shown in Fig. (1).

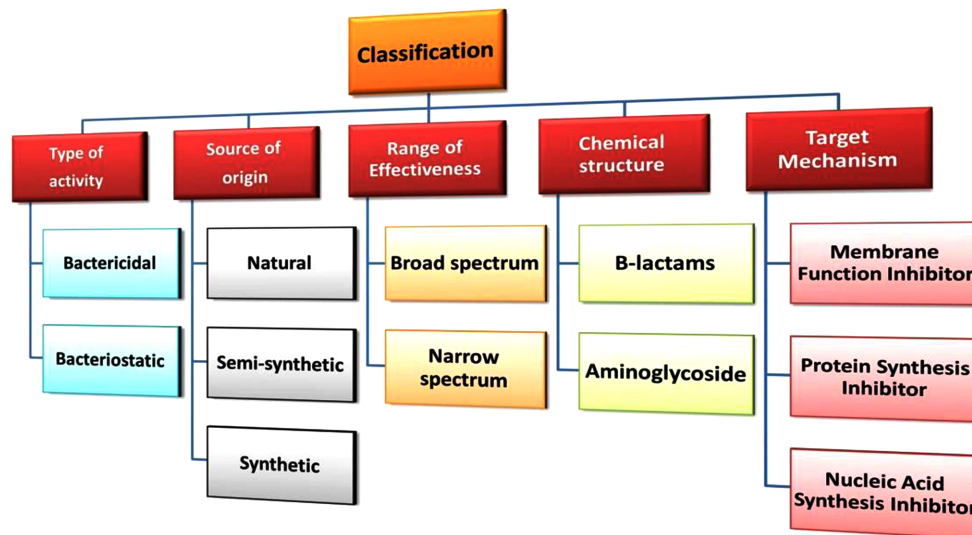


Fig. (1). Different modes of classification of antimicrobial agents.

MECHANISM OF ANTIMICROBIAL RESISTANCE

Infectious diseases are a major cause of death and disease, and the advent of antimicrobial resistance adds little to this. Factors contributing to the growing resistance in microorganisms include increased consumption/overuse of drugs, and inappropriate prescription of multi-drugs or broad-spectrum drugs [18 - 20]. In evolution, bacterial pathogens have developed resistance against various antimicrobials [21]. Such resistance against antimicrobials is achieved by systems involving the molecular and cellular-based machinery of the bacterial system [22]. Antibiotic resistance in bacteria has been declared one of the most important public health threats by the World Health Organization [23].

The organisms can develop “intrinsic resistance” on exposure to natural antibiotics by reducing the outer membrane permeability (like lipopolysaccharide, in the gram-negative bacteria) and the natural efflux pumps action. While a microorganism can develop the “acquired resistance” due to mutations in chromosomal genes or due to the acquisition of resistance through external gene transfer or modification by horizontal gene transfer (transformation, transposition, and conjugation) or mutations in its chromosomal DNA [24].

The resistance/susceptibility of antimicrobial agents depends on various factors. The establishment of susceptibility breakpoints (susceptible, intermediate and resistant) basically depends on the *in vitro* activity of the given antibiotic against the amount of microbial load applied, along with the various dependent pharmacological parameters (*e.g.*, the site of infection and a load of antimicrobials) [25]. The mechanism of antibiotic resistance in the bacterial population is depicted in Fig. (2).

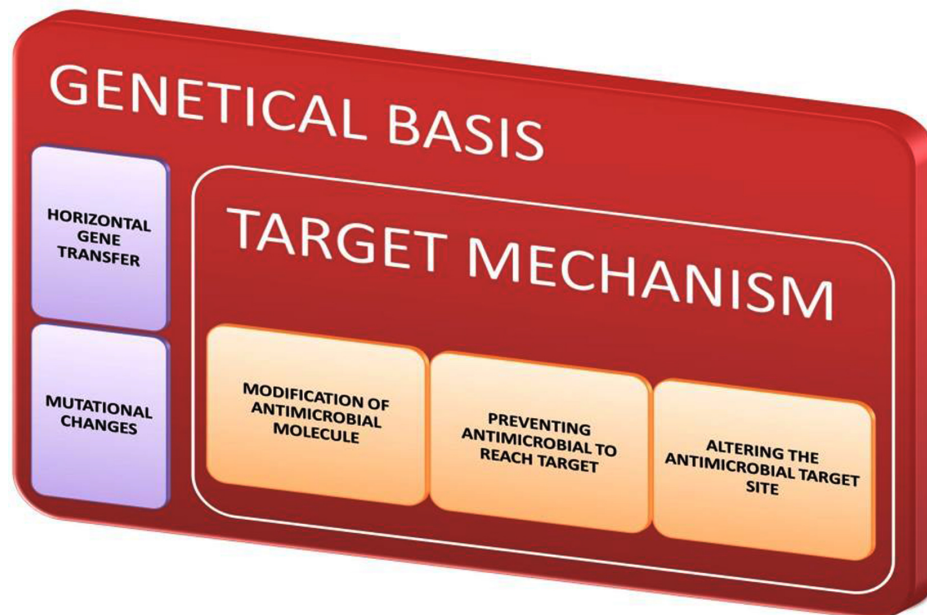


Fig. (2). Mechanism for antimicrobial resistance in bacterial population.

BIOMOLECULES OF MUSHROOMS AS A NATURAL ANTIMICROBIAL AGENT: MYCOTHERAPY

Mycotherapy is a treatment that uses a fungal regime, that is, mushrooms, as medicinal properties. The name was coined by Researchers at Hifas da Terra in 2006 and has since been used worldwide to refer to fungal treatment (or parts of it) for health, prevention and support of combined therapies for various pathologies. Finally, mushrooms contain more than 150 bioactive compounds in their structure. Their consumption provides us with the best of bioavailable alpha and glucans, but also enzymes, prebiotics, natural antibiotics, B vitamins, ergosterol, minerals such as selenium and zinc, essential amino acids and other nutrients that help homeostasis and/or body balance [26, 27].

The ability of mushrooms to produce a bioactive metabolism makes them a valuable source of drugs [28]. Fig. (3a) depicts mycoconstituents of mushrooms

with diverse medicinal uses as well as antimicrobial properties. Mushrooms contain organic matter and are good for the body. Mushrooms are traditionally used for medicinal purposes and are extremely important in the scientific and medical world. In addition, fungi are widely known as efficient producers of organic and products made from natural organic sources [29]. Therefore, mushrooms can be a different source of new antimicrobial compounds, especially secondary metabolites, such as terpenes, steroids, anthraquinones, benzoic acid compounds, and quinolones, as well as other key metabolites such as oxalic acid, peptides, and proteins. For example, it is well established that *Lentinus* manure has antibacterial properties against both gram-positive and gram-negative microbes [30]. Polysaccharides, glycosides, alkaloids, flavonoids, carotenoids, terpenoids, proteins, tocopherols, fats, trans fats, oils, folates, lectins, enzymes, minerals, ascorbic acid, phenolics and organic acids are mostly just several of the bioactive chemical substances found in macrofungi [31]. Polysaccharides have significant medicinal properties and glucan is the most abundant and versatile metabolite with a wide range of natural interactions [32, 33]. Eating mushrooms has produced many phytochemical bases such as alkaloids, glycosides, saponins, tannins, flavonoids, reducing compounds and polyphenols [34]. Isolation of antibiotic metabolites, specifically oudemansin, strobilurins A, D, Illudin S and Pterulone B from *Collybia nivalis*, *Omphalotus olearius*, *Flavolaschia* sp., and *Pterula* sp., respectively [35]. Throughout mycelial growth, the genus *Cyathus striatus* produces striatins A, B, and C, which act as crystalline antibiotics and are very effective in preventing fungal infections, various gram-negative microorganisms, and some gram-positive bacteria [36, 37]. The mode of action of various antibodies is divided into fungi with their own purposes, such as DNA, RNA and protein. Fig. (3b) depicts the potential antibacterial mechanism of action of mushroom mycoconstituents.

However, most antimicrobials have no target, and their effectiveness is unclear. *Pleurotus*, which shows good potential in the production of bioactive compounds. *Pleurotus ostreatus* was cultivated with a variety of ingredients. They confirmed that changing these agronomic metrics is a promising way of addressing both medicinal byproducts as well as improve antimicrobial activity, as evidenced by the presence of innumerable mycochemical metabolites. Literary data suggest that extracts of mushrooms and extracts show high levels of gram-positive and gram-negative antibacterial activity and MDR bacteria [2, 38]. At present, it is well established in the literature that basidiomycete *A. blazei* contains a variety of organisms that develop a variety of functional, individual and/or harmonious structures. Therefore, it is important to understand what active ingredients play a role in the action of antibiotics. However, the scientific literature does not provide sufficient information on the chemical composition of the mushrooms for this work or the machine for action [39].

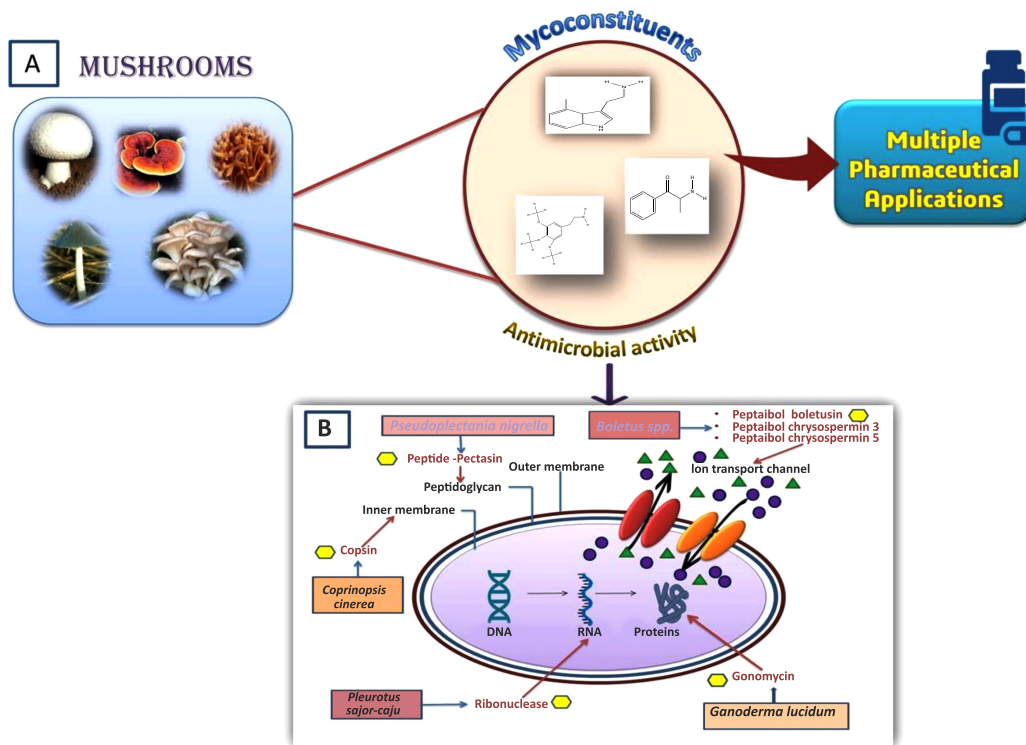


Fig. (3). [A] Mycoconstituents of mushroom having multiple pharmaceutical applications along with antimicrobial activity [B] Showing the possible antimicrobial mode of action of mycoconstituents of mushrooms (Source [2]:).

Other mushroom-derived proteins have also been shown to be effective against non-gram-negative bacteria. The protein CSAP isolated from *Cordyceps sinensis* had antibacterial activity against *Escherichia coli*, *Proteus vulgaris*, and *Salmonella typhi*, whereas the protein (N-terminal sequence SVQATVNGDKML) isolated from *Clitocybe sinopica* had antibacterial activity against *Agrobacterium rhizogenes*, *Agrobacterium tumefaciens*, *Agrobacterium vitis*, *Ribonuclease (Pleurotus sajor-caju)* has been shown to interact with *Pseudomonas aeruginosa* and *Pseudomonas fluorescens*, both of which work at the RNA level. Fracture B (*Pycnoporus sanguineus*) has been shown to be effective against *E. coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa* and *Salmonella typhi* [5, 30]. Glycopeptides consisting of semi-synthetic oritavancin are diverse antibiotics that combat gram-positive microorganism which includes MRSA and VRSA. Teixobactin, a bacteria-derived compound, may have antistaphylococcal activity [40].

FUTURE PROSPECTS AND CONCLUSION

The emergence of several MDR strains linked to nosocomial infections necessitates a new antimicrobial drug response. According to reviews, extracts and/or compounds from various mushroom species may have antimicrobial activity in such species. In recent years, an increasing number of reports have highlighted the potential capability of certain organisms in the performance of universal antibiotics [41]. Additional pharmacological research looking at the interactions between antibiotics and those herbal products should substantially enhance the capacity for mild toxicity of anti-MDR chemical compounds. Identifying individual antibodies to explain antibodies and explaining how they work is inevitable in identifying drugs. This paves the way for the improvement of powerful chemicals towards selected microorganisms which is in line with the growing anti-drug problem in recent decades; people are becoming resistant to traditional treatments.

Therapeutic mushrooms are considered the primary source of therapeutic agents [42]. Mushrooms can be used as a natural source of food and medicine. The traditional significance of edible and wild mushrooms, which have now been tested for their presence in various diseases, was known to the natives and their ancestors [43]. Herbal drugs are classified as natural, synthetic, or artificial natural products [44]. Mushrooms can be used as food, tonics, antiseptics, cosmetics, and biocontrol agents, and they are not uncommon in establishing flora with insecticidal, fungicidal, bactericidal, herbicidal, nematocidal and antiphytoviral activities [45, 46]. Mushrooms have evolved into a life-giving food in recent years and can be a source of drug-enhancing drugs.

Without a doubt, mushrooms will serve as a potential source of novel antibiotics and anti-parasitic drugs in the near future. To achieve the apex and specificity of effective antimicrobial and anti-parasite activity, collaborative research in genomics, bioinformatics, chemistry, and pharmacology is required. Furthermore, strategies to elicit the sleeping gene clusters linked to the production of bioactive compounds and their regulation must be implemented [42].

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Declared none.

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***In silico* Interactions of the Biomolecules of Edible Mushrooms Against Lifestyle Diseases**

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Abstract: Mushrooms are fungi that are consumed all over the world and contain bioactive nutritive components with nutritional and therapeutic qualities. Protein, minerals, vitamins and antioxidants are all found in edible mushrooms. Selenium, vitamin C, and choline are antioxidants that help the human body remove free radicals. Antimicrobial, antiviral, anticancer, anti-allergic, immunomodulation, anti-inflammatory, anti-atherogenic, hypoglycemic, hepatoprotective, and antioxidant properties of mushrooms. Primary and secondary metabolites can be found in mushrooms. The primary metabolites are energy-producing, but the secondary metabolites have therapeutic qualities. As the bioactive molecule has a pharmacological effect, researchers have recently focused on extracting it. As a result, the mushroom has the potential to be a recipe for human health and play a key role in the battle against COVID-19 pandemics and other infectious illnesses. Mushrooms and their biomolecules have therapeutic properties in a variety of diseases, including cardiovascular, diabetes, reproductive problems, cancer, and neurological disorders. A computer method, or *in silico* technology, is promising early evidence for drug development. Molecular docking studies have discovered bioactive chemicals from natural items like mushrooms as possible inhibitors against various diseases.

Keywords: Biomolecules, Diseases, *In silico*, Mushroom.

INTRODUCTION

Mushrooms have been used as food and nutritional value from ancient times to modern days. Mushrooms are a potential source of biomolecules that include large macromolecules (protein, carbohydrate, lipid, and nucleic acid) as well as small molecules (primary metabolites, secondary metabolites, and natural products) [1]. Mushrooms contain secondary metabolites, including polysaccha-

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rides and phenolic compounds. Secondary metabolites contain polyphenols, acids, terpenoids, alkaloid sesquiterpenes, lactones and sterols. In edible mushrooms, many vitamins B1, B2, B12, C, D, and E are present. A mushroom is a macro fungus with a distinctive fruiting body, either epigeous or hypogeous, and large enough to be seen with the naked eye and picked by hand [2]. In several countries, mushrooms are used as food and medicine. Mushrooms are a good source of protein, carbohydrates, minerals and vitamins (including thiamin, riboflavin, cobalamin, ascorbate, tocopherols, and b-carotene) [3]. Mushrooms are a rich source of phenolic compounds. Several studies reported that mushrooms are a nutritionally functional food and a rich source of biologically active agents responsible for medicinal properties, including antimicrobial, antioxidant, antiviral, anti-diabetic and anticancer substances [4 - 6]. Regular consumption of mushrooms in diet may enhance the immune system and cure several diseases [7]. Edible mushrooms possess polyphenolic compounds, and dietary fiber composition may help in the modulation of gut microbiota. The medicinal properties of mushrooms may help prevent several lifestyle diseases cancer, neurodegenerative disease, cardiovascular disease, and diabetes. Medicinal mushrooms such as *Hericium erinaceus* are used to cure tumor disease such as gastric cancer, and duodenal cancer [8, 9]. Several research reports show that some edible mushrooms, including *Pleurotus ostreatus*, *Lentinula edodes*, *Agaricus bisporus*, *Flammulina velutipes*, and *Auricularia auricular-judae* are used as a treatment for ND [10, 11]. Oudemansin, strobilurins A, D, illudin S and pterulone B are antibiotic metabolites extracted from *Collybia nivalis*, *Omphalotus olearius*, *Flavolaschia* sp. and *Pterula* sp [12]. Heart disease and diabetes are age-related diseases that have been treated by ingesting mushrooms. *Cordyceps sinensis* regulates insulin sensitivity and reduces cholesterol levels. Sun mushrooms, such as *Agaricus blazei* used to cure hepatitis, congested arteries, diabetes, and cancer, are found in Japan and China.

Mushrooms are a source of polysaccharides used as anticancer and immune-stimulating properties. Turkey tail mushroom extract uses polysaccharopeptide (PSP) and polysaccharide-K to stop cancer cells [13]. Chemotherapy drug paclitaxel is produced from fungus are used to cure lung, bladder, pancreatic, and breast cancer. Mushrooms that contain polysaccharides compound does not directly attack cancer cells but stimulate antitumor properties to enhance immune cells. There can be four categories of mushrooms such as edible, poisonous, medicinal and miscellaneous category- mushrooms are used as folk medicine in several countries. Most of the mushrooms' secondary metabolites possess drug-like structures (*i.e.*, Lipinski's Rule of Five compliant) and could be considered a significant natural inspiration for drug discovery purposes. Multi-target drugs have advantages over single-target drug co-administration, mainly higher efficacy, an improved safety profile, and better compliance.

Furthermore, virtual screening methods help identify sources of off-target drug effects and investigate their potential to cause adverse or desirable side effects. In this work, a database of compounds has been created from the extracts of mushroom species (both edible and toxic). Furthermore, docking studies were carried out to theoretically comprehend their polypharmacological activity and guide the design of promising new multi-target agents (MTAs). The genomic analysis of the gut microbiota and the changes that happened at the genetic level of the microbiota upon the mushroom feeding (metagenomics or ecogenomics) [14]. In this chapter, we also describe the interaction between the bioactive compound of mushrooms and lifestyle diseases. Various computational techniques, including molecular docking, virtual screening, and molecular dynamics simulation, are used against various life-threatening diseases.

