Evidence-based Functional Foods for Prevention of Age-related Diseases

Surajit Pathak
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Preface

This book, *Evidence-Based Functional Foods for Prevention of Age-Related Disorders*, deals with the beneficial impacts of functional foods on the health and well-being of older people. Many chronic diseases such as CVD, brain disorders, immune disorders, and cancers are more frequent in the aged population.

Nutrient requirements for optimum health and function of old physiological systems are often quite distinct from those for young people. Therefore, the unique nutrition problems of the elderly are being intensively investigated. The growing demand for healthy food has stimulated a rapid increase in research on functional foods to prevent or address nutrient deficiencies and improve the health of the aging population. Functional foods have been shown to modulate gene expression, cellular redox system, brain function, gut health, and immune function. Functional foods include omega-3 fatty acids, polyamines, minerals, probiotics, prebiotics, polyphenols, dietary fiber, etc. This book aims to provide an overview of recent developments in the role of functional foods in promoting healthy and active aging, with a specific focus on their effects on the nutritional status of older adults.

The primary objective is to describe the latest development as to how food components or supplements can help treat the aged population. This book has 20 chapters that aim to describe the roles of functional foods in preventing age-related disorders with the latest scientific developments in this area. The chapters describe the roles of diet-gene interactions, macronutrients, polyamines, omega-3 fats, minerals, and several other nutrients, including antioxidants and energy restriction in aging. This book provides current information on functional food components, including antioxidants, omega-3 fats, prebiotics, bioactive flavonoids, minerals, macronutrients, and many other bioactive food components. Each chapter details the roles of functional foods in aging challenges and offers innovative and impactful insights into those challenges and possible mechanisms. This book also presents innovative functional food ideas for managing healthy aging and the processes and investigation of aged people.

The chapters are written by recognized functional food specialists, medical scientists, and nutritionists and cover the basics of functional food science. Despite their busy schedules, these authors wrote chapters for this book. This book provides

the latest developments to food scientists, biochemists, medical doctors, nutritionists, food technologists, students majoring in food science, and public health professionals.

We hope that the book will be a valuable resource for older adult care providers and government entities worldwide who are seeking ways to improve elder care and may inspire collaborative opportunities to enhance the well-being of the aged population.

We sincerely thank Springer Nature for assistance in publishing this book.

Chennai, Tamil Nadu, India — Surajit Pathak
Chennai, Tamil Nadu, India — Antara Banerjee
Oslo, Norway — Asim K. Duttaroy

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Chapter 1
Cellular Aging: An Introduction, Principle, Hallmarks, and Aging-Associated Diseases

Meenu Bhatiya, Asim K. Duttaroy, Surajit Pathak, and Antara Banerjee

Abstract Aging is a complex natural biological process that shows progressive decline or deterioration in physiological function with age. It is a series of processes that rely on time. Cellular aging can be generally conceptualized by aging hallmarks that lead to aging processes as well as determining the phenotypic and molecular changes throughout the age. Aging is an impact of time, which shows changes in function at multiple levels, such as physiological (organ, tissue), cellular, molecular, physiochemical (enzymatic, hormonal), and metabolic levels. Aging is an accumulation of damage. Several research articles confirm that cellular senescence, oxidative stress, and reactive oxygen species play a crucial role in aging and age-related disease development. An imbalance among pro- and antioxidant species leads to oxidative stress, that damages cells at the molecular level. Overproduction and accumulation of ROS damage cellular macromolecules and influence lifespan. Here, we examine the fundamentals of aging and the hallmark of aging to explain the cellular and molecular-level alterations related to aging. For understanding the mechanism of cellular aging, we explain apoptosis, autophagy, and inflammation. Many diseases such as cardiovascular disease, cancer, diabetes, arthritis, and Alzheimer's disease is associated with aging. Here, we discuss the role of several natural bioactive compounds and flavonoids such as vitamin C in the treatment of supplementation in aging-related diseases.

Keywords Cellular senescence · Epigenetics · Telomeres · Hallmarks of aging Plant extract

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1.1 Introduction

1.1.1 Aging

Aging is a complicated biological process that, eventually leads to a time-dependent deterioration in the function of the physiological organs, tissues, and cells. The aging phenomenon is associated with a gradual deterioration of the systemic and physiological functions of the different cellular, molecular, and tissue elements, and can be affected by both environmental and genetic factors (Rozing et al. 2020). To sustain tissue homeostasis and function, a multicellular organism must achieve a balance between cell mortality rate and cell propagation rate. A variety of theories have been suggested to understand aging, such as the shortening of telomere, cellular senescence, accumulation of DNA damage in cells, and degradation of several cellular organelles, such as mitochondria and ER. There is no direct evidence supporting cellular senescence, but some evidence is available that suggests that telomere shortening happens in aged tissues and cells (Di Micco et al. 2021). Aging is the route for various risk factors such as cancer, diabetes, cardiovascular disorders, and neurodegenerative diseases (de Pablos et al. 2019).

1.2 Principles of Aging

Bio-gerontology is the branch of science that deals with the biological basis of aging, aging-related disease, and age-related changes in organisms, the progression, and rate of aging vary from organism to organism, even in organs and tissues within an organism also it varying (Harper and Holmes 2021). Thus, aging can be defined at a broad, macro, and micro-molecule levels. Furthermore, biogerontologists concluded that aging is programmed, stochastic, and individualistic based on these observations. Aging is a biosocial issue, underlying the basis of most of the major human diseases, such as cancer, cardiovascular diseases, diabetes, dementia, neurodegeneration, and osteoporosis (Agraharam et al. 2022). Whereas the effective diagnosis of every disease, despite age, is a social and moral requirement, the best approach for improving the quality of human life in old age is to minimize the risk of age-related diseases by interfering in the fundamental aging process. Accumulation of molecular damage is the major characteristic of aging. The main cause of age-related damage accumulation is the inefficiency and degradation, failure of the DNA repair system, and turnover of signaling pathways (Ogrodnik et al. 2019). The progressive failure in maintenance and repair mechanisms is the universal biochemical cause of aging and age-related diseases. In other words, aging is the impact of time on the human body. Aging shows variation at multiple levels such as enzymatic, hormonal, and biochemical levels.

1.2.1 Cellular and Metabolic Aging

Cellular aging is the limited number of times a cell can divide and after a particular number of divisions, cells will lose their division capacity. The cell division potential of a cell is based on telomere length. Normally, the cell can divide almost 50 times until the telomere is not able to replicate due to telomere shortening. The cell with more genetic damage, more free radicals, and other factors, would continue to replicate due to alteration in cellular functioning (Bernitz et al. 2016). Hormones have a tremendous role in aging. Hormone levels fluctuate throughout life, from fetus development to teenage maturity and age. At the time of puberty, the hormonal level carries acne and larger pores and at an older phase of life, hormones change leading to dry, saggy, and loose wrinkled skin and menopause (Affrald and Narayan 2023). The cells, as per our daily routine, utilize food. The cell converts macro biomolecules into absorptive micro biomolecules and produces energy and by-products. The alteration in the mechanism of metabolizing and producing energy enables the individual to accumulate damage over the lifespan with time. According to researchers, the alteration, slow and improper functioning of the metabolic function such as calorie restriction is the cause of delay in human aging (Katsyuba et al. 2020).

1.3 Hallmarks of Aging

Aging is affected by the multi-factorial biological process and the hallmark of aging provides a framework to study the primary or secondary cause of aging and explains the mechanism in a systematic manner (Kaushik et al. 2021) (Fig. 1.1).

1.3.1 Primary Hallmarks

1.3.1.1 Genomic Instability

DNA stability and integrity are continually challenged by endogenous risks, including defective DNA replication, accumulated (ROS) reactive oxygen species, and spontaneous hydrolytic reactions as well as exogenous risks such as physical agents, and chemical and biological agents (Kahroba et al. 2020). Genetic lesions are complex due to extrinsic or intrinsic damage, including spontaneous mutation, point mutations, gene destruction, chromosome translocations, chromosome addition and deletion, and telomeric shortening due to virus or transposon incorporation. The cellular system of organisms established a sophisticated system network known as a DNA repair system is the potential to repair any kind of nuclear DNA damage (Golato and Wilson III 2020). In addition, these specific nuclear DNA can even cause genome instability, resulting in premature aging syndromes or aging-related

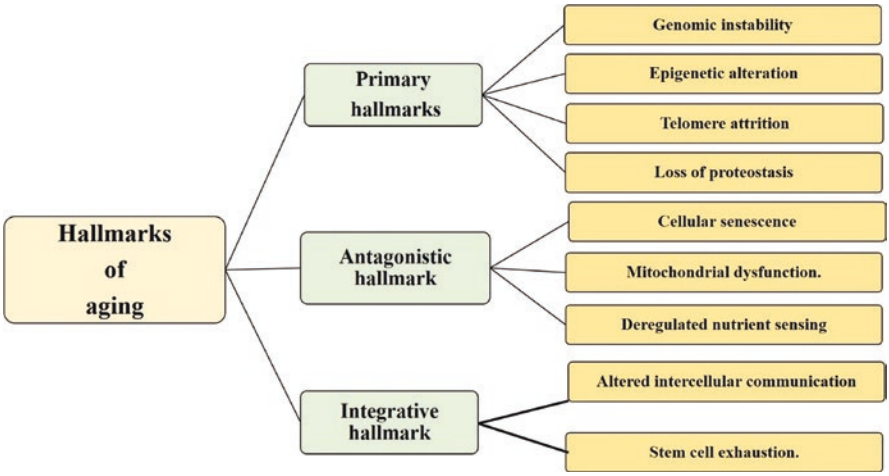

Fig. 1.1 Hallmarks of aging

diseases. This accumulated genetic damage during lifespan act as the basic denominator in aging (Ashapkin et al. 2019).

1.3.1.2 Telomere Attribution

Accumulated DNA damage during age directly affects the genome, although some specific chromosomal zones, such as the telemetric regions, are specifically prone to age-related diseases (Hu et al. 2022). A telomere at each end of a chromosome is a region of repeated nucleotide sequences. The telomere shields the chromosomal end from degradation and fusion with adjacent chromosomes. Specialized DNA polymerase called telomerase has the potential to synthesize the terminal ends of liner DNA known as a telomere. Sometimes, the telomerase loses its replication capacity. The exhaustion of telomere represents the limit of cell proliferative potential, so-called replicative senescence or Hayflick limit (Hall et al. 2017).

1.3.1.3 Epigenetic Alteration

Epigenetic alterations such as DNA methylation, alterations in Histone protein, Chromatin remodeling, Transcriptional alterations, and Inversion epigenetic alterations, affect all cells and tissues throughout their lifespan. Multiple enzymatic systems such as DNA methyl transferases, acetylases, histone deacetylases, histone methylases, and demethylases, as well as complexes of a protein involved in chromatin remodeling. A histone modification is a post-transcriptional modification such as histone methylation, acetylation, phosphorylation, and ubiquitination. These post-transcription changes in histone can affect the expression of genes by altering

the structure of chromatin. The epi-genome understanding and manipulation hold promise to strengthen age-related treatment and increase healthy lifespan (Ilango et al. 2020).

1.3.1.4 Loss of Proteostasis

Proteostasis is linked to aging and aging-related diseases (Lu and Guo 2020). All the cells have various advanced systems to sustain their proteomes stable and functional. Proteostasis mechanisms involve in stabilization and maintenance of folded proteins such as the heat-shock protein family, and the degradation of misfolded proteins by the proteasome or lysosome mechanisms. In the cellular systems, these mechanisms function in an ideal coordinated manner to restore protein and eliminate and degrade misfolded protein to prevent damaged protein accumulation and continuous renewal and folding of cellular proteins. According to many research studies, proteostasis can alter with aging. In addition, the accumulation and expression of misfolded proteins can develop many age-related diseases, including Alzheimer's disease, Parkinson's disease, and cataracts (Anirudhan et al. 2021).

1.3.2 Antagonistic Hallmarks

1.3.2.1 Deregulated Nutrient Sensing

Deregulated nutrient sensing is an important hallmark of aging. Nutrient sensing is the unique ability of cells to find out and respond to the fuel metabolic substrate, such as glucose. The nutrient-sensing mechanism involves the IGF-1 intracellular signaling pathway, which is the one triggered by insulin, which stimulates the cells and informs the availability of glucose. IGF-1 and insulin signaling are also known as the "insulin and IGF-1 signaling (IIS) pathway" which participates in glucose sensing (Smith et al. 2018). The other interconnected nutrient-sensing systems are mTOR, which senses high amino acid concentration, AMPK, which detects high AMP levels and senses low energy, and Sirtuin which detects high NAD+ levels and thereby senses low energy.

1.3.2.2 Mitochondrial Dysfunction

Mitochondrial activity has a major effect on aging and Mitochondrial dysfunction can accelerate mammalian aging (Zia et al. 2022). when the efficacy of the respiratory chain decreases then, the electron leakage starts increasing and the generation of ATP is reduced, in the aged cell. So, the mitochondrial dysfunction and aging relationship have been a major challenge suspected for research in aging. According to mitochondrial free radical theory, reactive oxygen species (ROS) production rate

rises because of the aging-related increasing mitochondrial malfunction, which furthers mitochondrial decline and damages cells (Giorgi et al. 2018).

1.3.2.3 Cellular Senescence

Cellular senescence was first described by Hayflick and his colleagues when they were working on cell culture. They noticed that normal human embryonic fibroblasts would differentiate only for several limited times and after a sequential passage cell undergo a permanent growth arrest state called proliferative or cellular senescence (Marotta et al. 2021). Cellular senescence is the process caused by the cells that have reached irreversible growth arrest which contributes to phenotypic aging. Cellular senescence is the beneficiary action to the damage when the tissues exhaust their proliferation potential. This eventually becomes deleterious for aging. Commonly, cellular senescence is an outcome of a variety of stresses, these cells accumulate and promote age-related disease which leads to the loss of tissue regeneration through the exhaustion of stem cells and progenitor cells (Di Micco et al. 2021). There are two general cellular senescence models which explain the contribution of cellular senescence with aging. First, senescent cells can multiply to the point where tissue strength and functional ability are impaired in tissues. A second model indicates that stem cell senescence limits their regenerative capacity, leading to a gradual loss of tissue strength and functional potential. Several mechanisms such as telomere shortening and DNA damage can trigger by cellular senescence (Borghesan et al. 2020).

The senescence of the cell is indicated by an increase in the size of the cell, lysosomal content, and the senescence-associated β -galactosidase [SA-β-gal] activity. It is induced by multi-factorial reasons such as oxidative damage oncogene activation, telomere attrition, and irradiation. It may cause the perturbation of homeostasis in mitochondria which may accelerate age-related phenotypes. The defect in the mitochondria can generate ROS, which can be solely responsible for cellular senescence; the supporting factor is a free radical aging theory (Bhatiya et al. 2021). In many cells types hydrogen peroxide act as a potent inducer of cellular senescence. Exogenous hydrogen peroxide treatment can promote cellular senescence even while endogenous ROS is involved in establishing and maintaining irreversible growth arrest. Excessive production leads to replicative senescence and oncogene-induced senescence. The cells accumulated due to senescence in tissues that are aged can be inferred using the markers that are surrogates such as DNA damage (Di Micco et al. 2021).

1.3.3 Integrative Hallmarks

1.3.3.1 Stem Cell Exhaustion

The cumulative effect of many aging-related damaging factors is stem cell exhaustion. Stem cell rejuvenation may be able to reverse the aging phenotype at the organismal level, according to recent promising findings (Sriramulu et al. 2018).

Reducing the tissue regenerative capacity becomes the most evident in aging characteristics when hematopoiesis decreases with age, leading to a decline in the development of adaptive immune cells called immune-senescence, and an increased occurrence of anemia and myeloid malignancies.

1.3.3.2 Altered Intercellular Communication

Aging is involved both cell-autonomic as well as intercellular communication changes such as endocrine and neuronal communication. Aging is not a biological phenomenon exclusively for cells. Cell with some growing intercellular communication alteration, providing the opportunity to modulate aging at this stage. Thus, neuro-hormonal signaling such as renin-angiotensin, and insulin-IGF1 signaling, appear to downregulate aging by increasing inflammatory reactions, Immune surveillance of pathogens, decreasing premalignant cells, and all tissue's functional and mechanical properties are impacted by changes in the peripheral and extracellular environment's composition (Mallick et al. 2019).

1.4 Oxidative Stress

Oxidative stress can be defined as a modification or imbalance of pro-oxidants and antioxidants which results in possible damage. Oxidant stress occurs as reactive oxygen species production overwhelms the endogenous antioxidant defenses. In many age-related disorders, oxidative stress plays a vital role (Reshma et al. 2022). The reactivity of oxygen allows it to participate in transfers of the high-energy electron, thus enabling the production of mass quantities of adenosine-5-triphosphate (ATP) by oxidative phosphorylation. Oxidative stress research has become an increasingly growing and evolving topic of study, particularly in the field of studies on aging. The oxidative stress aging theory is based on the principle of structural damage concept with age-related functional changes to the accumulation of oxidative damage to macromolecules (Zavadskiy et al. 2022).

1.5 Reactive Oxygen Species (ROS)

Free radicals can be defined as species containing more than one unpaired electron. The incomplete electron shell which providing high reactivity to these free radicals. Normally, reactive oxygen species (ROS) act as an intracellular signaling molecule at normal (Costa et al. 2021). Higher ROS levels disrupt cellular signaling processes by acting as an attacking molecule and start attacking protein, lipid, and nucleic acid (Phull et al. 2018) (Fig. 1.2). Under physiological conditions, superoxide anion ($O2^{\bullet-}$) is the most abundant oxygen-free radical, and

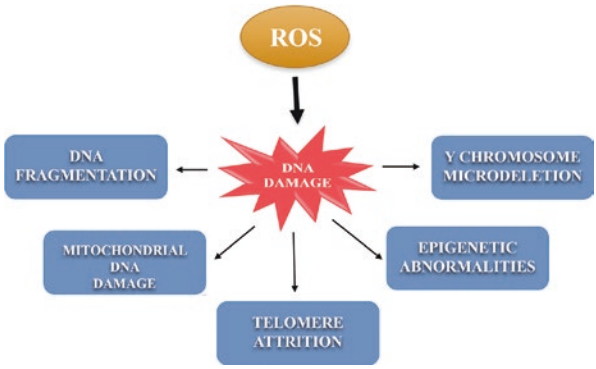

Fig. 1.2 Impact of reactive oxygen species

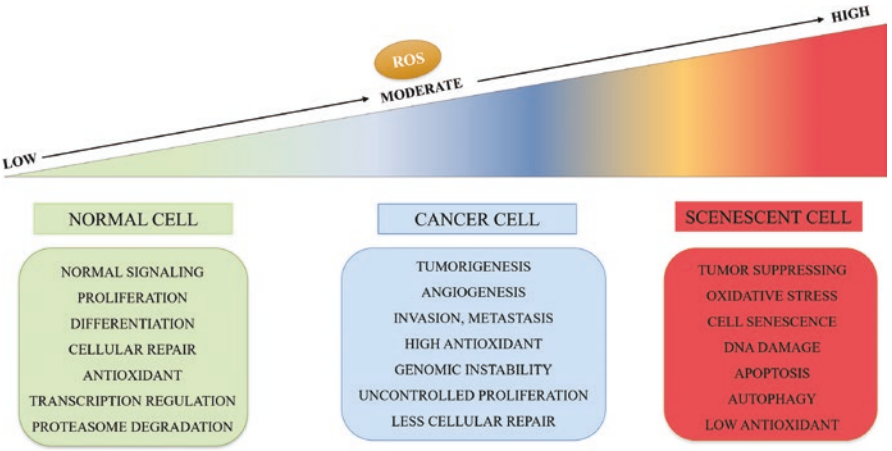

Fig. 1.3 Role of ROS in normal, cancer, and senescent cells

mitochondria are considered the primary source. Superoxide dismutase, an enzyme that changes superoxide into hydrogen peroxide, detoxifies free radicals such as superoxide (Costa et al. 2021). Despite not being a free radical, hydrogen peroxide falls under ROS due to its crucial function in the production and detoxification of free radicals. ROS affect cellular activity in a variety of ways at the homeostatic level, including via activating protein kinases and redox-sensitive transcription factors (Fig. 1.3).

1.6 Molecular Mechanism of Cellular Aging

As the burden of aging-associated disorders is increasing, our understanding of cellular changes that occur during aging also should increase. Molecular knowledge has important medical and social implications as it has the potential of being

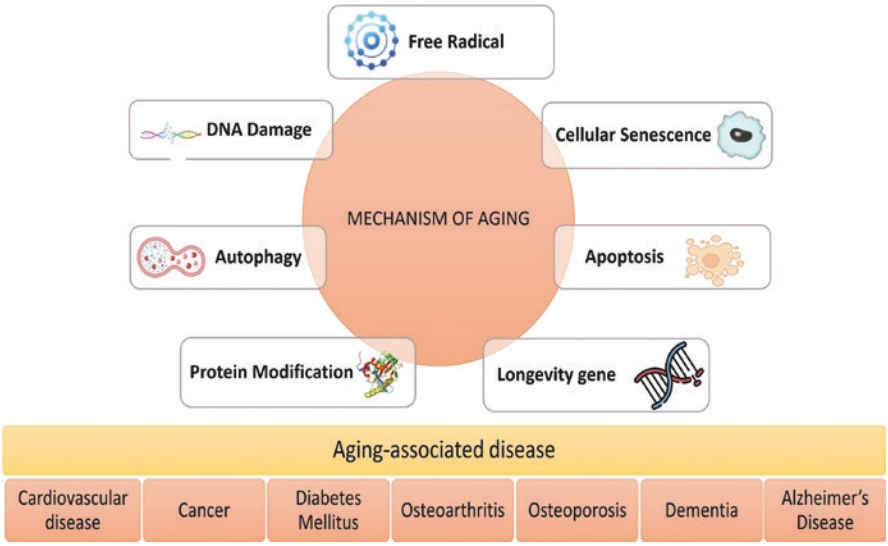

Fig. 1.4 Mechanism of aging and age-associated diseases

exploited to delay aging and the onset of aging-associated disorders. Current understanding of aging at the molecular level, and how targeting these aging-associated changes might increase health span and lifespan (Fig. 1.4).

1.6.1 Apoptosis

Apoptosis, a programmed cell death, is a life-long regulated cycle that helps to eliminate required or defective cells. Apoptosis plays a vital role in embryonic development during limb formation and eliminates damaged cells (Opferman and Kothari 2018). Alzheimer's and Parkinson's diseases were associated with an increase in apoptosis. Several pathways and proteins regulate apoptosis. The signaling protein p53 is capable of sensing damage. In the cell, catabolic processes start when the cell gets an apoptosis-induced molecular signal, and apoptosis-specific enzymes continue to degrade the cellular components and fragmentation of nuclear DNA. During apoptosis, chromatin condensates, shrinking of the cell due to a break in the integrity of the cell and irregular bulge in plasma membrane occur, finally the cell breakdown into smaller apoptotic bodies which contains cell organelles and nuclear components (Wallig and Janovitz 2022). These apoptotic bodies are then eliminated by macrophages.

1.6.2 Autophagy

Autophagy is another process that can induce cell death. Like apoptosis, this mechanism is strongly regulated and plays a normal role in the production, development, and homeostasis of cells (Basak et al. 2020). Autophagy enables a starving cell to reallocate nutrients from wasteful pathways to more essential ones, and it also plays an important role in housekeeping by extracting misfolded or aggregated proteins, sorting out degraded organelles such as mitochondria and endoplasmic reticulum, and eliminating intracellular pathogens (Wu et al. 2020). Some researchers suggest that mitochondrial dysfunction, which is believed to lead to cellular aging, exists in part due to cells' inability to extract their defective mitochondria. Moreover, autophagy degrades proteins so that they can be replaced and also degrades defective proteins that are no longer functional.

1.6.3 Inflammation

"Inflammation" is a notable intercellular connection modification linked to aging. Inflammation occurs due to the accumulation of pro-inflammatory tissue damage and the deterioration of a progressively compromised immune system. Secretion of pro-inflammatory cytokines promotion activation of the NF-πB transcription and development of defective autophagy resistance is the tendency of senescent cells (Lynch et al. 2020). Besides inflammation, emerging research suggests that aging-related alterations in tissue may result in aging-specific deterioration to the other tissues, due to inter-organ synchronization.

1.7 Aging-Associated Diseases

1.7.1 Cardiovascular Disease

Cardiovascular disease is still the most prevalent cause of death for older people. Cardiovascular disease includes chronic ischemic heart disease, congestive heart failure, and arrhythmia. Ischemic heart disease can be diagnosed at an early age whereas vascular remodeling and vascular stiffness develop in normal aging. Inflammation due to atherosclerosis and more vascular changes results in the risk of cardiac attacks, stroke, and promoting peripheral artery disease, and neurological dysfunction (Agraharam et al. 2022).