Biomolecules of Mushrooms

Medicinal mushrooms play a beneficial role in United Nations Sustainable Development Goal in Good health and well-being. Healthy human health problems are publically considered, including life-threatening diseases, cancer, diabetes, cardiovascular disease, and neurodegenerative disorders influenced by food consumption and lifestyle [13]. There are various drugs and therapeutics for human diseases, but they have some side effects. The Sustainable Development Goals (SDGs) of the United Nations challenge authorities globally to cease hunger, achieve food safety, and update nutrition through 2030, especially for the poor and vulnerable members, including children. Due to their therapeutic potential, mushrooms have recently generated a lot of attention as a source of physiologically functional food and medication. In the main world, researchers focus on a mushroom in their therapeutic properties. Mushrooms are not only utilized as food but also used as potential therapeutics against numerous ailments. Mushroom is the “elixir of life” for the remedy of human disease due to the proximity of different secondary metabolites. Secondary metabolites, such as phytochemical compounds and low molecular weight molecules, are generated in reaction to stress. Edible mushrooms are *Ganoderma lucidum*, *Lentinula edodus*, *Schizophyllum commune*, *Hericium erinaceous* and *Cordyceps sinensis* function as medicinal mushrooms [15]. *Ganoderma lucidum* is the unique power of medicinal mushrooms. Edible mushrooms include a vast amount of biochemical compounds, including polysaccharides, terpenes, bioactive proteins, phenolic compounds, Lentinan, Adenosine, Ling Zhi 8, Polysaccharide Krestin (PSK), Polysaccharide Peptide (PSP), Entadenine butyric acid and antioxidants that make therapeutic threatening many diseases [13, 16]. Medicinal mushrooms possess diverse pharmacological and remedial traits including immune improvement, maintenance of homeostasis and coordination of biorhythm, antioxidant, anti-atherosclerotic, anti-inflammatory, analgesic, anti-tumor, anti-bacterial, anti-viral,

hypolipidemic, hypoglycemic, anti-fibrotic, anti-diabetic, anti-androgenic, anti-angiogenic, anti-herpetic, and radical scavenging, anti-aging, estrogenic activity. Mushroom has enriched therapeutic potential for life-threatening therapy diseases such as cancer, diabetes mellitus, cardiovascular disease, and neurodegenerative disease. The most significant secondary metabolites of medicinal mushrooms are polysaccharides. Polysaccharides are the essential structural portion of the cell wall of mushrooms. The appearance of polysaccharide β -glucans or polysaccharide-protein complexes content in mushroom extract possesses unique therapeutic significance in human health. They have many properties such as anti-diabetic, anti-tumor, etc. anti-obesity, immunostimulating, hypocholesteremia, hepatoprotective activity along anti-aging are shown in Fig. (1) and Table 1 [7, 17].

Table 1. Bioactive compounds of mushrooms show various therapeutic activities.

Disease	Mushroom Species	Bioactive Compound	Therapeutics Activity	References	
Anti-tumor	Liver cancer	<i>Ganoderma lucidum</i>	Proteoglycans	Protect liver injury	[7]
	Breast cancer Liver cancer	<i>Pleurotus ostreatus</i> <i>Pleurotus pulmonaris</i>	Methanol Polysaccharide	Stop colon and breast cancer cell growth. It suppresses liver cancer by inhibiting PI3k/AKT signaling pathway	[7]
	-	<i>Agaricus bisporus</i>	Methanolic	Antiproliferative action that suppresses prostate cancer by regulating ERK/AKT and NF-kappa.	[1]
	-	<i>Grifola Frondosa</i>	Heteroglycan	It represents antitumor and immunomodulatory activity	[18]
Neurodegenerative disease	-	<i>Hericium Erinaceus</i>	Polysaccharides	Improve neurite outgrowth	[19]
	-	<i>Ganoderma lucidum</i>	Psilocybin	Protective effects for mild cognitive impairment	[19]
Anti-diabetic	-	<i>Pleurotus ostreatus</i>	Fruiting body	Reduces blood glucose levels as well as the effects of cholesterol.	[20]
	-	<i>Ganoderma lucidum</i>	Polysaccharides, triterpenoids	Increase insulin sensitivity	[21]
	-	<i>Inonotus obliquus</i>	Polysaccharides, polyphenols	Suppressed DPP4 enzyme induces GLUT4 translocation	[21]

(Table 1) cont....

Disease	Mushroom Species	Bioactive Compound	Therapeutics Activity	References
Cardiovascular disease	- <i>Agaricus bisporus</i> <i>Tricholoma matsutakei</i>	Crude extract Peptides	Inhibit the function of angiotensin	[22]
Anti-obesity	- <i>Pleurotus sajor-caju</i> <i>Grifola frondosa</i>	β -Glucan	Obesity prevention in people with a high-fat diet. Reduce the hydrolysis of 4-methylumbelliferyl to inhibit pancreatic lipase.	-
Anti-viral	- <i>Agaricus brasiliensis</i> <i>Pleurotus citrinopileatus</i>	Ethanol extracts Lectin	Inhibit poliovirus type 1 in HEp-2 cells Inhibit immunodeficiency virus type 1	[23]

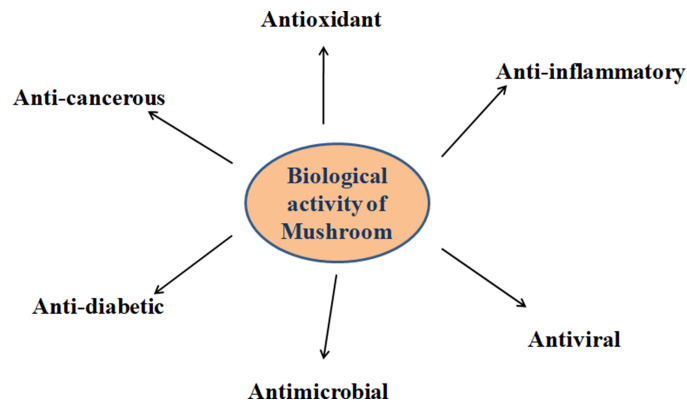


Fig. (1). Medicinal effect of the bioactive compound of mushroom.

Medicinal Properties of Mushroom

Anticancer Properties of Mushroom

Cancer-related mortality rate increases worldwide. Chemotherapy is the most common therapy for cancer which generally has side effects. Due to their great medical potential, mushrooms have received a lot of attention in recent times as a source of vital nutritious foods and medication. Mushroom bioactive substances, such as polysaccharides and polysaccharide-protein complexes, have medicinal potential and have no adverse effects [1]. Researchers reported that some medicinal mushrooms could stop/inhibit cancer cell progression by cytotoxic activity [24]. In therapeutic action, the most effective anticancer compounds are polysaccharides of mushrooms. Beta-glucan extracted from edible mushroom *Lentinula edodes* in the lab shows that anti-cancerous activity is available worldwide [25].

Some medicinal mushroom has been reported; they stimulate macrophages and strengthen the immune system. Medicinal mushrooms are *Schizophyllum commune*, *Tremella fuciformis*, *Dendropolyporus umbellatus*, *Hericium Erinaceus*, *Grifola frondosa*, *Lentinus edodes*, *Inonotus obliquus*, *Ganoderma lucidum*, *G. applanatum*, *Flammulina velutipes*. *Agaricus brasiliensis* containing three ergosterol derivatives and glycoprotein show antitumor activity. Nowakowski *et al.* [26] investigated mushrooms, *L. deliciosus* and *C. comatus* have significant anti-glioma potential against a brain tumor. The most effective treatment of medicinal mushrooms is anti-tumour properties. Medicinal mushrooms are used as a biological response modifier (BRM) in the treatment of cancer. BRM is maintained by immune system amplification, immune system regulation, and natural killer cells (NK cells) production by activating macrophages, cytotoxic T-cells, and natural killer cells (T-cells). It helps to cure cancer and reduces the adverse effects of treatments [13].

Antioxidant Properties of Mushroom

Another important activity of medicinal mushrooms is their antioxidant properties. Oxidants or free radicals damage the normal cell and cause autoimmune inflammation and malignant alterations. Antioxidants act as reducing agents and scavenge free radicals. Mushrooms contain anti-glycemic effects, and adenosine triggers insulin receptors, causing blood glucose to be metabolized and stored in the liver and improving glucose consumption by peripheral tissues [27, 28].

Anti-diabetic Properties of Mushroom

In a 12-week randomized, double-blind experiment, the *Agaricus Blazei* Murill extract was used as a dietary item with gliclazide and metformin to potentially reduce insulin resistance (IR) in T2DM patients [29]. *Agaricus blazei* and other therapeutic mushrooms are commercially available in mushroom products with claimed anti-diabetic and other medical characteristics, as shown in Table 2. Comatin, β -glucan, Tremellastin, and Lentinan KS-2 are the active compounds in mushrooms that significantly impact diabetes mellitus by modulating the cellular activity or biochemical pathways [20]. Mushroom consumption lowers lipid levels, such as low-density lipoprotein cholesterol, while increasing high-density lipoprotein cholesterol. Mushrooms have a lot of fibre and water in them as well. They are high in natural insulin-like enzymes, which help break down glucose in foods and lower IR. Most medicinal mushrooms, including *Ganoderma lucidum*, *Inonotus obliquus*, *Pleurotus spp*, *Phellinus linteus*, *Poria cocos*, and *Sparassis crispa*, have been found to help in DM therapy. Using *in silico* approach, drug targets were identified against diabetic patients. Compounds of edible mushrooms

are complex for researchers, so these compounds are classified into low molecular weight (LMW) and high-molecular-weight (HMW) based on chemical organization. HMW act as an oral diabetic drug, including Guanide, extracted from *Pleurotus* species that contain anti-hypoglycemic activity [20, 21].

Table 2. Some commercial mushroom-based products have medicinal properties.

Mushroom Species	Product	Activity	References
<i>Agaricus blazei</i>	ORIVEDA ® <i>Agaricus blazei</i> Murill capsules	Anti-hyperglycemic, support the immune system and normalize blood glucose level.	[29]
<i>Lentinus edodes</i>	Shiitake Gold capsules	For complete physical human health	[7]
<i>Ganoderma lucidum</i>	ReishiMax (RM) capsules	It inhibits adipocyte differentiation, activates AMPK and boosts glucose uptake in 3T3-L1 cells.	[30]
<i>Cordyceps sinensis</i>	<i>Cordyceps sinensis</i> capsules	Improve respiratory system, antitumor, and liver protection	[31]
<i>Ganoderma lucidum</i>	Pure Red Reishi capsules; Organic Reishi tablets	Increase body's resistance to stress	[7]
<i>Agaricus blazei</i> , <i>Pleurotus eryngii</i> , <i>Hypsizygus tessellates</i> , <i>Cordyceps militaris</i>	GlucoSANO-Diabetes Health Formula	Specially used for diabetic health and balanced blood sugar level	[7]
<i>Ganoderma lucidum</i> , <i>Lentinus edodes</i> , <i>Gri- fola frondosa</i> , <i>Agaricus blazei</i> and <i>Pleurotus ostreatus</i>	GanoSuper	Antitumor, antidiabetic	[1]
<i>Hericium erinaceus</i>	Amyloban 3399 Super Lion's Mane (Tablets)	Improve brain function	[1]
<i>Ganoderma lucidum</i>	Ganoderma herbal antidiabetic capsules	Enhance human body immunity.	[1]
<i>Maitake mushroom</i>	SX-Fraction®	Maintain blood sugar level	[32]
Mixture of several mushrooms	Dr. Myco San products DIMEMYKON	Optimally control blood sugar levels.	[32]

Mushrooms as Therapeutic Potential Against Neurodegenerative Disease

Medicinal mushrooms are used as therapeutics to prevent age-related neuronal diseases like Alzheimer's and Parkinson's diseases. Some mushroom species prevent and improve brain functions, including *Hericium erinaceus*, *Ganoderma lucidum*, *Antrodia camphorata*, *Pleurotus giganteus*, *Lignosus rhinocerotis* and *Grifola frondosa* [33]. It has been studied that the extract of the mushroom

compound *Ganoderma lucidum* reduces beta-amyloid-induced neurotoxicity. It also reduces the neuroinflammation, stimulation of neurons and synthesis of nerve growth factors. The bioactive compound of mushrooms is used as potential therapeutics in the treatment of neurodegenerative disease. *In silico* analysis identifies the bioactive compound against neuronal diseases [19]. Numerous (multi-target agents) MTAs have been *in silico* designed to identify significant applications against mentioned neurodegenerative diseases. Various researchers reported that the medicinal mushroom *Cordyceps sinensis* contain a cordysininaA compound that inhibits neuronal disorders. Some studies investigated cordysininaA and showed potential binding affinity to GSK3 β , AChE and COX-2 targets. Likewise, pterulone compound derived from mushroom *Omphalotus olearius* show therapeutic binding affinity with MAO-B, AChE, COX-2 and GSK3 β targets [34].

Anti-viral Properties of Mushroom

Mushrooms have a potential source of bioactive compounds fighting against viral disease. Some bioactive compound represents anti-inflammatory activity. In a recent study, Rangsinth *et al.* 2021 [35] reported that mushroom-derived 25 bioactive compounds have good binding affinity against SARS-CoV-2 main protease using bioinformatics approaches to molecular docking. In which mushroom-derived six compounds, including colossolactone VIII, colossolactone E, colossolactone G, ergosterol, heliantriol F and velutin have good therapeutic potential against SARS-CoV-2 virus [35]. *Grifola frondosa* and *Lentinus edodes* have been used to inhibit the AIDS virus. Extract of medicinal mushroom *Pleurotus urinaria* is acetone, ethanol, and methanol act as anti-herpes simplex virus-2 (HSV-2). While extract of *Grifola frondosa* is protein act as anti-HSV-1.

Mushroom Against Cardiovascular Disease

Coronary artery disease is the most common cause of death in most developed countries. *Lentinus edodes* reduce blood pressure and free cholesterol in plasma. Comparative study of medicinal mushrooms such as *Grifola frondosa*, *Pleurotus eryngii*, and *Hypsizygus marmoreus* can reduce cholesterol content in the human body. The crude extract of *Agaricus bisporus* and *Tricholoma matsutake* fruiting bodies contain bioactive inhibitory peptides that block the action of angiotensin, which transforms the enzyme responsible for hypertension and cardiovascular illness [36]. *Hericium erinaceus* ethanol extract improves lipid metabolism by preventing platelet aggregation caused by collagen.

Mushroom Bioactive Compounds Enhanced the Immune System

Medicinal and edible mushroom stimulates the immune system through phagocyte cells. Several studies investigated the effect of the bioactive compound of mushroom show action on the immune system by inhibiting tumor growth. Medicinal mushroom contains the potential compound β -glucan, which stimulates the immune system by affecting NK cells, macrophages, T-cells and cytokine production. Recent studies reported that *Agaricus blazei* Murill has immunostimulatory activity [29]. Various medicinal mushrooms, including *Pleurotus florida*, *Agaricus bisporus*, *Trametes pubescens*, *Flammulina velutipes*, and *Lentinus edodes*, have anti-inflammatory action measured by interferon- γ (IFN- γ) and lipopolysaccharide (LPS), both of which activate macrophages.

In silico Study of Biomolecules Against Various Life-threatening Diseases COVID-19

From a natural source, a bioactive compound extracted that can inhibit the main protease of the SARS-CoV-2 virus is being investigated as an alternate strategy for combating COVID-19. *In silico* technology is a shred of promising early evidence for drug development [37]. The bioactive compound from natural products has been discovered as a possible SARS-CoV-2 main protease inhibitor obtained from natural sources in molecular docking investigations. COVID-19 might be effectively treated with these two actions. Various bioactive compounds have been found to inhibit HIV protease, indicating that they may have an action against coronavirus proteases [35].

Cancer

In silico predictive pharmacological analysis of a flavonoid compound was isolated from *Fulvifomes fatuous* mushroom. The targeted compound was isolated from the mushroom using different chromatographic methods and identified by NMR spectrometry and mass spectrometry.

Using *in silico* approach predicted that hericerol A and erinacerin P compound extracted from *H. erinaceus* mushroom have good theoretical binding affinity versus anticancer target. Hericerol A shows the best binding affinity with Mesenchymal-Epithelial Transition Factor (c-Met) kinase. Maruca *et al.* 2017 [34] reported that in MEK1, Erinacerin P contains three H-bonds to Asp209, Lys97, and Ser 222 and one π - π interaction Phe209. The excellent theoretical binding affinity for serine/threonine-protein kinase 1 is due to six H-bonds to Val103, Ile104, Lys102, Ile179, and Tyr178. The researchers used an *in silico* approach based on the structural similarity of low-molecular-weight compounds (phenolics) to anticancer drugs and chemicals with epigenetic event modulatory

activities. The enzymes histone acetyltransferase (HAT), histone deacetylase (HDAC), and DNA methyltransferase (DNMT) were chosen as targets for the screening of mushroom compounds with potential epigenome regulatory effects. Saranea software was used to do the similarity analysis. Furthermore, using the programme Power MV 0.61, the chemical structural similitude of phenolic compounds from *Pleurotus ostreatus* (oyster mushroom) and anticancer reference compounds was determined [34].

Maruca *et al.* [34] analyse the docking result of the best multi-target agents of mushroom extracts with those of the co-crystallized ligand with the best binding affinity. Hericenol A, inotopyrrole, and crizotinib, the co-crystallized ligand of c-Met, share an H-bond with the residue Met1160. Similarly, when erinacerin P and the inhibitor are complexed with the anticancer target MEK1 (PDB code: 4ARK), they form two H-bonds with Lys97 and Asp208, with both aromatic rings involved in one π - π interaction with Phe209 and their side chains forming two H-bonds with Lys97 and Asp208. Ganomycin B and the inhibitor complexed with PDK1 share the creation of two H-bonds with Lys111 and Ser160 (PDB code: 3NAX)

Metabolic Disease

Metabolic diseases, such as diabetes mellitus, show high-risk complications related to cardiovascular disease. Recently, a group of naturally occurring pentacyclic triterpenes was studied as multi-target therapeutic agents for preventing and treating metabolic and vascular disorders when given orally. They were found to be both productive and safe. According to the virtual screening results, some natural chemicals exhibited a good theoretical affinity with diverse targets implicated in metabolic disorders, notably diabetes mellitus. Researchers reported in their study that O-xylotocopherol could prevent unsaturated fatty acids from oxidation by blocking the most reactive oxygen species. Peroxisome proliferator-activated receptor alpha (PPAR- α) and peroxisome proliferator-activated receptor gamma (PPAR- γ) are two key targets in metabolic disorders for O-xylotocopherol has a strong theoretical affinity. It creates one H-bond and one π - π interaction to Tyr314 and His440 of PPAR- α and Tyr473 and His449 of PPAR- γ , respectively, revealing a similar binding mechanism in both complexes. Furthermore, the interactions between PPAR- α and PPAR- γ are mediated by His440 and Tyr473 of PPAR- α and PPAR- γ respectively [34].

Neurodegenerative Disease

After docking analysis, literature reports that designed multi-target agents show a potent application toward neurodegenerative disease. Designed lipocrine inhibit the activity of AChE and protect them from ROS. Cordysin A extract of

Cordyceps sinensis shows the neurodegenerative effect reported in the literature. Cordysin A show the best binding affinity with GSK3 β , AChE and COX-2 by showing H-bond with residue Val130, Phe295 and Ser530, respectively (Table 3).

Table 3. Fungal component with best binding affinity against various diseases.

Disease	Fungal Component	Target
Cancer	Hericenol A Erinacerin P Inotopyrrole	c-Met MEK1 VEGFR2
Metabolic disease	Hericenone A O-xylotocopherol	PPAR- α , PPAR- γ , GSK3 β PPAR- α , PPAR- γ
Neurodegenerative disease	Erinacerin O Cordysin A	AChE, COMT GSK3 β , AChE, COX-2
Inflammatory disease	Illudacetic Acid Pterulinic Acid	COX-2 COX-1

Methods to Identify Interaction among Biomolecules and Diseases

Ligand Preparation

Bioactive compounds, such as palmitic acid, linoleic acid, and fomalactone A mushroom extract, were retrieved from the PubChem database. Ligand structures were plotted in 2-D.

Protein Preparation

The 3-D structure of the target protein was downloaded from the protein data bank in PDB format.

Determination of *In silico* Pharmacokinetic, Physicochemical Parameters and Drug Likelihood of the Compound

Assessment of *in silico* pharmacokinetic parameters (ADME), physicochemical parameters, drug likelihood, lipophilicity and medicinal chemistry friendliness properties for the molecule was performed using SwissADME web tool. Lipinski's rule of five (Molecular weight, not more than 500; H-bond donors ≤ 5 ; H-bond acceptors ≤ 10 ; Lipophilicity < 5 and molar refractivity ranging from 40-130) were considered to evaluate favourable drug-like properties of all compounds [37]. The toxicological properties of all the compounds were determined by the web tool admetSAR (<http://lmmd.ecust.edu.cn/admetSar2/>) [38].

Molecular Docking

Molecular docking techniques were used to investigate molecular interactions. Drug mechanistic interactions with target protein receptors have been studied and understood using molecular docking experiments [39]. Autodock Vina was used for molecular docking, and the Autodock tool was used for molecular interaction analysis. Autodock is an automated docking programme that predicts how tiny compounds, such as drugs, attach to a receptor's 3D shape [40].

Molecular Dynamic Simulation

Drugs with stable binding to the target protein can be studied using molecular dynamics simulation methods. It assesses the receptor-ligand complex's stability. For a long time, researchers ran molecular dynamics simulations and evaluated root-mean-square deviation (RMSD), root-mean-square fluctuation (RMSF), and radius of gyration (RG) plots. The atomic fluctuations of the interaction complex system may be analysed using RMSD, RMSF, RG, and other metrics. To evaluate individual residue dynamics of the target receptor, an RMSD plot was created. RMSF was calculated for amino acid side chains to investigate amino acid variations in the docked complex. GROMACS 2018 software and iMODS server were used to simulate molecular dynamics [39].

Using a computational approach, the bioactive compounds of mushrooms show interaction against the target protein of human diseases, as shown in Fig. (2).

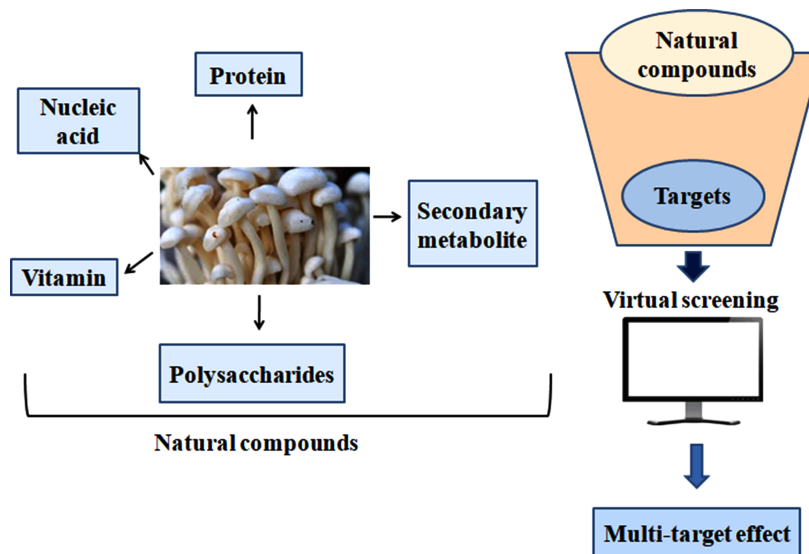


Fig. (2). *In silico* interaction of natural compound against the target protein.

Therefore, drug development, design, lead optimization and discovery procedures have accelerated because of powerful computer assistance and information-based technologies. It is used to speed up hit recognition, hit-to-lead optimization and simplify biomedical and computer-aided drug design processes that employ *in silico* methods in drug discovery criteria. The structure-based and ligand-based strategies for computer-aided drug design (CADD) have been used. Autodock Vina in PyRx was used to conduct structure-based VS of mushroom compounds and redocking of top-scoring hits using Autodock 4.2. The term “molecular dynamics” (MD) was used to describe the study of molecular dynamics.

CONCLUSION

To summarise, mushrooms and their bioactive components provide considerable protection, and play an essential role in preventing the development of lifestyle diseases. Mushrooms can be taken as a supplement to help prevent infections. Secondary metabolites, such as polysaccharides, polysaccharopeptides, β -glucans, and various polyphenolic substances, are commonly utilised to treat multiple diseases. Mushrooms also help to maintain redox and energy homeostasis and relieve the causes of illness development. They were using *an in silico* approach to identify an excellent binding affinity compound against a target that involves the cause of disease. The bioactive compounds, such as inotopyrrole, ganomycin B, hericenol A and erinacerin P extracted from mushroom *I. obliquus*, *G. lucidum* and *H. erinaceus*, have binding affinity to the anticancer target. Some other compounds, including illudacetalic acid and pterulinic acid, are isolated from *omphalotus olearius* and have binding affinity against the target of inflammation. In neurodegenerative disease, Cordysin A and pterulone show binding affinity against targets, whereas O-xylotocopherol against metabolic disease targeting. Some mushrooms with a variety of health advantages might be turned into functional foods or medications for the prevention and treatment of a variety of chronic illnesses. Creating the chemoinformatic database has resulted in a greater understanding of species that have yet to be thoroughly investigated and understood.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Declared none.

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An Eco-friendly Practice of Decontamination of Toxicants using Fungi

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Abstract: The advent of industrialization and urbanization has caused rapid production of various types of domestic, agricultural, medical and technological goods, such as different types of pesticides, herbicides, cyanotoxin, heavy metals, antibiotics, dyes, phthalates, *etc.* Production of these substances has led to the production of enormous amount of waste materials. Inappropriate discharge and uncontrolled drainage of these waste materials into the environment have caused their accumulation in the surrounding environment, causing serious health problems and destroying our ecosystem. Different methods such as physical, chemical and biological have been adopted to eliminate these waste materials. However, these methods are cost-effective and have some side effects. Hence, in this chapter, efforts have been made to understand the fungal enzymes involved in remediation processes, and their role and the mechanism of action of fungi have been depicted. Besides that, we have also discussed different categories of waste and their remediation using fungi, which is an eco-friendly biological approach to remediate toxic materials.

Keywords: Contaminants, Detoxification, Fungal enzymes, Mycoremediation.

INTRODUCTION

Production of anthropogenic waste has been increased in recent years. In the past centuries, it was limited both in terms of quantity and variety owing to smaller production and less industrialization. In the ancient period, only small amount of waste was contributed by industries, while majority was primarily due to domestic practices. In contrast, increased population augmented the human need and all sorts of requisites which led to the advent of urbanization and industrialization.

To alleviate the needs of the growing world population, the rapid progress in industrialization has led to the generation of more and more medicines, pesticides,

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and herbicides for human health as well as the betterment of agricultural fields. Apart from these, there are many medium and small industries that, along with their useful products, produce a massive amount of hazardous products, such as several types of useless inorganic and organic compounds. The hazardous products are considered waste materials which are mostly toxic and harmful. Improper disposal and continuous mixing of these wastes into the environment led to their accumulation many times higher than their tolerable limit, causing various kinds of health hazards that could be detrimental to living world.

In the report of the world health organization, it is mentioned that 144 million people are using contaminated water while 2200 million people are unable to get clean water for drinking as well as other purposes [1]. It is expected that 50% of the world's population will face water stress by 2025 [1].

Pollution caused by industrialization and urbanization has become havoc for developing countries leading to a loss of their GDP (5%), 16% global death, as well as 25% polluted regions. Besides its effect on the economy and the health of people, it can be responsible for threatening the availability of drinking water, food security, and biodiversity. Therefore, it is necessary to develop and generate some methods and strategies to overcome water pollution caused by toxicants.

In order to deal with the problem of water contamination, there is an urgent need to treat wastewater or effluents before their release into the aquatic environment. To decontaminate the contaminated water number, techniques like ion exchange methods, chemical precipitation, electrochemical method, and membrane technologies are used in different industries at large scales [2]. However, these techniques are not environmentally friendly, very costly, and also less effective [3]. Hence, it is important to develop an eco-friendly method that will be fast and cost-effective in eliminating polluted water. In recent years, the use of fungi has increased many folds to remediate toxic elements owing to their high metal binding capacity as well as a high percentage of the cell wall [4]. Although there are numbers of *in vitro* studies to remediate various toxicants from the synthetic media in which fungi are used, information regarding the *in vivo* studies to decontaminate natural waste using fungi is scanty. Mycoremediation, *i.e.*, the use of fungi for remediation purposes, is considered an economical and environmentally friendly method to mitigate the problem of contamination of water. The unique characteristics of fungi, like sturdy growth, resistance to toxicants, production of ligninolytic enzymes, vast hyphal network, resistance to changing temperature and pH, and presence of chelating proteins to combine metals make them crucial agents for the elimination of various toxicants [5, 6]. The present chapter discusses the role and importance of fungal species to degrade different toxicants such as heavy metals, pesticides, herbicides, pharmaceuticals,

antibiotics, dyes and phthalates. The role of various enzymes involved in mycoremediation processes has also been described. Moreover, the mechanism or cellular response in the mycoremediation process has been explained (Fig. 1).

ROLE OF FUNGI IN MYCOREMEDIATION

Bioremediation is considered a very effective, economical and eco-friendly method to decontaminate toxins and harmful compounds into nontoxic substances. This is the natural and biological way of decontamination [7, 8]. The use of plants, *i.e.*, phytoremediation has been recognized as an economical and environmentally friendly method to decontaminate waste materials. But researchers found some limitations, such as tolerance to toxicants, selectivity of plants and climatic inhibitors, which cannot solve all the strategies to decontaminate waste materials [9].

Fungi can be an effective alternative to plants to remediate contaminated waste materials [5, 6-9]. Some characteristics of fungi, such as robust morphology, diverse metabolic capacity, and resistance to extreme temperature and pH, play significant roles in removing the different toxicants. Fungi have metal-chelating proteins that bind with metals and make them hyperaccumulators [4]. Apart from these qualities, reactive oxygen species, which are produced directly or indirectly by toxicants, can be counteracted by an antioxidant system that exists in fungi.

Various fungi have been recognized to play an important role in the mycoremediation of varieties of toxicants [10]. Some filamentous fungi such as *Acrimonium*, *Aspergillus*, *Pithium*, and *Curvularia* species are known for their tolerance ability to various toxicants [11]. Some other fungi, like *Trametes versicolor*, *Pleurotus ostreatus*, *Hypholoma dispersum* and *Trametes pavonia* are also known to have the degradation ability of various toxicants [12, 13]. Similarly, *Aspergillus* and *Penicillium* are also involved in remediating different toxicants [14, 15].

ROLE OF FUNGAL ENZYMES INVOLVED IN MYCOREMEDIATION TECHNIQUES

Extracellular Oxidoreductases

Some specific enzymes, *i.e.*, extracellular enzymes of fungi, make them able to catalyze toxic substances into nontoxic forms. These enzymes are likely produced to enhance fungal growth on toxic substrates of various structures which are not accessible to most of the bacteria [16, 17]. Therefore, these enzymes contribute to

fungi biological advantage over bacteria [16]. The role of an extracellular enzyme in mycoremediation techniques has been depicted in Table 1.

Laccase, and copper-containing oxidase are well-known enzymes of some fungal species like basidiomycetes and ascomycetes. They oxidize toxicants using molecular oxygen [18]. These enzymes are mainly involved in the detoxification and degradation of dyes in different industrial effluents such as dyestuff industries, textile industries, paper industries, *etc.*, as well as detoxification of recalcitrant wastewater toxicants (endocrine disruptors, pesticides, chlorophenols and others) [19, 20]. Another enzyme, *i.e.*, tyrosinase, is also a copper-containing oxidase that oxidizes highly chlorinated phenols arising from contaminated media [21]. Other enzymes, including lignin peroxidase, manganese peroxidase, versatile peroxidase, dye-decolorizing haem peroxidases, and haem–thiolate peroxygenase are widespread among basidiomycetes, capable to oxidize toxicants with redox potential [22–24] while other peroxidases like *Coprinopsis cinerea* peroxidase (CiP) and *Caldariomyces fumago* haem–thiolate chloroperoxidase (CPo) are able to oxidize phenols and other contaminant having redox potential of very low level [23]. Manganese peroxidase has also shown an ability to break aromatic rings of chlorophenols and monoaminodinitrotoluenes.

Table 1. List of fungal enzymes involved in the catabolism of various toxicants.

Name of Enzymes	Fungal Taxa	Localization	Detoxifying Efficiency	References
Laccases	Basidiomycota & Ascomycota	Extracellular	Direct oxidation of different aromatic amines, phenols and dyes	[18, 19]
Tyrosinases	Basidiomycota, Ascomycota & Mucormycota	Intracellular but sometimes extracellular	Oxidation of various chlorinated phenols	[21, 69]
Manganese peroxidase	Basidiomycota	Extracellular	Oxidation of a variety of aromatic amines & phenols mediated by Mn ³⁺	[22, 23]
Lignin peroxidase	Basidiomycota	Extracellular	Oxidation of different aromatics having a high redox potential	[22, 23]
Versatile peroxidases	Basidiomycota	Extracellular	Direct oxidation of dyes & phenols	[22, 23]
Dye decolorizing peroxidase	Basidiomycota	Extracellular	Oxidation of anthraquinone dyes	[23]
<i>Coprinopsis cinerea</i> peroxidase	Basidiomycota	Extracellular	Oxidation of dyes & phenols having a low redox potential	[23, 70]

(Table 1) cont....

Name of Enzymes	Fungal Taxa	Localization	Detoxifying Efficiency	References
Caldariomyces fumago haem-thiolate chloroperoxidase	Ascomycota	Extracellular	Not effective on non-substituted aromatic rings and n-alkanes	[23]
Haem-thiolate peroxxygenases	Basidiomycota	Extracellular	Oxygenation of dibenzofuran, polycyclic aromatic hydrocarbon, d monohydroxylated & polyhydroxylated products	[23]
Cytochrome P450 monooxygenases	Basidiomycota, Mucoromycotina, Ascomycota, & Chytridiomycota	Cell-bound	Hydroxylation & Epoxidation of aliphatic or aromatic structures of many pollutants, including polycyclic aromatic hydrocarbon, alkanes and alkyl-substituted aromatics, and polychlorinated dibenzo-p-dioxin	[25, 26, 71]
Phenol 2-monooxygenases	Basidiomycota & Ascomycota	Cell-bound	Ortho-hydroxylation of different (halo) phenols into catechols	[19]
Nitroreductases	Mucormycotina, Ascomycota & Basidiomycota	Cell-bound	Reduction of 2,4,6-trinitrotoluene to hydroxylamine dinitrotoluene & amino dinitrotoluene	[72, 73]
Quinone reductases	Basidiomycota	Cell-bound	Detoxification of quinone	[31, 32]
Reductive dehalogenases	Basidiomycota	Cell-bound	Dechlorination of chlorohydroquinones	[74, 75]
Miscellaneous transferases	Mucormycotina, Ascomycota & Basidiomycota	Cell-bound	polycyclic aromatic hydrocarbon metabolism	[25, 76]

Cell-bound Enzymes

Several cell-bound enzymes involved in chemical catabolism do not have substrate specificity. Cytochrome P450 is one of them, which can initiate the metabolism of polycyclic aromatic hydrocarbon, dioxins, nolyphenol, *etc* [25, 26]. It is also involved in the metabolism of different pharmaceutical compounds, lipid regulators as well as anti-inflammatory drugs [27, 28]. Cytochrome P450 monooxygenase enables *Cunninghamella elegans* to oxidize Polycyclic aromatic hydrocarbons with 2–5 aromatic rings [25]. Aromatic nitroreductases can reduce Trinitrotoluene to hydroxylamino- and amino-dinitrotoluenes and are widespread among fungi [29, 30]. Quinone reductase is a very common enzyme among brown-rot and white-rot basidiomycetes [31], efficient in the redox cycling of

quinone [32]. It also reduces quinones by the transformation process using extracellular oxidoreductases.

MECHANISMS OF ACTION OF FUNGI FOR DETOXIFICATION OF TOXICANTS

There are a number of physical and chemical methods for the detoxification of toxicants. However, these methods are unsuitable, very costly, and generate harmful byproducts. To overcome those problems, mycoremediation seems to be a good strategy.

The cellular mechanism of action of fungi for the detoxification of toxicants is poorly known. Therefore, an attempt has been made to depict how fungi detoxify the toxicants (Fig. 1).

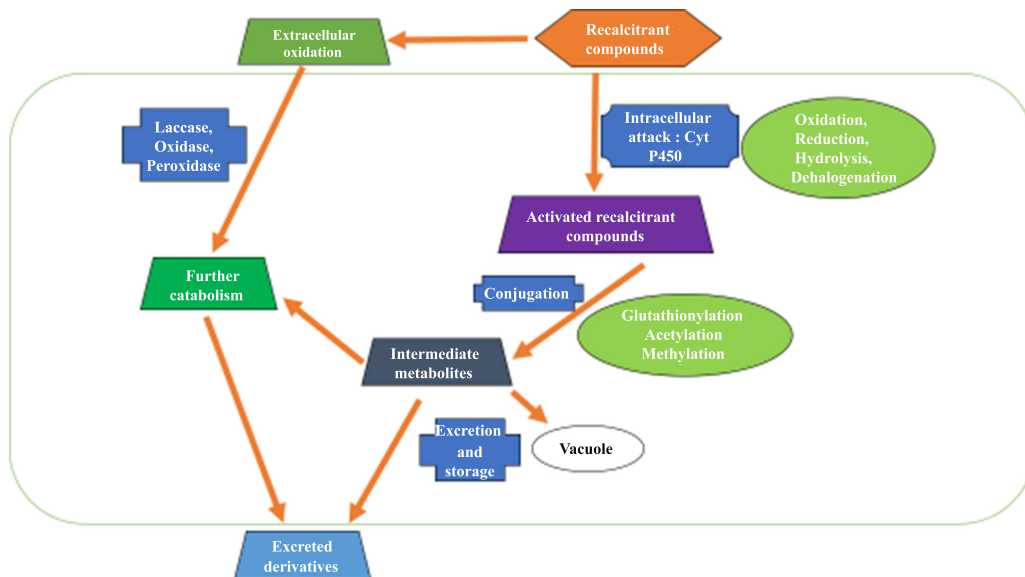


Fig. (1). Mechanism of action of fungi for bioremediation of toxicants.

Two types of enzymes are involved in the detoxification process: extracellular enzymes (laccase, oxidase and peroxidase *etc.*) and cell-bound enzymes (cytochrome P450 monooxygenase, nitroreductase, quinone reductase, *etc.*). Extracellular catabolism of toxicants is done by the release of extracellular enzymes which can further undergo catabolism to completely detoxify the toxicants and ultimately release their derivatives. In the same way, an initial intracellular attack is carefully made by the cell-bound enzymes to activate the

toxicants, which subsequently generates the intermediate metabolites *via* the involvement of glutathionylation, acetylation and methylation. Some intermediate metabolites are stored in vacuoles and some of them again can further undergo catabolism to detoxify the toxicants and the end products are excreted out.

BIOREMEDIATION OF DIFFERENT KINDS OF TOXICANTS

Mycoremediation of Heavy Metals

There are several types of heavy metals, such as chromium, lead, arsenic, mercury, silver, nickel, copper, *etc.*, observed at the contaminated sites, which can enter into the water bodies by means of natural as well as human activities [33]. The release of these toxic metals into the environment can lead to their accumulation in flora and fauna, including human beings, by consumption of contaminated food and water. These metals impair many vital functions of the body and cause cancer and other health problems [5, 34].

Fungi-mediated bioremediation can be used as a promising method to remove heavy metals from contaminated sites. *Pleurotus ostreatus* were reported to remediate manganese from polluted water as well as copper, zinc, chromium, lead, nickel and cobalt from coal washery effluents [9, 35]. Similarly, various fungi like *Absidia cylindroslora*, *Trichoderma ghanense*, *Rhizopus microsporus*, and *Fomitopsis meliae* are also capable to accumulate different heavy metals (lead, iron, cadmium, copper, and arsenic) [36, 37]. Further, *Penicillium rubens* and *Aspergillus* species demonstrated their capability to detoxify Cadmium and Chromium [38]. Therefore, it could be suggested that various species of fungi are responsible to remediate different kinds of heavy metals from the environment to protect the environment as well as human health.

Mycoremediation of Chemicals [Pesticides and Herbicides]

Various pesticides and herbicides containing different chemicals like endosulfan, paraquat, fipronil, aldrin, and glyphosate are considered carcinogenic and neurotoxic, and also able to cause severe damage in the reproductive system as well as different vital organs like the kidney and liver. Despite their ban, the use of these herbicides and pesticides is still in practice. Most of these pesticides and herbicides can be released into nearby water bodies and accumulate in the bodies of living organisms such as aquatic plants and animals [39]. Various strategies such as volatilization, chemical treatment, and incineration, are used to detoxify various toxicants, but these methods have some limitations. Therefore, mycorem-

ediation seems to be a plausible, economical, and eco-friendly method for the decontamination of pesticides as well as herbicides.