1.7.2 Cancer

Aging is an irreversible time-dependent deterioration in functional organ activity, which is the main risk factor for one of human morbidity mortality's most important factors, including cancer (Figuer et al. 2021). According to the Surveillance Epidemiology and End Results (SEER) Database of the US National Cancer Institute, 43% of men and 38% of women will develop a lifetime invasive cancer. Among these, 23% of men and 19% of women will die from cancer. More than half of cancers arise in people aged 70 years. In most developed countries life expectancy now exceeds 80 years, according to the World Health Organization (WHO). Cancer is becoming an increasingly critical health problem worldwide as the population ages. The underlying mechanism in both cancer and aging is the time-dependent accumulation of cellular damage (Deka et al. 2021)**.**

1.7.3 Osteoarthritis

Osteoarthritis is the second most prevalent chronic disease in senior citizens and a major source of chronic pain and disability. In one survey, 52% of 85-year-olds had an osteoarthritis diagnosis. Osteoarthritis tends to have a higher prevalence in females than males and the chances of knee and hip arthritis increase with the age. Another risk factor for osteoarthritis is Obesity. The treatments for osteoarthritis often require extensive joint replacement surgery.

1.7.4 Diabetes Mellitus

Diabetes rates have increased and become more overweight as populations age. Diabetes incidence in older adults in the United States could increase 2050 by more than 400%. At age 85 (32), diabetes is a major risk factor for cardiovascular disease. Diabetes and peripheral arterial disease are associated which contributes to diabetic foot ulcers (Azhar et al. 2021). The approaches to treating diabetes should be individualized. a major risk of hypoglycemia is having Sulfonylureas and insulin, so the use of more prone older adults should be cautiously weighed up. For patients diagnosed with hypoglycemia, post-acute treatment is provided during problematic periods.

1.7.5 Osteoporosis

Osteoporosis is a natural reduction of bone mass with aging. Older age, have osteoporosis, which is a more extreme loss of bone mass. Osteoporosis disease is associated weakness of bone and with increased bone fracture rates with age. Bone density

in women starts decreasing with the age for that bone density test recommended over 65 ages. While the incidence of fractures decreases with the age of men over age 85. To increase bone density and reduce the rate of bone fracture supplements of calcium and vitamin D are recommended, however, the effectiveness of these supplements is still controversial.

1.7.6 Dementia

Cognitive deterioration is a common problem of age-related brain changes whereas dementia, is not a result of natural aging. The term Dementia is the collection of all conditions triggered by disabilities that affect the capacity of memory profoundly it impairs the ability to perform regular activities such as feeding. Loss of memory is a common symptom of dementia, but memory loss alone is not dementia. Patients having dementia are having increasingly serious issues with activities such as memory, vocabulary, and loss of problem-solving capacity. It can also trigger changes in personality and difficulties in regulating emotions.

1.7.7 Alzheimer's Disease

The most prevalent form of dementia is Alzheimer's disease. it affects approximately 5.2 million people in the US, according to the National Institute of Aging. Alzheimer's disease is a chronic, systemic brain disorder that is gradually affecting memory, vocabulary, cognitive skills, and planning capacity (Rajagopal et al. 2022). The ability to perform the basic activities of everyday life is reduced over time. Symptoms first appear in most Alzheimer's patients after age 60. A protein called amyloid precursor protein (APP) is usually found in brain tissue. The enzymes cut off into fragments referred to as beta-amyloid as part of the recovery of this protein and are usually discarded. Nevertheless, these sticky protein fragments bind to each other in Alzheimer's disease and build up spaces between two neurons. Neurofibrillary tangles are defects in the brain cells within the microtubules. During the early stages of Alzheimer's symptoms will not appear till or up to 10 years but the plaques and the neurofibrillary tangles are accumulating and killing damaging most of the brain cells. As the number of neurons dies rises, the affected part of the brain starts to shrink. The deterioration is common in the final stages of Alzheimer's disease, and brain tissue has been significantly diminishing. Individuals in the end stage of Alzheimer's disease cannot carry on communication or react to their environment.

1.8 Alternative Treatment Strategies for Aging Associated Diseases

Many natural compounds were proposed for supplementation treatments. Among them, more attention has been given to a few specific molecules and bioactive compounds such as Vitamin C, Quercetin, Rutin, Curcumin, and Resveratrol.

1.8.1 Vitamin C

The primary source of vitamin C is ascorbic acid. Vitamin C acts as both a reducing and antioxidant agent. Ascorbate can also react with reactive oxygen species and inactivate ROS. Various cellular functions are mediated by vitamin C for enhancing the bioavailability of nitric oxide needed to maintain homeostasis in endothelial cells. However, the role of vitamin C associated with aging-related diseases is not investigated extensively since this antioxidant has always been used in association with other molecules (Barbosa et al. 2020).

1.8.2 Quercetin

Quercetin has shown tremendous ability not only to minimize inflammation caused by dysfunctional senescent cells but also to prevent healthy cells from senescent cells. Treatment with quercetin also promotes natural cell activity and delays the cycle of cell aging. Quercetin, as an antioxidant, can neutralize harmful free radicals, and unstable molecules that damage high concentrations of cells. Free radicals play a major role in chronic disease growth, such as cardiovascular disease, diabetes, cancer, and other age-related diseases (Akbari et al. 2022). Today, further research going on its biological activity has revealed how it can also delay or prevent cellular aging, and even induce cell death in cancer cells.

1.8.3 Rutin

Rutin, a quercetin glycoside is a member of a class of bioflavonoids believed to possess antioxidant properties. Rutin, a glycoside of quercetins, is a member of the bioflavonoid family. Previous research established Rutin as an anti-aging, anti-inflammatory, and anti-carcinogenic antioxidant capable of scavenging radicals of superoxide (Pandey et al. 2021). It has also been demonstrated that rutin is capable

of inhibiting collagen-stimulated human platelet aggregation, reducing capillary fragility, prolonging the activated partial thromboplastin duration, and exerting anti-thrombotic activity. The present research indicates that rutin decreases skin aging by increasing dermal density and elasticity by controlling the enzyme.

1.8.4 Curcumin

Curcumin is phenol derived lipophilic bioactive compound extracted from the *Curcuma longa* rhizome (Borghesan et al. 2020). Oral administration of curcumin is absorbed by the body as an active metabolite from tetrahydrocurcumin, which is converted by an enzyme found in the intestinal epithelium called reductase. Extensive research has been suggesting that curcumin has highly therapeutic and pharmacological potential as an anti-oxidant, anti-aging, anti-mutagenic, and anti-bacterial agent (Zia et al. 2021). The medicinal properties of curcumin are high with anti-cancer and neuroprotective effects.

1.8.5 Resveratrol

Phytoalexin compound, resveratrol is a bioactive compound belonging to the stilbene family, extracted from plants, such as nuts, berries, and grapes, mostly in the glycosylated form. It is synthesized by plants in response to environmental stress such as temperature, ozone, ultraviolet irradiation, and fungal infection (Bhatiya et al. 2020). Resveratrol targeting and controls various signaling enzymes such as AMPK and NAD-dependent Sirt-1 deacetylase to modulate various aging-related cell signaling pathways. Resveratrol is a strong antioxidant and also inhibits LDL degradation in vitro, which is related to coronary heart disease (Kaur et al. 2021). Resveratrol's anti-inflammatory characteristics raise the possibility that it has neuroprotective effects on neurodegenerative diseases, which are studied in cellular models of age-related illnesses including Alzheimer's disease.

1.9 Discussion

Aging is a complex biological phenomenon. Aging is a multifactorial process composed of both genetic and environmental components. Every physiological process within an organism system, every tissue within a system, and every type of cell within a tissue has its aging direction. The aging process must therefore be studied as part of a whole and understood as the sum of its parts. Cellular and molecular basis study of aging is the best way to understand the study of aging-related disease. Cellular level changes of aging can be studied, as changes in cellular

components, cellular dynamics, cellular communication, and progressive deterioration of functional integrity with time. There are several hallmarks of aging which provides a framework for the study of aging in a linear form. These hallmarks also contribute to understanding the aging mechanisms at the cellular and molecular levels and to determining their phenotypic changes. In aged people, endogenous antioxidant systems decline in effectiveness which makes them more susceptible to oxidative stress. As we know, oxidative stress indirectly promotes age-related diseases such as diabetes, aging, cardiovascular disease, and osteoporosis. Oxidative stress forms in cells due to the overproduction and accumulation of ROS and the imbalance between antioxidants and ROS (Moraes et al. 2020). According to previous research, clinical trials focusing on the treatment of bioactive compounds rich in antioxidants analyze the positive or negative effects of aging and aging-associated diseases. A linear relationship of dose-response between overproduction of ROS and biological damage, culminating potentially in disease and mortality. Oxidative stress would also be the primary cause of aging and a significant determinant of lifespan.

1.10 Conclusion

The aging process is universal, multiplex biological process. Cellular and molecular biology are powerful tools in the research field now being applied by scientists for the study of the mechanism of aging and aging-related disease. The results of these studies should serve to advance our understanding of aging and to focus future research efforts. As antioxidant play a protective role in the pathogenesis of age-related diseases. Hence, the bioactive compound enriches antioxidant and can be proving a useful approach for lifespan extension and therapeutic approach for aging-related disease.

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Chapter 2
Anti-oxidant and Anti-ageing Mechanism of Bioactive Compounds in Modulating the Ageing-Related Epigenetic Factors

Diptimayee Das, Amit Dey, Asim K. Duttaroy, Antara Banerjee, and Surajit Pathak

Abstract Ageing is the multifaceted reduction in physiological function of all living organisms. Several characteristics of ageing have been identified, including epigenetic dysregulation. Epigenetic dysregulation is receiving a lot of attention right now as a key component in ageing and age-related neurodegenerative diseases including Alzheimer's, Parkinson's and Huntington's disease, where it may influence interactions between genetic and environmental risk factors. Life expectancy diversity is influenced by epigenetic factors such as DNA methylation and histone modifications. Histone variations, changes in chromatin accessibility, histone and heterochromatin loss, aberrant histone modifications and unregulated miRNA expression are all epigenetic alterations that contribute to ageing and ageing-related diseases. Oxidative stress, which is caused by the build-up of reactive oxygen species (ROS), can cause lipid, protein, nucleic acid and organelle damage, resulting in an unbalanced homeostasis and the induction of cellular senescence, which is one of the key processes driving ageing. The senescent-associated phenotype includes chronic, pro-inflammatory signals which cause risk in developing ageing-related disorders (ARDs). Researchers have discovered that anti-ageing bioactive components have promising anti-ageing properties in vitro, in animals and in humans. Recent research has revealed that bioactive compounds have distinct modes of action, enhanced effectiveness and reduced toxicity. Hence, this bioactive compound has the ability to suppress the ROS formation and can be investigated as therapeutics interventions in ARDs.

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Keywords Ageing · Epigenetic dysregulation · Oxidative stress · Ageing-related disorders · Bioactive compounds

2.1 Introduction

Ageing is a natural process defined by increasing degradation of physiological function, with chronic illnesses and poor health being the primary risk factors. According to prominent evolutionary scientist Ernst Mayrl, there are primarily two distinctions between living and non-living organisms. First, organisms reproduce themselves, and subsequently, they evolve over time. The two differences are the indirect products of the biological hierarchy which gives rise to the features such as phenotypic plasticity, ageing, adaptability and death (Macedo et al. 2017).

A sudden loss of weight and a slow contraction of muscles are signs of the degradation of the cells' physiological integrity during the ageing process. There are several risks associated with ageing, including reduced bone density, changes to the cardiovascular system, cognitive decline and a pro-inflammatory state in the organism, which leads to various cancer, diabetes, cardiovascular disorders and neurodegenerative diseases as well as increases the possibility of death (Campisi 2012).

Towards the end of one's life, cellular damage accumulates and causes ageing. It is primarily the nine hallmarks that contribute to cellular ageing and determine its phenotypic characteristics that may be used as a means of defining cellular ageing. Epigenetic changes, genomic instability, torn telomeres, stem cell fatigue and impaired nutrition sensing are some examples of these changes.

Individually hallmark ideally highlights the requirements that (1) it should age naturally; (2) ageing should not be accelerated by experimental aggravation; (3) ageing should not be increased by experimental aggravation; and (4) the ageing process should be normally retarded by experimental amelioration and increase healthy lifespan (Gems and Partridge 2013). For the long duration of period, ageing was considered as the passive process which occurs randomly and was not subjected to any kind of gene regulation or stress response. The ageing of the organism can be delayed or altered using active constituents isolated from the natural bioactive components which have a potent ability to reduce inflammation. Ageing is affected by the multi-factorial biological process which affects the entire process. The hallmark provides a framework to study the primary or secondary cause of ageing and explains the mechanism in a systematic manner (Pitt and Kaeberlein 2015). To find possible therapeutic targets to halt the ageing process, numerous research studies have been conducted to decipher ageing's signs. All these factors indicate ageing, such as stem cell fatigue, impaired intercellular communication, senescence, genomic instability and epigenetic dysregulation (López-Otín et al. 2013).

2.1.1 Cellular Senescence

Cellular senescence is the process caused by the cells that have reached the irreversible growth arrest which contributes to the phenotypic ageing. It is the beneficiary response to damage that eventually becomes the deleterious and accelerates ageing when the tissues exhaust their capacity for regeneration.

The cellular senescence an outcome of a variety of stresses, these cells accumulate and promote age-related disease which leads to the loss of tissue regeneration through exhaustion of stem cells and progenitor cells. They secrete different kinds of growth factors, cytokines and proteases which are collectively called as senescence-associated secretory phenotype (SASP). These SASP factors due to its paracrine and autocrine activities are capable to alter the tissue homeostasis. Hence, cellular senescence is the after effect of the numerous pathological conditions affected in an organism in the association with the ageing (Zivanovic 2012).

The senescence of the cell is indicated by an increase in the size of the cell, lysosomal content and the senescence-associated b-galactosidase (SA-β-gal) activity. It is induced by multi-factorial reasons such as oxidative damage oncogene activation, telomere attrition and irradiation. It may cause the perturbation of homeostasis in mitochondria which may accelerate age-related phenotypes. The defect in the mitochondria can generate ROS, which can be solely responsible for the cellular senescence; the supporting factor is a free radical ageing theory (Hu et al. 2012).

The free radical theory of ageing explains the study of cellular senescence. The hydrogen peroxide is a potent inducer of cellular senescence in many cells types. The exogenous treatment of hydrogen peroxide can promote cellular senescence while endogenous ROS is implicated on the establishment and maintenance of irreversible arrest of growth. Excessive production leads to replicative senescence and oncogene-induced senescence.

2.1.2 Epigenetics and Ageing

A reversible heritable mechanism called epigenetics changes gene expression through modifications of chromatin rather than underlying DNA sequences. Nucleosomes, which are repeated structural components of eukaryotic chromatin, are highly condensed structures. The N-terminal histone tails and core histones interact via the histone-fold domains. It has been found that post-translational modifications to these tails influence gene expression frequently. In addition to acetylation and methylation, histones are also phosphorylated and ubiquitinated (Torres and Fujimori 2015). A new paradigm in ageing epigenetics is developing, which promises exciting discoveries in the near future, including a DNA methylome and histone modification map that will help identify a ‘young’ cell from an ‘old’ one, and identify all the chromatin modifier enzymes involved. Figure 2.1 illustrates this process.

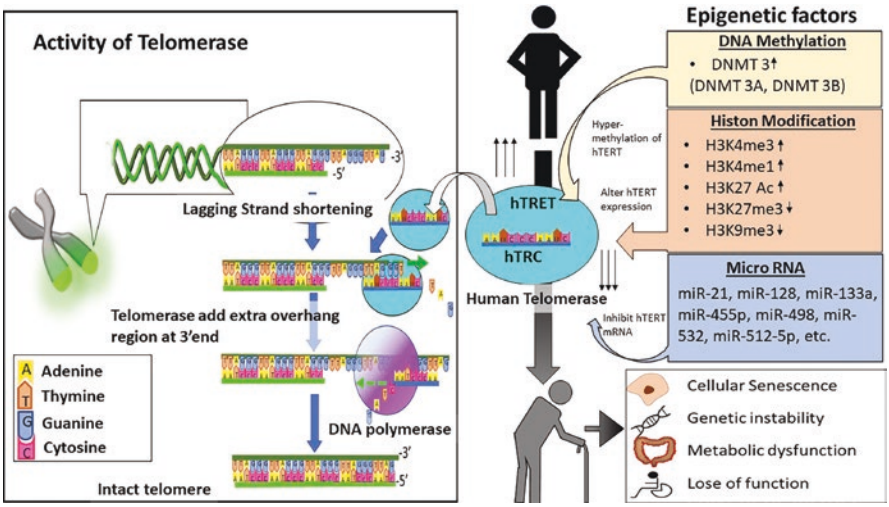

Fig. 2.1 The role of epigenetic factors in the maintenance of telomeres in ageing

2.1.2.1 DNA Methylation and Ageing

DNA methylation occurs, predominantly in CG dinucleotides. DNA methyltransferases are enzymes that add methyl groups to DNA (DNMTs). DNMT3A and DNMT3B initiate DNA methylation, but DNMT1 maintains DNA methylation during DNA replication. In DNA replication, DNMT1 maintenance methyltransferase activity can be reduced passively or actively, resulting in DNA demethylation. The methylation of DNA changes both globally and locus-specifically with ageing, according to several studies. Methylation levels were positively connected to ageing among the age-associated sites, and these sites were mostly found in CpG islands. These worldwide methylation changes may result in genomic instability and telomere integrity degeneration, both of which may contribute to the ageing cellular phenotype (Florath et al. 2014). As humans age, changes in the expression and/or activity of DNMTs or other epigenetic modifiers involved in DNA demethylation may explain this ageing-related methylation. Ageing-related DNA hypermethylation, on the other hand, is produced by an increase in the expression of DNMT3, which is known to be involved in de novo DNA methylation (Casillas et al. 2003). Furthermore, a recent research (Mcclay et al. 2014) revealed that ageing-related hypomethylation is associated to a variety of histone markers detected utilising whole blood DNA on ageing-related differentially methylated regions (DMRs) from people ranging in age from 25 to 92. Hypomethylated areas in DMRs are related with histone changes such as acetylation and methylation (McClay et al. 2014). These findings imply that the coordination of DNA methylation and histone modifications during the ageing process may influence age-related epigenetic alterations and chromatin structure.

2.1.2.2 Histone Modifications and Ageing

The occurrence of various types or combinations of histone modifications across the lifespan is also characterised by a gradual decrease in histone levels, which has a significant influence on chromatin structure. Trimethylation of H4K20 rises with age, as it does phosphorylation of H3S10, although trimethylation of H3K9 and H3K27 decreases and acetylation of tH3K9 increases (Bártová et al. 2008). Both histone levels and post-translational modifications alter during the replicative age of Saccharomyces cerevisiae cells. Indeed, overall protein levels of H3, H4, and H2A were decreased in aged cells, as was the expression of acetylated H3K56 (Feser and Tyler 2011). Furthermore, Caenorhabditis elegans study revealed that ASH-2 trithorax complex components, ASH-2 itself, WDR-5, and the H3K4 methyltransferase SET-2 were harmful to longevity, and that H4K5 acetylation, but not total H4 protein levels, decreased with age (Feser et al. 2010). H4K12 acetylation changes in mice have been linked to age-related cognitive decline (Greer et al. 2010). Furthermore, as seen in Fig. 2.2, loss of SIRT6, an H3K9 deacetylase implicated in telomere function, ageing-associated gene expression, and recruitment of the DNA-PK catalytic subunit to chromatin in response to DNA damage, may result in a premature ageing-like phenotype (Peleg et al. 2010). Histone-modifying enzymes also play an essential role in ageing. The Sirtuin family, a class of evolutionary conserved NAD-dependent histone deacetylases (HDACs) involved in a variety of intracellular processes such as chromatin remodelling, apoptosis, transcriptional silencing, and lifespan, is responsible for the regulation of two critical histone post-translational modifications, namely the acetylation of H3 and H4 at lysine 9 and 16,

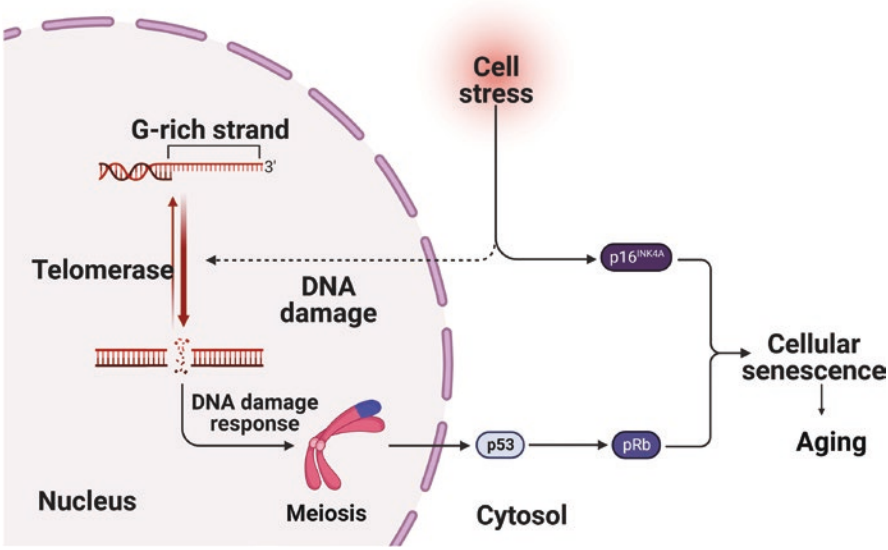

Fig. 2.2 Telomerase-mediated stress response in ageing

respectively (Burgess and Zhang 2010). In replicatively aged yeast cells, Sir2 protein levels decreased with age, which was connected to an increase in H4K16 acetylation and histone loss at certain subtelomeric locations (McGuinness et al. 2011).

2.1.2.3 Non-coding RNA and Ageing

According to studies, non-coding RNAs (ncRNAs) are produced by the majority of eukaryotic genomes and are involved in a number of intracellular processes as well as being part of the epigenetic machinery. MicroRNAs (miRNAs) are small noncoding single-stranded RNAs (19–22 nucleotides) that have recently emerged as an important research topic in the field of ageing. MiRNAs can impede translation or induce mRNA degradation by binding to their gene targets in a sequence-specific way (Kinser and Pincus 2020). As a result, they control a wide range of biological functions, such as cell proliferation, differentiation, and death (Lai et al. 2019). In humans, around 2000 miRNAs have been found, and they appear to be involved in the regulation of approximately 60% of all human genes (Kozomara and Griffiths-Jones 2014). One of the first ncRNAs to be linked to the ageing process was miRNA lin-4, which targeted the transcription factor lin-14 and was revealed to influence longevity in C. elegans (Kinser and Pincus 2020). A Drosophila research found that deleting mir-125 (a lin-4 homolog) reduced male fly longevity (Chawla et al. 2016). However, the function of this miRNA in humans is unknown. While little is known about the roles of miRNAs in animal ageing, a recent research examined whole-blood samples from 5000 people and discovered 127 miRNAs that were expressed.

2.2 Oxidative Stress-Induced Ageing

The imbalance in the oxidative and anti-oxidative systems in cells is known as oxidative stress. The anti-oxidative system contains enzymes such as SOD and GSH-Px, while the oxidative system comprises reactive oxygen and nitrogen species (ROS and RNS). Irreversible growth arrest occurs in cells as a result of time-dependent damage accumulated during numerous culture passes, also known as replicative senescence. They are resistant to apoptosis and undergo malignant growth by induction and maintenance of cell senescence, cytostasis. Senescent cells are continually changing but cannot grow like cancer cells. In in-vivo experiments, senescent cells had a broad and flat form with abundant cytoplasmic and vacuolar granularity, as well as high levels of lysosomal-galactosidase activity (SA-gal), p16, p21, and IL-6 (Rossiello et al. 2022).

Cell senescence can be caused by oxidative stress, mitochondrial dysfunction, oncogene expression, DNA damage, and the loss of tumour suppressor genes such as INPP4, NF1, PTEN, and RB1. Provocation of endogenous cues causes a phenomenon known as replicative senescence, which differs from stress-induced premature senescence. The two processes have functional and molecular characteristics,

although the extrinsic and intrinsic events apoptosis and cell senescence differ depending on the degree of cell homeostasis disruption (Ziegler et al. 2015).

The autocrine and the paracrine activities in the senescent cells are highly maintained by the tissues secreting molecules and they act at multiple levels such as metabolic control, epigenome, gene expression and protein processing. The senescence process which contributes to the specific mitochondrial pathway through which there is an alteration in the mitochondrial redox state. The chemicals released by senescent cells have a role in pathological and physiological events such as wound healing, tissue remodelling during embryogenesis, and the onset of ageing as well as age-related disorders in diverse animals.

The secretome produces essential cytokines for cancer cell development, encouraging carcinogenesis, which is connected to cellular metabolic status. Mitochondrial DNA damage (mtDNA), signalling pathways via p53, Ras, p21, and p16, and autophagy can all be implicated in the cause-effect link between cell senescence and cellular ROS generation.

2.3 Ageing-Related Diseases (ARDs)

Many age-related problems are caused by ageing, and it has a significant influence on social and economic stability. The ageing-associated diseases are the complications arising from the senescence. Ageing involves risk in developing cardiovascular disease (CVD), osteoarthritis, diabetes, cancer and numerous neurodegenerative diseases. The main reason for the ageing- related disease is disturbed metabolism with the mitochondrial damage. The increase in the frequency of ageing-associated diseases found to increase with the senescence. Cell senescence is recognised as an ageing signature for two reasons: (1) the buildup of senescent-related cells in organism tissue parallel to age progression; and (2) stem and progenitor cell depletion occurs when senescent cells accelerate the age-related reduction in tissue regeneration (Sarikhani and Firouzamandi 2022).

2.3.1 Neurodegenerative Diseases

The most common risk factor for the development of neurological diseases is ageing. Alzheimer's disease (AD) is the most common neurological disorder worldwide, and its prevalence increases with age (Trevisan et al. 2019). Alzheimer's disease is characterised by extracellular amyloid plaques, intracellular neurofibrillary tangles (NFTs), and Tau protein hyper-phosphorylation (Harini et al. 2022). Parkinson's disease (PD) is another neurological disorder and almost doubles between the ages of 50 and 80 (Pringsheim et al. 2014). Parkinson's disease (PD) is defined by the loss of dopaminergic neurons in the substantia nigra (SN) (Kanaan et al. 2007). Several studies have shown that Parkinson's disease has the same cell function decline as ageing.

2.3.2 Cardiovascular Disease

Ageing has a substantial impact on the cardiovascular and arterial systems, increasing the prevalence of cardiovascular disorders (CVD) such as stroke, atherosclerosis, myocardial infarction and hypertension (Donato et al. 2018). Increased arterial stiffness, altered diastolic performance, decreased LV systolic reserve capacity, Hypertrophy, and decreased endothelial function are all pathological alterations in ageing cardiovascular tissues (Metkar and Girigoswami 2019). Telomere shortening has been associated to vascular cell ageing, cardiovascular illness, arterial thrombotic events, cardiovascular risk factors (including obesity, hypertension, smoking and type-2 diabetes) and aortic valve stenosis.

2.3.3 Musculoskeletal Disorders

The elderly are more prone to injury and degenerative musculoskeletal disorders. Sarcopenia and osteoarthritis (OA) are two of the most prevalent musculoskeletal illnesses associated with ageing, and they both have considerable economic consequences (Grote et al. 2019). Sarcopenia is characterised as a decline in muscle mass and function as people age. Increased inflammation causes an increase in ROS generation in the skeletal muscles, resulting in cell death and impacting skeletal muscle catabolism (Musci et al. 2020). Impaired mitochondrial activity and antioxidant defences have also been related to the development of sarcopenia. Inconsistently, some individuals reach advanced age in the good clinical conditions demonstrating the fact that healthy ageing can be achieved. The research and the observations are trying to find a treatment which can intercept to prevent and delay ageing-related disease development, to increase health span and compressing the morbidity. Most of the research work conducted recently mainly focuses on hypertension and cholesterol, the levels of triglyceride and cancer. However, evidence for the most effective strategy would be the target the molecular mechanisms shared by all the age-related disease (Crimmins 2015).

2.4 Modern Therapies Related to Ageing

There is no proven methodology to stop or delay, human ageing process. Much valid scientific data is not available in the field of anti-science and longevity. It is possible to delay some ageing process by avoiding unprotected exposure to the sun, balanced diet can lower the cardio-vascular diseases; however, a single age-related disease cannot be scientifically considered as delaying ageing. Ageing refers to the changes that occur during an organism's life span, with the pace at which the changes occurs varying (Tungmunnithum et al. 2022). Many widely accepted

hypotheses explain why ageing occurs, although it is typically seen as planned development. The ageing is the attributed through the free radical-induced damages, molecular cross-linking, telomere shortening, presences in the genes of senescence in the DNA and changes in the immulogical functions. The theories of the ageing are categorised into three such as Programmed theory, Combined theory and Damage theory (Cohen et al. 2022).

The technological advancement aims at explicit purpose of curing the ageing which would prolong a healthy life. There is multi-factorial process in the ageing. Following therapies were suggested to delay the ageing such as Caloric restriction, Hormonal therapies, Antioxidants, Stem cells, telomere-based therapies and ALT-711.

The stem cell was the other therapy used for ageing-related issues. It demonstrated that the stem cell had the potency to cure the health issues ranging from blindness, liver restoration and nerve regeneration as well as potent therapy for the autoimmune diseases and other age-related diseases namely skin carcinogenesis, wound healing and muscular dystrophies. The stem cells have been used for treating various diseases of ageing and rejuvenation. It has been postulated that mitochondrial metabolism is an essential regulator in ageing in somatic stem cells. The difference in the embryonic stem cell can affect both therapeutic potential as well as research application. Further studies and potential application is required to investigate the variation in the signaling pathways and mechanism which may yield to the delay in ageing process.

The hormones are used for the therapy of anti-ageing, the patients with the deficiencies of GH and IGH-1 exhibit early signs of ageing. On the study conducted, growth hormone was used as an anti-ageing medication, GH has been demonstrated to have extremely favourable benefits on the elderly, and hGH pills have showed an increase in muscular mass and libido, as well as an improvement in the immune system. There are also some worries that hGH might promote cancer, particularly in individuals who already have malignant or pre-malignant tumours. The general view is that it can be employed as an anti-ageing therapeutic agent, but additional study is needed to analyse potential side effects and assure therapeutic agent safety (Burke 2022).

Antioxidants are employed in anti-ageing treatment to combat ROS and their effects on lipids, proteins, and nucleic acids, which display an array of endogenous anti-oxidant system, which is increased by input from co-factors and ingestions of exogenous anti-oxidants. The most popular anti-oxidants include vitamins A, E, and C, as well as coenzyme Q10, which was widely utilised. Few studies have found that antioxidants do not slow down the ageing process, but rather lead to increased longevity. Antioxidants are often utilised as anti-ageing treatments and can be found in dietary supplements. Few studies found that marketed products had no effect on mortality, either favourably or adversely, but in certain mice, it has been demonstrated to increase cancer growth. High-dose antioxidant supplements can do more harm than benefit, although low-dose antioxidant combinations can occasionally have a positive impact, depending on food and lifestyle (Lim et al. 2022).

Telomere-based therapeutics has the potential to slow the ageing process by increasing cell proliferative capacity in vitro and reversing tissue degeneration in mice. The fundamental idea behind the commercialisation of telomerase kits is to estimate an individual's biological age and, for some, the risk of telomerase shortening linked diseases such as liver cirrhosis, coronary heart disease, and arthrosclerosis.

2.5 Currently Proposed Treatments Involving Bioactive Compounds in Age-Related Disorders

The bioactive compound which is naturally present in the food is known as 'nutraceuticals'. The studies have been conducted to identify the nutraceuticals to prevent the pathological conditions especially ageing-related diseases (ARDs) or that mimic the anti-ageing action. Plants are a rich source of biologically active natural products known as secondary metabolites, the most notable of which are phenolic and polyphenolic compounds (Oroian and Escriche 2015). Diet is an important part of everyday living, and dietary patterns and specialised nutritional supplements may play an important role in boosting human health and extending life. According to current research, adopting a Mediterranean diet and supplementing with particular vitamins may reduce morbidity and death. Rhodiola, Curcumin, Quercetin and Gallic acid has the most relevant anti-ageing property.

2.5.1 Rhodiola rosea

The *Rhodiola rosea* is widely distributed in higher altitudes in the Arctic and mountainous region throughout Europe and Asia. It is the plant popularly found in the regions of Eastern Europe and Asia, with the capability of enhancing performance, eliminating fatigue enhancing work and preventing high altitude sickness. The *Rhodiola rosea* has six distinct groups of chemical compounds such as Phenylpropanoids, Flavonoids, Phenyl ethanol derivatives, Monoterpenes, Triterpenes and Phenolic acids. The extract from the root solely contains about 140 bioactive compounds mainly rhodioloside or salidroside which has capability to protect cells from pre-mature ageing when exposed to the oxidative-stress (Polumackanycz et al. 2022). The extract of the *Rhodiola rosea* has proven to show the protective effect and increasing immunity and can fight against age-related immune deficiency issues known as immune-senescence (Amintas et al. 2022) and has anti-ageing, neuroprotective activities, anti-cancer, possess adaptogenic properties and anti-oxidative as well (Sun et al. 2022).

2.5.1.1 Effects of Rhodiola on Ageing-Related Diseases

Rhodiola rosea contains bioactive substances such as salidroside, which has the capacity to reduce the effects of neurodegenerative illnesses such as Alzheimer's. It is an age-related neurodegeneration that causes memory and learning problems in the early stages. Salidroside protects neurons from oxidative stress by activating anti-oxidant enzymes such as hemeoxygenase 1 (HO-1), thioredoxin (TRX), and peroxiredoxin 1 (PRX1). Salidroside also enhances the amount of the anti-apoptotic protein BCL-XL while decreasing the level of the pro-apoptotic protein BAX (Ajdert et al. 2022). Salidroside protects against both myocardial hypoxia and ischemia-reperfusion damage. The cardioprotective properties of salidroside were demonstrated in studies showing salidroside dramatically lowered levels of lactate dehydrogenase, CK, and CK-MB caused by strenuous swimming. Salidroside reduces MDA concentration while increasing GSH-Px and SOD activities, indicating that it can protect the heart from repetitive strenuous damage (Xiong et al. 2022).

2.5.2 Curcumin

The hydrophobic yellow polyphenol CUR is a bioactive chemical ingredient of the Curcuma longa Linn rhizome that is often used in cooking as a food colouring and preservation. CUR is the primary active component in turmeric, accounting for about 2–5% of the plant (Kapakos et al. 2012). Curcumin's antioxidant benefits may be achieved via the stimulation of anti-inflammatory responses. Its ability to decrease inflammatory enzymes such inducible cyclooxygenase-2 (COX-2) and nitric oxide synthase (iNOS) and lipoxygenase (LOX) is most likely responsible for its anti-inflammatory properties (Menon and Sudheer 2007). Furthermore, curcumin's anti-inflammatory activities are linked to its capacity to block NF-κB activity and lower TNF-α levels, which is a known NF-κB pathway activator (He et al. 2015). Curcumin has the ability to modify the low-grade chronic inflammatory state (inflamm-ageing) that is widespread in the ageing process and is thought to be a common driving factor in various age-related disorders (Furman et al. 2019).

2.5.2.1 Effects of Curcumin on Ageing-Related Diseases

Curcumin's varied actions provide a sound theoretical foundation for considering it as a prospective option for the treatment of age-related diseases (Abrahams et al. 2019). Curcumin has been demonstrated in various in vitro and in vivo studies to have antioxidant, anti-inflammatory, anti-microbial, immunomodulatory, cardioprotective, hepatoprotective, nephroprotective, anti-neoplastic, hypoglycaemic and anti-rheumatic properties (Balaji et al. 2022). Curcumin can be used to treat a variety of clinical problems, including age-related renal and eye diseases, rheumatoid arthritis, atherosclerosis, cardiovascular, type 2 diabetes, neurological illnesses,

cancer, and osteoporosis (Sundar Dhilip Kumar et al. 2018). Curcumin supplementation, according to Derosa et al. (2016), can significantly lower circulating interleukin 6 (IL-6) concentrations, which are known to be a crucial role in inflammatory reactions; astonishingly, the most profound impacts were reported in individuals with greater levels of systemic inflammation.

Curcumin is without a doubt one of the most promising phytobioactive substances in terms of metabolic effects. It has been demonstrated to aid in the prevention and treatment of type-2 diabetes in adults (Zhang et al. 2013). Curcumin has been proven in animal models to reduce hyperglycemia, improve β-cell function, prevent β-cell death, lower insulin resistance, and delay the establishment of type-2 diabetes (Zhang et al. 2013). A variety of experimental and clinical investigations have completely proven curcumin's usefulness in the prevention and treatment of cardiovascular disease (Wongcharoen and Phrommintikul 2009). A number of in vitro studies have shown that curcumin has anti-atherogenic properties. A reduction in cholesterol build-up has been shown to mediate this impact (Zhao et al. 2012). The relevance of micro-RNAs such as miR-126 in investigating the molecular processes behind such effects has been demonstrated (Li et al. 2019). Long-term treatment of curcumin to mice resulted in decreased plasma and hepatic cholesterol levels as well as suppression of early atherosclerotic lesions (Jayakumar et al. 2016). Changes in immune gene expression were responsible for these effects. Curcumin also prevented atherogenesis in an atherosclerosis animal model, such as apoE/LDLR-double knockout mice given a fat-rich Western diet (Olszanecki et al. 2005).

Curcumin has been shown to have neuroprotective properties in both in vitro and in vivo Alzheimer's disease models. In the human neuroblastoma cell type SH-SY5Y, it was shown to protect against mitochondrial and synaptic damage (Reddy et al. 2016). Curcumin's anti-AD effect in animal models is due to its ability to penetrate the BBB, which reduces aggregation and protects neurons from toxic insults (Reddy et al. 2018). Curcumin has been shown to improve synaptic function, cognitive decline, and tau clearance in Alzheimer's disease mice models.

Curcumin has been shown to have therapeutic promise for age-related musculoskeletal problems such as osteoporosis (Peddada et al. 2015). Curcumin's therapeutic potential in osteoporosis is supported by recent in vitro and in vivo data. It was proven in animal models of this condition to enhance several aspects of bone health by influencing multiple processes in differentiation and osteoclast activation, as well as mineral density and bone mechanical characteristics. NO generation, receptor activator of NF-κB ligand (RANKL) repression, cytokine synthesis, nuclear factor kappa B (NF-κB), and ROS creation are most likely involved activities (Peddada et al. 2015). Curcumin, for example, was discovered to prevent bone structure deterioration and to promote favourable changes in bone turnover when taken orally; the likely involvement of pro-inflammatory cytokines such as IL-6 and TNF-α in these effects was revealed (Girigoswami et al. 2020).

Curcumin's anti-cancer potential has been investigated in a number of human Phase I and II clinical studies. Its therapeutic potential has been studied most thoroughly in patients with pancreatic cancer, one of the world's deadliest cancers

(Bimonte et al. 2016). In a Phase II research, Dhillon et al. (2008) discovered that oral curcumin was well tolerated and, despite modest absorption, exhibited strong anti-inflammatory and anti-neoplastic effects in a large number of patients with advanced pancreatic cancer. This medicine lowered the expression of inflammation-related proteins such as NF-kB, COX-2, and phosphorylated signal transducer and activator of transcription 3 (p-STAT3) in these patients' peripheral blood mononuclear cells when provided orally. Curcumin's therapeutic effectiveness in colorectal cancer patients was also proven in a Phase IIa clinical trial, including the reduction of aberrant crypt foci (Carroll et al. 2011).

2.5.3 Quercetin

Quercetin has been used to treat inflammation, cancer, arthritis, allergic responses, and cardiovascular disease. The flavonoid also has a crucial function in platelet aggregation, lipid peroxidation, and mitochondrial biogenesis (Batiha et al. 2020). Quercetin is a powerful chemical that may be utilised to treat a variety of health problems. In vivo and in vitro, quercetin has antioxidant effects. The antioxidant activity of quercetin protects against a variety of age-related diseases (Ulusoy and Sanlier 2020). A diet high in quercetin provides a number of health advantages. It works to reduce inflammation, coagulation, hypertension, and hyperglycemia. Several clinical studies indicate that quercetin supplementation is used to prevent and treat a wide range of chronic illnesses, including cardiovascular disease (Huang et al. 2020).

2.5.3.1 Effects of Quercetin on Ageing-Related Diseases

Flavonoids have been shown to be effective in the prevention of neurodegenerative illnesses and may even postpone the progress of neurodegeneration. Quercetin has been shown in studies to have neuroprotective properties. Quercetin inhibits the neuroinflammatory process by downregulating pro-inflammatory cytokines such as iNOS and NF-kB, hence stimulating neuron regeneration. Quercetin inhibits lipid peroxidation and hence protects neurons from oxidative injury. Neuronal cells serve as antioxidants at lower doses of 5 M and 10 M quercetin, but become toxic at greater concentrations of 20 M and 40 M (Khan et al. 2019).

Quercetin treatment improved dyslipidaemia, decreased serum blood glucose levels, increased insulin levels, and reduced oxidative stress in diabetic rats. Oral administration of quercetin to rats decreased sexual activity, sperm count and motility, and diabetes-induced testicular damage. Quercetin reduced blood pressure in hypersensitive rats when given intravenously (Shabbir et al. 2021). Quercetin mitigates the effects of oxidative stress and protects pancreatic cells from β-cell damage. It has been demonstrated that the chemical reduces hepatic cell oxidative stress and increases antioxidant enzymes such as catalase and heme oxygenase.

Quercetin is a potent flavonoid with chemo-protective activities in a range of in vivo and in vitro studies. Its anti-cancer properties, such as decreased proliferation, the ability to cause apoptosis, mitotic inhibition, and cell cycle arrest, make it a reliable chemical in cancer therapy (Reyes-Farias and Carrasco-Pozo 2019). In the case of human leukaemia, quercetin was demonstrated to stop the cell cycle at G2. Quercetin has also been linked to changes in p53-related pathways in cancer cells. It inhibits the activity of cyclins A, B, and CDK2, maintaining MCF-7 breast cancer cells in the S phase of the cell cycle. Quercetin inhibits malignant cell apoptotic pathways, causing cancer cells to die.

2.6 Conclusions and Perspectives

With an ageing population, healthy ageing has emerged as a critical public health priority. Genetics and environmental factors have been linked to ageing for decades. Furthermore, epigenetic modifications influence the ageing process. Hence, epigenetic indicators such as histone alterations and DNA methylation are linked to ageing. Several studies have found epigenetic biomarkers, most notably DNA methylation, that can predict the biological age of specific tissues. These findings imply that epigenetic techniques might be exploited to develop effective anti-ageing medications. Nutrients and their metabolites play critical roles in epigenetic control as well as antioxidant substrates. Nutritional availability modifications, such as calorie restriction and direct supplementation with bioactive substances, have been related to ageing via epigenetic mark alterations and ROS generation. The physiological alterations generated by dietary intervention in rhodiola and trachurus extract may be responsible for epigenetic modifications and the suppression of ROS generation. R-L bioactive substances often contain anti-oxidant and anti-ageing qualities that can protect cells from damage caused by intrinsic and extrinsic causes, and oxidative stress created by the cells may prevent cellular senescence. This bioactive compound might open the path for researchers to target and understand the therapeutic impacts of ageing-related diseases. However, more research into the anti-ageing and anti-oxidant properties of the R-L bioactive component therapy will help to verify this finding. As a result, it is critical to establish direct proof of nutritional benefits of R-L bioactive chemicals in the future, as well as to research epigenetic markers that can predict individual responses and whether it can effectively regulate the anti-ageing process and ageing-related disorders.

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Chapter 3
Diet-Gene Interactions that Regulate Longevity and Diseases

Tripti Nair, Sonia Verma, and Arnab Mukhopadhyay

Abstract Aging, an almost universal phenomenon, encompasses a gradual yet constant deterioration of the metabolic functions of the body. Aging is characterized by an increased homeostatic imbalance and an elevated risk of systemic metabolic failures leading to diseases, with the ultimate outcome being death. Age-related metabolic disorders, such as cardiovascular diseases and type-2 diabetes, are among the major causes of mortality worldwide. A plethora of research has established that aging is regulated by genes functioning in important metabolic pathways. Thus quite expectedly, the nutrient content of a diet has been found to modulate the lifespan of an organism and define the severity or course of several age-related or other illnesses. Under normal conditions, an organism can modulate its gene expression to adapt to these diet-induced metabolic changes to display normal health and lifespan. However, in the presence of an altered allele, the effects of diet or one of its components may become apparent in terms of health, disease, or longevity effects. Identifying such diet-gene pairs and the associated molecular mechanisms is necessary for developing dietary and therapeutic interventions that would prevent or treat diseases and promote healthy aging.

Keywords Diet-gene pairs · Aging · Metabolism · Age-associated disorders · Gene polymorphism · Diet supplementation · Disease susceptibility

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Abbreviations

AD	Alzheimer's disease
ALH-6	ALdehyde Dehydrogenase
AMD	Age-related macular degeneration
APOA5	APOlipoprotein A-V
APOE	APOlipoprotein E
ATP7B	ATPase copper transporting 7 Beta
ATPsynD	ATP synthase subunit D
BCAA	Branched-chain amino acids
BRS-3	Bombesin Receptor Subtype 3
CCHa2R	CCHamide-2 Receptor
CVD	Cardiovascular diseases
DGRP	Drosophila genetic reference panel
DTT	Dithiothreitol
ech-6	Enoyl-CoA hydratase
FLR-4	FLuoRide resistant 4
FTO	FaT mass and Obesity
GLUT	GLUcose Transporter
GSTM1	Glutathione S-Transferase Mu
HC	High caloric
HDL	High-density lipoprotein
HMGCR	3-Hydroxy-3-MethylGlutaryl-Coenzyme A Reductase
HNF4	Hepatocyte Nuclear Factor 4
HP-LS	High protein and low sugar
HS-LP	High sugar and low protein
IRS1	Insulin Receptor Substrate 1
LD	Lipid droplets
LDL	Low-density lipoprotein
LPS	LipoPolySaccharide
MAPK	Mitogen activated protein kinase
MEF2	Myocyte Enhancer Factor 2
MRPL-2	Mitochondrial Ribosomal Protein Like 2
MTHFR	MethylTetraHydroFolate Reductase
MUFA	Monounsaturated fatty acids
NAD(P)H	Nicotinamide adenine dinucleotide phosphate reduced
NHR-114	Nuclear Hormone Receptor 114
NMUR-1	NeuroMedin U Receptor 1
NRF2	NF-E2-Related transcription factor
OSM-3	OSMotic avoidance abnormal
P5C	1-Pyrroline-5-carboxylate
P-80	Polysorbate 80
PLP	PyridoxaL 5'-phosphate
PMT-2	Phosphatidylethanolamine MethylTransferase 2
PNPO	Pyridox(am)iNe 5-Phosphate Oxidase

PUFA	PolyUnsaturated fatty acids
RANKL	Receptor Activator of Nuclear factor-Kappa-B Ligand
RICT-1	Rapamycin-Insensitive Companion of TOR
RIPS-1	Rhy-1-Interacting Protein in Sulfide
RPE	Retinal pigmented epithelium
SAM	S-adenosyl methionine
SIRT-6	NAD^+-dependent deacetylase (SIRTuin-6)
SKN-1	SKiNhead 1
SNP	Single nucleotide polymorphism
SOD2	SuperOxide Dismutase 2
Spen	Split ends
T2DM	Type-2 diabetes mellitus
TCF7L2	TransCription Factor 7-Like 2
TG	Triglyceride
TNFα	Tumor Necrosis Factor-alpha
UPR^{mt}	Mitochondrial unfolded protein response
ZPR1	Zinc finger PRotein-1

3.1 Introduction

Aging is the major risk factor for chronic diseases that are more prevalent in the elderly. The gradual decline in the activity of various biological processes with age increases the risk of individuals developing age-associated pathologies. Impaired mitochondrial function, DNA repair system dysfunction, dysregulated immunity, hormonal imbalance, proteostasis collapse, and altered metabolic signaling are a few biomarkers of aging. These hallmarks of aging are also the driving factors involved in the initiation as well as the advancement of age-associated disorders. Few instances of such diseases include cardiovascular diseases (CVD), neurodegenerative disorders, arthritis, and type-2 diabetes (T2DM). The frequency of these diseases increases exponentially with age. An individual's genetic predisposition also substantially influences aging and age-associated or other disorders. For example, variations in the genes coding for APOlipoprotein E (*APOE*), Receptor Activator of Nuclear factor-Kappa-B Ligand (*RANKL*), TransCription Factor 7Llike 2 (*TCF7L2*) have been associated with Alzheimer's disease (AD), osteoporosis, and T2DM, respectively (Cluett and Melzer 2009). In the coming decades, with advancements in wellness programs, the population with age above 65 is predicted to double. Therefore, to meet the healthcare needs of the growing aging population, identifying strategies that can improve the conditions of individuals predisposed to age-associated or related disorders is crucial.