A number of studies have demonstrated the remediation capabilities of a variety of fungus species for pesticides and herbicides; most of these studies are focused on indigenous species of fungi grown in a contaminated environment. Many species like *Aspergillus tamarii* and *Botryosphaeria laricina* are reported to be very efficient in the degradation of many chemicals and their metabolites e.g., sulfate, endosulfan, alpha endosulfan, and beta endosulfan [40]. *Aspergillus glaucus* has been reported to break fipronil and its various active substances by Gajendiran A, Abraham J, 2017 [41]. Degradation of atrazine has also been shown by *T. maxima* as well as *Paecilomyces carneus* in the same culture and enzyme extracts of *Trametes maxima* [42]. Paraquat could be degraded by *Trametes species*. Likewise, another toxicant, glyphosate, can be degraded by *Aspergillus* and *Penicillium species* as well as *Hypholoma dispersum* and *Trametes pavonia* due to involvement of different ligninolytic enzymes [13]. White rot fungus (*Pleurotus ostreatus*) has also been illustrated for degradation of aldrin and dieldrin by the mechanism of epoxidation and hydroxylation [43]. In many studies esterification, dehydrogenation, demethylation and dechlorination processes have been reported during the alteration of these toxicants by fungi [39] (Fig. 2).

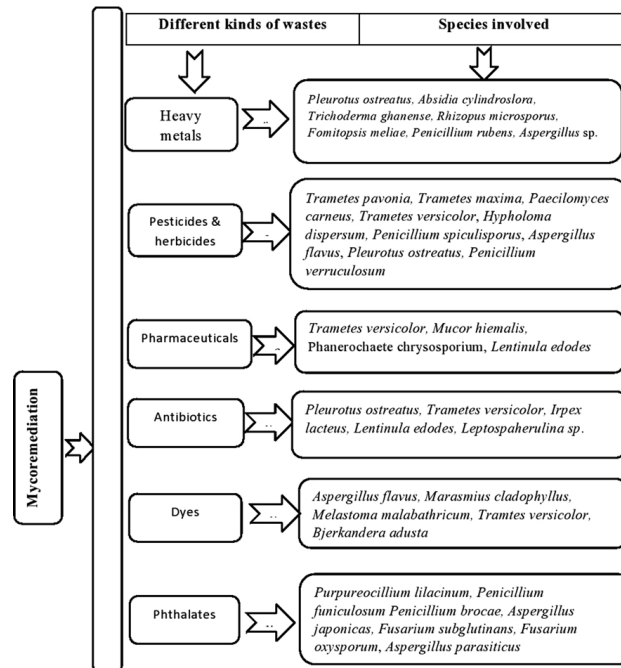


Fig. (2). Bioremediation of different kinds of toxicants using fungal species.

Mycoremediation of Pharmaceuticals

Release of pharmaceutical products from different drug industries are also adding a great threat to the already severely polluted wetlands and affecting the entire ecosystem including plants, animals, and human beings. Many of the aqueous fungi as well as white rot fungi, are being used for the degradation of pharmaceutical products. *Mucor hiemalis*, an aqueous fungus, can be utilized for the removal of acetaminophen from contaminated water bodies and diclofenac [44, 45].

Trametes versicolor has been reported to accumulate and degrade the naproxen and its various derivatives to below detectable levels within 6 h [46]. Similarly, *T. versicolor* also showed the ability to degrade an analgesic, *i.e.*, ketoprofen [28]. The importance of ligninolytic enzymes as well as cytochrome 450, have been analyzed to degrade ketoprofen and naproxen *T. versicolor* [28, 46]. *T. versicolor* is also reported to detoxify other pharmaceuticals such as carbamazepine, diazepam and codeine [47]. *Lentinula edodes*, an edible fungus, can degrade endocrine disruptors [17α -ethyl-estradiol and synthetic testosterone] as well as an anti-inflammatory drug [piroxicam] by using its various enzymes in order to degrade the contaminants [48].

Mycoremediation of Antibiotics

Antibiotics can be considered important drugs which are widely used and released in the form of effluents from different sources such as hospital waste, discarding of expired antibiotics, fecal materials and urine of human, pharmaceutical industries, and uncared usage in aquaculture and animal husbandry, and causing a harmful impact on the economy, animal as well as human health [49, 50]. Toxicity caused by antibiotics has been reported in aquatic organisms due to antibiotic accumulation in water bodies [51]. Some strategies include sonolysis, ozonation, oxidation *via* potassium permanganate, membrane bioreactors, photocatalysis by means of titanium dioxide, Fenton oxidation, and adsorption of charcoal used to treat polluted water caused by antibiotics. However, these practices are costly, energy-consuming, and also produce toxic byproducts [50]. Moreover, some antibiotics have been shown to counteract the different physical and chemical methods because of their chemical reaction [52].

Different fungal species were found to be observed to remove various antibiotics, such as sulfonamides, clotrimazole, oxytetracycline, oxacillin, bifonazole, and fluoroquinolone [50, 52]. *Pleurotus ostreatus*, which is reported as ligninolytic fungi, can absorb oxytetracycline drugs and also be able to remove the various antibiotics from the culture media. However, it was observed that the laccase

enzyme has no involvement in the breakdown of oxytetracycline [53]. Different isoxazolyl-penicillins like dicloxacillin and oxacillin were degraded by *Leptosphaerulina sp.* in which the role of two enzymes, such as laccase and versatile peroxidase, was reported [52]. Various fluoroquinolone antibiotics, such as ofloxacin and ciprofloxacin, were degraded by *Trametes Versicolor*, and the involvement of cytochrome 450 was conveyed with ligninolytic enzymes [54]. *Irpex lacteus* has shown the ability to degrade fluoroquinolone antibiotics, such as flumequine, ofloxacin, and ciprofloxacin, very rapidly and efficiently [55, 56]. *Irpex lacteus* also showed the ability to remove different antibiotics like ofloxacin and norfloxacin, and the role of manganese peroxidase has been observed for it [55]. Likewise, it was also reported to remove antifungal drugs clotrimazole and bifonazole by edible fungi *Lentinula edodes* [57].

Mycoremediation of Dyes

In everyday life, large amount of contaminated water is being discharged into the environment by means of several dyes manufacturing industries, printing, and textile industries. Dyes act as recalcitrant and are able to remain in nature for a long time to have some intrinsic characteristics which make them resistant to fading, stable, and not affected by light and microbial degradation. It is inexpensive and easier to discharge the wastes from the industries into the environment than to decontaminate them [58]. Most of these dyes are mutagenic, carcinogenic, and toxic [59]. Different enzymes like lignin peroxidase, laccase and manganese peroxidase can reduce the various dyes due to their non-specific activity [58, 60]. There are numbers of fungal species which are able to degrade a variety of dyes. *Aspergillus flavus*, obtained in soil samples near a paper processing industry, has shown the accumulation and biodegradation properties of Congo red dye [58]. It is reported that different synthetic dyes can be degraded by the endophytic fungus *Marasmius cladophyllus* isolated from *Melastoma malabathricum* [59]. A strain of *Trametes versicolor* is involved in degrading various azo-anthraquinone-type dyes [60]. Another fungal species, *i.e.*, *Bjerkandera adusta*, which is matured in an airlift bioreactor, can decolorize various reactive and acid dyes rapidly [61]. It is reported that manganese peroxidase and laccase enzymes have shown higher activity in *T. versicolor* while the enhanced activity of lignin peroxidase has been reported in *Bjerkandera adusta* [60, 61]. These studies show that endophytic and ligninolytic fungi can be represented as an effective strategy for treating industrial effluents that perform on varied dyes and do not generate harmful substances [60, 61].

Mycoremediation of Phthalates

Phthalates are considered an important environmental contaminant used in various fields, such as films, capacitors of medical devices, toys, and vinyl tiles [62]. They offer elasticity to the different plastics. Nevertheless, uncontrolled discharges of these substances to the aquatic environment cause imbalance in the food chain, ultimately affecting human health. It is reported that phthalates can reduce testosterone and thyroid hormone levels in humans. These are considered effective carcinogens [63, 64]. There are several methods, such as Hydrolysis, UV irradiation, and photocatalysis *via* TiO₂, which can break down the phthalates, however, these processes are very lengthy [62]. Therefore, the rapid and effective treatments of phthalates could be done *via* the mycoremediation technique.

Two important enzymes, *i.e.*, cutinase and esterase, which are obtained from *Fusarium oxysporum*, have shown ability to degrade various phthalates such as dipropyl phthalate, di-hexyl phthalate, dipentyl phthalate, di-2-Ethylhexyl phthalate and butyl benzyl phthalate. Another enzyme, Cutinase, can degrade these toxic substances rapidly without the formation of any harmful byproduct, while esterase can degrade slowly and form toxic byproducts, which may affect the activity of enzymes [65, 66]. Di-2- Ethylhexyl phthalate, which is noticed in PVC blood bags, can be completely degraded by several fungi such as *P. brocae*, *A. japonicas*, *P. lilacinum*, *F. subglutinans*, *A. parasiticus*, and *P. funiculosum* found from sites heavily polluted with plastics [67, 68].

EFFICIENCY OF MACROFUNGI (MUSHROOMS) FOR BIOREMEDIATION OF TOXICANTS

Mushrooms have been used for consumption purpose as food product for a long time owing to their flavor and richness in protein [77]. They are also recognized as a mycoremediation tool because they are used in decontamination of different kinds of toxicants (Table 2). The Mycoremediation technique depends on different efficient enzymes which are produced by mushrooms for degradation of different types of toxicants.

Mushrooms are known to produce various types of enzymes involved in breakdown of different contaminants, such as cellulases, ligninases (laccase, lignin peroxidase, and manganese-dependent peroxidase), pectinases, oxidases, xylanases and also extracellular peroxidases [78]. These enzymes are also capable to oxidize recalcitrant toxicants in *in-vitro* conditions. These enzymes are usually induced by their substrates.

Table 2. Macrofungi (Mushrooms) and their degradation efficiency for various toxicants.

Mushroom Species	Toxicants	Degradation Efficiency	References
<i>Pleurotus ostreatus</i>	Oxo-Biodegradable plastic	Efficient to degrade plastic and grows on it	[85]
<i>Lentinula edodes</i>	2,4-dichlorophenol	Capable to degrade 2,4-dichlorophenol (DCP) by using vanillin as an activator	[86]
<i>Pleurotus pulmonarius</i>	Radioactive cellulosic-based waste	Acts as the first barrier against the release of radio contaminants	[87]
<i>Coriolus versicolor</i>	Polycyclic aromatic hydrocarbon	Able to degrade Poly-R 478, which decides its suitability to degrade polycyclic aromatic hydrocarbon.	[88]
<i>Pleurotus pulmonarius</i>	crude oil	Capable to degrade crude oil	[89]

These enzymes are also known to degrade non-polymeric and recalcitrant toxicants such as polycyclic aromatic hydrocarbons [79, 80], pentachlorophenol [81], organic and synthetic dyes [82, 83] and nitrotoluenes [84] under *in-vitro* conditions. Recently, it has been reported that mushroom species can degrade polymers such as plastics [85].

The biodegradation mechanism by these enzymes is very complex. It is influenced by other biochemical systems and interactions of ligninolytic enzymes with cytochrome P450 monooxygenase system, hydroxyl radicals and the level of H_2O_2 which are produced by mushroom itself.

CONCLUSION AND FUTURE PERSPECTIVES

It is concluded that the mycoremediation technique represents a safe and inexpensive approach to degrade the different contaminated substances, such as heavy metals, pesticides, herbicides, pharmaceuticals, antibiotics, dyes, and phthalate. Different extracellular ligninolytic enzymes and cytochrome P450 have been used to degrade various toxicants in most of the studies. Whole or functional proteomic analysis can be another important area that needs to be explored to recognize the role of various genes as well as proteins in the technique of mycoremediation which will help in the development of genetically modified and improved fungi for rapid and effective detoxification of the toxicants from the contaminated site. In addition, at a large scale, the fungi may be grown-up in bioreactors for the elimination of contaminants. The optimizing conditions inside the bioreactors need to be studied for efficient remediation practice. The native fungi present in contaminated sites can also be used for this process as they are

capable of adapting themselves in adverse environmental conditions having higher concentrations of various toxicants. Nonetheless, there is a promising indication that the mycoremediation technique can remove various toxicants and make this globe a secure habitat.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Application of Mushroom in Bioremediation of Toxic Heavy Metal Ions

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Abstract: Heavy metals have economic importance in industrial applications and are presently becoming a significant environmental concern. Components of heavy metals like As, Cd, Cr, Pb, Se, and Hg are considered systemic toxicants and induce various organ damage even at lower levels of exposure. Natural sources include metallurgy of metal-bearing rocks and volcanic eruptions, whereas mining and different industrial and agricultural operations are human sources to release them into the environment. In recent times, remediation of toxic metal pollution has been a major environmental and technological challenge all over the world. Several physicochemical strategies have been used in the past to remove heavy metals from the environment. But, it has adverse repercussions, including power dissipation, incompetence for inherently dangerous ions, pernicious by-products, and high cost; hence, alternative strategies are necessary. Biosorption and its operational processes have been very effective in the removal of hazardous heavy metals and display features like eco-friendly, high efficiency, and economic viability, and can be used repeatedly, showing selective metal binding, effective desorption, and recycling of adsorbents. Different biological agents like algae, bacteria, fungi, and yeast can be employed to carry out bioremediation, especially mycoremediation. The potential of fungal biomass (Mushrooms) as a biosorbent is well accepted for the removal of toxic heavy metals and radionuclides from the environment because of its excellent metal-binding characteristics and tolerance towards metals and unfavourable environmental conditions like diverse pH and temperature conditions. Mushrooms, macro-fungi, have fruiting bodies that grow out of a mass of mycelium and can build up heavy metals in high concentrations in their bodies above maximum permissible concentrations and may also act as an effective biosorption tool. High

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accumulation potential and shorter life span are some of the advantages of using mushrooms as biosorbents and exhibiting excellent mycoremediation potential.

Keywords: Bioremediation, Macro-fungi, Miosorbents, Mycoremediation.

INTRODUCTION

Heavy metals are naturally occurring elements having high atomic mass and at least five times the density of water, prevalent mainly in the earth's crust [1]. The heavy metals also include metalloids like arsenic (As), antimony (Sb) and silicon (Si), and can induce toxicities even at low levels of exposure to the living organism, including humans [2]. These metals have numerous agricultural, domestic, industrial, medical, and technological applications to meet the demands of the ever-growing modern human population [1, 2]. Several inorganic metals like calcium (Ca), chromium (Cr³⁺), copper (Cu), magnesium (Mg), manganese (Mn), nickel (Ni), sodium (Na), and zinc (Zn) are vital components for living organisms and required in a small amount for various biochemical, metabolic and physiological functions [3, 4]. However, metal ions like arsenic (As), cadmium (Cd), chromium (Cr), lead (Pb), mercury (Hg), and silver (Ag) do not have significant biological roles but adversely affect the environment and living organisms. These metals enter the environment by various natural and anthropogenic means, such as mining, natural weathering of the earth's crust, industrial effluents, fossil fuel burning, soil erosion, sewage discharge, urban runoff, insect or disease control agents to crops, and many others [5 - 7]. An increasing ecological and global public health concern has been associated with environmental contamination by these metals. Heavy metals are non-biodegradable and persistent in the environment, contaminate the food chains, and cause different health abnormalities due to their toxic nature. At present, there is a significant rise in bio-accumulation and bio-intensification of heavy metals (above threshold levels) in biological species, which causes various anomalies in humans and the environment [8 - 10]. Bioaccumulation of these metals above the permissible limits exhibits its lethal toxic effects and negatively affects the microbiota and ecological equilibrium of soils, animal species, and humans. Therefore, remediation of heavy metals requires special attention to protect air quality, water quality, soil quality, human and animal health, and all spheres as a collection. In this scenario, it is critical to choose economically viable and effective treatment methods free of shortcomings and translate the need for heavy metal alleviation from the environment in terms of an eco-friendly approach [11, 12]. Bioremediation is the most potent and ideal for removing heavy metals and degrading various pollutants, recognized as heavy metal hyper-accumulators by numerous studies as efficient and sustainable. Additionally, it poses multiple

advantages over conventional methods, including economic viability and repeated use of biomass, selective metal binding, effective desorption, and recycling of bio-adsorbents [13, 14]. Mycoremediation, for example, is a biological approach for removing trash from the environment that relies on the usage of fungi or mushrooms. Fungi have chitin in their cell walls, which can tolerate high concentrations of metals, grow in diverse pH and temperature conditions, and exhibit excellent mycoremediation potential [15]. Macro-fungi, a member of Phylum Basidiomycota and Ascomycota of the Fungi kingdom, have diverse epigeous or hypogeous fruiting bodies that grow out of a mass of mycelium and are collectively called a mushroom. The ability of mushroom species to digest heavy metals by secretion of a range of hydrolysing and oxidizing enzymes has attracted researcher's attention toward its application in waste remediation/mycoremediation [16, 17]. Mushroom is a multicellular, heterotrophic and achlorophytous species that belongs to Basidiomycetes family and mycota kingdom. The present review paper discusses about bioremediation of heavy metals and biodegradation with mushroom diversity. The edible mushroom *Lactarius deliciosus*, *Russula delica* and *Hizopogon roseolus* are known to dissociate Cd, Cr, Cu, Pb and Zn. *Agaricus bisporus* assimilates heavy metals like Cr, Cu, Cd and Zn whereas, *Pulveroboletus amarellus* absorbs Zn metal. *Agaricus macrospores* accumulate Cd metal. *Pleurotus ostreatus* absorbs more heavy metals like Cd, Hg, Zn and Cu [18 - 20].

SOURCE OF HEAVY METAL TOXICITIES

Sources of heavy metals in the environment are both natural and anthropogenic. The natural or geological sources of heavy metals in the environment include weathering of metal-bearing rocks and volcanic eruptions. The primary rocks, such as magmatic or igneous rocks, crystallize upon the cooling down of magma. Magma contains a large amount of heavy metal in small quantities [21 - 23]. These heavy metals are incorporated into the crystal lattice of magma during the cooling of magma. Magma crystallization is a function of temperature and pressure conditions, which change constantly during cooling. Different metal ions concentrate according to their stability field at limited ranges of temperature, pressure and chemical composition conditions. One such example is Cr deposited as chromite, and another is Zircon contains uranium and other rare earth materials. These infiltrate into the enclosing rocks; a chemical reaction takes place between enclosing rock and hydrothermal fluids and mineral precipitate as ores such as arsenic as arseno-pyrites (FeAsS), lead as galena (PbS), Zinc as sphalerite. Repeatedly, the ore is an assemblage of several minerals, so smelting and processing of one metal often result in releasing other metals in the environment. Physical and chemical weathering dissolves these heavy metal ions and is

transported to sedimentary basins, where they deposit and eventually enter into the food chain. Upon consuming these food items, it enters the body of the living organism and exhibits toxic effects [24 - 28]. The sources of heavy metal ions in the environment are shown in Fig. (1).

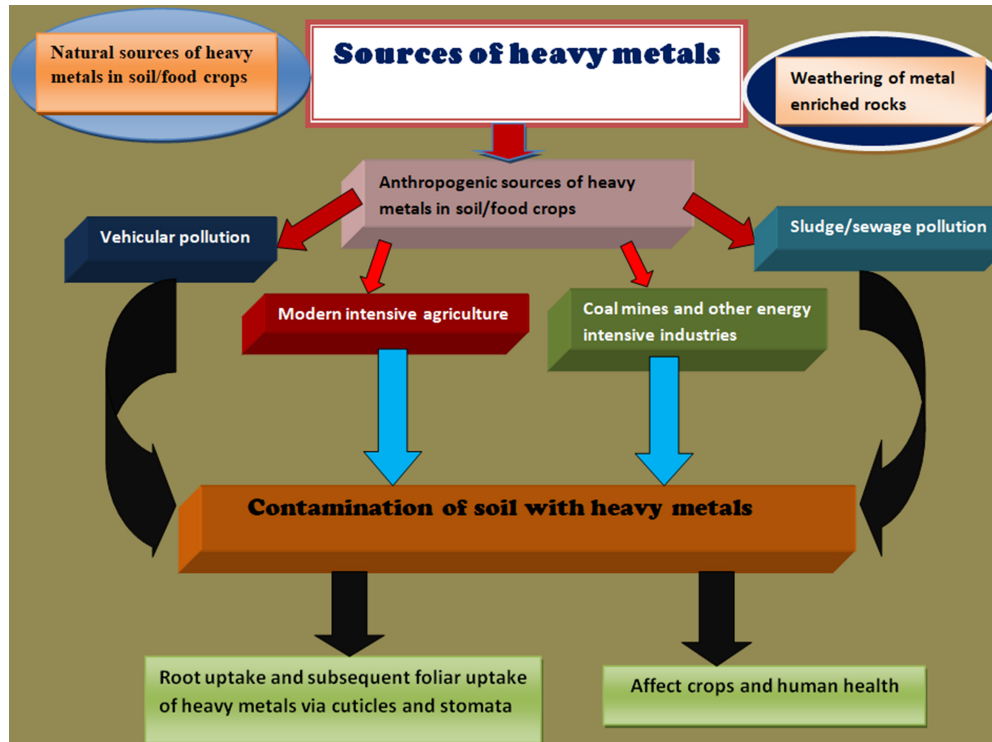


Fig. (1). Diagrammatic representation of sources of heavy metals and their impacts.

Moreover, in the context of human activities, the emission of toxic metals upon combustion of fossil fuels led to release in the environment such as arsenic, selenium, mercury, chromium, lead, and cadmium, as present in significant amounts in fossil fuels (coals and petroleum), and many municipal and industrial effluents/wastes [29]. Several elements present in coals, fuel oil, gasoline, and the combustion of these fuels cause them to mobilize their components and may emit into the atmosphere primarily as constituents of particulate matter. Further, these toxic elements/metals are classified as non-volatile (barium, beryllium, chromium, nickel), semi-volatile (antimony, arsenic, cadmium, lead), and volatile (mercury, selenium), depending on their volatility at stack temperatures [30]. Over the past centuries, the magnitudes of toxic metals contamination in air, soil, and water have risen significantly and caused air pollution, surface water pollution, groundwater pollution, and raised other ecological concerns. Predominance of

these metals in the environment (air, soil, water) can be easily entered into the living body through direct exposure, such as ingestion, inhalation, and surface/dermal contact or through food chain pathways, endangering human health and causing a variety of diseases. Some heavy metals, like As, Cd, Hg, and Pb, will lead to hazardous health problems like renal insufficiency, liver injury, skin cancer, and painful osteoporosis, while others, such as Cu, Mn, Zn, *etc.*, are necessary for the healthy growth of plants or animals but the accumulation of these above the threshold levels will lead toxicity to organisms. In the recent past, the accumulation of toxic heavy metals in the environment and their assessment in context of ecological-health has become a widespread concern and drawn significant attention worldwide. A lot of research has been carried out on spatial distribution, migration process, source analysis, ecological risk assessment, and possible remediation to remove these toxic heavy metals from the environment and ecology [31].

SUBSTRATE FOR MUSHROOM CULTIVATION

Mushroom, which is grown mostly above ground, on soil, or on some substrates, is the spore-bearing fleshy body of a fungus [32, 33]. It is also called a toadstool and is widely used as an edible item. It is also being used extensively as single-cell proteins. The standard features of the most cultivated mushrooms are the presence of a stem (stipe), a cap which is also known as pileus and gills, known as lamellae, present underneath the cap. The most common cultivated mushrooms are the *Agaricus bisporus*, more often known by the common name white button mushroom. Mushrooms can be categorised mainly into two categories- ‘edible’ and ‘poisonous. Macrofungi are fruit-bearing structures that are large enough so that they can easily be seen with the naked eye. These species of fungi mainly constitute the edible varieties of mushrooms. They are either cultivated or harvested wild. A mushroom needs a substrate to grow, which is a material required by the mushroom mycelium to establish itself [33]. It serves to provide the essential factors for the growth of mushrooms, like nutrients, energy and moisture. A variety of mushroom substrates are used depending on the species of mushroom to be cultivated. Different species of mushrooms have different specifications for substrates [34].

Requirements for a Good Mushroom Substrate

Some of the essential or desired characteristics for a material to be suitably used as mushroom substrates are [35]:

1. Substrates should desirably have a nitrogen content of 1 to 2 percent. Some substrates like straw or sawdust require the addition of some other materials to them so that they can reach the threshold of this much nitrogen content.
2. A small amount of sulphur, phosphorus, potassium, magnesium, and calcium should also be present in the substrates [36, 37]. It is important to mention here that most of the substrates generally contain these minerals, but there can be some variations depending on the source material of the substrate. It is a matter of experiment to determine whether supplementation with some additional minerals is required. Acidic substrates are preferred, with pH ranging from 5 to 6.5. Some mushrooms, for example, oyster mushrooms, are capable of tolerating pH up to 8.
3. For the mycelium to grow and colonise optimally, it is essential for the substrates to have a structure conducive to the exchange of air.
4. Moisture content of 50-70%.
5. With the purpose of providing a non-competitive canvas so that mycelia can grow efficiently and thrive, there should be an absence of competing organisms.

Commonly used Substrates for Mushroom Cultivation

It is again noteworthy to mention here that the substrates are chosen according to the purpose and types of mushrooms to be cultivated as they affect the growth, yield, and nutritional composition of mushrooms, still straw, coffee grounds, vermiculite, coco coir, sawdust, rice straw, wheat straw, *etc.* are most used as a basic substrate for mushroom cultivation. Total C, total N, C/N ratio, pH, EC, and mineral content are important factors for mycelium colonization and the development of fruiting bodies. It is very important to determine the chemical and nutrient composition of the substrates, especially those used for commercial purposes [38].

REMOVAL OF HEAVY METALS

The industrialization has led to the introduction of heavy metals in the environment. Heavy metals are known to persist in the environment and pose a risk to microorganisms. Microorganisms have evolved various metabolic dependent or independent strategies to cope with these pollutants. One such strategy is biosorption which is the binding of metal ions with metal-binding proteins present on the cell wall of bacteria, algae, fungi, and yeasts. Different factors, such as temperature, pH, nature of biosorbents, initial metal ion concentration, *etc.*, are known to affect the process of biosorption. Recovery of absorbed metals can be made by using agents, such as thiosulfate, mineral acids, and organic acids [39, 40].

Methods for Removal of Heavy Metals

There can be many methods implied for the removal of heavy metals. Chemical methods include chemical precipitation, oxidation/ reduction, and electrochemical treatment, whereas physical methods include membrane technology, recovery, reverse osmosis, evaporation, and ion-exchange. Biological methods involve microorganisms, including algae, fungi, and bacteria. These approaches, are, however, not efficient and economical. They also fail to offer a selective treatment strategy. Bioremediation is being used and explored to a much greater extent due to its cost-effective and natural treatment strategies.

Biosorption is one of the techniques wherein biological materials accumulate heavy metals from waste substrate either by ATP-dependent metabolic pathway or by virtue of ATP- independent physicochemical pathway. It can also be attributed to some non-living, inactive microbial biomass that tends to uptake and concentrate heavy metals even from diluted polluted aqueous solutions. Mycoremediation which uses fungi for the removal of toxicants, is another biotechnique. It offers benefits in terms of being cost-effective and effective. Mushrooms, or the macro-fungi (especially *Pleurotus sp.*), are considered one of the most efficient mycoremediation. Mycoremediation is one of the biotechniques that recruits fungi to remove toxic pollutants from the environment in an efficient and economical manner. Mushrooms, macro-fungi, are among nature's most important mycoremediation [41]. Biosorption is associated with the utilisation of biomass for heavy metal removal. Biosorption is capable to remove multiple heavy metals simultaneously. Biomass used for heavy metal removal is capable to remove multiple heavy metals simultaneously. However, active site saturation of metal binding ligands and reversibility of the process is a major limitation [42].

A natural biological phenomenon exhibited by microorganisms wherein they recruit proteins to take up metal ions and sequestration of the same occurs in the intracellular space. It can then be further used for various cellular processes such as catalysis of enzymes, charge stabilisation on biomolecules and signalling [43]. It is important to mention here that there is an evident difference between biosorption and bioaccumulation; thus, they should not be used interchangeably. Biosorption is a surface phenomenon wherein the adsorption of heavy metal ions, or other particles occurs mediated by various interactions such as chemical interactions and displacement of proton or ion, chelation, complexation, or some physical forces such as electrostatic interactions [44]. Microorganisms' extracellular surfaces may contain anionic moieties that may act as binding sites for cationic heavy metals at neutral pH [45]. On the contrary, bioaccumulation is a process mediated metabolically in which microorganisms are used to take up

heavy metals from the surroundings into their intracellular space aided by an import system that serves to create a translocation channel across the lipid bilayer, the sequestration of which. It has gained much attention and importance in recent years due to its various attributes, majorly applicability and scientific novelty. Bioremediation can be mediated either by passive or active pathways, and microorganisms are very efficient in bioremediation [46 - 48].

Heavy metal pollution creates environmental stress for human beings, plants, animals and other organisms. A complete understanding of the process and various alternatives for remediation at different steps is needed to ensure effective and economical processes. Bioremediation employs microorganisms to remove heavy metals. Microorganisms have adopted different mechanisms for bioremediation. These mechanisms are unique in their specific requirements, advantages, and disadvantages, the success of which depends chiefly upon the kind of organisms and the contaminants involved in the process. Bioventing, biostimulation, bioattenuation and biosparging are the techniques involved in in-situ bioremediation. Whereas bioreactors, biopile windrows and land farming are the techniques associated with ex situ bioremediation [49, 50].

APPLICATION OF MUSHROOM IN BIOREMEDIATION OF TOXIC METAL IONS

Heavy metals are toxic substances and non-degradable in nature. These metal ions can remove from the contaminated site by biosorption and accumulation through living cells. The living cells can change the more lethal metal ions into less lethal ones by reduction or oxidation. Mushrooms are one of the very potential bio accumulators and show a fascinating potential of accumulating almost 1540 more times than the background nickel level when they grow in areas that are heavily polluted, such as the smelters vicinity. For the bioaccumulation of metals, such as Mn, Fe, Zn, and Cu, the evaluation of the accumulation potential of *P. ostreatus* has been done. The variation is observed in the potential of accumulation of species with different metal ions, which may be ascribed to the varied ecosystems due to the presence of different growth substrates. For example, the fruiting bodies of *P. ostreatus* were shown to accumulate more Hg than Cd, whereas, in the case of *P. fabellatus*, Cd was accumulated to a greater extent. Bioaccumulation is a “metabolically-active” phenomenon, which implies that the host should be alive and thus have its own intricacies. Proper consideration should be given to nutrient requirements and aeration levels to optimally cater to aerobic or anaerobic needs. Proteins of the cytosol and lipid membrane-embedded proteins are also involved, which further impose some more challenges, such as a decrease in the viability of the cell due to the expression of some proteins which

are not necessary for the growth of the cell (for example, heterologous import storage proteins), excess aggregation of proteins and the competitive native environment resulting in the phenotype losses [47, 48].

Mushrooms such as *P. Florida* secrete extracellular enzymes which are able to degrade the solid substance. *P. florida* can also uptake heavy metal ions from solid substances. The mechanism of *P. florida*, which is involved in the degradation of biomass and removal of heavy metal ions, is shown in Fig. (2).

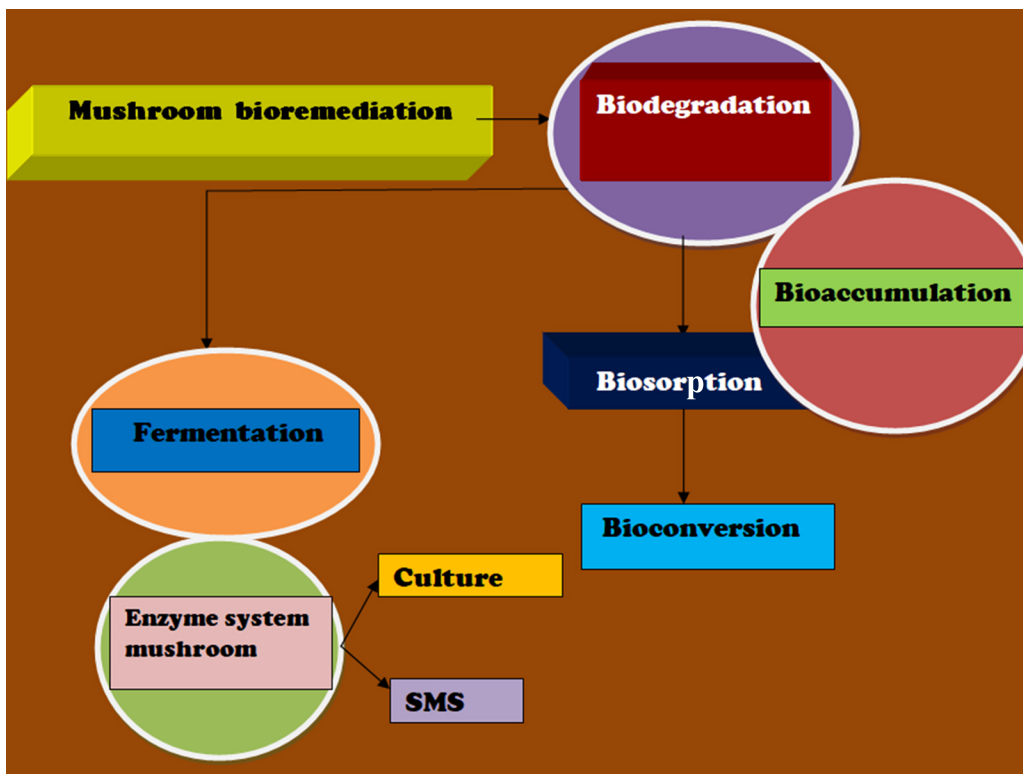


Fig. (2). Heavy metal removal mechanism using mushroom.

Microorganisms tend to adapt and concentrate the heavy metals present in the contaminated areas by various mechanisms of bioremediation. Heavy metals may get attached to some of the extracellular polymeric substances on the cell wall of biomass, thus providing a means for micro-precipitation or exchange of protons. Different mechanisms, such as adsorption, ion-exchange, electrostatic interactions, complexations, redox process, etc., mediate the bioremediation process. Mobilization or immobilization of metals may be initiated by redox

reactions and thus can influence the process of bioremediation. Heavy metals, such as Hg, Cr, Fe, and As, may undergo cycles of reduction and oxidation. It facilitates bioremediation as it converts a stationary and insoluble form of elements in sediments into soluble and mobile forms. Microorganisms may initiate metal mobilization/immobilization by redox reactions; and hence, impact bioremediation processes [51, 52].

Factors Affecting the Heavy Metal Removal

There can be many parameters that can affect the process of bioremediation. The prominent among them are-

Temperature

Temperature, as well as soil moisture, are one of the very significant environmental factors in the process of heavy metal bioremediation. Optimisation of these variables can maintain and enhance the *in-situ* bioremediation of hazardous metals in cold conditions, that too at reduced cost/or maintenance [53]. An elevation in moisture and temperature may also lead to an increase in desorption and bioavailability as was observed with soil laboratory microcosms.

pH

Mushroom-mediated bioremediation is reported to be increased with an increase in pH. The soil pH of about 5 (low pH) may result in reduced bioremediation activity but not complete inhibition. It has been shown that mushroom growth prefers a neutral pH.

Growth Medium or Substrate

Heavy metal bioremediation also depends on the growth substrate medium used for mushroom cultivation. It becomes very significant to provide the optimum growth conditions for the growth of mushrooms that are to be deployed for bioremediation, and hence, the selection and maintenance of a suitable substrate growth medium is a pre-requisite since it would directly affect the growth of mushrooms [54].

Other factors that can influence the bioremediation process are the contact time, concentration of heavy metals in the substrate, and the presence of other contaminants that need to be considered to select the most suitable bioremediation approach [55, 56].

CONCLUSION

The application of mushrooms in heavy metal bioremediation from solid waste and wastewater is an eco-friendly method. The mushrooms can be grown on several inexpensive agricultural or forest wastes, such as rice straw, corn cobs and sawdust. The fungal inoculum can also be mass-produced by current simple techniques used to produce fungal spawn in the quest for economical and ecologically sound methods for environmental remediation. The use of mushrooms is a very good approach and solution. More intensive research needs to be carried out on the heavy metal bioremediation potentials of mushrooms. The challenges faced in the field application, such as technology development for the treatment of heavy metal ions by mushrooms at a large scale, need to be also investigated.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Mushrooms - A Promising Candidate for the Bio-sorption of Heavy Metals from the Environment

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Abstract: Heavy metal pollution has become an emerging issue worldwide owing to its high toxicity, non-biodegradability and persisting nature. Thus, it shows high bioaccumulative ability in the living system that may lead to carcinogenicities and several health complications in humans, even at trace concentrations. Their genesis occurs *via* both natural as well as anthropogenic activities that have contributed to an unusual increase in the concentration of toxic heavy metals across the globe. Several conventional methods, namely chemical precipitation, ion exchange, and membrane filtration, are being implied for the elimination of recalcitrant metals persisting in the ecosystem. But these methods have their own shortcomings and offer many limitations when applied to large volumes and fewer metal concentrations. In this regard, an alternative treatment method is needed that will overcome major demerits while remediating pollutants at a large scale without generating any secondary pollutants. Hence, a variant of the sorption technique, *i.e.*, biosorption, appeared as economical and eco-friendly alternative treatment technology which is characterized by utilizing a material of biological origin. Further, in this process, the binding of passive cations might occur through living or nonliving biomass and aid in the elimination of contaminants from the aquatic system. The origin of biosorbents may vary in terms of the different microorganisms used. However, the biomass of macrofungi or mushrooms has been apprehended as a reassuring class of low-cost adsorbents in effacing toxic ions. This is because the cell walls of macrofungi are enriched with several functional groups that provide key aspects in the biosorption process. In this chapter, the biosorptive propensity of different mushrooms toward metal ions has been accented, and also insights into mechanisms of biosorption are discussed.

Keywords: Biosorption, Environment, Heavy metal, Mushroom.

INTRODUCTION

During the last centennial, industrialization and urbanization have increased progressively to meet human necessities. This leads to increased demand for the

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exploitation of natural resources at a high level and thus aggravates pollution across the globe [1]. The environment is gradually contaminated through the entrance of many pollutants; inorganic ions are of great concern. Since the 1940s, heavy metal pollution has been alarmingly increased owing to their high rates of mobilization and transport in the living systems [1]. These are considered leading contaminants because of their toxicity, perseverance and bioaccumulative nature. Their genesis occurs through both natural as well as anthropogenic sources in which natural activities include weathering of metal-bearing rocks, soil erosion, and volcanic eruptions and anthropogenic activities comprise mining and several other manufacturing and farming activities [2]. Therefore, the term 'heavy metal' is used to represent the metallic chemical elements and metalloids that show a negative impact on the environment and living organisms. However, certain metalloids and lighter metals (like selenium, arsenic, and aluminum) also have toxic effects. Some elements (such as gold) are non-toxic even though they are known to be heavy metals [3, 4]. Although, some heavy metals appear to show biological importance when trace amounts occur. The elements with biological significance especially belong to the 4th period in the modern periodic table. These elements involve the functioning and production of many enzymes, hormones, and the cellular and metabolic growth of the living organism. But their importance is limited to only low concentrations and above the required concentration, which instigates many adverse impacts on human health [5]. Several industries of chemical fertilizers, pesticide, metallurgy, tannery, mining, electroplating, iron, and steel discard their heavy metal-containing wastes into the aquatic ecosystem and contribute negative consequences to aquatic biota also. The most widely distributed heavy metals which have engrossed the researcher's attention due to their ubiquitous nature are chromium (Cr), lead (Pb), zinc (Zn), arsenic (As), copper (Cu), nickel (Ni), cobalt (Co), cadmium (Cd), mercury (Hg) and others [3]. Hence, it becomes vital to remove such non-biodegradable and recalcitrant pollutants from the environment.

Various efforts have been made to eliminate such pollutants using conventional methods like chemical precipitation, cation or anion exchanger, membrane filtration, ultrafiltration, microfiltration, nanofiltration, reverse osmosis, electrolysis, photocatalysis, and activated carbon adsorption [6]. These treatment methods have their shortcomings and offer many limitations when applied to large volumes and fewer metal concentrations. Furthermore, other drawbacks are they precipitate metals slowly, remove metals partially, require expensive reagents, are less effective for mixed metal concentrations, and release secondary pollutants in high quantities that further need proper disposal. In this criterion, it becomes essential to elite such processes that are fast, worthwhile, eco-friendly, and efficient approaches for the treatment. Moreover, it should be devoid of the limitations and enhance the ability to translate the need for eliminating toxic

heavy metals released from industries or originating from other sources [7 - 9]. Recent research has approached green technologies for cleaning and remediating recalcitrant pollutants. Hence, the process of adsorption is found to be efficient, reasonable, and worthwhile for the eradication of these pollutants and shows a high degree of efficaciousness while using feasible biosorbents. In addition to other advantages, biological methods have the propensity to remediate huge quantities of effluents using low biomass concentration in a short period. In the biosorption process, microbial biomass is a biosorbent for detoxification and removal of several recalcitrant pollutants, particularly toxic inorganic ions, from the ecosystem [10]. Moreover, it can perform dual mechanisms as active and passive transport. The first phase is generally signified as passive uptake that exhibits fast and reversible accumulation at the earliest, whereas the second phase represents active uptake owing to slow bioaccumulation inside the cell's organelles, often irreversible and associated with metabolic activities [11]. Initially, dead microorganisms were used mostly for decontamination, but a later approach initiated the utilization of living microorganisms to express better endures in the contaminated environment and high metal accumulation [12].