To support growth and cellular functions, food is critical for all organisms. Most organisms have a wide variety of dietary choices. These vary in nutrient composition, which can affect life-history traits such as development, survival, and health by altering the metabolic status of an organism. Therefore, deficiency or excess of

nutrients has been found to affect aging and influence the progression and/or severity of various age-associated disorders. Diet can have immediate as well as long-lasting effects on animal physiology and that of its future generations (Pang and Curran 2012). Importantly, the genetic make-up of an individual also plays a crucial role in determining the outcome of dietary choices. Genes modulate metabolism depending upon the nutrient availability to maintain physiological homeostasis so that the organism can display normal life-history traits. The metabolic flexibility brought about by gene interactions, when an organism is exposed to different nutrient source and composition, help it adapt to a diverse nutritional environment, providing evolutionary advantages. With aging, this metabolic flexibility progressively declines and may thus increase susceptibility to age-dependent metabolic disorders. Additionally, mutations in such genes disrupt the adaptive capacity to the diet leading to an altered rate of aging in a diet-specific manner. Studies in *Caenorhabditis elegans*, *Drosophila melanogaster*, and mice have uncovered several such instances of diet-gene pairs, where the outcome of mutations in a particular gene is evident only on a specific diet. Similarly, in humans, we are aware of multiple polymorphisms in metabolic genes that cause diseases treatable with a modified diet or diet supplementations.

Mechanistic studies in elucidating the nature of diet-gene interactions are few and primarily driven by research in model organisms. In this chapter, we highlight some instances of diet-gene interactions that regulate aging. We also provide some examples of human age-associated or other diseases caused by gene mutations that can be treated with dietary interventions. We posit that more studies providing mechanistic insights into diet-gene interactions are required as they can be capitalized to prevent/treat diseases and promote a healthy lifespan.

3.2 Dietary Composition and Aging (for More Details, Refer to Chaps. 10 and 12)

The nutritious component of a diet primarily consists of carbohydrates, proteins, and fats as essential macronutrients as well as vitamins and minerals as micronutrients. The quantity and quality of any of these factors in each diet have been demonstrated to alter the rate of aging in different model organisms and, importantly, promote/prevent disease incidences in humans.

3.2.1 Carbohydrates

Carbohydrate metabolism plays a key role in maintaining homeostasis of cellular energy levels, synthesis of cellular components, and development and reproduction of an organism (Mattila and Hietakangas 2017). Dysregulation in carbohydrate flux may cause increased incidences of chronic inflammatory diseases as well as

multiple metabolic disorders such as obesity, diabetes, diabetic nephropathy, increased triglyceride (TG) storage, and cancer (Mattila and Hietakangas 2017; Parkhitko et al. 2020), negatively affecting life span.

3.2.2 Lipids

Lipids aid in energy storage, membrane synthesis, and cellular signaling. Supplementation of fatty acids such as arachidonic, linoleic, oleic, palmitoleic, and eicosapentaenoic acid improves lifespan and stress tolerance and decreases α-synuclein aggregation, and delays onset of amyloid-β toxicity, along with other health-span benefits. Aberrant lipid metabolism is the cause of obesity, insulin resistance, diabetes, Alzheimer's disease (AD), atherosclerosis, and other geronto-metabolic disorders (Johnson and Stolzing 2019).

3.2.3 Amino Acids

Maintaining a balanced dietary quotient of protein is essential for multiple aspects of cellular homeostasis, systemic immune response, and stress response as they are modulated by amino acids, peptides, and proteins (Timmerman and Volpi 2008). Protein restriction in *Drosophila* and mice significantly extends lifespan. Methionine restriction and manipulation of methionine metabolism increase lifespan in yeast, worms, flies, and mice (Parkhitko et al. 2019). On the other hand, supplementation of branched-chain amino acids (BCAA) leucine, valine, and isoleucine increases chronological lifespan in yeast and worms (Alvers et al. 2009; Edwards et al. 2015; Mansfeld et al. 2015). BCAA supplementation to middle-aged mice improves mitochondrial biogenesis and enhances cardiac and skeletal muscle functions (D'Antona et al. 2010). Therefore, amino acids play a multifaceted role in regulating an organism's health span and longevity.

3.2.4 Vitamins

Vitamins, required in small quantities, significantly regulate multiple aspects of organism physiology and health. They are cofactors to enzymes that play important roles in maintaining metabolic and epigenetic homeostasis (Vitamin B1-B12 and A), neuro-cognitive functions (Vitamin B6-B12 and K), behavioral responses (Vitamin B1 and B12), mitochondrial respiration (Vitamin B2, B5, B7, and B12), cellular growth and differentiation (Vitamin B1, B2, B5, B9, C, A, D, E, and K), cellular detoxification and stress responses (Vitamin B3, B9, C, A, D, and E), embryonic morphogenesis, tissue morphology and functioning

(Vitamin B1, B5, B9, B12, and A), and immune response and inflammation (Vitamin B5, B7, B9, B12, C, A, D, E, and K) (Thomas 2006). Deficiency of Vitamins, as well as hypervitaminosis (specifically Vitamin A), can adversely affect health.

3.2.5 Minerals

Minerals are classified into two major classes, macro-minerals and micro-minerals. Minerals play diverse roles, ranging from skeletal development to transmission of nerve impulses. They also regulate the production of different hormones and play an important role in heart functionality. Macro- and micro-elements are found in the dentitions (Ca, F and P) and bones (Ca, Mg, P, B, Mn, and F), while most micro-elements (Cu, Fe, Mg, Mn, Se, and Zn) function as structural components of various enzymes. Macro-minerals (Ca, P, Na, K, and Mg) function in nerve cell signaling and transmission. Micro-minerals regulate erythrocyte formation (Co, I, and Fe) and activate antioxidant enzymes (Mo). Minerals also regulate immune responses (Ca, Se, Cu, Mg, and Zn) and neuronal functioning (Cr and Mn). Thus, minerals affect a vast range of molecular, cellular, and physiological processes required for life and well-being (Gharibzahedi and Jafari 2017).

3.3 Diet-Gene Interactions Modulating Aging and Disease in Model Organisms

Research on longevity and healthy aging requires model organisms that have a short lifespan, inexpensive maintenance, and an easily manipulable genome. Invertebrates like *Drosophila*, *C. elegans,* and mammalian models such as mice have contributed immensely to our understanding of the aging processes and disease mechanisms. The feasibility of performing dietary and genetic interventions in these species has been useful in identifying diet-gene pairs required for maintaining normal aging patterns or ameliorating disease pathologies. This section discusses a few such pairs studied using *C. elegans, Drosophila,* or mice that regulate aging, metabolism, stress response, and disease phenotypes (Table 3.1).

Considering the word limitation, the chapter could not include all the published reports of diet-gene interactions and their effects on organismal lifespan, health, and disease.

Table 3.1 Summary of diet-gene pairs modulating aging and disease in model organisms

S. no.	Dietary modifications	Effects	Genes maintaining homeostasis	References
Caenorhabditis elegans				
1	↑↑↑ vitamin B12	• Lifespan extension • Lower phosphatidylcholine levels • p38 MAPK pathway activation • Elevated cytoprotective gene expression • Heightened stress tolerance	*flr-4*	Verma et al. (2018), Nair et al. (2022)
2	↓↓↓ tryptophan	• Sterility • Germline defects • Lower detoxification gene expression	*nhr-114*	Gracida and Eckmann (2013)
3	↓↓↓ vitamin B12	• DTT-induced – Developmental toxicity – Depleted SAM levels – Intensified ER proteotoxic stress	*rips-1*	Gokul and Singh (2022)
4	↓↓↓ lipopolysaccharide	• Lifespan extension	*nmur-1* *osm-3*	Maier et al. (2010)
5	↓↓↓ feeding on HB101	• Lifespan extension	*rict-1* *skn-1*	Soukas et al. (2009)
6	↑↑↑ proline catabolism	• 1-pyrroline-5-carboxylate build-up • Reduced mitochondrial function • Increased ROS • Lifespan suppression • Reduced fecundity and fertility	*alh-6* *nmur-1*	Pang and Curran (2014)
7	↑↑↑ fat	• Energy homeostasis disruption	*ech-6*	Liu et al. (2022)
8	↓↓↓ vitamin B12	• Low methionine synthase activity • Methionine restriction • Lifespan extension • UPR^{mt} activation • Enhanced mitochondrial function	*mrpl-2*	Amin et al. (2020)
Drosophila melanogaster				
1	↑↑↑ protein	• Lifespan extension	*Sirt6*	Shukla and Kolthur-Seetharam (2022)

(continued)

Table 3.1 (continued)

S. no.	Dietary modifications	Effects	Genes maintaining homeostasis	References
2	↑↑↑ sugar ↓↓↓ protein	• Lifespan extension • Heightened stress tolerance in muscles	*Mef2*	Zhao et al. (2020)
3	↑↑↑ carbohydrate	• Lethality	*CG4607*	Francis et al. (2021)
4	↑↑↑ protein ↓↓↓ carbohydrate	• Heightened stress resistance • Lifespan extension	*ATPsyn-d*	Sun et al. (2014)
5	↑↑↑ sugar	• Lifespan extension in mated females	*Spen*	Gillette et al. (2020)
Mice				
1	↑↑↑ zeaxanthin	• Inducing antioxidant response • Preserved RPE structure and function	*Sod2*	Biswal et al. (2018)
2	↑↑↑ n-3 fatty acids	• Lowered pro-inflammatory cytokines • Increase anti-inflammatory response • Delayed progression or reversion of retinal lesions	*Ccl2 and Cx3cr1*	Tuo et al. (2009)

3.3.1 Serine Threonine Kinase Gene (flr-4)

FLR-4 is involved in moderating vitamin B12-mediated effects on cellular metabolism and, thus, longevity. The *flr-4* gene was initially identified in a forward genetic screen for genes required for fluoride resistance in *C. elegans* (Katsura et al. 1994). Later, it was found that the kinase-dead allele, *n2259*, possesses a longer lifespan on the *E. coli* HT115 compared to *E. coli* OP50 (Verma et al. 2018). OP50 and HT115 have been reported to differ in nutrient and metabolite contents, thus affecting the expressions of various genes in the worm and their normal physiology (Soukas et al. 2009; Pang and Curran 2014). The OP50 strain was also found to possess lower vitamin B12 levels compared to HT115. The elevated dietary vitamin B12 level in *E. coli* HT115 was shown to activate the p38 MAPK pathway, induce cytoprotective gene expression, and increase stress tolerance and lifespan in the *flr-4* mutant (Verma et al. 2018; Nair et al. 2022). Mechanistically, the higher vitamin B12 levels increase the flux through the one-carbon cycle in the mutant, thereby transcriptionally downregulating the phosphatidylethanolamine methyltransferase 2 (*pmt-2*) gene, leading to lower phosphatidylcholine levels that activate the p38 MAPK pathway (Nair et al. 2022). Thus, *flr-4* prevents ectopic activation of the p38 MAPK pathway on food with different vitamin B12 levels to maintain a normal life span.

3.3.2 Nuclear Hormone Receptor Gene (nhr-114)

The mammalian HNF4 is a nuclear factor that functions in the hepatocytes, regulating lipid and glucose metabolism, thereby maintaining metabolic homeostasis (Hayhurst et al. 2001; Van Gilst et al. 2005). In *C. elegans,* the HNF4 ortholog NHR-114 regulates germline development. Interestingly, the *nhr-114* depletion results in sterility when fed *E. coli* OP50 but not HT115 (Gracida and Eckmann 2013). On downregulating *nhr-114*, germline defects such as nuclear aberrations, irregularly differentiated oocytes, and condensed germline are visible on OP50 but not on the HT115 diet (Gracida and Eckmann 2013). Interestingly, supplementing tryptophan to *E. coli* OP50 significantly diminishes the *nhr-114* knock-down-associated sterility and upregulates the expression of detoxification genes (Gracida and Eckmann 2013). Meanwhile, the wild-type worms do not exhibit any dietary tryptophan-dependent germline defects and sterility. Thus, NHR-114/HNF4 assures germline health, regardless of dietary inputs, by compensating for dietary variations in tryptophan levels between the *E. coli* diets and mounting a variety of stress responses to protect the developing germ line. Therefore, a mutation in the gene seems to accelerate germline aging on a diet lacking enough of the amino acid.

3.3.3 S-Adenosyl Methionine (SAM)-Dependent Methyltransferase Gene (rips-1)

RIPS-1, a protein with a putative SAM-dependent methyltransferase domain, is involved in developmental toxicity caused by the presence of dithiothreitol (DTT). Interestingly, wild-type worms develop normally when DTT is added to *E. coli* HT115 feed but display toxicity on *E. coli* OP50 containing DTT. DTT causes developmental defects by inducing the expression of *rips-1* gene, depleting SAM levels, and intensifying endoplasmic reticulum proteotoxic stress. The loss of function allele of *rips-1* improves worm development on *E. coli* OP50 containing DTT. Since RIPS-1 functions in the one-carbon metabolism by transferring a methyl group from SAM to a substrate, supplementing vitamin B12 to *E. coli* OP50 containing DTT can also alleviate and reverse the toxicity of DTT by restoring SAM levels (Gokul and Singh 2022). The upregulation of RIPS-1 in *E. coli* OP50 or low vitamin B-12 conditions suggests a defense response elicited by organisms against reagents such as DTT.

3.3.4 Kinesin Motor Protein (osm-3) and Neuromedin U Receptor (nmur-1) Genes

The *C. elegans osm-3* gene is essential for cilia formation in the sensory neurons (Snow et al. 2004), while the *nmur-1* is the worm ortholog of mammalian NMUR expressed in neurons. Compared to wild-type, the *osm-3* and *nmur-1* mutants

display lifespan extension on the *E. coli* OP50 but not on HT115 (Maier et al. 2010). Interestingly, a double mutant of *osm-3* and *nmur-1* does not display an additive effect, suggesting that both the genes regulate lifespan via similar mechanisms. The sensory neurons expressing *osm-3* and *nmur-1* aid in perceiving dietary cues by differentiating between the lipopolysaccharide (LPS) structure of the two *E. coli* strains. The outer core of the LPS of the *E. coli* HT115 (a K-12 strain) is longer than the *E. coli* OP50, a B strain (Klena et al. 2005). The effect of *nmur-1* on lifespan is indeed LPS-dependent as the mutant worms live longer on the LPS-truncated K-12 strain but not on the parent strain (Maier et al. 2010).

3.3.5 *Mechanistic Target of Rapamycin Complex 2 Subunit (RICTOR) Gene (rict-1)*

Mutants of the conserved *RICTOR* gene ortholog, *rict-1* in *C. elegans*, exhibit variations in life-history traits on different bacterial diets. *Rict-1* functions as a critical sensor of organismal energy status and appropriately guides calories into crucial metabolic processes such as energy storage, growth, lifespan maintenance, and reproduction. The *rict-1* mutants are short-lived on *E. coli* OP50 and long-lived on *E. coli* HB101 as well as HT115 (Soukas et al. 2009). The HB101 (and HT115) and OP50 diet have similar protein and fat content; however, HB101 (and HT115) have many folds higher carbohydrate content, qualifying them as high-quality worm food (Brooks et al. 2009). The reduced lifespan of the mutants on OP50 is due to excessive feeding. On HB101, the consumption of bacteria is reduced, thereby extending lifespan. This extended lifespan is suppressed if the transcription factor *skn-1* gene is knocked down. Since SKN-1, a mammalian Nrf2 ortholog, is required for dietary restriction-induced longevity (Bishop and Guarente 2007), the short lifespan of *rict-1;skn-1* on HB101 suggests the role of RICT-1 in regulating the rate of feeding on different diets. The absence of the functional protein disrupts this feeding behavior, reducing HB101 consumption, inducing dietary restriction, and extending longevity.

3.3.6 *Aldehyde Dehydrogenase Gene (alh-6)*

Another gene required by *C. elegans* adaptive response to diet is *alh-6*, an ortholog of the human aldehyde dehydrogenase. This enzyme catalyzes the two-step breakdown of proline by converting 1-pyrroline-5-carboxylate (P5C) into glutamate. The *alh-6* mutant worms show lifespan suppression, reduced fecundity, and fertility only when fed on OP50, but not HT115, as they accumulate toxic levels of P5C that affect mitochondrial function, producing reactive oxygen species. Antioxidants such as ascorbate and N-acetylcysteine rescue the lifespan defects of *alh-6* mutants on the OP50 diet (Pang and Curran 2014). This suggests that proline catabolism is

activated in worms when fed OP50. Active ALH-6 efficiently metabolizes P5C to sustain mitochondrial homeostasis that is otherwise disrupted by toxic levels of P5C build-up in the absence of the functional protein. This, however, does not occur in HT115. Interestingly, without functional NMUR-1, *alh-6* mutants no longer present mitochondrial defects and live a normal lifespan on an OP50 diet (Pang and Curran 2014). Thus, in addition to providing energy, diet can also impose physiological challenges like mitochondrial dysfunction on an organism and negatively affects the rate of animal aging; however, neuronal and metabolic tissues function together to promote mitochondrial adaptation and maintain physiological homeostasis.

3.3.7 Enoyl-CoA Hydratase Gene (ech-6)

Excessive dietary fat disrupts energy homeostasis, leading to a shorter lifespan in *C. elegans*. However, a mutation in the *ech-6* gene that is suggested to function in the branched-chain amino acid (BCAA) catabolic pathways prevents lifespan shortening when the worms are grown on media supplemented with oleic acid-rich dietary fat polysorbate 80 (P-80). Knocking down *ech-6* under normal conditions shortens lifespan, possibly suppressing mitochondrial metabolic functions and aberrant amino acid catabolism. However, in P-80 treated *ech-6* mutants, fat-enriched diets had little effect on lipid levels, possibly because the fuel may be burnt by beta-oxidation to produce energy, contrary to storage as triglyceride (TG) seen in wild-type. During *ech-6* deficiency, supplementing P-80 upregulates biological processes involved in the production of energy and lysosome-related processes that contrasts with the broader metabolic effects seen in wild-type worms. Thus, the gene *ech-6* represents a factor that can fine-tune metabolic flexibility in response to excessive dietary fat intake to modulate lifespan (Liu et al. 2022).

3.3.8 Mitochondrial Ribosomal Protein Gene (mrpl-2)

Mitochondrial unfolded protein response (UPR^{mt}) is a cellular defense response stimulated by multiple types of mitochondrial dysfunction and regulated by a coordinated mito-nuclear cross-talk that recovers normal mitochondrial function. The *mrpl-2* gene helps maintain mito-nuclear balance, negatively regulating UPR^{mt} in *C. elegans*. Compared to the wild-type strain, the *mrpl-2* loss-of-function mutation activates UPR^{mt}, in a diet-dependent manner, increases mitochondrial function, extends lifespan, and boosts resistance towards infection only when fed low vitamin B12 diet *E. coli* OP50. This is because on the low vitamin B12 diet, a reduction in the activity of methionine synthase, which converts homocysteine to methionine in the SAM/methionine cycle, activates UPR^{mt}-induced longevity. In wild-type worms on low B12 diet OP50, functional MRPL-2 prevents this aberrant stimulation of UPR^{mt} and maintains the normal rate of aging. However, on *E. coli* HT115, the

higher vitamin B12 levels lead to an increased supply of methionine and the mito-nuclear imbalance in *mrpl-2* mutant is insufficient to induce the UPR^{mt} resulting in normal aging rates (Amin et al. 2020).

3.3.9 *NAD$^+$ -Dependent Deacetylase Gene* (Sirt6)

Nutrient inputs regulate physiological fitness during development and adulthood. Developmental dietary inputs have often been shown to determine lifespan and health span in adults, but the mechanisms are poorly characterized. In this regard, the study by Shukla et al. has illustrated how differential carbohydrate and protein ratios during development lead to the programming of adult physiological measures from aging to metabolic homeostasis. Moreover, the study identified SIRT6 as one of the key components necessary to control plasticity and memory of responses later in life because of varied diets during development. Interestingly, while loss of SIRT6 led to accelerated developmental progression, it also resulted in a detrimental impact on physiological fitness in adults. Besides clearly establishing the tunable adaptation of life history changes, the study also proposed epigenetic mechanisms and metabolic sensing as possible mediators of such memory (Shukla and Kolthur-Seetharam 2022).

3.3.10 *Myocyte Enhancer Factor Gene (Mef2)*

An evolutionarily conserved transcription factor, MEF2 controls biological processes such as lipid metabolism and mitochondrial function. Muscle-specific attenuation of MEF2 activity in *Drosophila* leads to the accumulation of large intramuscular lipid droplets (LD) in a diet-specific manner. LD are cellular organelles that store neutral lipid and provide energy substrates for mitochondrial beta-oxidation. Diet and nutrient availability are factors that shape lipid droplet diversification. High sugar and low protein (HS-LP) or high protein and low sugar (HP-LS) diets increase LD size compared to a high calorie (HC) diet in wild-type flies. When *Mef2* is non-functional, large intramuscular lipid droplets with higher cholesterol ester and low TG are accumulated in response to HS-LP and HC diets, but not in the HP-LS diet. The accumulation of intramuscular lipid droplets also enhances organismal lifespan and stress protection of muscles. This *Mef2*-diet mediated accumulation of lipid and lifespan extension depends on cyclin E function; however, the exact mechanism is not yet known (Zhao et al. 2020).

3.3.11 *Putative Glucose Transporter Gene (CG4607)*

Not all individuals respond similarly to the same diet due to the diverse genetic variations. The effects of different dietary exposures to starvation resistance were compared using 178 inbred strains from the *Drosophila* genetic reference panel

(DGRP) that covers various genetic polymorphisms. DGRP consists of fully sequenced inbred lines derived from a natural population; therefore, it is a powerful tool for understanding genetically-driven metabolic responses. Adult male flies show variable resistance to starvation-induced death when fed a diet with different macronutrient combinations (high carbohydrate or high-fat). A majority of the single nucleotide polymorphism (SNP) that contributed to this diet-gene effects are located in the noncoding regions of genes; for example, a SNP >500 bp upstream of the start site of gene *CG4607*, a homolog of the human glucose transporters *GLUT6* and *GLUT8*, may affect transcription, splicing or post-transcriptional processing of RNA. By reducing glucose utilization, silencing of *CG4607* produced lethality in flies on high carbohydrate but not on high protein or high-fat diet. The *CG4607* knock-down flies also exhibited higher levels of glycogen post-starvation and broke down more TG under starvation conditions (Francis et al. 2021). Thus, genetic variations play a determining role in the response of an organism to different diets, thereby affecting life history traits.

3.3.12 Neuropeptide CCHamide-2 Receptor Gene (CCHa2R)

Diet restriction has been demonstrated to have pro-longevity effects in most model organisms. Importantly, natural genetic variations found among the wild population of organisms can affect diet-dependent longevity. One such example is a SNP in *CCHa2R* gene (2R_1939249_SNP) that reduces the levels of metabolites such as pipecolate, valine, serine, and methionine. Neuron-specific attenuation of *CCHa2R* leads to a longer lifespan under dietary restriction but not on an *ad libitum* diet. CCHa2-R is a neuron-enriched G-protein coupled receptor that exclusively binds to the neuropeptide CCHa2 that expresses mostly in the fat body, and at low levels in the gut and neurons. This axis is involved in the regulation of insulin signaling and satiety in response to nutritional status. The human homolog of *CCHa2R* is bombesin receptor subtype 3 (BRS3), expressed in the central nervous system and gastrointestinal tract, similar to the expression pattern of CCHa2R peptide in *Drosophila*. Since BRS3 is also involved in mammalian gut-brain axis signaling, it is tempting to speculate that the mechanisms may be conserved between flies and mammals (Jin et al. 2020).

3.3.13 ATP Synthase Subunit Gene (ATPsynD)

ATPsynD is a component of the mitochondrial electron transport chain complex V. Silencing of *D. melanogaster* ATPsynD reduces TOR signaling, enhances protein homeostasis, and activates antioxidant defences in a sex and diet-specific manner. The ATPsynD knock-down mediated stress resistance, and longevity occurs only when the flies are fed a diet low in a carbohydrate-to-protein ratio (Sun et al. 2014). Interestingly, knocking down the gene in *C. elegans* also increases life span; however, it is not known whether diet has any effect on this phenotype (Hansen et al. 2005).

3.3.14 RNA-Binding Protein Split Ends Gene (Spen)

Genetics plays a critical role in the development of obesity and metabolic syndrome. The Spen is a transcriptional regulator of fat catabolism. The fat body-specific knock-down or mutation in *Spen* leads to blockade of fat catabolism, higher levels of stored TG, decreased lipase expression, and increased adiposity. These are also accompanied by a compensatory increase in glycolytic flux and protein catabolism. Interestingly, diets supplemented with yeast early during development partially rescues these metabolic dysfunctions and developmental defects in the *Spen* mutant. On the other hand, high sugar moderately improves the longevity of mated females (Gillette et al. 2020). Interestingly, diet supplementation was heavily dependent on the developmental timings, with yeast supplementation in adulthood being detrimental. Since *Spen* is a conserved gene, such studies point at the possible use of dietary interventions in humans to improve metabolic dysfunction associated with certain genetic factors.

3.3.15 Pyridox(am)ine 5-Phosphate Oxidase Gene (PNPO)

The brain-localized PNPO enzyme catalyzes the rate-limiting step in the synthesis of the active form of vitamin B6, known as pyridoxal 5′-phosphate (PLP). SNPs in *PNPO* have been associated with neonatal epileptic encephalopathy and early-onset epilepsy. The *PNPO* variants can cause mild to complete inactivation of this enzyme. The R116Q, D33V, and R95H are a few of the *PNPO* mutations reported in patients with neonatal epileptic encephalopathy. The *Drosophila* transgenic lines expressing the human *PNPO* mutant alleles demonstrate allele-dependent variation in seizure onsets and seizure types. These alleles also display a variable reduction in *PNPO* level and different degrees of lifespan shortening effect. Interestingly, these mutants show more diversified phenotypes upon dietary treatments. For example, on a sugar-only diet, the R116Q but not D333V homozygotes become hyperactive (Chi et al. 2022). This suggests that allele-diet interactions contribute to the ultimate phenotypic manifestations of these polymorphisms.

3.3.16 Genes Associated with Age-Related Macular Degeneration

Age-related macular degeneration (AMD) is one of the leading causes of irreversible blindness among the population > 50 years of age. Diet-gene interactions have been found to alleviate AMD-associated pathologies in mice models. Retinal pigment epithelium-specific deletion of *Sod2,* the mitochondrial Superoxide Dismutase 2, results in the development of AMD-like pathologies in mice due to massive

oxidative stress. Daily zeaxanthin, a carotenoid, supplementation to *Sod2*$^{flox/flox}$ *VMD2-cre* mice increased retinal pigmented epithelium (RPE) expression of NRF2-regulated enzymes, such as catalase, NAD(P)H quinone dehydrogenase 1 and heme oxygenase 1, thus inducing an antioxidant response (Biswal et al. 2018). Zeaxanthin supplementation also reduced RPE thinning and preserved RPE structure and function. It would be interesting to study whether zeaxanthin supplementation slows disease progression once retinal and/or RPE degeneration has initiated.

In another AMD model, *Ccl2*$^{-/-}$*/Cx3cr1*$^{-/-}$ mice treated with a high n-3 fatty acid diet showed a delayed progression, or even reversion of retinal lesions, compared to the low n-3 fatty acids group. The ocular transcript levels of pro-inflammatory cytokines, TNFα and IL6, were lowered while anti-inflammatory eicosanoids, prostaglandin D_2, and leukotriene B4 were increased in the mice fed on high n-3 fatty acids (Tuo et al. 2009). The study supports the epidemiological retrospective studies on the protective relationship between n-3 fatty acids intake and advanced AMD (Lawrenson and Evans 2015).

3.4 Diet-Gene Interactions in Human Aging and Associated Diseases

Aging is a critical risk factor for a variety of human pathologies, including neurodegenerative diseases, cancer, and metabolic diseases. Diet-gene pairings also have crucial implications for human physiology and disease progression. In randomized clinical trials focusing on the effects of dietary interventions on weight maintenance, insulin resistance, and lipid profile, individuals' genotype was found to be an important determinant (Qi 2014). In multiple nutrigenetic and nutrigenomic studies, the effect of genetic background in response to diet interventions in multiple cohorts with diverse genetic predispositions has begun to explicate. Few such examples have been detailed below (also see Fig. 3.1).

3.4.1 TCF7L2 and IRS1 in Type-2 Diabetes Mellitus

The interplay between genetics and environmental factors results in variable severity of T2DM. At least 200 genetic variants have been identified as T2DM-related alleles. The polymorphism is present in genes regulating pancreatic β-cell function, insulin secretion pathway, and insulin signaling. Some of these variants would increase susceptibility to T2DM and dietary factors can interact with these genetic variants to modulate the risk of T2DM development. Genetic polymorphisms in the gene *TCF7L2* are associated with an increased risk of T2DM. A high fiber intake increases the T2DM risk in carriers of allele rs12255372 or rs7903146 while non-carriers display a reduced risk of T2DM (Hindy et al. 2016; Ortega et al. 2017).

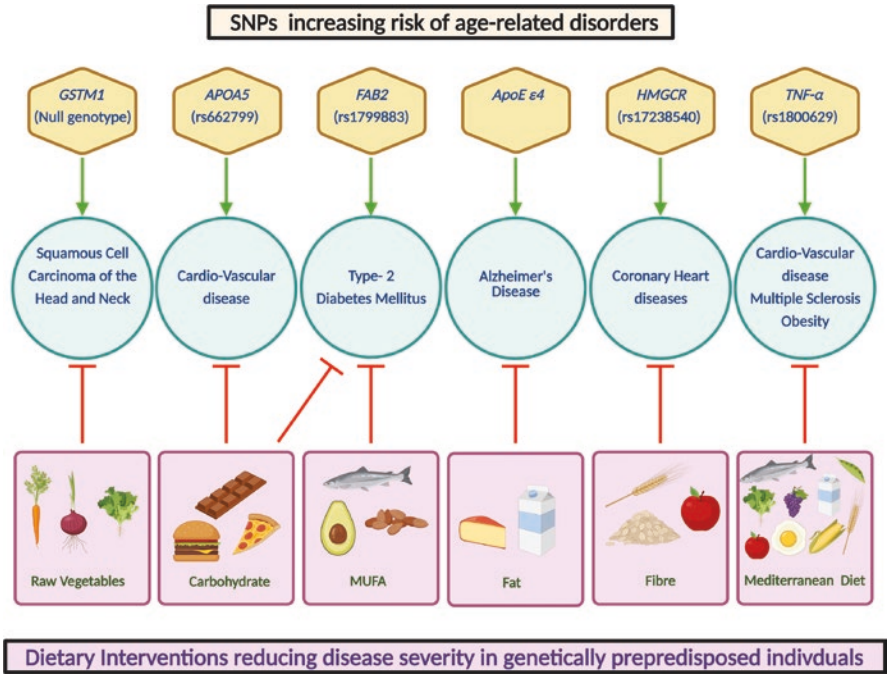

Fig. 3.1 Gene-diet interactions in age-associated diseases. Diet interventions have crucial implications on the effect of genetic background in human physiology and disease progression. For instance, consumption of raw vegetables reduces incidence of carcinoma among individuals with the *GSTM1*-deletion genotype. High carbohydrate intake lowers plasma triglyceride levels in individuals carrying *APOA5* (rs662799) allele. Replacing saturated fatty acids by MUFAs and carbohydrates improves insulin sensitivity in the carriers and reduces T2DM susceptibility in individuals homozygous for *FABP2* (rs1799883) allele. Cognition and plasma AD biomarkers in aged *APOEε4* carriers is improved when fed a high-fat diet. Consuming more fibre proves beneficial to *HMGCR* (rs17238540) carriers at high risk of coronary heart diseases. Mediterranean diet interacts with the TNF-α (rs1800629) allele and reduces risk of obesity, CVD, and multiple sclerosis. SNP- Single Nucleotide Polymorphism; MUFA- Monounsaturated Fatty Acids; *GSTM1*- Glutathione S-transferase Mu; *APOA5*- Apolipoprotein A-V; *FAB2*- Fatty Acid-Binding protein 2; *HMGCR-3*-Hydroxy-3-Methylglutaryl-Coenzyme A Reductase; *TNF-α*-Tumor Necrosis Factor-alpha

Genetic variants near the gene encoding insulin receptor substrate 1 (*IRS1*) have been associated with T2DM. The variant rs2943641 T allele lowers the risk of insulin resistance which is further modulated by dietary factors like monounsaturated fatty acids (MUFAs), and carbohydrate quantity. Low consumption of MUFAs and low total fat consumption decrease resistance to insulin. Carriers of Ala54Thr polymorphism (rs1799883) in intestinal fatty acid-binding protein 2 are more susceptible to T2DM than homozygous individuals (Qiu et al. 2014). Replacement of saturated fatty acids by MUFAs and carbohydrates improves insulin sensitivity in the carriers. Thus, individuals with higher genetic predisposition should change their dietetic patterns depending on the effect of diet on the variation-specific T2DM phenotypes (Ortega et al. 2017).

3.4.2 *APOE and ATP7B in Alzheimer's Disease*

The most significant genetic risk factor for AD is the ε4 allele of the *APOE* gene, increasing the risk for AD up to ~tenfold in homozygous persons. *APOE* ε4 is associated with weakening neuronal repair, overwhelming amyloid plaque formation, and heightened oxidative stress. When aged *APOE* ε4 carriers with cognitive impairment or non-carriers with normal cognition were fed a high-fat diet, cognition and plasma AD biomarkers in ε4 carriers improved but worsened in ε4 non-carriers (Hanson et al. 2015). Interestingly, *APOE* ε4 carriers also demonstrate resistance to improvement on a ketogenic diet (Henderson et al. 2009).

The defects in copper homeostasis caused by variations in genes like *ATP7B* are associated with a significant increase in AD risk. *ATP7B* encodes a plasma membrane copper-transport protein, and carriers of a loss-of-function *ATP7B* variant ($ATP7B^{K832R}$) have higher levels of free copper in serum than non-carriers. This copper overload leads to the intoxication of various organs, including the brain, where it enhances the A-β deposition and increases oxidative stress, while a low copper diet lowers the risk of AD in $ATP7B^{K832R}$ carriers (Squitti et al. 2014).

3.4.3 *APOA5 and ZPR1 in Cardiovascular Diseases*

CVDs, a group of disorders of the heart and blood vessels, include coronary artery disease, hypertensive heart disease, rheumatic heart disease, etc. The major risk factors associated with CVD include elevated TG and low-density lipoprotein (LDL) cholesterol levels in serum and reduced activity of lipoprotein-lipase. Apolipoprotein A-V (*APOA5*) rs662799 and rs2266788 minor alleles elevate the risk of increased TG and decreased high-density lipoprotein (HDL) cholesterol concentrations in the bloodstream. APOA5 is predominantly expressed in the liver and is an important determinant of plasma TG levels. Interestingly, low fat intake increases plasma TG levels while high carbohydrate intake lowers plasma TG concentration in individuals carrying the minor alleles. Individuals who are carriers of rs662799 and have low calcium intake display higher plasma TG concentrations than those with moderate calcium intake (Jiang et al. 2010). Further studies on such diet-gene interactions may promote genotype-based personalized nutrition to manage the risk of age-related disorders.

The zinc finger protein-1 *ZPR1* is an essential gene in mice and is required for transcription and cell proliferation. The rs964184 C > G variation in the gene has been associated with elevated levels of fasting and postprandial TG, thus increasing the risk of myocardial infarction in patients with CVD. The G-carriers on Mediterranean Diet have higher fasting and postprandial TG, while their levels are reduced to that of non-carriers when on a low-fat diet (Alcala-Diaz et al. 2022). Such evidence supports the notion of precision nutrition, based on diet-gene interactions, to benefit the health of genetically predisposed individuals.

3.4.4 Methyltetrahydrofolate Reductase Gene (MTHFR)

One-carbon metabolism gene *MTHFR* plays an essential role in the folate-methionine cycle. MTHFR helps convert 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, thus facilitating crucial cellular processes such as DNA, RNA, and protein methylation. The *MTHFR* 677TT genotype reduces the activity of the reductase and results in suboptimal plasma folate and elevated plasma homocysteine levels. Polymorphism of *MTHFR* is associated with an increased risk of CVD (Liew and Gupta 2015). Supplementing the diet with folate has been found to effectively increase folate and normalize homocysteine levels in TT homozygotes (Ashfield-Watt et al. 2002). It would be interesting to carry out detailed studies on the effect of folate supplementation on the incidence and severity of CVD in individuals homozygous for the *MTHFR* 677TT allele.

3.4.5 Tumor Necrosis Factor-Alpha (TNFA)

Tumor necrosis factor-alpha is a pro-inflammatory cytokine and plays a vital role in the inflammatory responses in obesity, insulin resistance, dyslipidemia, and cardiometabolic disease. Individuals with the -308G → A rs1800629 promoter polymorphism in the *TNFA* gene exhibit higher BMI, higher leptin levels, and disproportionately higher levels of soluble TNFR2, making them genetically predisposed to increased risk of obesity, CVD, and multiple sclerosis (Dalziel et al. 2002; Babu et al. 2012). A 12-month regime of a Mediterranean diet was found to interact with the rs1800629 allele and reduce TG levels as well as inflammation status, qualifying it as a potential treatment of the metabolic syndrome (Gomez-Delgado et al. 2014).

3.4.6 Fat Mass and Obesity-Associated Gene (FTO)

FTO or alpha-ketoglutarate-dependent dioxygenase enzyme regulates energy homeostasis, and it is expressed highly in brain regions involved in controlling nutrition and energy expenditure. The A allele of *FTO* (rs9939609) leads to high adiposity and increased BMI, alterations in appetite, altered ghrelin synthesis and secretion, as well as type 2 diabetes. Individuals carrying *FTO* polymorphism have been found to benefit more from consumption of a Mediterranean diet or Eastern European diet, again highlighting the important of considering diet-gene interactions in designing treatment options for metabolic syndrome (Xiang et al. 2016; Di Renzo et al. 2018; Chmurzynska et al. 2019).

3.4.7 *Glutathione S-Transferase Mu Gene (GSTM1)*

GSTM1 catalyzes the phase II detoxification of toxins, carcinogens, drugs, and products of oxidative stress, by conjugation to the tripeptide glutathione. Polymorphisms in *GSTM1* lead to null activity of the enzyme, which causes increased incidences of squamous cell carcinoma of the head and neck (Geisler and Olshan 2001). Weekly consumption of raw but not cooked vegetables has been associated with reduced incidence of carcinoma among individuals with the *GSTM1*-deletion genotype (Gaudet et al. 2004).

3.4.8 *3-Hydroxy-3-Methylglutaryl-Coenzyme A Reductase Gene (HMGCR)*

HMGCR is a critical enzyme in cholesterol biosynthesis. The *HMGCR* polymorphism like T > G SNP (rs17238540) causes hypercholesterolemia and hypertriacylglycerolemia and thus, increases susceptibility toward coronary heart diseases (Freitas et al. 2010a, b). The type of allele present in an individual influences serum lipid and TG response to dietary supplements. For example, with a higher intake of saturated fatty acids, the G allele carriers present lower HDL levels than TT individuals. In response to dietary fibre intake, the G allele carriers present lower serum TG compared with TT individuals (Freitas et al. 2010a, b). Therefore, consuming more fibre and less saturated fat would benefit individuals at high risk of coronary heart diseases.

3.5 Conclusion

Both environmental and intrinsic cues, such as diets and genes, respectively, have been independently identified as significant regulators of organismal aging and disease. Studies on model organisms have discovered various aging-regulating genes and advanced our understanding of the biological processes that modulate the rate of aging. The type of dietary intake has pro- or anti-longevity effects, but these are counterbalanced mainly by organismal metabolic responses, controlled by a complex genetic network, to maintain homeostasis. Nevertheless, no two individuals are genetically similar. Owing to the mutations that accumulate during development, minor genetic differences are also present even in monozygotic twins. Based on the host's genotype, the same diet may exert distinct effects on the life history traits of different individuals. Thus, diet and genetic background can interact to maintain the normal rate of aging, and animals that can adapt to different food sources are in an evolutionary advantageous state as their survival would not solely depend on the availability of a specific diet.

During aging, the gradual loss of metabolic plasticity increases susceptibility to age-related disorders. Several alleles have been identified that predispose individuals to various age-associated disorders and modulate the severity of diseases. Interactions between an individual's genotype and diet further dictate the incidence of the diseases and phenotypic variations among patients, amplifying the heterogeneity of the disease among individuals. This may have significant implications in developing treatment strategies. Therefore, dietary intervention based on an individual's genetic makeup may provide a novel therapeutic strategy for better management of age-associated or other debilitating diseases.

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Chapter 4
Antioxidants and Ageing

Sayantan Chakraborty

Abstract Antioxidants are compounds which react with free radicals and neutralise them. Various metabolic processes in the body produce free radicals as their by-products. Free radicals can damage DNA, lipids and proteins of cell membranes. They can peroxidise several lipids, including low-density lipoproteins, which accumulate in the wall of blood vessels and disrupt blood circulation throughout the body. Free radicals are also involved in Alzheimer's disease, acute and chronic kidney disease, atherosclerosis, myocardial infarction. Antioxidants break down free radicals, remove them from the site, and delay ageing. Telomere shortening by free radicals is directly linked with ageing and age-related diseases. Various antioxidants are present in our body as water-soluble, fat-soluble, enzymatic, non-enzymatic, small, and large molecular antioxidants. Enzymatic antioxidants are mainly present in mitochondria and cytosol, and non-enzymatic antioxidants are present in blood plasma. To avoid oxidative damages, consumption of antioxidant-rich foods are suggested. Foods are divided depending on the amounts of antioxidants. Guava, red grapes, spinach, carrots, raisins, turmeric, ginger, cumin, and green tea are rich sources of antioxidants. Antioxidants in coloured vegetables and fruits boost immunity, prevent age-related diseases, delay ageing and reduce mortality.

Keywords Antioxidants · Ageing · Age-related diseases · Free radicals · Oxidative stress

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4.1 Introduction

Ageing is a complex biological process; in humans, it has a multifactorial origin. Ageing results from long-term cellular and molecular damages, with which free radicals are inherently involved. Ageing leads to an increasing number of diseases and disorders and a gradual decrease in physical and mental capacity. Biological changes, environmental conditions, and life transitions such as loss of loved ones, death of parents, friends, siblings, separation from children, and retirement accelerate the ageing process (Olshansky and Carnes 2010).

Besides the genetic factors, several factors such as diet, exercise, pollution, and lifestyles also assume great importance. Social isolation, lack of mobility, dental problems, food faddism, and inadequate nutrition are major problems of old age. Reactive oxygen species (ROS) and reactive nitrogen species (RNS), such as superoxide, hydroxyl, and nitric oxide radicals damage the DNA and lead to the oxidation of lipid and proteins in cells (Metodiewa and Kośka 1999). Oxidation-Reduction reaction is the primary source of energy. Dehydrogenation is the most common form of biological oxidation (Xu et al. 2017).

Immunity decreases with age, called immunosenescence. Disease prevalence increases due to reduced cellular and humoral immune responses. Both the humoral and cellular adaptive immune systems protect cells by destroying microbes. Primarily it is regulated by antibody response, then by cytotoxic T-cell mediated immune response.

Oxygen-derived free radicals are responsible for cellular damage, leading to several diseases, including cancer, retinopathy, cataracts, etc. In addition, antioxidants have a strong influence on the immune system of the elderly.

Any substance impedes cell oxidation by free radicals or prooxidant radicals is an antioxidant. According to the Free radical theory in 1956 Denham Harman, free radicals are produced during aerobic respiration because cumulative oxidative damage is the cause of ageing and death (Blumberg 2000). Free radicals have unpaired electrons. These highly reactive unpaired electrons react with molecules and damage proteins, lipids, carbohydrates, cell membranes, peptide bonds, and nucleic acids (Phaniendra et al. 2015). Several experimental evidence favouring the free radical theory of ageing comes from invertebrates (Viña et al. 2013). In a study by Schriner et al., mice that have extra catalase in their mitochondria live 18% longer and were less likely to develop cataracts, but they did not appear to age slower (Schriner et al. 2005). Free radical theory is one of the most promising explanations for the process of ageing (Jayanthi et al. 2010).

Since antioxidants can neutralise free radicals by electron donation, the most logical approach was to use them as supplements to prevent ageing. Free radicals are atoms or molecules with unpaired electrons that damage our tissue. Antioxidants combine with free radicals in the body and neutralise their damaging effects. Therefore, the use of medicinal plants as a source of bioactive compounds, particularly natural antioxidants, has increased substantially worldwide. Beta-Carotene, lycopene (abundant in tomatoes), lutein (found in green vegetables), zeaxanthin, cryptoxanthin, and polyphenols found in some fruits, olive oil, tea, grapes, and oranges have antioxidant effects.

This chapter describes the relationship between free radicals, ageing-related physiological changes, antioxidants' impacts, and defence mechanisms.

4.2 The Physiological Process of Ageing

Aging involves various physiological changes:

4.2.1 Gastrointestinal Tract

From gum disease to tooth decay and other pathophysiological factors, adequate dietary intake is reduced. Loose, painful teeth and ill-fitting dentures cause difficulties in mastication. Lips, tongue, salivary glands and teeth play a role in chewing, breaking down and swallowing food. Swallowing food without proper chewing results in digestive problems. In the case of the tongue, due to the decreasing number of taste buds, taste sensitivity is reduced, and food may seem less appetising. People over 70 years old have a common problem of xerostomia. Decreased secretion of saliva leads to xerostomia (dryness of the mouth) which makes swallowing difficult. After swallowing, the bolus reaches the posterior pharyngeal wall, where the musculature contracts around it, but the intestine's motility decreases, leading to impaired absorption of nutrients. The absorptive capacity of the small intestine is reduced by 30%. Gastric emptying diminishes progressively with age, and the acidity and pepsin content in gastric juice also decreases. Food stays in the stomach for a longer period, which gives a feeling of fullness. Fat and carbohydrate absorption decreases to a lesser extent with age. Fat tolerance decreases because of inadequate secretion of fat-digestive enzyme lipase (Nigam and Knight 2017).

4.2.2 Telomere Shortening

A telomere is a region of repetitive DNA sequences at the end of a chromosome (Blackburn et al. 2006). Telomeres perform many vital roles; the three main roles of telomeres are: (a) it protects the end of chromosomes. Without their protection cap DNA gets damaged. It also protects chromosome ends from degradation and illegitimate recombination; (b) they ensure the replication of chromosomes during cell division; and (c) they help in arranging each of the 46 chromosomes. Telomere function is inextricably linked with cell age (Shammas 2011). With each cell division, chromosomes become shorter. In cells without telomeres, DNA becomes broken and damaged, which causes cells to stop dividing, cell fate and ageing. Telomere density is higher in rapidly dividing cells such as eggs, sperm, and stem cells. It's concentration is less in somatic cells. The number of telomeres decreases by 20 to 40 per year. Ageing is not the only cause of telomere shortening. Factors such as

lifestyle, diet, smoking, obesity, etc. are responsible for telomere shortening. Maintaining a healthy diet can prevent telomere shortening and protect against various chronic diseases (Jennings et al. 2000).

4.2.3 Changes in Cardiovascular System

The risk of cardiovascular disease also increases with age. The progressive accumulation of atheromatous plaques on veins, arteries wall or vascular walls leads to narrowing of the lumen of blood vessels and decreased blood flow. Not only does it alter the mechanical and structural properties of the vascular wall, but it also decreases arterial elasticity. The decline in cardiac output reduces the efficiency of other organs. Due to reduced blood flow, the digestion, absorption and distribution of nutrients are less efficient. We should take care of our hearts from childhood. Fatty material, fats, and collagen accumulate in the artery and form plaque; as a result, there is difficulty in blood flow in the arteries. As the age increases, a thick layer of fat falls in the artery, in which case the size of the lumen of the artery decreases, because of which blood cannot flow smoothly. This plaque reduces blood flow or completely stops blood flow and causing heart diseases.

4.2.4 Renal Changes

With increasing age, chronic and acute kidney diseases are possible. Blood flow decreases with age, and the number of functioning nephrons also decreases. The smaller number of functioning nephrons lessens the glomerular filtration and tubular reabsorption of essential nutrients. Thus, the excretion of wastes and return of nutrients to the circulation is less efficient. According to research from Johns Hopkins University researchers, more than 50% of seniors over the age of 75 are believed to have kidney disease. The National Kidney Foundation (NKF) urges everyone over the age of 60 to be screened for kidney disease. NKF also recommends that people with diabetes, hypertension, and kidney failure in their families are a high-risk group. Swelling of the face and feet, frequent urination (especially at night), urinary sensation and presence of blood or pus in the urine, difficulty urination, and dribbling urine are symptoms of kidney diseases (Kolman 2019).