However, the biomass of various microbes is being employed as biosorbents. While numerous biosorbents have also been designed using different live or dead constituents of mushrooms, such as mycelium, fruiting bodies, and spent mushroom substrates (SMS). These are found to be effective in heavy metal sorption, and their mechanism of action, including extracellular and intracellular accumulation in the biosorption process, displayed the tolerance potential of heavy metals to macrofungi [13]. Further, they have huge dimensions to accumulate heavy metals above their threshold concentration inside the fruiting body and other parts, so the mushrooms emerged as an operative agent for biosorption [14]. Various species related to the genera, such as *Agaricus*, *Boletus*, *Armillaria*, *Polyporus*, *Russula*, *Pleurotus*, and *Termitomyces*, have been explored for the sorption of toxic heavy metals [15]. Hence, the macrofungi or mushrooms are considered a scavenger of pollutants and the foremost part of the ecosystem. This chapter aims to highlight the mechanisms of biosorption, the potentials of macrofungi (mushrooms) in heavy metal sequestration, the efficiency of different biosorbents, and comparative analysis of dead and live fungal biomass as biosorbent for heavy metal removal from the contaminated sites.

BIOSORPTION

In the early 1970s, nuclear power stations discarded their wastewater containing heavy metals and radioactive elements in large amounts into the aquatic system; meanwhile, many microorganisms have appeared to show a remarkable process called biosorption which aid in the concentration of these toxic elements.

Biosorption is a physicochemical sorption process where biological materials or polymers are wielded as sorbents for target species like inorganic metals. In this process, two phases are actively involved, such as a solid phase that acts as a biosorbent (for instance, plants, bacteria, and fungi), whereas an aqueous phase usually represents metal-containing water which is referred to as the sorbate [16]. Furthermore, their quick and reversible binding to ions from the solution occurs through the functional groups which are found on the biomass surface. In other words, the essential site for the biosorption process in biological sorbents is mainly their cell walls [17]. This is because the cell walls of biological sorbents are enriched with several functional groups that provide key aspects in the biosorption process. Among them, some functional groups are observed as most crucial in the sorption of heavy metals that includes the hydroxyl group (-OH), which is mostly present in alcohol and carbohydrates, carboxyl group (-COOH) present in fatty acids, proteins, and organic acids, amino groups (-NH₂) are basic constituents of proteins and nucleic, ester group (RCOOR') present in lipids, sulfhydryl group (R-SH) mainly found in amino acid cysteine and proteins, carbonyl group (>C=O) occurs at the end of aldehydes and polysaccharides while internally in ketones and also in some polysaccharides and phosphate group (PO₄-3) found in the backbone of DNA, RNA, and also in tissue plasminogen activator [18]. These functional groups show immense affinity to metals which aids in effective removal *via* sorption and can be analyzed *via* different analytical methods titration, Atomic Force Microscope based infrared spectroscopy (AFM-IR), raman spectroscopy, wavelength-dispersive X-ray spectroscopy (WDX), X-ray photoelectron spectroscopy (XPS), energy-dispersive X-ray spectroscopy (EDS), and extended X-ray absorption fine structure (EXAFS) [18]. In addition, other techniques such as Fourier Transform Infra-Red (FTIR), transmission electron microscopy (TEM), X-ray diffraction (XRD), energy dispersive X-ray (EDX) spectrofluorometry, and nitrogen gas adsorption-desorption, etc. are used in different combination with classical methods for a comprehensive understanding of the biosorbent structure, morphology, and its constituents. However, the combination of these techniques completely relies on the type of biosorbent [19].

Influence of Parameters on Biosorption

The enhanced rate of biosorption can be achieved by optimizing some factors in which the pH and temperature values play a significant role generally, 3-9 pH value and 4-90 °C temperature values show high sorption capacity. Optimizing the particle size of biosorbent is also found essential for rapid adsorption and desorption and also helps in attaining the equilibrium state [20]. Other factors, including contact time, metal concentration, and amount of biosorbent, have also shown the elevated ability in increased sorption phenomenon. Hence, in view of

ideal biosorbents, it becomes indispensable to select such standout biosorbents that have high biosorption capacity. Thus, it aids to overcome the limitation and reduces frequent replacement during the process. Besides, some other features have also contributed significant aspects while opting for biosorbents. These must have a degree of sustainability regarding any adverse impact on the environment, property of immobilization, and rapid removal through selected species [21]. Nevertheless, fungi as biosorbents are found to have additional merits over algae and plants as they can be grown through simple cultivation methods and fermentation procedures in huge amounts with less expenditure [22]. Many research has documented the role of functional groups in the biosorption of various heavy metals. Yan *et al.* 2008 reported the biosorption of some heavy metals such as lead, cadmium, nickel, and zinc occurs mainly *via* the amine and phosphate groups, which were analyzed through the FTIR technique in *Mucor rouxii*. However, the function of lipid fraction is not yet vital [23]. Hence, the process of biosorption appears as a remarkable biotechnological approach for sustainable development that furnishes an environment-friendly, feasible, and effective technique for wastewater treatment [24, 25]. Thereupon, it helps in minimizing the concentration of several water pollutants to the permissible limits suggested by several federal regulations [26]. Further, the usage of bio-waste in this process aids several benefits; these are the bio-waste to have the ability of recycling and can be used in their native as well as altered forms directly to minimize the wastes for rectifying various problems persisting in the ecosystem [27].

Fungi - a Felicitous Biosorbent

Much research has indicated the immense properties of microorganisms for the uptake of heavy metals in high concentrations. The microorganisms have shown surface specificity towards the biosorption of heavy metals while using them as biosorbents [28]. However, bacteria displayed less resistance towards toxic heavy metals than algae and fungi, whereas algae need a continuous supply of oxygen, and carbon sources for survival and growth. Moreover, other demerits related to bacteria and algae are their small size which resulted in difficulty in their harvesting and needed more labor for separation. Fungi are ubiquitous across the globe, and the fungal hyphae range in diameter between 2 and 10 μm , whereas fungal mycelia comprehend an intertwined network that ranges in size from mm to cm. Owing to these vegetative features, fungi have appeared as the most reasonable and eco-friendly biosorbents [29]. Further, their biomass can be grown at a large scale simply by utilizing an inexpensive growth medium. Fungi are found in large quantities, mainly in the fermentation industries, and hold more advantages than other microorganisms, such as bacteria [22, 30]. On this account, fungi were found to be suitable as a biosorbent for the uptake of heavy metals in

huge amounts with great tolerance resistance when compared to other microbial biomass.

Mushroom/Macrofungi-aided Biosorption of Heavy Metals

Hence, the fruiting bodies of macrofungi or mushrooms are regarded as ideal biosorbents in the process of biosorption owing to their high potential for metal uptake [31]. Several studies have reported the efficacy of mushrooms in the reduction of different metals, such as cadmium, copper, nickel, and chromium, from a polluted environment [32, 33]. During mushroom production, various byproducts are released that also play a significant role, and these wastes can be classified into cuttings and substrates. The stalk of edible mushrooms that is unfit for consumption is known as cuttings, but they contain an essential component, for instance, chitosan, in their cell walls [34]. The fungal cell wall is usually constituted of polysaccharides up to 80% of the dry weight and shows several advantages, for example, a polymer of N-acetyl D-glucosamine occurs in chitin that increases the metal binding property and also the uptake capacity [35]. Further, chitosan and chitin are promising bioactive polymer that has the ability to chelate metals, such as Pb [36]. Similarly, the fungal (*Cunninghamella elegans*) mycelium was grown to obtain a biopolymer, chitosan for the absorption of heavy metals from the aqueous solution. It resulted in high affinity and better absorption for Pb^{2+} than Cu^{2+} at the concentration range of 100-300 ppm [37]. Moreover, an extracellular polymeric substance, β -1,3-glucan, is also being used for metal biosorption to reduce the management of waste generated during mushroom production. β -1,3-glucan isolated from the Shiitake mushroom is employed as a biosorbent for the eradication of heavy metals, such as Ni^{2+} , Cd^{2+} , Zn^{2+} and Pb^{2+} from the contaminated water. This emerged as a significant biosorbent due to its advantageous features, such as high carbon content, numerous metal-binding sites, and pores on the surface. However, they are insoluble in water and thus show efficient sorption capacity [38]. Many studies have shown the efficiency of several mushrooms and their maximum sorption ability of different heavy metals, which are illustrated in Table 1. Moreover, the efficiency of biosorption can be enhanced by pretreating the biosorbents. The hot alkali-treated biomass of *Fomes fasciatus* was found to absorb more Cu (II) in comparison to untreated biomass [39]. Furthermore, *Pleurotus platypus*, *Agaricus bisporus*, and *Calocybe indica* have appeared to uptake Cu, Zn, Fe, Cd, Pb, and Ni significantly from the contaminated water [40].

Table 1. Comparison between different mushroom species for biosorption of heavy metals.

Species	Heavy Metals	Total Biosorption	Concentration	References
<i>Pleurotus ostreatus</i>	Pb	25%	500 mg/L	[41]
	Cr	55%	500 mg/L	[42]
	Ni	89%	500 mg/L	[43]
	Cu(II)	51.77%	23.56 mg/L	[44]
	Zn(II)	60.50%	42.87 mg/L	[44]
<i>Armillaria cepistipes</i> , <i>Xerocomus badius</i>	V	40-90%	51.3 mg/L	[45]
<i>Panellus stipticus</i> , <i>Psilocybecubensis</i> , <i>Schizophyllum commune</i> , <i>Stropharia rugosoannulata</i>	Hg	82% 15% 96% 96%	20 mg/L	[46]
<i>Pleurotus eryngii</i>	Cd(II)	99.9%	20 mg/L	[47]
<i>Lepiota Hystrix</i>	Pb	3.89%	300-500 mg/L	[48]
	Cu	8.50%	300-500 mg/L	
<i>Pleurotus florida</i>	Fe ²⁺	100%	150 mg/L	[49]
<i>Pleurotus eous</i>	Pb	93.2%	5 mg/L	[50]
	Cr	27.6%	5 mg/L	
	Ni	39.8%	5 mg/L	
<i>Penicillium simplicissimum</i>	Cu	33.1%	100 mg/L	[51]
	Zn	28.3%	100 mg/L	
	Cd	33.1%	100 mg/L	
	Cr	88.6%	100 mg/L	
	Pb	73.7%	100 mg/L	
<i>Oudemansiella radicata</i>	Cd	93.3%	30 mg/L	[52]
<i>Agaricus macrosporus</i>	Cu	96%	100 mg/L	[53]
	Pb	89%		
	Cd	96%		
<i>Ganoderma lucidium</i>	U(VI)	80%	100mg/L	[54]
<i>Coprinus atramentarius</i>	Cd ⁺²	76%	1 mg/L	[55]

Mechanism of Biosorption

Biosorption is a process that involves various mechanisms to perform the complete process while eliminating the heavy metals from the contaminated sites. Their mechanism has been categorized into different subcategories, which count upon the microbial metabolism and the locality of sorted metals [56, 57]. In context, metabolism is further divided into (i) metabolic dependent or (ii) metabolic independent mechanism, whereas according to the location of sorted metals within the cells, it includes three sub-types that are (a) Extracellular

accumulation/precipitation; (b) Cell surface sorption/precipitation; (c) Intracellular accumulation [56]. However, the biosorption process, which utilizes cell metabolisms, is termed bioaccumulation instead of the biosorption sub-type [58]. Mostly, their mechanisms involve transport *via* the cell membrane and precipitation, whereas physisorption, ion exchange, precipitation, and complexation take place in the mechanisms of non-metabolism-dependent processes [59]. Sometimes free diffusion is also noticed in the majority of biosorption mechanisms [60]. The transport of heavy metals that occurs across the cell membrane is found to be accumulated inside the cells, and this mechanism was also observed to consume the cell's energy. Hence, it indicated the usage of visible cells only in the process. Moreover, it is usually linked to the active defense system of fungi that becomes functional while reacting to recalcitrant heavy metals [56]. The metal binding was remarked to be a two-step process in which the first step contributes to stoichiometric interaction between the heavy metal and the active functional groups found in the cell wall while the second step performs deposition of inorganic metals in huge quantities. Generally, the metal comes first in contact with cell walls before reaching the cell membrane and cytoplasm. Therefore, the cell walls appeared to be the initial substance that reached in contact with inorganic ions, and the function of these cell wall components is to provide several active sites for active binding, as illustrated in Fig. (1). Owing to this, the process is considered as a complex ion exchanger that seems like commercial resins. Although the cell wall composition varies greatly among various biosorbents, which leads to the difference in the intra-groups. It may further be consequent to alteration in the type and quantity of heavy metal binding, and this type of biosorption, metal-binding, takes place in a quite fast and reversible manner thus, it represents a metabolism-independent process [22]. Furthermore, the physicochemical aspect of biosorbents, for instance, solvability, molecular size, surface charge, chemical combination, reactivity, and hydrophobic nature, affects the rate of biosorption, while some basic factors have great capability for controlling and characterizing the mechanisms that include the chemical, stereochemical, and coordination characters of inorganic ions such as molecular weight, ionic radii, and degree of oxidation of the selected heavy metals, nature of the biosorbents *viz.*, the type and structure of living or dead biomass, different kinds of binding sites, the essential parameters like pH values, range of temperature, the concentration of sorbate and sorbent dose, and different participated inorganic ions; and the presences of binding sites [61].

The pH values influence the sorption mechanism greatly. In the increasing acidic medium, the concentration of H^+ ions also increased, which resulted from the competition with pollutants having a positive charge for sorption onto the biosorbent, whereas, in the basic medium, the enhanced concentration of OH^- ions resulted in competition with pollutants having negative charge for sorption

onto the biosorbent [62]. Nevertheless, it is noteworthy that a combination of many mechanisms functions unassisted to each other to perform the comprehensive uptake of metals. However, there is a lack of proper attention related to the specific mechanism that is solely involved in the sequestration of metals from the surroundings. So, there is a need to clarify the otherwise confusing aspects of the biosorption mechanism for their proper defining [22].

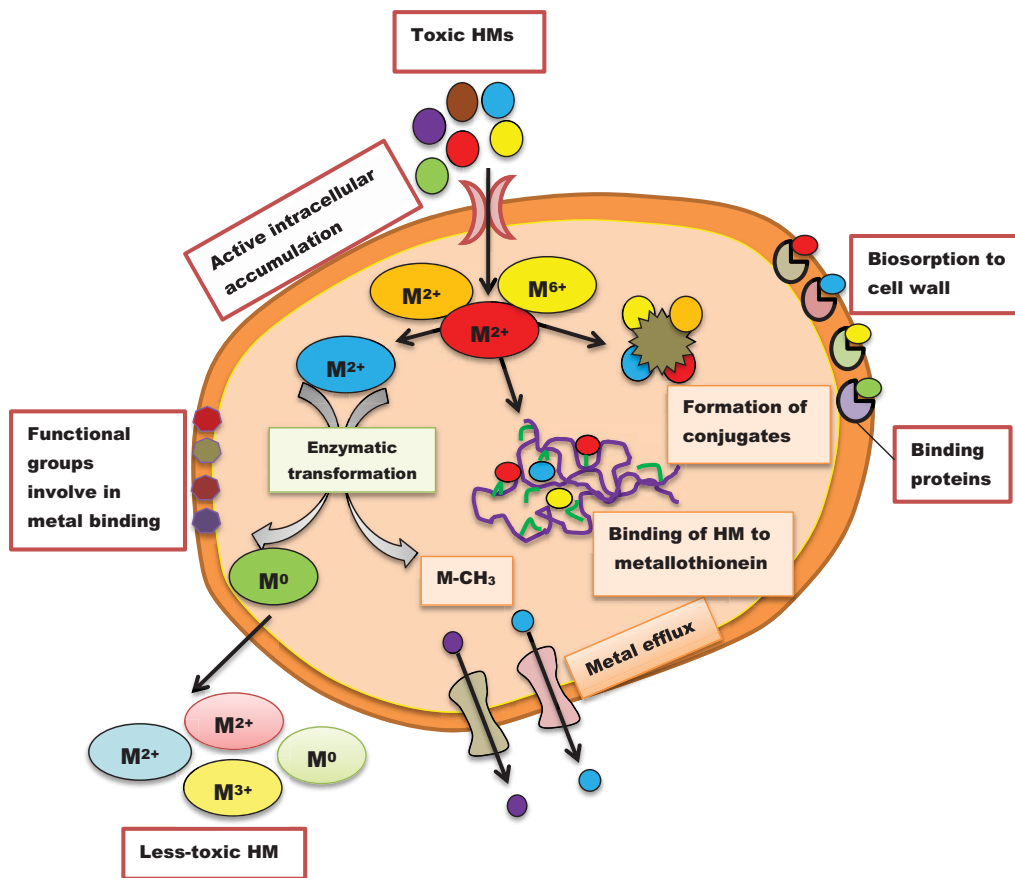


Fig. (1). An insight mechanism of biosorption.

CONCLUSION

With the increasing advancement in technologies, many inventions are made to ease our life. But over time, these also lead to the addition of several recalcitrant pollutants like inorganic ions and organic compounds into the environment. These pollutants are introduced into terrestrial and aquatic ecosystems *via* different natural and anthropogenic activities. Among these pollutants, heavy metals are

polluting the globe in so many ways and remain to persist in the environment for a long time which ultimately shows an adverse impact on living organisms as well. However, as mentioned above, biosorption is an adjunct biotechnology process that continues to offer very significant output for the eradication of toxic pollutants. It further includes many processes depending on the nature of sorbents and the location of sorted metals that aid a great diversity of options and represent great flexibility for its application. In this process, the biosorbents are generally prepared through biomass of different microorganisms, but mushroom residues have shown enormous efficiency for the sorption of environmental pollutants in a wide range. It is a green approach that offers a cost-effective, eco-friendly, and effective removal of heavy metals from contaminated sites. Their sorption efficiency can be enhanced by optimizing the physicochemical parameters. Despite the knowledge of basic biosorption mechanisms, it is still insufficient to implement in real industrial circumstances, and also there is a lack of proper attention related to the specific mechanism that is solely involved in the sequestration of metals from the surroundings. Therefore, there is a need to clarify the otherwise confusing aspects of the biosorption mechanism for their proper application.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Application of Fungal Xylanase Enzymes

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Abstract: The enzyme xylanase breaks down the linear polysaccharide β -1,4-xylan into xylose, therefore breaking down hemicellulose, one of the primary components of plant cell walls. It is essential for the breakdown of plant materials into usable nutrients by microorganisms that thrive on plant sources. Fungi, bacteria, yeast, marine algae, protozoans, snails, crustaceans, insects, seeds, and other organisms generate xylanases. However, the amount of xylanase produced by fungal cultures is generally significantly larger than that produced by yeasts or bacteria. There is a growing demand for low-cost microbial xylanolytic enzymes that have industrial uses and are commercially manufactured. The chlorine-free whitening of wood pulp preparatory to the papermaking process and the enhanced digestibility of silage are two commercial applications for xylanase. Aside from the pulp and paper industry, xylanases are used in wheat flour for ethanol production, improving dough handling and quality of baked products, as food additives in poultry, clarification of fruit juices, biofuel production, textiles, pharmaceuticals, and chemical industries. Improved knowledge of the biological characteristics and genetics of fungal xylanase will allow these enzymes to be used in a variety of novel biotechnological and commercial applications.

Keywords: Biofuels, Biotechnological applications, Pharmaceuticals, Textiles, Xylanase.

INTRODUCTION

Global demand for sustainable renewable fuels has been spurred by rising energy costs and environmental concerns [1]. Governments are now funding considerable research into the development of alternative transportation fuels generated from renewable energy sources, recognising the impending global energy problem caused by the depletion of petroleum-derived fuels. The US Department of Energy has launched a programme to produce biofuels, with a goal of 60 billion gallons per year by 2030. Europe has set a similar goal of replacing 25% of petroleum-based liquid transportation fuel with biofuels by that time [2].