4.2.5 Change in BMR

The basal metabolism decreases by about 2% for each decade from 25 years of age due to increased body fat and lesser muscle tension. Age is the most important factor that changes basal metabolic rate. Physical activity and energy consumption

decrease with age. Energy requirements decrease in the elderly. As a result, the uptake of vitamins, minerals, and antioxidants gradually decreases. Walking, doing heavy work, and going to the office decrease with age. As a result, older adults usually lead a sedentary lifestyle. And if energy consumption increases during this time, fat accumulates in the body. Body fat tends to accumulate in the abdominal cavity in the elderly. According to the Food and Nutrition Board/ Institute of Medicine, the USA average decreases of 2.9% and 2% per decade, respectively, for men and women of average body weight (Basal metabolic rate of 18.5–25.0 kg/m^2). Healthy lifestyle and physical activity decrease BMI. The ability to maintain a normal body temperature is also lessened, this condition is called Hypothermia, which is deadly for elderly people (Shimokata and Kuzuya 1993).

4.2.6 Carbohydrates and Fat Metabolism

With age, the level of bad cholesterol (LDL, VLDL) and triglycerides in the blood also gradually increases (Roberts and Rosenberg 2006) (Fig. 4.1).

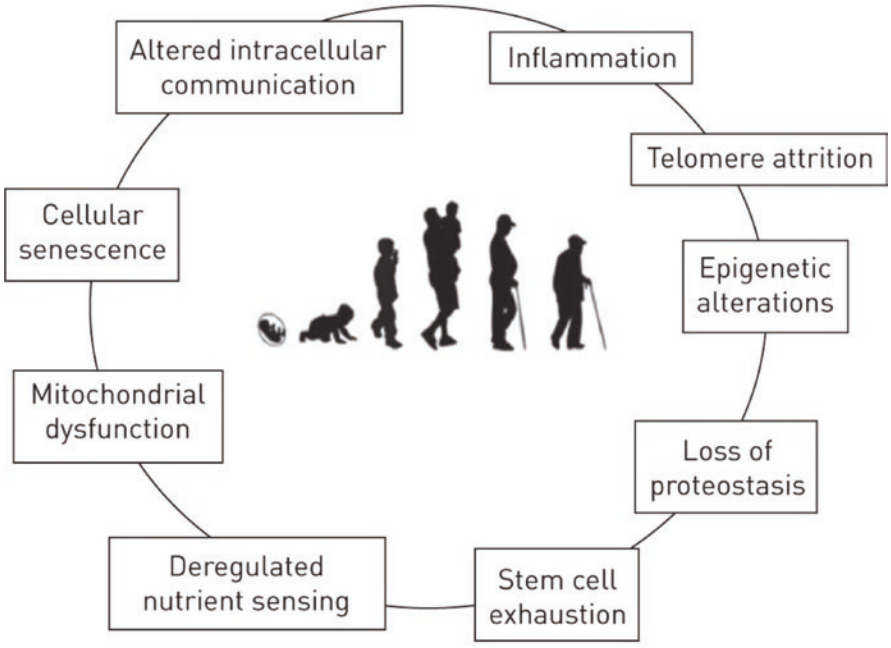

Fig. 4.1 Process of ageing. (Source: https://erj.ersjournals.com/content/44/5/1332)

4.3 Antioxidants

Components that combine with free radicals in the body and neutralise their damaging effects are called antioxidants. All antioxidants work together to protect our cells from damage and keep our body healthy. Although antioxidants have many definitions. According to chemical definition, a substance that opposes oxidation or inhibits reactions promoted by oxygen or peroxidase is called an antioxidant. The biological definition of antioxidant is: antioxidants are synthetic or natural substances that prevent or delay the deterioration of a product or are capable of counteracting the damaging effects of oxidation in animal tissues. The Institute of Medicine defines an antioxidant as a substance that significantly decreases the adverse effects of reactive species such as ROS or RNS on normal physiological function in humans. ROS and RNS mean reactive oxygen species and reactive nitrogen species, respectively.

4.4 Classifications, Locations and Functions

Antioxidants can be classified in different ways. Based on their *activities*, they are classified as: enzymatic antioxidants and non-enzymatic antioxidants (Moussa et al. 2020).

Depending on the *solubility*, antioxidants can be differentiated into two types, as water-soluble and lipid-soluble antioxidants (Azat Aziz et al. 2019). Few examples of water-soluble antioxidants are ascorbic acid, glutathione, uric acid, etc. Few examples of lipid-soluble vitamin E, carotenoids, etc.

The antioxidants can also be classified according to their *size*, the small-molecule antioxidants and large-molecule antioxidants (Nimse and Pal 2015). Ascorbic acid, retinol, β-carotene, tocopherol and polyphenolic compounds are small molecule antioxidants. Vitamin C, vitamin E, carotenoids, and glutathione peroxidase are large molecule antioxidants (Fig. 4.2).

Endogenous Antioxidants		Exogenous Antioxidants
Enzymatic	**Non-Enzymatic**	**Non-Enzymatic**
Catalase (CAT)	Myoglobin	**Vitamins**
Superoxide dismutase (SOD)	Ferritin	Vitamin C (ascorbic acid)
Glutathione peroxidases (GPxs)	Metallothioneins	Vitamin E (tocopherols)
Glutathione reductases (GRs)	Transferrin	Vitamin K
Glutathione-S-transferases (GSTs)	Lactoferrin	**Mineral elements**
Phospholipase A2	Albumin	Selenium
	Ceruloplasmin	Zinc
	Glutathione	Manganese
	Coenzyme Q10	Copper
\	Uric acid	**Nutritional**
	Bilirubin	Carotenoids
	Melatonin	Phytonutrients
	Vitamin A (retinol)	**Supplements**
		Lipoic acid
		Polyphenol
		D-Methionine
		Carnosine
		Omega-3 fatty acids
		Acetyl L-carnitine

Fig. 4.2 Classification of antioxidants. (Source: https://images.app.goo.gl/2DduSh99Rt4s14rA9)

4.5 Enzymatic Antioxidants

Enzymatic antioxidants break down free radicals, such as superoxide radicals and hydrogen peroxide and remove them from the site. Some enzymatic antioxidants are: superoxide dismutase (SOD), glutathione peroxidase (GSH), catalase (CAT), glutathione reductase, etc. (Jeeva et al. 2015). These antioxidants react chemically in the presence of various cofactors (zinc, copper, manganese, iron) to convert free radicals first into hydrogen peroxide and then into the water.

4.6 Superoxide Dismutase (SOD)

Superoxide dismutase is located in mitochondria and cytosol. This antioxidant destroys superoxide radicals and helps the conduit in transmitting the injury caused by free radicals. Copper-zinc containing enzymes are found in the cytoplasm, and manganese SOD is located in the mitochondria.

4.7 GSH and Glutathione Reductase

The oxidative form of glutathione is not protective, but the reduced form is defensive in nature. Three main reduced forms of glutathione which play as enzymatic antioxidants are Glutathione reductase, Glutathione peroxidase and Glutathione

transferase, located at mitochondria and cytosol. Glutathione peroxidase reduces lipid hydrogen peroxides to their corresponding alcohol to remove hydrogen peroxide and organic peroxide (Lubos et al. 2011). Some studies suggest that glutathione peroxidase and superoxide dismutase play an essential role in celiac disease. Glutathione peroxidase and glutathione reductase play a key role in preventing increased levels of oxidative stress. Type 2 diabetes with microalbuminuria, diabetic nephropathy—all these patients have low levels of glutathione peroxidase in serum or blood.

4.8 Catalase

One of the most important enzymatic antioxidants present in cytosol and mitochondria is Catalase. In a two-step reaction, Catalase breaks down two hydrogen peroxide molecules into one molecule of oxygen and two molecules of water and then removes hydrogen peroxide (Nandi et al. 2019). In 1948, the first prokaryotic catalase was purified from the organism of an aerobic bacterium Micrococcus lysodeikticus. Catalase malfunctioning or deficiency is associated with many diseases such as anemia, Alzheimer's disease, cardiovascular disease, Wilson disease, bipolar disorder, etc. Low catalase activities have been reported in schizophrenic patients.

4.9 Non-enzymatic Antioxidants

In addition to enzymatic antioxidants, human blood plasma has highly efficient small molecular weight compounds which act as antioxidants called non-enzymatic antioxidants. Few non-enzymatic antioxidants are vitamin E, vitamin C, uric acid, carotenoids, bilirubin, ubiquinones, nitric oxide, etc.

4.9.1 Vitamin E

Vitamin E is a group of eight fat-soluble compounds with potent antioxidant effects. Alpha-tocopherol is the most biologically active form of vitamin E (Ref) Dutta-Roy, A.K., Gordon, M.J., Campbell, F.M., Duthie, G.J., James, W.P.T: Vitamin E requirements, transport, and metabolism: Role of α-tocopherol-binding proteins. Journal of Nutritional Biochemistry, 5, 562-570, 1994. Plant oils such as rapeseed (vegetable oil), sunflower, soya, corn and olive oil, nuts, and seeds are good sources of vitamin E (Miller 2006). In the human body, vitamin E is mainly present in the cell membrane. Vitamin E breaks antioxidants in cell membranes and helps proper immune function and cellular signalling. Vitamin E supplements significantly reduced systolic and diastolic blood pressure and triglycerides, low-density lipoproteins (refs).

4.9.2 Uric Acid

Uric acid inhibits lipid peroxidation and scavenges free radicals. The major limitation of uric acid is it acts only in the hydrophilic environment (Sautin and Johnson 2008). Urate is a very efficient scavenger of highly reactive oxygen species (hydroxyl radicals, singlet oxygen, etc.). Uric acid is the product of purine metabolism.

4.9.3 Carotenoids and Flavonoids

The two primary antioxidants available from plants are carotenoids and flavonoids. They are very potent natural and lipid-soluble antioxidants. Both of them are located in membrane tissues. Flavonoids scavenge hydroxyl and superoxide radicals from cells. According to the World Health Organization, cancer is a primary cause of death and accounted for around 13% of all deaths in 2008. Carotenoids and flavonoids protect against many diseases related to ageing, such as neurological disorders, various types of information, diabetes, cardiovascular disease, cancer, etc. Cantaloupe, carrot, papaya, and kale are good sources of carotenoids. Berries, red cabbage, tea, and onion are good sources of flavonoids.

4.9.4 Vitamin C

Water soluble vitamin C is the most effective antioxidant in plasma. It is protective against ageing-related problems and neurological disorders. Few clinical studies suggest that vitamin C (ascorbic acid) reduces wrinkles and improves skin texture and appearance. It is essential for the growth, development and repair of all tissues in the body. It is indispensable in many vital body functions, including collagen formation, iron absorption, immune system strengthening, wound healing, etc. Parkinson's disease and arthritis are significant problems in the elderly; daily vitamin C intake can reduce these problems. All sour fruits such as lemons, oranges, tamarinds, tomatoes, grapes, and bitter gourds are good sources of vitamin C (Nimse and Pal 2015; Jeeva et al. 2015).

4.10 Foods Containing Antioxidants

Antioxidants from dietary sources can protect from various diseases, such as cardiovascular disease and cancers, and it is also very effective as antiaging agent.

Fruits, vegetables, nuts, and seeds are good sources of antioxidants. Scientists at NIH (National Institute of Health and Aging) develop ORAC scores to measure

antioxidant capacity in different foods. Foods with higher ORAC values can neutralise more harmful free radicals. Free radicals damage cells and cause many age-related degenerative diseases. According to researchers, 3000-5000 antioxidant or ORAC units are able to meet the body's daily requirements. Many times, due to eating higher antioxidant-containing foods (apple, cherry, cloves, turmeric, peaches, broccoli, etc.), the antioxidant in the body increased by 15–20%. But antioxidant capacity in the blood is tightly regulated. Excess antioxidants are simply excreted by the kidneys. Five serving varieties of fruits and vegetables give an approximate ORAC score of 3500, according to UK FSA and FDA (Carlsen et al. 2010).

4.11 Antioxidants and Their Sources

USDA researches 100 foods from each food category and gives a list of the top 20 foods. Among them, small red beans, blackberries, wild blueberries, strawberries, black beans, sweet cherries, plums, and red delicious apples are quite significant. American Dietetic Association gave an authoritative list of the highest antioxidants containing the top 20 foods (Reilly 2015).

Food group	Highest antioxidants containing foods
Fruits	Guava, red grapes, cherries, peaches, oranges, strawberries, etc.
Vegetables	Spinach, broccoli, carrots, potatoes, cabbage, avocados, pumpkin, etc.
Dried fruits	Dried pears, apples, raisins, dates, etc.
Spices and herbs	Turmeric, parsley, curry powder, basil, ginger, cumin, etc.
Cereals and nuts	Walnuts, almonds, cashews, etc.
Beverages	Green tea, pink grapefruit juice, apple juice, pomegranate juice, etc.

4.11.1 Guava

Guava is one of the antioxidant-rich fruits. The first highest vitamin C content fruit is amla, and the second highest vitamin C content fruit is guava. Not only in guava fruit but the leaf, root and bark of this tree are also very useful. Guava leaves also have a high content of antioxidants. We get a few important antioxidants from guava; they are quercetin, ascorbic acid, ferulic acid, caffeic, and gallic acid. Quercetin has high reducing power, it breaks down hydrogen peroxide to form water. Elderly people often suffer from arthritis, brain dysfunction, and arteriosclerosis. Antioxidants present in guava are beneficial in many degenerative diseases including arthritis, cancer, heart disease, arteriosclerosis and brain dysfunction (Naseer et al. 2018).

4.11.2 Spinach

Spinach contains many active antioxidants. Both glucuronic acid derivatives of flavonoids and coumaric acid derivatives are present in aqueous extract of spinach leaves. Spinach leaves also contain two phyto-pigments xanthine and lutein. It also contains carotenoids. We find that the tendency to develop cataracts increases with age. Xanthine, lutein, beta carotenoids prevent cataracts. Vitamin A present in spinach, which protects the mucous membrane of the eye and increases eyesight. Besides these, carotenoids are also very good for the eyes. Spinach is very useful in reducing blood pressure, weight loss, constipation, etc. Spinach is also very effective in removing various skin problems such as wrinkles, acne, etc. (Bergman et al. 2001).

4.11.3 Dates

Dates are rich in phenolic antioxidants, such as sinapic acid, p-coumaric, ferulic, flavonoids and procyanidis. It also contains vitamin B1, B2, B3, B5, vitamin A and vitamin C. Dried dates have more sugar content (sucrose). Due to its high antioxidant content, it is included in functional food. Traditional use of dates can be seen in several diseases such as bronchitis, wound healing, fever, intestinal disorder, etc. Sinapic acid, p-coumaric, ferulic, and flavonoids have antibacterial and anti-inflammatory activity. Dates are also a good source of carotenoids. 100gm dates contain 3942 mg phenolic compounds and carotenoids. Dates cure anemia, improve brain function and increase the body's immune system (Rahmani et al. 2014).

4.11.4 Turmeric

Turmeric contains a very powerful antioxidant called curcumin. Curcumin reduces blood pressure and blood sugar, enhances immunity power, protects neurons and postpone the onset of age-related disease such as Alzheimer's disease, rheumatoid arthritis, metabolic syndrome, cancer, etc. As a result of oxidative stress, the amount of pro-inflammatory cytokines such as 1L-6 and 1L-1 increases in tissue and causes low-grade inflammation (inflame-ageing). It has been confirmed through various in vitro experiments that curcumin is an anti-cancer agent. So, curcumin antioxidants in turmeric can also prevent terrible diseases such as cancer. It triggers the Nrf2/ARE signalling pathway, which activates a few antioxidative enzymes such as heme oxygenase and thioredoxin reductase, which play vital roles in oxidative stress-related diseases. Turmeric is also called a natural antibiotic. For a long time, we have seen that turmeric is applied to the wound. Turmeric oil helps to stop bleeding and protects that area from infection. Curcumin is a highly lipophilic compound

which crosses the blood-brain barrier (BBB) and reaches the brain to protect the brain against ageing, and neurodegenerative disorders. Curcumin also reduces melanin production and makes our skin fair and glowing (Sikora et al. 2010).

4.11.5 Walnuts

When you hear about nuts, the first thing that comes to mind is its fat content. But nuts contain many useful antioxidants. Vinson analysed antioxidants in nine types of nuts such as walnuts, peanuts, hazelnuts, pistachios, almonds, Brazil nuts, pecans, macadamias, and cashews. He said that walnuts have the highest level of antioxidant content. Useful antioxidants in walnuts are ellagic acid, ellagitannins, catechin, melatonin, and vitamin E (32). Deposition of fatty materials on the inner walls of arteries increases with age, causing atherosclerosis. Melatonin and vitamin E reduce low-density lipoproteins (bad cholesterol) and prevent atherosclerosis. Ellagic acid decreases the levels of inflammation and melanin production (Chen et al. 2018).

4.11.6 Green Tea

The antioxidant presents in green tea is epigallocatechin-3-gallate (EGCG). This natural antioxidant, catechin, reduces the formation of free radicals and protects cells from damage. Catechin plays a leading role in shedding belly fat (Gunnars 2020).

4.11.7 Antioxidant Activity of Fresh Fruits

Name	Antioxidant activity DPPH[a] (Trolox equivalent) mg/100 g
Guava	891
Apple	330
Grapes (green)	137
Indian plum	500
Papaya	46
Orange	167
Mango	211
Pomegranate	149
Water melon	32
Sweet lime	149
Chiku	141
Banana	41

[a]2, 2′-Diphenyl-1-picrylhydrazyl (DPPH) radical scavenging activity. (Source: Nutrition News NIN, 31 or book source: Food Science, B Srilakshmi)

4.12 Mechanism of Antioxidants and Ageing

Antioxidants have immense importance in keeping the body healthy and disease-free. Free radicals are typical by-products of various physiological processes that continue throughout the day in our bodies. These free radicals damage our cells and tissues. Antioxidants neutralise these free radicals and protect the body from damage (Lobo et al. 2010). Free radicals cause oxidative stress, accelerating the ageing process. Antioxidants reduce several age-related diseases such as arthritis, glaucoma, cardiovascular disease, neurological diseases, etc. (Fig. 4.3).

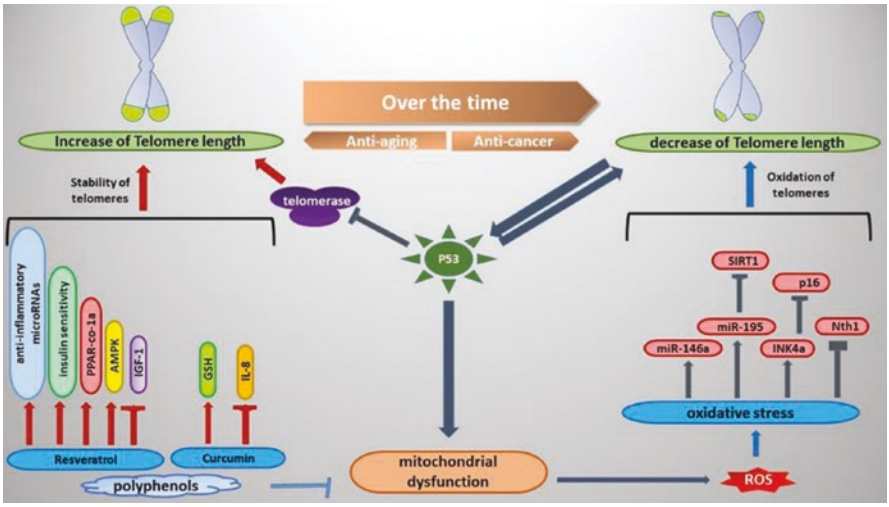

Fig. 4.3 Free radicals, gene expression, telomere and antioxidant as a model figure. (Source: https://ars.els-cdn.com/content/image/1-s2.0-S0024320520310936-ga1_lrg.jpg)

4.13 Antioxidant Defence System

A variety of antioxidants exist to control enzymatic and non-enzymatic damage by reactive oxygen species (ROS).

The *enzymatic defence system* includes Glutathione peroxidase, Glutathione reductase, Glutathione transferase, Catalase, and Superoxide dismutase.

The *non-enzymatic system* includes:

(a) Ascorbic acid, Selenium, Glutathione, Alpha-tocopherol, Beta Carotene.
(b) Ceruloplasmin, Uric acid, Anserine, Transferrin, Carnosine.

Superoxide dismutase, Glutathione peroxidase, and Catalase these enzymatic antioxidants and non-enzymatic antioxidants such as albumin and bilirubin are endogenous antioxidants. When the concentration of ROS in tissue increases, endogenous antioxidants cannot neutralise all free radicals. So, endogenous antioxidants fail to give complete protection to our bodies. That is why exogenous antioxidants are needed. These exogenous antioxidants are available in foods, nutritional supplements, and pharmaceuticals. There are several metals containing enzymes which scavenge and destroy free radicals. Various essential nutrients act as cofactors for all these enzymes. Some examples are given below.

4.14 Selenium

The amount of free radicals in the body increases due to various reasons. Consuming certain drugs, various radiations, and being exposed to heavy metals such as cadmium, lead, etc. increases the body's free radicals (Jaishankar et al. 2014). When the concentration of ROS exceeds the concentration of antioxidants, this extra ROS causes lipid peroxidation and damages the lipid layer of the cell membrane. Polyunsaturated fatty acids (PUFA) are very useful in maintaining membrane permeability. But polyunsaturated fatty acids are more susceptible to peroxidation (Catalá 2013). As a result of the damage to the cell membrane, nutrient absorption decreases in the cell, which results in a deficiency of various essential elements, vitamins, and minerals.

Not only the cell membrane but also the ROS extensively damage the DNA. At first, reactive oxygen species break the double strand of DNA and then damage the base and DNA protein, creating lesions in chromatin and sugars. This process is done by oxidation, methylation, deamination and depurination. Natural or dietary antioxidants help living organisms to live healthy in an oxygen-rich environment. Free radicals also cause protein oxidation. Protein peroxidation, damage in the amino acid chain and loss of parent amino acid is linked with ageing. Selenium is a component of a wide range of antioxidants such as glutathione peroxidase, thioredoxin reductase, selenophosphate synthetase, selenoprotein H, selenoprotein K, methionine sulfoxide reductase B1, etc. These antioxidants protect tissues from

damage caused by protein oxidation and lipid oxidation. Selenium-containing antioxidants decrease free radicals production and convert peroxidised lipids to stable and harmless products. Low dietary intake of selenium leads to Kashin-Beck disease, Keshan disease, male infertility, etc. (Zoidis et al. 2018).

Zinc and copper are components of redox-inert metal of copper/zinc superoxide dismutase. According to some studies, zinc, copper, and their dependent enzymatic antioxidants are responsible for age-related variations. Low or high zinc concentration causes cellular oxidative stress, which is very harmful to cells. Zinc-containing antioxidants Superoxide dismutase converts superoxide radicals to hydrogen peroxide to oxygen. Zinc increases immunity power, making our skin healthy. Zinc is also important for neural functions (Sfar et al. 2009; Lee 2018).

Iron-containing enzymatic antioxidant Catalase alters hydrogen peroxide to water and oxygen.

4.15 The Mechanism for Disposal of Free Radicals

- Zinc containing superoxide dismutase converts superoxide radicals to hydrogen peroxide (H_2O_2).
- Selenium-containing glutathione peroxidase converts hydrogen peroxide (H_2O_2) to water (H_2O).
- Glutathione reductase regenerates reduced glutathione.
- Iron-containing enzyme catalase alters two molecules of hydrogen peroxide into two molecules of water and oxygen.
- Vitamin E reacts with free radicals and is oxidised, and forms water.
- Vitamin E also reacts with lipid peroxyl radical, oxidises itself, and forms stable hydroperoxide.
- In the presence of vitamin C, vitamin E can be regenerated from oxidised vitamin E (Nimse and Pal 2015) (Fig. 4.4).

Colourful fruits and vegetables are the richest sources of antioxidants. Other major plant pigments besides chlorophyll are carotenoids, lycopene, lutein, flavonoids, etc. Plant pigments such as anthocyanin are present in pink, red, and

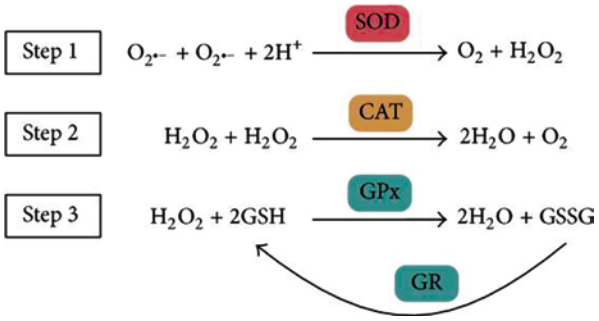

Fig. 4.4 Role of dietary antioxidants. (Source: https://images.app.goo.gl/PXF32L1CqD1SkyjbA)

blue-coloured fruits and vegetables such as berries, red cabbage, etc. *Anthocyanin* is a water-soluble pigment belonging to the flavonoid group. Currently, 500 types of anthocyanin have been discovered. 'Anthos' means flower, and 'cyanine' means blue. Anthocyanin is normally present in the cytoplasm of a cell. It protects cells from ultraviolet rays. This pigment reduces the risk of cardiovascular disease, cancer, neurological disorders, and age-related diseases (Sudhakar et al. 2016).

Carotenoids give plants and fruits yellow, orange and bright red colours. Various health benefits are available from carotenoids. Few sources of carotenoids are carrots, watermelon, cantaloupe, papaya, spinach, mangos, kale, etc. About 600 types of carotenoids have been found in plants, bacteria, and algae. Beta carotenoid is notable among them. Xanthophyll contains fruits and vegetables, primarily red and orange Oxygen. Containing molecules are found in dark green leafy vegetables such as spinach, kale, and broccoli. Few forms of carotenoids, such as beta-carotenoids, convert into vitamin A, which is crucial for vision (Anthony 2018). Foods rich in carotenoids can prevent the growth of cancer cells and keep the eyes healthy (Sudhakar et al. 2016).

Lycopene is a tetraterpene compound belonging to the family of carotenoids. Tomato is a rich source of lycopene. Lycopene hinders the onset of several diseases, including diabetes, oxidative stress-mediated malfunctions, skin and bone disease, neural and reproductive disorders, liver disease, etc. (Imran et al. 2020). Lycopene is responsible for the red and orange colour of fruits and vegetables. The bioavailability of lycopene in the body also decreases with age. Lycopene can remove more singlet oxygen than beta-carotene and alpha-tocopherol. A higher intake of lycopene reduces the risk of prostate cancer. Lycopene is one of the most potent anti-inflammatory nutraceuticals. Increasing the amount of lycopene in the blood reduces the risk of cancer.

Lycopene has anticarcinogenic effects, reducing the risk of several cancers such as lung cancer, stomach cancer, ovary cancer, breast cancer, and prostate cancer. Research suggests that a proper dose of lycopene reduces the number and size of ovarian tumours. It protects cells from cell damage caused by free radicals and cell necrosis. Lycopene supplementation protects the liver and lung by hindering nicotinic acetylcholine receptors expressed in the lung and CYP2E1 in the liver. Lycopene also acts as an antidiabetic by increasing insulin secretion.

Lycopene is also helpful in pancreas injury and urination problems caused by diabetes. Cardioprotective compound lycopene decreases very low-density lipoproteins (VLDL), low-density lipoproteins (LDL), triglycerides (TG) and total cholesterol and increases the level of high-density lipoproteins (HDL) (Dullaart et al. 1987). Thus, lycopene reduces blood pressure and protects the heart from various types of fatal heart diseases such as atherosclerosis, myocardial infarction, etc. (Imran et al. 2020).

As age increases, the ability of the intestine to absorb vitamins also decreases. Then we have to take more vitamins or vitamin supplements from outside. *Vitamin E* is essential for muscle health. Fat-soluble vitamin E reacts with loose electrons, oxidises itself and protects cells from oxidative damage. Alpha-tocopherol is the most active and abundant vitamin E. Sedentary lifestyle and malabsorption of

vitamin E cause several chronic age-related diseases, so vitamin E is involved in reaching longevity. The moisturising power of vitamin E makes our skin healthy and protects our skin from oxidative damage sunburn (2014).

Vitamin C decreases the formation of wrinkles, fine lines, age spots. It fights against harmful toxins or free radicals and improves skin texture and appearance. It also protect cells from sunburn. It increases immunity power and helps eliminate diabetes, hypertension, cardiovascular disease, and Alzheimer's disease. It accelerates the production of collagen and elastin and regenerates cells, delaying the skin's ageing process (Monacelli et al. 2017; Oregon State University 2021).

Oxidative stress is the result of an imbalance between prooxidants and antioxidants. The chemiluminescence process is used a lot to study oxidative stress in living organisms in vitro. In vivo, this process has been proposed as a non-invasive method to assess free radical skin damage. Tropical application of vitamin C or ascorbic acid before exposure to UVA decreases the UVA-induced chemiluminescence signal. This is very effective process to assess oxidative damage by UVA in the skin and how vitamin c protects our skin from UVA. According to American Dietetic Association spokeswoman Dee Sandquist, vitamin C obtained directly from fruits and vegetables is better than a supplement. Vitamin C nourishes the cell well from the inside to the outside. A study about this has been published in the American Journal of Clinical Nutrition, where the nutrient intake and skin ageing of 4025 people aged 40–75 years were observed. It has been seen here that people who have taken more vitamin C have less tendency to dry skin and fewer wrinkles on the skin (Ou-Yang et al. 2004; Zelman 2020).

4.16 Conclusions

Ageing is the result of long-term cell damage, molecular damage by free radicals produced as a result of various chemical reactions occurring in the body for a long time. Ageing is a biological process which depends on environmental factors, mental factors, etc. Free radicals such as ROS and RNS cause extensive damage to the cell membrane, protein, lipid, DNA and accelerate the ageing process. The unpaired electron in free radicals is the cause of ageing and death. Oxidative damage leads to several age-related diseases, including retinopathy, cataract, hypertension, diabetes, atherosclerosis, etc. Antioxidants neutralise free radicals by combining with unpaired electrons. Antioxidants are of different types depending on activities, solubility, and size. The mitochondria and cytosol of the cell usually contain enzymatic antioxidants. SOD, GSH, CAT destroys superoxide radicals and remove hydrogen peroxide and organic hydrogen peroxide. Human blood plasma also contains highly effective small molecular weight non-enzymatic antioxidants. Among them, vitamin E, uric acid, and vitamin C are quite significant. High triglyceride levels and hypertension are common problems for every elderly person. Vitamin E supplements reduce systolic, and diastolic blood pressure and total cholesterol. Urate reacts with highly reactive free radicals like singlet oxygen, and hydroxyl radicals

and neutralises them. Water soluble vitamin C reduces wrinkles and improves skin condition. It has a vital role in collagen production, wound healing and iron absorption. As we get older, some changes happen in our bodies. Gum diseases, tooth decay, loose, painful teeth, and reduced saliva causes mastication and swallowing difficulties. Telomere is also crucial for cell division and replication. Smoking, obesity, and alcohol consumption are responsible for telomere shortening. The risk of atherosclerosis, myocardial infarction, and Alzheimer's disease also increases with age. Progressive accumulation of fats on blood vessels leads to narrowing of the lumen. As a result, blood cannot flow properly in all organs such as the kidney, brain, etc. Thus, most elderly people suffer from chronic and acute kidney and neurological diseases. The number and the capacity of nephrons also decrease. The antioxidant defence system is made with different antioxidants, including glutathione peroxidase, glutathione reductase, ceruloplasmin, transferrin, etc. The amount of free radicals increases due to various drug consumption, pollution, etc. The risk of several chronic diseases decreases with diets rich in colourful vegetables and fruits. Because colourful vegetables and fruits contain many powerful antioxidants such as carotenoids, lutein, lycopene, etc., higher intake of these antioxidant-rich foods reduce the risk of diseases, delay ageing and lower the risk of mortality.

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Chapter 5
Nutrition and the Ageing Brain

Emily Connell, Matthew Pontifex, and David Vauzour

Abstract As the detrimental impacts of the ageing process accumulate, individuals become increasingly susceptible to cognitive dysfunction and neurological disorders. Diet has emerged as a key 'modifiable factor' that over a life course can have considerable implications upon cognitive function. This stems from its ability to modulate multiple processes such as neuroinflammation, endogenous antioxidant defence system and gut microbiota structure and function, which have an integral role in memory, learning and cognitive function. This chapter aims to highlight some of the key dietary nutrients, as well as whole diet approaches which may promote healthy neurological function, particularly during ageing. The emergence of novel pathways by which diet may influence healthy ageing (e.g., gut microbiome), and the advancement of new methodological approaches (neuroimaging, metabolomics, biomarkers) has enabled researchers to uncover novel mechanisms that may underpin this relationship. Despite this, the translation of these findings into a clinical setting remains challenging, marred by inconsistent and often contradictory results, suggesting further research using more standardised approaches is needed.

Keywords Ageing brain · Cognitive function · Polyphenols · Polyunsaturated fatty acids · Vitamins · Mediterranean diet

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5.1 Introduction

The global population is ageing. In 2015, the elderly proportion of society (e.g., 60 years or over) comprised of 901 million people accounting for 12.3% of the global population. By 2050, this number is expected to reach 2.1 billion, or 21.3% of the population (United Nations Department of Economic and Social Affairs, Population Division 2019). Given that age is the primary risk factor for cognitive decline; age-related neurological diseases such as dementia will undoubtably become increasingly prevalent over the coming decades. While some decline in cognition is to be expected as an inevitable part of the ageing process, approximately 15% and 11% of the population over 65 years develop more extensive cognitive impairment, namely mild cognitive impairment (MCI) and age-related dementias such as Alzheimer's disease (AD) respectively. Although more complex in reality, MCI generally describes a decline in mental abilities which exceeds normal ageing, without functional impairment and dementia (Petersen et al. 1999). Dementia (of which AD is the most common form), often follows MCI, and presents when the degree of cognitive decline reaches a level in which an individual's ability to carry out everyday tasks and activities becomes impaired. Debilitating conditions such as AD and dementia have a profound societal and economic impact, which are projected to intensify to overwhelming proportions over the forthcoming years. To address this global challenge, strategies to mitigate disease burden are urgently required. In the case of AD, it has been estimated that delaying disease onset by as little as 2–5 years could result in a 20–35% reduction in predicted AD prevalence by 2050 (Lewis et al. 2014), highlighting how preventative measures could be used to significantly lessen overall disease burden. Targeting lifestyle factors is an attractive option in the prevention of neurodegenerative disease given their modifiable nature. Therapeutic interventions/strategies targeting these lifestyle factors (e.g., diet and exercise) can be used to shift an individual to a more favourable status which promotes healthy brain ageing, while resisting aberrant changes (Fig. 5.1).

Nutrition is a key influencer of cognitive function. Indeed, current evidence indicates that nutritional strategies can delay or ameliorate neurodegenerative disease progression (Trichopoulou et al. 2003; Dangour et al. 2010). Individual dietary components, such as vitamin B, selenium and omega-3-fatty acids have been associated with protective roles during brain ageing (Trichopoulou et al. 2003; Dangour et al. 2010). However, long-term exposure and individuals with low baseline exposure are often required to observe a meaningful effect. Therefore, synergistic dietary patterns which encompass numerous bioactive compounds, such as the Mediterranean diet, DASH (Dietary Approaches to Stop Hypertension) diet and the hybrid MIND (Mediterranean-DASH Intervention for

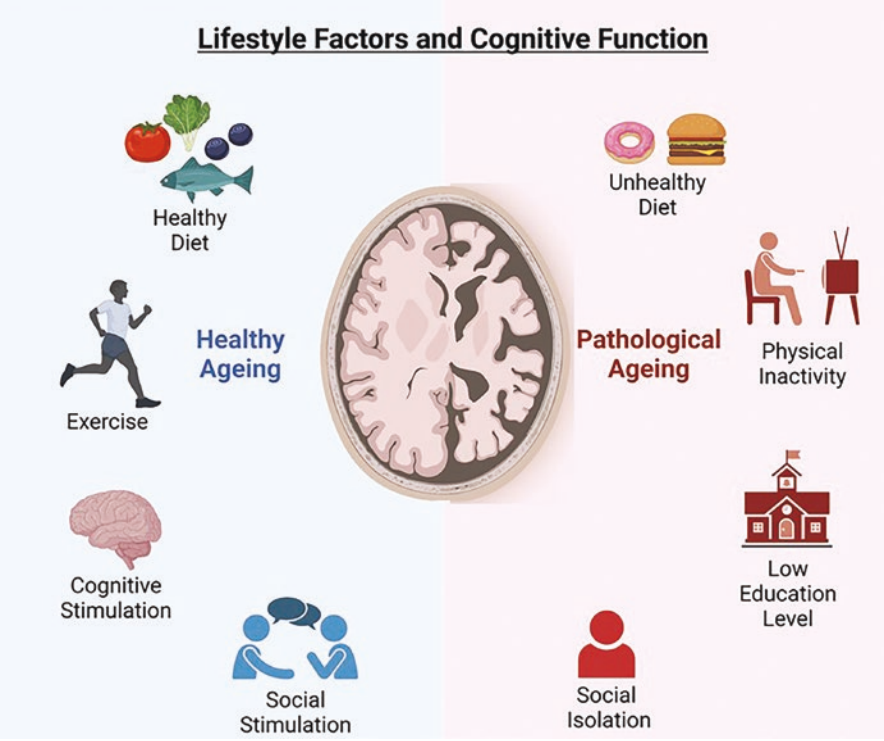

Fig. 5.1 Lifestyle factors associated with healthy and pathological ageing. (Figure created with BioRender)

Neurodegenerative Delay) diet, have become increasingly popular (Trichopoulou et al. 2003). This is supported by the World Health Organization and Public Health England, who are now promoting whole diet approaches to delay or prevent cognitive decline (Scientific Advisory Committee on Nutrition 2018; World Health Organisation 2019). The mechanistic basis by which diet exerts its neuroprotective actions is diverse and nutrient dependent. Dietary factors modulate a wide range of processes and pathways including neuroinflammation, endogenous antioxidant defence systems and gut microbiota structure and function, which will in turn affect learning/memory and ultimately cognitive function. Given the complexity of these interactions, the exact biological effects of many single nutrients remain unclear. This chapter aims to summarise current evidence and future directions of both single nutrient and combination dietary approaches in the context of healthy brain ageing (Table 5.1).

Table 5.1 Impact of the Mediterranean, MIND and DASH dietary patterns on health and cognitive function

Study	Dietary pattern	Participants	Findings
Gkotzamanis et al. (2022)	Mediterranean	The HELIAD study: 1226 adults over 65 years	Higher adherence to the Mediterranean dietary pattern was associated with more favourable trajectories in ageing
Tsivgoulis et al. (2013)	Mediterranean	REGARDS study: 17,478 participants 45 years and over with no history of cognitive impairment at baseline	Higher adherence to the Mediterranean diet correlated with lower incidences of cognitive impairment
Trichopoulou et al. (2003)	Mediterranean	22,043 adults from Greece	44-month follow-up showed higher adherence to the Mediterranean diet was significantly associated with a reduction in mortality
Féart et al. (2009)	Mediterranean	1410 participants 65 years and older	Higher Mediterranean diet adherence was linked with slower cognitive decline on the mini-mental state examination test only and was not associated with dementia
Wu and Sun (2017)	Mediterranean	Systematic review and meta-analysis of 9 cohorts with 34,168 participants	A linear relationship was found between Mediterranean diet score and incidence of cognitive decline
Rodríguez-Rejón et al. (2014)	Mediterranean	PREDIMED trial: 2866 non-diabetic participants	A Mediterranean diet supplemented with extra virgin olive oil or nuts lowers glycaemic load and glycaemic index
Berti et al. (2018)	Mediterranean	70 participants (30–60 years old)	Lower Mediterranean diet adherence was associated with progressive AD brain biomarker abnormalities
Gu et al. (2015)	Mediterranean	674 elderly adults without dementia	Mediterranean diet adherence was associated with less brain atrophy, equivalent to 5 years of ageing
Zbeida et al. (2014)	Mediterranean	Analysis of the US National Health and nutrition survey (NHANES) 1999-2002 and from the Israeli National Health and nutrition survey (MABAT ZAHAV) 2005–2006	Mediterranean diet adherence was associated with better health outcomes and cognitive functioning

(continued)

Table 5.1 (continued)

Study	Dietary pattern	Participants	Findings
Mosconi et al. (2014)	Mediterranean	52 cognitively healthy adults (mean age 54 years)	Lower adherence to the Mediterranean diet was associated with cortical thinning in similar regions to AD patients
Shannon et al. (2019)	Mediterranean	EPIC-Norfolk study: 8009 adults from the UK	The Mediterranean diet improved global cognitive function equivalent to 1.7 fewer years of cognitive ageing
Wengreen et al. (2013)	DASH and Mediterranean	3831 adults over 65 years	Greater adherence to both the DASH and Mediterranean dietary patterns was linked with higher cognitive function over 11 years
Tangney et al. (2014)	DASH and Mediterranean	826 memory and aging project participants	Both the DASH and Mediterranean diet patterns were linked with slower rates of cognitive decline
Haring et al. (2016)	DASH and Mediterranean	6425 postmenopausal women between the ages of 65–79	Adherence to the dietary patterns did not modify the risk of cognitive decline in a 9-year follow-up
Morris et al. (2015)	MIND	960 participants from the memory and aging project	The MIND diet was found to significantly slow cognitive decline (both global cognitive score and each of the five cognitive domains) with age
Melo van Lent et al. (2021)	MIND	2092 participants (mean age of 61 years)	Greater MIND diet adherence is linked with better cognitive performance and larger total brain volume, but not with cognitive decline
Arjmand et al. (2022)	MIND	50 healthy obese women	The MIND diet was associated with the reversal of the destructive effects of obesity on cognition and brain structure

5.2 The Gut Microbiota-Brain Axis, Nutrition and Ageing

The involvement of the gut microbiota in health and disease dramatically emerged over the last decade. It is becoming increasingly apparent that this involvement extends to cognitive function and neurodegenerative disease development. The gut microbiota, a dense population of 10^{14} microorganisms living in a mutualistic

relationship with their host, plays many important roles: shaping immune system development, metabolising dietary nutrients, forming vital bioactive compounds, digesting complex polysaccharides and synthesising essential vitamins. The intestinal microbiome is dynamic and rapidly responds to various intrinsic (e.g., genetics, immune response, metabolites) and extrinsic factors (e.g., diet, lifestyle, antibiotic intake). Diet can account for up to 57% of changes in gut microbiota composition (Clark and Mach 2016) and therefore is one of the most influential factors. Long-term dietary consumption modulates the structure and activity of the gut microbiota population, while the short-term intake of animal or plant products can overcome inter-individual variances in microbial gene expression and modify microbial community structure. Hence, an individual's microbial community is significantly impacted by their dietary intake, this community in turn shapes the individual's development and health, suggesting that diet can be used as a valuable therapeutic tool to promote human health, including cognitive disorders.

Dietary compounds can elicit a substantial influence upon cognition by communicating through a gut microbiota-brain axis. The gut microbiota-brain axis is a bidirectional communication system connecting the gut, liver, and central nervous system (CNS) that is modulated by the microbiome. The gut sends signals to the brain via numerous neurocrine, endocrine and neuroimmune mediated pathways, while the brain controls the secretory and sensory function of the gut. Once dietary components reach the gut, they are broken down by the gut microbiota to form key microbial-derived metabolites. These bioactive compounds exit the gut and enter the systemic circulation where they can induce direct effects by crossing into the brain or indirect effects by activating the vagus nerve.

As we age, gut microbiota composition and function changes. In humans, this has been correlated with a reduction in species diversity, a decline in Clostridiales and *Bifidobacterium* and an increase in Proteobacteria and pathobionts such as Enterobacteriaceae. While most of these changes are harmless, major shifts in composition, known as 'dysbiosis', can trigger harmful local and systemic inflammation, which are associated with shifts in gut-derived metabolites. For example, the abundance of *Bifidobacterium,* a commensal species that produces the important short-chain fatty acid metabolite from dietary fibres, is inversely related to inflammageing in the elderly population (Ragonnaud and Biragyn 2021). Older age is associated with an increase in dysbiosis, with pro-inflammatory gut microbiota populations increased, replacing more beneficial microbes. Together, these changes can have detrimental consequences and therefore identifying nutritional approaches to modulate the gut composition could assist with longevity.

5.3 Inflammation, Nutrition and Ageing

Inflammation is an essential process of innate (non-specific) immunity. Generally, inflammation is the local response reaction to injury, pathogens, irritants or oxidative stress, which stimulates increased blood flow, capillary dilation, leucocyte

infiltration and the production of host chemical mediators to remove toxic agents and restore damaged tissue. Importantly, the termination of inflammation requires both the production of cytokines and other anti-inflammatory mediators, as well as the elimination of pro-inflammatory pathways. Despite the essential role of inflammation in host immunity, when inflammation is prolonged (known as chronic low-grade inflammation) it becomes detrimental and is present in many chronic conditions such as type-2 diabetes, cardiovascular disease and even neurological disorders such as dementia. However, although the relationship between chronic conditions and inflammation is well recognised, the extent to which inflammation plays a role and its causation remains unclear.

Ageing is associated with the development of low-level systemic, chronic inflammation, known as 'inflammageing', a term coined by Claudio Franceschi in 2000. Inflammageing has been highlighted as a key factor that may promote and worsen cognitive decline in older adults, as baseline levels of inflammatory biomarkers have been found to increase with age (Sartori et al. 2012). Therefore, although inflammation with age may be a natural effect of immune senescence, it also increases the susceptibility of the host to pathogenesis, including in the brain. Studies also suggest modulatory factors of the immune response may become less effective as we age, decreasing the regulation of the immune response. This process may explain why we observe changes in cytokine profiles in elderly individuals (Kim et al. 2011), particularly proinflammatory cytokines such as interleukin-1 beta (IL-1β), tumor necrosis factor-alpha (TNF-α), and interleukin-6 (IL-6), which present in higher concentrations in brain regions such as the hippocampus and cortex.

In the mammalian brain, neuroinflammation activates microglia, macrophages and inflammatory mediators such as cytokines, chemokines and complement proteins, which in turn generate a significant number of pro-inflammatory factors that are detrimental to neuronal cells. Limbic and related neuronal structures, including the hippocampi and basal ganglia (brain regions that modulate key cognitive processes such as memory, attention, emotion, and perception) are comprised of a larger number of enzymes associated with the inflammatory response and consequently, are more at risk to progressive damage (Raz and Rodrigue 2006). Accumulating evidence also implicates low-grade chronic inflammation in the pathogenesis of neurodegenerative disorders. Amyloid plaque depositions and neurofibrillary tangles, two key pathological features of AD, are correlated with markers of inflammation. Ownby and colleagues also suggest AD patients may have increased body temperature, further associating the inflammatory processes (Ownby 2010).

Dietary compounds can modulate the neuroinflammatory process. Polyphenols, unsaturated fats and antioxidant vitamins have been found to inhibit oxidative stress and neuroinflammation, while saturated fats can promote inflammation, particularly in the hypothalamus. Westernised dietary patterns, including high fat and fibre deficiency, have been associated with neuroinflammation and neurodegeneration. As mentioned in the previous section, dietary patterns can significantly influence gut microbiota composition and as such can modulate brain function through the microbiota-gut-brain axis. For example, high-fat diet-induced gut microbiota

alterations can decrease cognitive function in mice. Furthermore, the transplantation of obese-type microbiota into healthy mice leads to intestinal barrier disruptions and increased cognitive dysfunction (Bruce-Keller et al. 2015). Gut microbiota can influence inflammatory responses in the brain by influencing microglia maturation and function, and therefore changes to the gut microbiota caused by diet can be a major modulator of the initiation of neuroinflammatory processes and subsequent dysfunction caused by this. Identifying a safe, cheap and easily implementable nutritional approach to regulate microbiota could therefore be of great importance to improve harmful aspects of the microbiota-gut-brain axis dysregulation, subsequently reducing neuroinflammation and cognitive impairment that arises with age. For example, in mice, microbiota-accessible carbohydrates prevented high-fat diet-induced cognitive impairment by preventing gut microbiota dysbiosis, increasing colonic mucus thickness, tight junction protein expression and decreased colonic systemic inflammation and neuroglial activation (Shi et al. 2020).

5.4 Individual Dietary Components

5.4.1 Dietary Polyphenols

Polyphenols are a diverse group of phytochemicals that are present in fruits, vegetables, nuts, seeds and other plant products. They are comprised of multiple hydroxyl groups on aromatic rings, forming two main groups, flavonoids and non-flavonoids, depending on the number and interaction of their phenol rings. Flavonoids, such as flavones (found in celery and parsley), flavonols (found in onions, broccoli and leeks), isoflavones (found in soy products), flavanones/flavanonols (found in citrus fruits and wine), flavonols (found in green tea and red wine) and anthocyanins (found in red wine and berries), consist of a C6-C3-C6 structure with two aromatic carbon rings, benzopyran (A and C rings) and benzene (B ring). The degree of oxidation of the C ring, the hydroxylation pattern of the ring structure and the substitution of the 3-position vary between subclasses of flavonoids. The non-flavonoid group is comprised of two classes known as phenolic acids (found in many fruits and vegetables) and stilbenes (found in grapes, wine and peanuts).