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However, because biofuel production utilising substrates such as sugar cane and corn has limited ability to produce such large volumes, it is a difficult goal to achieve. Researchers discovered that lignocellulose biomass, which contains 75 percent polysaccharide sugars, may be used as a significant feedstock for biofuel production as a solution [3]. If that isn't enough, lignocellulose biomasses are a sustainable energy source that can be procured mostly from agricultural wastes and are plentiful in nature [4].

Agricultural and industrial activity, notably related to agro-allied industries like breweries, paper pulp, and textiles, creates lignocellulosic wastes worldwide. Wood residues (such as sawdust and paper mill waste), waste paper and agricultural leftovers (such as straw and bagasse), household garbage (lignocellulose waste), food industry residues, and municipal solid wastes are just a few examples of waste [5].

These wastes tend to build up in the environment, resulting in pollution [6]. These wastes, on the other hand, are biodegradable and may be turned into useful goods like biofuels, chemicals, and low-cost energy sources for fermentation-improved animal feeds, food processing, sugar, paper pulp, ethanol, pharmaceutical, and agro-industries [7 - 9]. There has been much concern regarding the use of lignocellulosic wastes in the production and recovery of various value-added products because of their availability and renewability [10, 11]. Its increasing need for more efficient usage looks to be transforming into one of the most crucial areas of enormous industrial interest.

Plant biomass wastes that are mostly made up of lignin, cellulose, and hemicelluloses are referred to as lignocellulosic wastes. Hemicellulose has a significant structural component called xylan, which accounts for 20–40% of total plant biomass. The degradation of lignocellulosic biomass necessitates the use of a variety of hydrolyzing enzymes. The availability of enzymes for lignocellulosic biomass hydrolysis remains a key problem in the efficient degradation of plant biomass. Under ideal industrial conditions, biomass may be degraded successfully by combining multiple enzymes that hydrolyze complex polysaccharides into fermentable sugars. These enzymes must function in a range of environments, including those with high temperatures and pH [12].

Xylanases are a kind of depolymerizing enzyme that hydrolyzes xylan, which is a major component of hemicellulose. The development of thermophilic xylanases that are more efficient at higher temperatures than those currently accessible commercially is essential. The relevance of xylanase-producing thermophilic bacteria is critical, and they are well-suited for industrial applications. As a result, researchers are increasingly interested in studying thermophilic bacteria from

harsh environments for biotechnological applications in biomass breakdown. Xylanases are most often generated from microorganisms for industrial purposes due to their biotechnological features. Xylanases have recently piqued the curiosity of the industry for biofuel production, chemical and pharmaceutical production, bioleaching of wood pulp, papermaking, food and beverage production and animal nutrition.

XYLAN

Plant biomass that remains in agricultural trash contains an essential structural component called xylan [13, 14]. It is the second most common biopolymer after cellulose and the most abundant hemicellulosic polysaccharide in plant cell walls [15]. The angiosperms, grasses, and grains constitute a family of structurally varied plant polysaccharides [16]. It is a heterogeneous polymer composed largely of a linear-(1,4)-D-xylose backbone that is partially acetylated and partially replaced by a variety of side chains, principally-D-glucuronosyl and L-arabinosyl units, to varying degrees.

Multiple hydrolases are necessary for full xylan breakdown due to their structural complexity. Endo-xylanase (EC3.2.1.8) is the main enzyme in this process, which cleaves the xylan backbone into xylooligosaccharides [17, 18]. Its primary role appears to be structural, preserving the cell wall's integrity in conjunction with other components, such as hemicellulose, cellulose, pectin, and lignin. It also works in tandem with lignin to protect cellulose microfibrils from biodegradation [19 - 22].

Xylans have characteristics that influence our well-being. One of the essential functional ingredients in baked goods is xanthan gum. They may be turned into xylitol, a natural food sweetener. They affect the brewing characteristics of grains. They can also aid in the diagnosis of various human illnesses. Due to the variety and complexity of plant xylan's chemical composition, it takes a combination of hydrolytic enzymes with distinct specificities and modes of action to completely break it down. As xylan has a complicated structure, it necessitates the use of many enzymes for full hydrolysis. However, endo β -1, 4-xylanase plays a significant role in xylan depolymerization [23].

XYLANASES

Biological catalysts, such as enzymes, mediate the vast majority of metabolic processes that make life possible. Enzymes are the catalytic cornerstones of metabolism, and as such, they are the area of extensive research worldwide, not just among biologists but also among process designers/engineers, chemical engineers and other scientists. Enzymes perform a number of functions inside

living organisms. Several enzymes play important roles in a variety of industrial applications, including biofuel production, brewing, dairy production, paper production, and starch production, to name a few (Fig. 1).

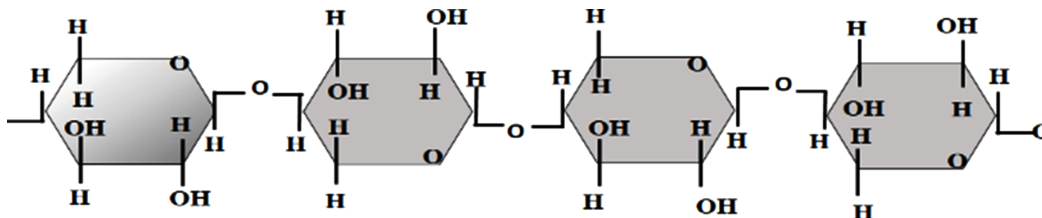


Fig. (1). Structure of Xylan.

Industrially important enzymes, particularly those of microbial origin, have cheap manufacturing costs and, due to their low cost of production, are in high demand. As microbial enzymes are so diverse, they exhibit a wide range of characteristics that make them useful for a variety of applications. A variety of microbial enzymes, such as protease, amylase, xylanase, cellulase, tannase, lipase, and others, are used in the food, agriculture, pharmaceutical, cosmetic, and other biotech industries in our country and abroad.

Microbial enzymes offer a lot of potential in a variety of applications. Enzymes have become a need in recent years since they provide effects similar to chemical additions while also being regarded as harmless natural additives. Enzymatic therapy achieves the same production level as traditional techniques that rely on harsh chemicals. As a result, the use of enzymes at various industrial levels has gained traction.

The major enzymes involved in the degradation of xylan are xylanases (EC.3.2.1.8) (Sharma and Sharma, 2016c). Endo-1,4-xylanases (1,4- -xylan xylohydrolase; EC 3.2.1.8) and -D- xylosidase (1,4-b-xylan xylohydrolase; EC 3.2.1.37) depolymerize polymeric substances, converting them to xylooligosaccharides and xylose [24]. These enzymes play an important function in the role of bacteria that eat plants for food.

Xylanases are found all over the world. Both prokaryotes and eukaryotes have these [25]. Bacteria and cyanobacteria from maritime settings generate xylanases among prokaryotes [26]. Microorganisms, protozoans, snails, crustaceans, insects, seeds, and molluscs, all generate xylanases, and they are [27] also found in the rumen of higher animals. Microorganisms such as bacteria, fungi, and actinomycetes produce the majority of xylanases that are used on an industrial

basis [28]. However, filamentous fungi are the most common commercial source of xylanases.

Xylanase is a fascinating protein not just from an industrial and agricultural standpoint, but also from a scientific standpoint. The use of xylanases in many industries has risen dramatically during the last decade. Due to its hydrolysis and other characteristics, Xylanases are employed in a variety of dietary supplements, biofuel, veterinary, and agricultural processes, as well as in the pulp and paper business and the degumming of plant fibre technologies such as those related to flex, hemp, jute, and ramie [29]. The use of xylanase in many sectors such as pulp and paper, food and feed, and others, has been mandated by a rising concern for environmental pollution and sustainable development, which reduces the use of hazardous chemicals in their operations.

As filamentous fungi produce large amounts of plant cell wall hydrolyzing enzymes such as xylanases in the culture medium, they are receiving more interest than bacteria as possible sources of plant cell wall hydrolyzing enzymes. Some cellulolytic microfungi, including a wild strain of *Aspergillus niger* (ANL301), were identified from decaying wood waste in Lagos, Nigeria, in the hunt for microorganisms capable of effectively digesting lignocelluloses.

Several bacterial species generate a lot of extracellular xylanases, whereas filamentous fungi secrete a lot of extracellular proteins, with xylanase secretion being one of them, frequently occurring with cellulolytic enzymes [30]. Due to their excellent specificity, moderate reaction conditions, low substrate loss, and side product formation, microbial endo-1,4-xylanases (1,4-D-xylan xylano-hydrolase, EC 3.2.1.8) are the ideal catalysts for xylan hydrolysis. Sectors related to papermaking, animal feed, breadmaking, juice and wine industries, xylitol synthesis, and other sectors employ fungal xylanases. This study will focus on current advancements in the understanding of fungal xylanases as well as their industrial applications.

Recently, there has been a surge in interest in xylanase due to its numerous biotechnological applications, including pre-bleaching of pulp, improving the digestibility of animal feedstocks, modification of cereal-based stuffs, elucidation of bioconversion of lignocellulosic material and agro-waste to fermentable products, fruit juice clarification, and degumming of plant fibres [31, 32]. In addition to their usage in the food, paper and pulp sectors, microorganisms create a significant number of xylanases capable of degrading xylan to renewable fuels and chemicals [33 - 35]. In recent years, there has been a rising interest in using green biotechnology in bleaching operations to reduce pollution while also improving pulp quality.

Sources of Xylanases

Marine, terrestrial, and rumen bacteria [36], mesophilic and thermophilic fungi [37, 38], protozoa [39, 40], and crustaceans [41] are all known to have the xylanase enzyme, *etc.* Aerobes, anaerobes, mesophiles, thermophiles, and extremophiles are among the bacteria and fungi that generate xylanases. The ability of fungus and bacteria to create a wide range of hydrolytic enzymes has been widely utilised [42]. Bacteria and cyanobacteria from maritime settings generate xylanase among the prokaryotes [43]. There is information about the presence of xylanase in plants, such as endoxylanase in Japanese pear fruits during the mature stage, and higher animals, such as molluscs, may also produce xylanase [44].

There have been instances of xylanase being isolated and purified from a variety of different sources, including the anaerobic bacteria *Clostridium acetobutylicum*, immature cucumber seeds, and sprouting barley [45]. It has been observed that under solid-state fermentation, *Myceliophthora thermophila* SH1, a thermophilic fungus, produces xylanase [46]. Bacteria and fungi are commonly employed in the manufacture of xylanase in the industrial sector. By synthesising 1,4-Dendroxylanases and -xylosidases, they have been shown to easily hydrolyze xylans. Filamentous fungi are particularly intriguing among microbial sources since they produce these enzymes and have considerably higher xylanase levels than those in yeasts and bacteria.

Xylanase genes have been discovered in a variety of bacteria and expressed in *E. coli*. Xylanases are generated at lower activity levels in bacteria than in fungi and are likewise confined to the intracellular or periplasmic fractions. Furthermore, post-translational modifications, such as glycosylation are not applied to enzymes produced in bacteria.

E. coli recombinants expressing genes from alkalophilic *Aeromonas* and *Bacillus species* were used to produce extracellular xylanases, as well as alkalophilic and thermophilic *Bacillus species* [47]. In the yeast, *Saccharomyces cerevisiae*, heterologous production of the gene xyn A, which encodes a *Bacillus* endoxylanase, has also been reported [48]. Endoxylanase genes from *Trichoderma reesei* and *Aspergillus kawachii* have been successfully cloned and expressed in *S. cerevisiae* [49]. Microbial xylanase is found throughout nature and has a wide range of uses in a number of disciplines. As a result, there are several papers on the study of microbial xylanase. Bacteria and fungi have recently become the most studied and used sources of xylanase. Bacteria can make both alkaline and acidic xylanase, but fungi can only make alkaline xylanase. Extracellular enzyme secretion is greatest in a filamentous fungus. Currently,

xylanase fermentation is mostly carried out by microorganisms such as fungi and bacteria.

Bacterial Xylanases

The presence of xylanolytic bacteria has been documented in the majority of bacterial groupings. Extracted and purified xylanases have been obtained from a variety of microorganisms, including extremophilic bacteria, with good thermostability, cold adaptivity, and alkalostability. *Bacillus stearothermophilus*, *Bacillus circulans*, *Bacillus subtilis*, *Bacillus amyloliquefaciens*, *Bacillus pumilus*, and *Bacillus halodurans* have all been discovered as potential sources of xylanases [50 - 52].

Bacillus spp., *Clostridium thermocellum*, *Thermotoga sp.*, *Rhodothermus marinus*, *Stenotrophomonas maltophilia* and *Streptomyces sp.* have all been shown to contain thermostable xylanases active at temperatures as high as 60–70°C [53, 54]. Although cold-adaptive xylanases are uncommon, they have been found in bacteria such as *Flavobacterium frigidarium* and *Clostridium sp.* PXYLY1 [55, 56]. Bacteria have the edge over fungi in terms of xylanase production since the pH optimum for bacterial xylanases is neutral or alkaline, whereas the pH optimum for fungal xylanases is acidic.

Bacterial taxa that have been found to generate xylanases include *Arthrobacter*, *Bacillus*, *Paenibacillus*, *Cellulomonas*, *Micrococcus*, *Microbacterium*, *Staphylococcus*, *Pseudoxanthomonas*, and *Rhodothermus* [57 - 60]. The low pH necessary for fungus growth and xylanase production necessitates additional procedures in subsequent phases, making fungal xylanases less desirable. *Actinomycetes*, such as *B. pumilus*, *Streptomyces sp.*, *Geobacillus thermoleovorans* and *B. halodurans* [61], as well as firmicutes, such as *B. halodurans*, *B. pumilus* and *Geobacillus thermoleovorans* and *Actinomadura sp* [62, 63] have been identified as possible sources of alkali stable xylanases. Xylanases with such distinct characteristics have a wide range of applications in a variety of sectors.

Bacillus sp., *Pseudomonas sp.*, and *Streptomyces sp.* generate xylanases that are efficient in a pH range of 5-9, with the optimal temperature for xylanase activity being between 35°C and 60°C [64]. Table 1 lists the bacterial strains that were tested for xylanase activity [64 - 67]. At alkaline pH and high temperature, *Bacillus spp.* demonstrated increased xylanase activity. As a result of their alkali tolerance and thermostability, bacterial xylanases are employed in industrial applications.

Table 1. Characteristics and applications of Xylanases from different fungal species.

Microorganism	Molecular mass (kDa)	Optimum pH	Optimum temperature (°C)	Application	References
<i>Trichoderma harzianum</i>	20	5.0	50	Pharmaceutical applications	[91, 92]
<i>Acrophialophora nainiana</i>	22	7.0	55	Textile processing	[93, 94]
<i>Aspergillus niger</i> ANL-301	13.5-14.0	5.5	45	Pulp Industry	[95]
<i>Aspergillus caespitosus</i>	26.3	6.5	50	Industrial effluent treatment	[96, 97]
<i>Aspergillus ficuum</i> AF-98	35	5	45	Commercial production of Phytases	[98, 99]
<i>Aspergillus niger</i> BCC14405	21	5	55	Bio-bleaching and Pulp Industry	[100, 101]
<i>Trichoderma viridae</i> VKF3	14	7	50	Bio-bleaching of newspaper	[102]
<i>Humicola insolens</i> Y1	44	6-7	70-80	Brewing Industries and XOS generation	[103]
<i>Aspergillus oryzae</i> LC1	35	5	25	Hydrolysis of Agro-residues and XOS Production	[104]
<i>Pichia stipitis</i>	31.6	6	50	XOS generation	[105]

Fungal Xylanases

Xylanase is produced in large quantities by fungi [68]. Filamentous fungi are especially intriguing for producing xylanase because they release enzymes into the medium and have greater activity levels than yeast and bacteria. Although the temperature optima and stability of xylanases from eubacteria and archaeobacteria are far greater than those of fungus, the amount of enzyme generated by these bacteria is significantly lower than that produced by fungi. In general, the amount of xylanase produced by fungi is significantly higher than that produced by yeasts or bacteria [69].

For the past five decades, filamentous fungi have been used as the most effective industrial enzyme makers in contrast to bacteria. Filamentous fungi create an abundance of xylanolytic enzymes in the medium used for the experiment. Lignocellulolytic fungi, such as *Trichoderma reesei*, *Aspergillus niger*, and *Myceliophthora thermophila*, produce a wide range of enzymes that break down

complex cell wall components [70 - 72]. Fungal genera *Aspergillus*, *Trichoderma*, *Fusarium*, and *Pichia* are well recognised for their ability to generate xylanase and are the most commonly utilised ones for commercial production [73]. *Thielavia terrestris* [74], *Talaromyces thermophiles* [75], *Paecilomyces thermophile* [76], *Achaetomium* sp. X2-8, *Rhizomucor pusillus* [77], *T. Leycettanus* [78], *Melanocarpus albomyces* [79], and *Aspergillus oryzae* LC1 [80] were discovered to be hyperthermophilic active xylanase producers.

Paenibacillus barcinonensis [81], *Aspergillus fumigatus* MA28 [82], *Cladosporium oxysporum* [83], and *Aspergillus oryzae* LC1 were among the fungal strains that produced alkali-stable xylanases. Extracellular xylanases produced by white-rot fungi have been shown to function on a wide range of hemicellulosic substrates. *Phanerochaete chrysosporium*, for example, generates a lot of glucuronidase [84], while *Coriolus versicolor* produces a complicated xylanolytic combination of enzymes [85].

The focus on xylan-degrading enzymes has resulted in the discovery of a slew of new enzymes with unique properties from a variety of microorganisms [86]. Thermophilic fungi, a special type of microbe that thrives in hot environments, are frequently found in piles of agricultural and forestry waste, as well as in other composting materials. *M. thermophila*, a strong cellulolytic organism, was employed in new sophisticated commercial enzyme production methods, such as biomass-derived fuels. *M. thermophila* differs from other xylanase producers, such as *A. niger* and *T. reesei*, due to its unique characteristics. It is the best source of genes for extracellular thermophilic xylanases. It possesses a high concentration of enzymes that degrade (glucurono) arabinoxylan. It includes lignocellulolytic enzymes, which create a full complement of cellulose-degrading enzymes. *M. thermophila's* genome and sequence analysis have shown carbohydrate-active enzymes, proteases, oxidoreductases, lipases, and xylanase, which are among the many genes involved for the production of thermostable lignocellulolytic enzymes [87, 88].

Other thermophilic fungi, such as the nonpathogenic and harmless fungus *Humicola*, produce a broad range of hemicellulases and cellulases. Thermophilic *Humicola insolens* Y1 is a prolific generator of xylanolytic enzymes, including thermophilic xylanases from the GH10 and GH11 families [89]. Another possible fungus with the ability to generate thermostable cellulases and xylanase, *Thermoascus aurantiacus*, has been discovered in the Aravali forest region of the University of New Delhi [90]. As a consequence of its inoculum preparation process, the fungus was able to create antioxidant chemicals, which may be exploited to harness agricultural wastes for biofuel generation. Other auxiliary enzymes required for xylan breakdown are produced by fungi. Extracellular

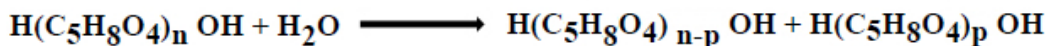
xylanases produced by the basidiomycete group of fungi operate on a wide spectrum of hemicellulosic materials, producing metabolites which can be used in medicinal, cosmetic, and food applications sectors. When cultivated on plant cell walls, for example, *Phanerochaete chrysosporium*, *Trametes versicolor*, and *Cunninghamella subvermispora* produce xylanolytic enzymes.

Catalytic Mechanism of Xylanase Action

The existence of several substituents (arabinose, glucuronic acid, galactose, acetyl group, feruloyl group, and p-coumaroyl group, among others) discovered to be associated with the free hydroxyl groups of xylose residues is responsible for xylan's variety and complexity. As a result, simplification of the specific biomass necessitates the simultaneous action of numerous hydrolytic enzymes with diverse modes of action. Endo-1,4-xylanases (EC.3.2.1.8), β -xylosidase (EC.3.2.1.37), α -arabinofuranosidase (EC.3.2.1.55), acetylxylan esterase (EC.3.1.1.72), glucuronidase (EC.3.2.1.139), p-coumaric acid esterase, ferulic acid esterase, and other enzymes are found in microorganisms [106].

The endo-1,4-xylanases, also known as endoxylanases (E.C. 3.2.1.8), are the most significant of these because they cleave the main chain, the structure's 1,4-glycosidic bond, leading to the production of lower molecular weight xylan fragments and xylooligosaccharides. Multiple isoforms of xylanases have been discovered in studies. Various pre- or posttranslational changes, such as differential mRNA processing, partial proteolysis, or variations in the degree of amidation and glycosylation, have been shown to result in the formation of these isoforms [107]. β -xylosidase is an enzyme that reacts with endoxylanase products to produce the monomer xylose. Aside from these two enzymes, there are other enzymes that cleave the substituents according to their specificities, such as α -arabinofuranosidase, acetylxylan esterase, and glucuronidase [108] (Fig. 2).

Endoxylanase hydrolysis of xylan can be expressed as follows:



Applications of Fungal Xylanases

The biotechnological and commercial usage of xylanase enzymes has increased dramatically during the last few decades. Xylanases are widely used in the food, paper, and feed industries, as well as in the production of xylitol and ethanol, biofuels, oligosaccharides, cellular proteins, liquid fuels, and other chemical substances, and in pharmaceutical industries [109 - 111]. *Humicola insolens*, *Aspergillus niger*, and *Trichoderma spp.* are some of the most often utilised microbes for this purpose. Xylanase, cellulase, and pectinase account for around

20% of the global enzyme market. Xylanolytic enzymes are utilised in the baking and brewing sectors because of their potential efficacy in bread production. Xylanases are employed in animal feed, where they break down arabinoxylans found in feed components, lowering the viscosity of the raw material.

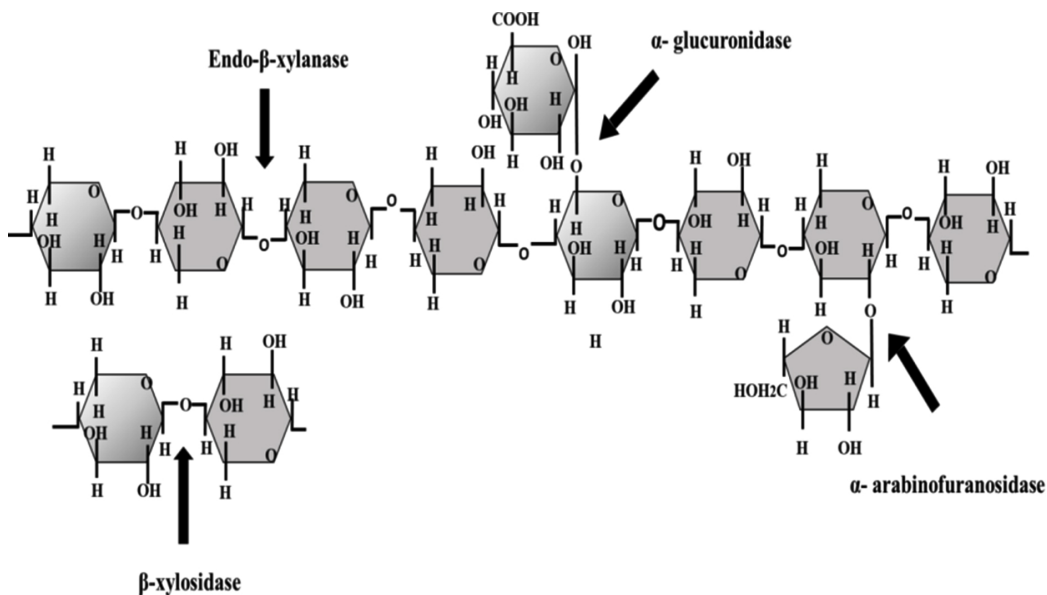


Fig. (2). Xylanase: Mechanism of action.

Xylan and xylanases are also utilised in the pharmaceutical industry. Indigestion is treated using xylanases, as well as enzymes, such as proteases and hemicellulase. Xylan hydrolytic products can be used to create fake sweeteners, solvents, ethanol, and other goods. Xylanolytic complex is also utilised in the textile industry and is used to make plant fibres such as linen and hessian. Xylanases are also employed in cellulose pulp bleaching. Xylanases are also utilised to improve the recovery of sugar from agricultural wastes. The majority of agricultural waste is composed of cellulose and hemicellulose, which must be transformed into component sugar [112]. Waste produced by the agro-business and food sector is dispersed around the world and is posing a health risk. We need strategic planning and chemicals to hydrolyze the constituents in order to use the waste and prevent this risk. Because xylan is the most abundant polymer in plant structures, xylanases and microorganisms that produce xylanase enzymes can be used to process food, paper pulp, sugar, ethanol, and in agro-industries. Fungal xylanases have enormous potential for industrial applications. Xylanase, in conjunction with other enzymes, can help businesses (Fig. 3).

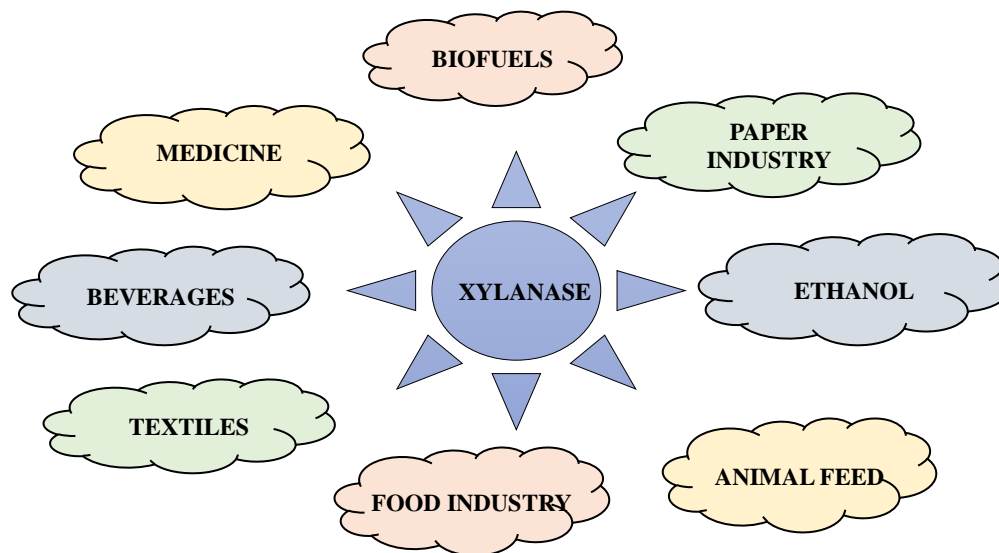


Fig. (3). Applications of Fungal Xylanases.

Biofuel Industry

Overconsumption of fossil fuels in recent decades has not only resulted in rapid depletion of the stock, but has also had a negative influence on the ecosystem. Due to the negative effects of using fossil fuels, it is necessary to consider alternatives that are both eco-friendly and sustainable in nature.

Renewable energy in the form of biofuel derived from the lignocellulosic substrate is now one of the most significant sources of sustainable energy generation. The output of lignocellulosic biomass is estimated to be between 10 and 50 billion dry tonnes globally [113, 114].

Enzyme conversion of most agricultural wastes necessitates the conversion of both cellulose and hemicelluloses to their component sugars. Agro-industrial and food-processing wastes are plentiful across the world, and they have mostly become a cause of health concerns. Utilizing these wastes for the manufacture of strategic chemicals and fuel necessitates the hydrolysis of all components. Xylanases and the microorganisms that produce them might be used in food processing, paper and pulp manufacture, ethanol, sugar, feed, and agro-fibre production because xylan is a major plant structural polymer.

Traditionally, xylanase has been used primarily for the bioconversion of lignocellulosic materials, particularly agricultural and forestry wastes and residues, into high-value products such as biofuel.

The generation of ethanol from this biomass does not compete with food production and is also cost-effective. However, this biomass is recalcitrant in nature and requires pretreatment, which includes the introduction of an acidic environment, which weakens the structure and accelerates the penetration of active molecules that can cleave the bonds within it, thereby increasing the ethanol yield [115].

This pretreatment procedure includes the addition of dilute sulfuric acid, which enhances the accessible surface area of the biomass and efficiently solubilizes the hemicellulosic component of the biomass [116]. As a result of the sulfuric acid pretreatment procedure, the medium becomes acidic, and the employment of acidophilic xylanases at this stage would be advantageous since no pH adjustment step for the downstream process is required.

Ethanol Production

Using microbial strains or biocatalysts to create value-added products of different types, such as biofuels, organic solvents, microbial enzymes, and other metabolites from easily available agricultural, and industrial wastes, offers an advantage over traditional chemical techniques in this context. All photosynthetic components are made up of simple carbohydrates, but they are intertwined in complicated ways as polymers of cellulose, hemicellulose, and lignin. As a result, the digestion of these compounds to create simple monomeric forms necessitates a strong alkali or acidic environment.

This process of chemical hydrolysis produces xenobiotic effluents, which pollute the environment. A better option is to use specialised hydrolyzing enzymes. Due to their widespread use in a variety of industries, particularly in the bioconversion of hemicellulosic waste materials to ethanol, xylitol, and arabitol, as well as their use in animal feed and other biotechnological applications, xylanases are gaining popularity among hemicellulosic material hydrolyzing enzymes.

Plant biomass delignification and hydrolysis of cellulose and hemicelluloses to monosaccharides are steps in the ethanol manufacturing process from lignocellulosic biomass. The hydrolysis process can be carried out by acid treatment at high temperatures or through enzyme action. Acid hydrolysis necessitates a considerable amount of energy and acid-resistant equipment, which raises the cost of the operation. These drawbacks do not apply to enzymatic hydrolysis.

Due to the sheer complex composition of lignocellulosic biomass, full hydrolysis requires the synergistic activity of multiple enzymes (β -glucosidases,

EC3.2.1.21; endoglucanases, EC 3.2.1.4; xylosidases, EC 3.2.1.37 and xylanases, EC 3.2.1.8).

Xylanases in Animal Feed

The utilization of enzymes in the production of feed is a significant agricultural industry, with an annual global output of more than 600 million tonnes and a turnover of more than \$50 billion dollars. Animal feed contains xylanases, as well as glucanases, pectinases, cellulases, proteases, amylases, phytases, galactosidases, and lipases. These enzymes break down arabinoxylans in feed components, reducing raw material viscosity [117]. The arabinoxylan found in grain cell walls is anti-nutritional for hens.

When such substances are present in soluble form, they may raise the viscosity of the ingested feed, preventing other components from moving about and being absorbed. If xylanase is added to feed containing maize or sorghum, both of which have low viscosity, it may improve nutrient digestion in the initial section of the digestive tract, resulting in increased energy usage. Furthermore, this type of diet has been shown to minimise undesirable residues in the excreta (phosphorus, nitrogen, copper, and zinc), which might help to prevent environmental pollution. The collaboration of xylanases, glucanases, proteinases, and amylases in feed formulations lowers viscosity and enhances nutrient adsorption. Enzymes either hydrolyze non-degradable fibres or release nutrients that have been occluded by these fibres [118].

Xylanase is used in the feed business to enhance the digestibility of animal feed, therefore boosting feed viability. Xylanase is added to poultry feed components such as wheat bran and rice bran to improve nutrient absorption, particularly in birds. The amount and concentration of nutrients in bird droppings would eventually be reduced as a result of this. Xylanase is also used in fodder digestion, when it is sprayed over forages alongside other fibrinolytic enzymes. The forages are subsequently given to cows in order to increase milk output.

Bread, Food and Drinks Manufacture

Xylanases, along with α -amylase, glucose oxidase and proteases, can be used in bread production. Xylanase is frequently used in the food business. Bread manufacture has received a lot of attention among the many sorts of food businesses in which xylanase is used. Bread is widely consumed all around the world. Enzymes such as fungal amylases are commonly utilised in the bread-making process. Enzymes have grown in relevance and popularity in the bread-

making business over the years because they increase the quality and characteristics of the dough. Other enzymes, such as proteases, amylases, and cellulases, act in tandem with xylanase to reinforce the gluten network in bread.

Xylanase destroys the glycosidic connections in arabinoxylans during the baking process. This process enhances the dough's handling characteristics as well as the bread's volume. Like other hemicellulases, xylanases help redistribute water in wheat flour, making the dough softer and easier to knead. They allow the dough to expand by delaying crumb formation during the baking process. Bread volume increases, water absorption increases, and fermentation resistance improve with the application of xylanases [119, 120]. Xylanases, in conjunction with cellulases, amylases, and pectinases, are now used to increase juice yield by liquefying fruits and vegetables, stabilising fruit pulp, recovering aromas, essential oils, vitamins, mineral salts, edible dyes, pigments, and other compounds, reducing viscosity, and hydrolyzing substances that obstruct the physical or chemical clearing of juice. Xylanase helps to clarify the end products of wine and fruit juice. With the presence of xylanase, xylans, pectins, and hemicelluloses in fruits are broken down into simpler molecules such as xylose and glucose. Hemicelluloses are plant cell wall polysaccharides that are not cellulose (polymer of -1,4-D-glucose) and pectins (polymer of galacturonic acid). The juice from the fruits is extracted once the cell wall is broken down.

Xylanase and endoglucanase act together to hydrolyze arabinoxylan and starch in wheat flour, separating and isolating gluten from starch. This enzyme is also utilised in the production of coffee bean mucilage. High stability and optimum activity at an acidic pH are the xylanases' most attractive characteristics for application in the food sector. Other applications for xylanases are being discovered as molecular biology techniques advance.

Pharmaceutical and Chemical Applications

Xylanase and xylan are rarely used in the pharmaceutical industry. Xylanases can be used as a dietary supplement or to treat impaired digestion when coupled with a complex of enzymes (proteases and hemicellulases), but there are few medicinal products that use this formulation. The first step is to delignify xylan-rich hemicellulose, which is subsequently hydrolyzed by xylanases and hemicellulases to produce D xylopyranosyl units. The chemicals are subsequently fermented by yeasts (mainly *Pichia stipitis* and *Candida shehatae*) to produce xylitol or ethanol [121]. Xylitol is a polyalcohol that has comparable sweetening characteristics to sucrose [122]. It is a sweetener that is not cariogenic and is safe for diabetics and obese people, and it helps prevent osteoporosis and respiratory infections, lipid metabolic abnormalities, and renal and parenteral diseases as well.

Chemical catalysis is used to manufacture commercial xylitol on a big scale. This is a high-cost method, owing to the fact that the xylose must first be purified in multiple stages. Furthermore, chemical reactions frequently produce by-products that are toxic to fermentation; for example, in the decomposition of lignocellulosic material, additional compounds (aromatic and phenolic compounds and aldehydes) generated from the breakdown of xylose, glucose, and lignin may be formed due to the release of sugars.

Acetic acid and extracted material (for example, terpenes and their derivatives, tropolones, and phenolic chemicals like flavonoids, quinones, stilbenes, quinones, and lignans), as well as substances liberated from the lignocellulose structure (chromium, iron, copper, and nickel) can be effective microbial inhibitors. The invention of a more appropriate method for xylitol synthesis has raised hopes for its greater application in the food, pharmaceutical, and odontological sectors.

Textiles

One of the most rapidly expanding disciplines in industrial enzymology is the use of enzymes in the textile industry. Xylanases, amylases, catalases, and lactases are enzymes used in the textile industry to extract starch. Excess hydrogen peroxide is broken down, textiles are bleached, and lignin is degraded. As enzymes become more widely available, their use in different aspects of textile production is quickly expanding. As these enzymes are non-toxic and environmentally benign, they might substantially help the textile sector. Xylanases in blends with cellulases can be used to remove noncellulosic substances from bast fibres, such as lignin and hemicelluloses.

In the textile business, the xylanolytic complex can be used to treat plant fibres such as hessian or linen. This requires that the xylanase be devoid of cellulolytic enzymes. In one method, dried ramee (China grass) stems are incubated using xylanase to release the lengthy cellulose fibres intact. There is no need to use an abrasive bleaching stage after employing this approach since the lignin does not oxidise, which results in the darkening of the fibres [123, 124]. Despite the fact that little research has been done on the enzymatic preparation of textile fibres, this appears to be a lucrative sector in need of innovative techniques.

Paper and Cellulose Pulp

Another major use for xylanase is in the pulp and paper industries for bleaching kraft pulp. The majority of xylanases discovered to date are most active at or below 50°C and at acidic or neutral pH 6 [125]. The incoming pulp in the

enzyme-assisted pulp bleaching process has a higher temperature and an alkaline pH, making the employment of thermostable alkaline xylanases highly appealing. Xylanase has been employed in bleaching during paper manufacture, resulting in less chemical usage and improved brightness.

Furthermore, interest in xylanase has lately increased, owing to its use in the pulp and paper sector. Xylanase enhances the chemical bleaching of pulps, resulting in more cost-effective and environmentally friendly results as compared to the chemical approach of employing chlorine [125]. Xylanase strengthens cellulose fibres in bleached kraft pulp and increases pulp fibrillation water retention. Indeed, microscopic examination indicates that xylanase has the potential to open up fibre surfaces, resulting in detached material on xylanase-treated pulps. When compared to chlorine-based treatments, this enzyme improves pulp bleaching by up to 25%.

The ultimate brightness value of the pulps is increased by enzymatic processing. Fungal xylanase producers include *Aspergillus sp.*, *Fusarium sp.*, and *Penicillium sp.* *Trametes trogii* [126], *Aspergillus awamori* [127], and *Streptomyces sp.*, all of which have shown to generate xylan-induced xylanases, with xylan acting as a powerful inducer. In *Sclerotium rolfii* and *Trichoderma reesei*, L-sorbose in medium promotes xylanase synthesis [128, 129]. In *Trichosporon cutaneum*, positional isomers have been found to trigger xylanase [130].

CONCLUDING REMARKS

Increased awareness of environmental contamination caused by chemical processes in many sectors has cleared the door for the use of more energy-efficient, commercially feasible, and environmentally acceptable methods, such as the use of enzymes. Xylanases are hydrolases that depolymerize xylan polysaccharides. As a cell component, xylan is also the second most frequently accessible polysaccharide. Microbial xylanases offer enormous potential and a wide range of applications in a variety of sectors. Insects, snails, bacteria, fungus, crustaceans, hulls and husks, seeds, protozoans, and other organisms have been found to generate xylanase, although filamentous fungi are the primary commercial suppliers. Due to its varied applications spanning from fruit pulp manufacturing to medicinal applications, fungal xylanase is gaining rising demand as an essential industrial enzyme. In a nutshell, xylanase piques the interest of many researchers due to the enormous earnings created in the global market for industrial enzymes. Until date, the majority of known xylanases have been derived from fungi. They provide more competitive and better working conditions, positioning them as a fast replacement for bacterial xylanases.

Combining different approaches would assist in accelerating research and knowledge of fungal xylanases, resulting in an efficient enzyme to meet the desire for environmental protection. A thorough understanding of the biology and biochemistry of fungal xylanases will allow researchers to search more effectively for and tailor highly efficient xylanases for industrial use. This also makes it possible to isolate novel fungal species for the production of recombinant xylanases.

Using better technological advancement systems, the creation of recombinant fungal expression systems via a genetic method will aid in the hyper-expression of xylanases and xylanase families for industrial production management. Xylanases have enormous promise in a wide range of commercial and scientific domains, including pulp and paper, animal feed, drinks and food, biofuels, ethanol manufacturing, textiles, pharmaceutical, and chemical industries. Due to their excellent specificity, moderate reaction conditions, low substrate loss, and side product formation, microbial xylanases are the ideal catalysts for xylan hydrolysis. However, one of the major problems limiting the economic viability of this method is the expense involved in the enzymatic hydrolysis of biomass. As a result, xylanase production must be increased by finding more efficient fungal or bacterial strains or by generating mutant strains that can secrete greater amounts of the enzyme. Therefore, xylanase output must be enhanced by identifying more powerful fungal or bacterial strains or by developing mutant strains that can produce more enzyme. To summarise, lignocellulosic biomass and enzyme-producing microbes are intriguing to study topics aimed at investigating the rising relevance of xylanases in diverse industrial products. Furthermore, as public awareness of the harmful effects of chemicals on the environment, ecosystems, and human and animal health has grown, so has the pressure on the chemical industry to transition from chemical-based catalytic processes to biobased and eco-friendly processes. Furthermore, there is a significant growth in demand for xylanases in the food and feed sectors to provide safe and high-quality products. All of this adds up to support our current forecast of steady growth in xylanase demand in a variety of industrial applications.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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