Epidemiological studies suggest polyphenols confer a broad variety of health benefits. For example, the intake of chocolate and tea was found to be inversely related to cardiovascular disease (Djoussé et al. 2011). Intervention trials also suggest cardiovascular benefits; however, the majority of these studies use coca-derived flavanols and modulate markers associated with inflammation, reducing incidences of atherosclerosis, insulin resistance, lipid profiles, blood pressure and vasodilation/endothelial function. Indeed, cardiovascular risk is intimately connected to cerebral blood flow and neuronal metabolism, and thus, they covary with the development of age-related cognitive impairment, AD, and mood.

Accumulating research is uncovering the beneficial properties of polyphenols in the CNS. They have been heavily associated with AD prevention via numerous pathways. First, polyphenols are suggested to be anti-amyloidogenic and therefore prevent the fibrillisation of amyloid beta (Aβ) both in in vivo and in vitro models. For example, gallic acid and catechin-rich grape seed polyphenol extract repressed cognitive decline corresponding with decreased concentrations of soluble oligomers of Aβ (Pasinetti et al. 2010). The mechanism underlying this process remains unclear, however, it is suggested that non-amyloidogenic processing of amyloid precursor protein (APP) may be increased by promoting the activity of α-secretase, an enzyme capable of cleaving APP at a site which avoids the formation of Aβ species and plaques, a hallmark feature of AD (Rezai-Zadeh et al. 2005). On the other hand, polyphenols may decrease Aβ plaque pathology by preventing amyloid aggregation and fibrillisation due to metal chelation activity (Mandel et al. 2007) or by promoting the formation of nontoxic oligomers. Second, they improve metabolic function, a process highly linked with AD and suggested to exacerbate neurological symptoms (Cai et al. 2012). Finally, polyphenols have a widespread neuroprotective role in the brain though exerting an anti-inflammatory, anti-apoptotic and antioxidant effect. They are implicated in a variety of vital pathways including the sirtuin-FoxO pathway, the NF-κB pathway, and the Nrf-2/ARE pathway associated with neuroprotective benefits (Vauzour 2012).

Curcumin is a polyphenol that forms a major component of the spice turmeric. Recent evidence highlights its neuroprotective benefits in humans and rodents. Indeed, curcumin displays anti-Aβ and anti-tau phosphorylation properties to protect against AD pathology, as well as playing a role in antioxidant, anti-cholesterol and anti-inflammatory activities. In adult mice, curcumin was found to increase the proliferation of hippocampal progenitor cells and improve spatial and non-spatial memory in high concentrations (Kim et al. 2008). Furthermore, curcumin has been linked with neurogenesis through the modulation of histone deacetylases and histone acetyltransferases (Kang et al. 2006). However, it is of note that curcumin's neuroprotective effects may be dose-dependent as curcumin has low bioavailability due to its hydrophobic nature and is reported as having sub-optimal systemic absorption from the gastrointestinal tract. Others report the benefits of curcumin may not solely rely on its bioavailability, but instead come from its interactions with the gut microbiota (Lopresti 2018). Together, these mechanisms in humans have led to significant improvements in attention, selective memory and visual memory when given twice a day (90 mg) (Small et al. 2018).

Berry fruits are also rich in polyphenols and commonly investigated regarding neuroprotective properties due to links with antioxidant, anti-inflammatory, microbiota modulation and cell-protecting effects. For example, blueberry intake has been associated with reduced oxidative stress, inhibition of inflammatory pathways and improve vascular health. The mechanisms underlying these protective effects have been attributed to a high anthocyanin content. Indeed, blueberry and strawberry extracts have been found to significantly reverse age-related declines in aged rodents, with improvements in working memory. In vitro, blueberries can also reduce the activation of the ERK1/2 pathway, a pathway that is stimulated from Aβ,

to inhibit Aβ aggregation. Whereas, in rodents, blueberry supplementation increased the proliferation of precursor cells in the dentate gyrus.

Overall, there is a large body of evidence demonstrating the neuroprotective and beneficial effects of polyphenols on brain health. As a result, polyphenols represent a promising treatment opportunity for the promotion of healthy ageing and the prevention of neurodegenerative diseases. However, there remain many challenges in the use and research of polyphenols. First, many studies highlight the hugely beneficial effects of polyphenols in vitro when supplied at a supraphysiological dosage. This means that in many cases, the research dosage cannot be achieved by normal food consumption in vivo and does not consider differences in bioavailability and bioactivity. Moreover, polyphenols can interact with the gut microbiota to produce a variety of microbial-derived metabolite products, which cannot be accounted for in in vitro studies. Therefore, moving studies into randomised controlled trials (RCTs) in humans is essential to extend our knowledge.

5.4.2 Polyunsaturated Fatty Acids

Polyunsaturated fatty acids (PUFAs) form essential elements of neuronal cell membranes, preserving membrane fluidity that is crucial for synaptic vesicle fusion and enabling neurotransmitter communication within neural networks. Additionally, membrane PUFAs form precursors for lipid messengers that stimulate signalling pathways that promote neuronal protection or neuronal dysfunction (Bazan 2005). However, as we age, the concentration of PUFAs in the hippocampus, cortex, and cerebellum, brain regions implicated in cognitive and motor processes, is reduced, with further decreases occurring in AD.

A variety of PUFAs perform different roles within the CNS and body. Each PUFA is characterised by an acyl chain consisting of one acid end (-COOH) and one methyl end (-CH_3). «Omega-3» (ω-3) reveals that the first double bond is located at the third carbon from the methyl end (H3C-C-C=), however, «omega-6» (ω-6) specifies that the double bond nearest to this end is at the sixth carbon. The most abundant PUFAs in the brain are arachidonic acid (ARA, 20:4(ω-6)), which consists of 20 carbon atoms with 4 double bonds, and docosahexaenoic acid (DHA, 22:6(ω-3)), which consists of 22 carbon atoms with 6 double bonds. Together, these two PUFAs account for approximately one-fifth of the brain's dry weight. The concentration of another important PUFA, eicosapentaenoic acid (EPA, 20:5(ω-3)), is relatively low due to it being quickly metabolised. Both ARA and DHA are needed for brain development and functioning. ARA is found in animal products such as eggs and meat, while DHA and EPA are found in oily fish and cod-liver oil. At birth, although the brain is fully developed, it is only 25% of its total adult volume. Therefore, as we grow, glial cells and neurons' axons and dendrite expand, and nerve fibres are myelinated. This expansion is greatly reliant upon long-chain PUFAs and therefore deficiencies can result in permanent mental deficiencies (Bentsen 2017).

In adults, the effect of PUFAs on cognitive functioning remains inconclusive. A recent meta-analysis of the cognitive effects of ω-3 PUFA supplementation in the general population showed no significant benefit, and may only have marginal effects on individuals who are PUFA deficient (Cooper et al. 2015). On the other hand, a three-month randomised double-blind intervention (EPA 270 mg + DHA 180 mg or placebo) in moderately malnourished Mexican school-aged children, indicated improvements in 11 of the 18 neuropsychological variables studies, including IQ scores, executive functioning, visuoperceptive capacity and processing speed (Portillo-Reyes et al. 2014). However, notably, these children had significantly lower baseline seafood intake than the meta-analysis.

In epidemiological studies, PUFAs from fish oils have frequently been associated with reduced AD and reduced cognitive decline (Joseph et al. 2009). DHA reduced Aβ 42 in AD mice (Lim et al. 2005) and production by cultured human neurons. It is suggested this may be due to a variety of mechanisms including changes in lipid raft structure (Stillwell et al. 2005), modifications in APP processing, initiation of anti-amyloidogenic chaperones for APP, and Aβ transthyretin. However, there is some evidence that PUFAs may have limited protection in *APOE4* carriers, the largest genetic risk factor of AD (Cole et al. 2009). PUFAs may also increase survival signalling as in vitro evidence suggests they can block Aβ oligomers toxicity, thereby protecting synaptic and dendritic function.

DHA and EPA have been found to decrease chronic inflammation by reducing NF-κB activation, which subsequently regulates the expression of pro-inflammatory cytokines TNF-α and IL-α and β. However, the specific mechanisms behind DHA and EPA's interaction with the NF-κB pathway remain unclear. During the ageing process, when inflammation is typically increased, ω-3 PUFAs concentrations are seen to be decreased, alongside neural membrane plasticity. Neurobiological studies found a markedly decreased concentration of DHA in the neural membrane of aged healthy individuals and patients with neurological dysfunction. However, these changes can be reversed by the intake of ω-3 PUFAs (Dyall et al. 2007). In rats, ω-3 PUFA supplementation can reverse age-related changes and maintains learning and memory performance (Farooqui et al. 2007). Overall, the results of the protective effects remain inconclusive. Future studies should perhaps examine cognitive outcomes associated with PUFAs in the context of genotype (e.g., *APOE*).

5.4.3 Vitamins

Vitamins are organic compounds that are critical for the normal functioning of cellular and physiological processes, as well as growth and development. All vitamins, except vitamin D, must be attained from the diet. In the developed world, vitamin supplements form the most chosen supplements, being taken by approximately a third of US and European populations (Li et al. 2010). However, ageing is linked with a higher risk for lower vitamin consumption (Thomas 2006).

Vitamin E (tocopherols) have been linked with decreases in cases of AD or dementia (Mangialasche et al. 2012). However, the supplementation of vitamin E did not show positive effects on the risk of AD. This may be as vitamin E supplements often only contain the α-tocopherol and not the range of vitamin E found in foods such as mangoes, spinach and tomatoes. Consequently, increased intakes of vitamin E from food sources were linked to a reduction in AD cases (Morris et al. 2005). The mechanism underlying vitamin E's beneficial properties is unclear, but may be related to its lipophilic antioxidant properties, as vitamin E can be transported across the blood-brain barrier by lipoproteins (Mardones and Rigotti 2004).

B vitamins play important roles at all levels of the brain as co-enzymes and precursors of co-factors in enzymatic processes. Sufficient concentrations of folate and B12 are necessary for the remethylation of the amino acid homocysteine, while B6 forms as a coenzyme in the metabolism of homocysteine to cysteine. High homocysteine levels (e.g., by a shortage of folate and/or vitamins B6, and B12) are suggested to increase dementia risk by promoting a range of negative effects on cellular, haemodynamic, oxidative and vascular factors (Kennedy and Haskell 2011). Importantly, vitamin B12 deficiency occurs in 5–20% of the elderly population (Andrès et al. 2004). Vitamin B6 also contributes to metabolic processes and is vital to the production of a variety of neurotransmitters, such as dopamine and serotonin, through its role as a cofactor for aromatic l-amino acid decarboxylase, an enzyme that catalyses the decarboxylation of a variety of aromatic l-amino acids. However, these beneficial effects do not seem to translate to clinical investigations. O'Leary and colleagues conducted a systematic review of 35 cohort studies, of which 21 were good quality. Of these 21, only seven studies showed beneficial associations between vitamin B12 and cognition (O'Leary et al. 2012). A meta-analysis of RCTs investigating the effect of vitamin B concluded overall that there was no underlying effect on cognition in individuals both with and without cognitive decline (Behrens et al. 2020). Nevertheless, the randomised, double-blind Folate after Coronary Intervention Trial (FACIT) study investigated 818 participants with daily folic acid and found a decrease in serum homocysteine concentrations and a significant increase in memory, processing speed and sensorimotor speed in comparison to a placebo group (Durga et al. 2007).

Vitamin C (ascorbic acid) is commonly obtained from citrus fruits and leafy vegetables and accumulates in high concentrations neuron dense areas in the brain, including the hippocampus, cortex and cerebellum. It plays a role as a powerful antioxidant, decreasing oxygen, sulfur and nitrogen-oxygen radicals produced through normal cellular metabolism, as well as converting additional radicals to their prior structures (e.g., tocopheroxyl to α-tocopherol). It is also involved in tyrosine, carnitine, catecholamine neurotransmitters and peptide hormones production and plays roles in neural maturation and the neuromodulation of the activity of acetylcholine and the catecholamine neurotransmitters (Kennedy and Haskell 2011).

Vitamin D is also heavily investigated in relation to cognitive function. It is estimated a large proportion of the general population, particularly the elderly, are

vitamin D deficient. Vitamin D receptors have been detected in the brain. It is suggested these may play a neuroprotective role through regulating neurons from excessive calcium entry, regulation of inducible nitric oxide synthase (iNOS), upregulation of the endogenous antioxidant glutathione, and improving synaptic function and nerve transmission in the neo-cortex and hippocampus via upregulation of neurotrophic factors (Buell and Dawson-Hughes 2008). The NAME (Nutrition and Memory in Elderly) study also supports these neuroprotective benefits of vitamin D, finding vitamin D concentrations <50 nmol/L were correlated with a greater prevalence of possible or probable AD (Scott et al. 2006).

5.5 Dietary Patterns and the Ageing Brain

5.5.1 The Mediterranean Diet

The Mediterranean diet refers to a diet composed of a high intake of fruits, vegetables, olive oil, whole grains and unsaturated fatty acids, moderate intake of fish, low to moderate intake of dairy products (in the form of yoghurt and cheese) and restricted consumption of red meats, but regular consumption of alcohol (especially wine) (Trichopoulou et al. 2003). This diet has been linked to reduced risk of numerous age-related diseases, including stroke, type 2 diabetes, and cardiovascular disease, which are all risk factors for dementia. Beneficial cognitive effects have been reported in elderly adults adhering to the Mediterranean diet, particularly in the domains of global cognition and episodic memory (Loughrey et al. 2017). Adherence to the Mediterranean diet is associated with a slower decline in cognition (Tsivgoulis et al. 2013), improved cognitive performance (Zbeida et al. 2014), decreased risk of cognitive impairment and reduced risk of MCI to AD conversion (Féart et al. 2010). In fact, a meta-analysis of 34,168 participants linked a high Mediterranean diet score to a 21% decreased risk of developing cognitive decline and a 40% decreased risk of AD (Wu and Sun 2017). Furthermore, when investigating where these beneficial effects may extend the ageing process, the Hellenic Longitudinal Investigation of Aging and Diet (HELIAD) study discovered that Mediterranean diet adherence was strongly associated with preserving or even improving healthy ageing status, independent of age, sex and lifestyle factors, suggesting this diet may promote longevity (Gkotzamanis et al. 2022). The benefits of the Mediterranean diet was also found to occur in non-Mediterranean countries, an analysis of an older UK population indicated high adherence to the Mediterranean diet improved global cognitive function equivalent to 1.7 fewer years of cognitive ageing (Shannon et al. 2019). However, the relationship between the Mediterranean diet and cognition is disputed, with some research studies finding no correlation (Psaltopoulou et al. 2008; Féart et al. 2009). Contradictory findings may occur due to heterogeneity in research methods, including dietary intake and cognitive status methods, follow-up time and population characteristics, which can hinder comparisons. For example, a systematic review highlighted a 30% increase in positive significant findings in

Mediterranean countries, in comparison to non-Mediterranean regions (Aridi et al. 2017).

Potential mechanisms underlying the protective effect of the Mediterranean diet include anti-inflammatory, antioxidant, and microbiome modulation due to the beneficial roles of major components of the dietary pattern, including fatty acids, vitamins, minerals, fibre and bioactive compounds (Fig. 5.2). The Mediterranean diet is high in fibre, omega-3, polyphenols, arginine, nitrate and melatonin, which have been associated mechanistically with improved cognition (Radd-Vagenas et al. 2018). The Mediterranean diet is also linked with a lessening glycaemic load (Rodríguez-Rejón et al. 2014), which is associated with better cognitive function in adults (Philippou and Constantinou 2014). Furthermore, a low calories Mediterranean diet was found to reduce circulatory advanced glycation end-products (AGEs) which are known to contribute to increased stress and inflammation (Rodríguez et al. 2015).

The Mediterranean diet is also linked to changes in neurological structure and brain integrity. Observational studies link Mediterranean diet adherence to increased cortical thickness (Mosconi et al. 2014), larger brain volume, reduced rates of hippocampal atrophy and improved structural connectivity (Gu et al. 2015), supporting the notion that the Mediterranean diet may protect against neurodegeneration. In fact, greater adherence has also been linked to a reduction in amyloid (Aβ) accumulation, a protein that forms senile plaques in early AD pathogenesis, in adults and the elderly (Berti et al. 2018).

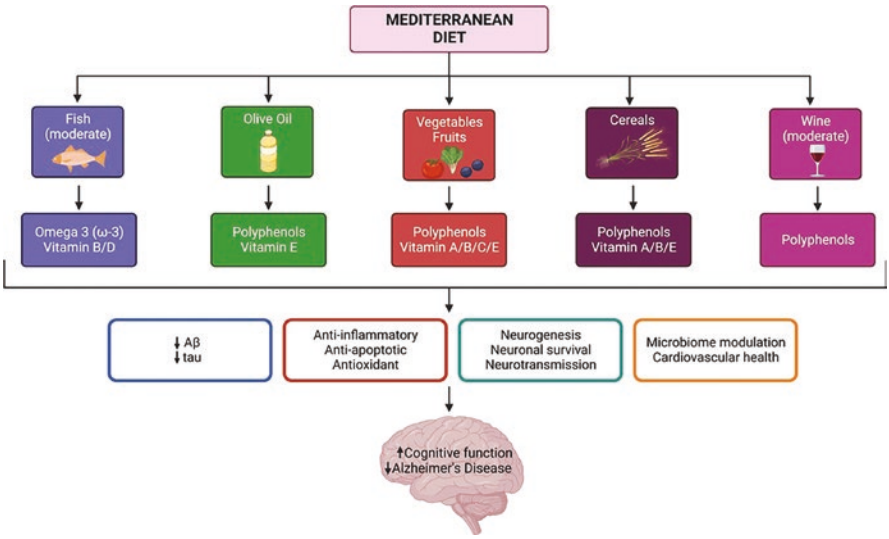

Fig. 5.2 Components of a Mediterranean diet pattern and potential mechanisms underlying their cognitive benefits. (Figure created with BioRender)

5.5.2 DASH

The Dietary Approaches to Stop Hypertension Diet (DASH), similarly to the Mediterranean diet, promotes a diet rich in fruits and vegetables, nuts and cereals. However, it places greater importance on a reduction in dairy products, sodium and alcohol consumption. DASH is currently recommended for improving cardiovascular health, however, more recently has been investigated for cognitive benefits. Greater adherence to the DASH diet has been associated with increased cognitive scores in adults (Wengreen et al. 2013), with reduced declines in cognition (Tangney et al. 2014). However, not all evidence supports these claims, with some comparative studies suggesting the Mediterranean diet and MIND dietary patterns have better impacts on cognition (Haring et al. 2016). This may be because the DASH diet does not alleviate symptoms of neurodegenerative disorders such as AD; but instead reduces the risk of disease occurrence by preventing cardiovascular disease, a risk factor of AD.

5.5.3 MIND

The combination of the DASH and the Mediterranean diet is known as the MIND diet (Mediterranean-DASH Intervention for Neurodegenerative Delay). Unlike the DASH diet, this dietary pattern was designed specifically to improve cognitive performance, while reducing the risk of developing neurodegenerative diseases based on findings from the diet-dementia field. The MIND diet promotes an intake of leafy green vegetables and berries up to six times a week, as these food products have been linked to better brain health. Similarly, to the Mediterranean and DASH diets, the MIND diet recommends the intake of vegetables, nuts, whole grains, as well as pulses, red wine and fish. On the other hand, it suggests restricting the consumption of red meats, cheese, sweets and fried foods. Research suggests that this combination approach is more effective in preventing dementia than the Mediterranean diet and DASH diet alone (Morris et al. 2015). Specifically, the MIND diet has been found to significantly improve global cognitive function, working memory, visual memory and verbal recognition memory, processing speeds and attention (Melo van Lent et al. 2021; Arjmand et al. 2022). MRI results suggest the MIND diet may also modulate neurobiology, increasing the surface area of the inferior frontal gyrus and total brain volume (Melo van Lent et al. 2021).

5.6 Conclusions

There is compelling evidence describing the neuroprotective potential of nutrition throughout the ageing process. The pathological manifestation of neurological conditions such as AD begins decades before clinical symptoms become

apparent. As such, the identification and implementation of suitable dietary interventions across an individual's lifespan could represent a cost-effective and efficacious preventative approach to curb disease incidence. Ageing is linked to an increase in oxidative stress, neuroinflammation and vascular dysfunction, the exacerbation of which can promote the development of age-related neurodegenerative diseases. Cell, animal and human epidemiological studies suggest that a diet rich in key nutrients such as long-chain ω-3 PUFAs, B vitamins, antioxidants such as vitamins C, E, carotenoids, and polyphenols is beneficial for the ageing brain. However, despite this, RCT evidence investigating these compounds often presents limited and/or contradictory outcomes. This may in part be due to underpowered studies (cognitive performance not the primary outcome), or a lack of adequate trial set-up (duration, dosage, target group or sensitivity) in the methodology to evaluate the effect of dietary compounds. In this regard, identifying relevant and sensitive biomarkers of disease progression becomes increasingly vital. For example, MRI and fMRI scans outline how changes in dietary interventions can affect neuronal brain structure. Furthermore, it is becoming increasingly apparent that large metabolic heterogeneity exists from factors such as genetics, epigenetics, microbiome and lifestyle, meaning individuals can differ in their requirements and responses to nutrients and bioactive molecules. Therefore, future research may look towards more personalised nutritional approaches by subcategorising the population based on markers of metabolic variation and use this knowledge to better estimate each group's dietary requirements for improved recommendations and interventions. Finally, current research methods into dietary intake often involve participants completing an in-depth food frequency questionnaire in which an individual may have to remember their intake of between 10–300 food items from the previous year. This may introduce inaccuracies to food intake measures and therefore multiple 24 h recalls and food records may be more expensive, yet appropriate. New technology such as web-based and smartphone food-based assessments are becoming increasingly popular as they can be easily accessible to large cohorts and reported near after the time of food consumption. However, as with all questionnaires, these methods are still suspectable to recall bias and self-reporting inaccuracies. Therefore, some studies turn to biomarkers as an accurate and unbiased measure. However, currently there is only a handful of validated food biomarkers, such as plasma vitamin C for fruits and vegetables, and as such are yet to cover the vast variety of the human diet.

Nevertheless, although significant work remains to fully develop comprehensive methods and uncover the complex role of nutrition as a modulator of ageing, the current evidence provides a promising outlook. Dietary changes, combined with other lifestyle factors and enrichment may provide the simplest and most efficacious method thus far. Intriguingly, although many of the mechanisms underpinning the beneficial impacts of these dietary approaches still need to be understood, it is evident that they incorporate reductions in oxidative/inflammatory stress signalling and increases in protective signalling to defend against the detrimental processes of ageing and promote healthy cognitive function.

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Chapter 6
Omega-3 Fatty Acids and Ageing Brain

Navya Sree Boga and Sanjay Basak

Abstract Inflammation plays a key role in the pathogenesis of age-related brain diseases. Hence, it is appropriate to target inflammation for disease prevention. The long-chain omega-3 polyunsaturated fatty acids (LCPUFAs), such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), play essential roles in supporting human health and offer protection due to their anti-inflammatory roles. Higher incorporation of DHA into the synaptic membrane improves signal transduction and increases the glutamatergic and dopaminergic synaptic activities. Despite several unsaturated double bonds in DHA, it can still empower its protection by the novel antioxidant defence in the brain. The molar ratio of DHA/ARA acts as an indicator of antioxidant defence. Excess n-6 LCPUFA like ARA levels has reflected the cells undergoing oxidative stress by increased lipid peroxides. Although intervention studies in older people could not establish an apparent causal effect with a disease state, nutritional factors like LCPUFAs showed promising benefits in delaying age-related brain disease. The review highlights the mechanism of brain dysfunctions & ageing and the roles of omega-3 fatty acids in its protection.

Keywords DHA · Brain dysfunctions · Ageing · Omega-3 · Neuroinflammation · Oxidative stress · MicroRNA

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Abbreviations

AD	Alzheimer's disease
ALP	Autophagy lysosomal pathway
ARA	Arachidonic acid, 20:4n-6
AREs	Antioxidant response elements
ASD	Autism Spectrum Disorder
ASEAN	Association of Southeast Asian Nations
ATP	Adenosine triphosphate
Aβ	Amyloid-beta
BBB	Blood-brain barrier
BDNF	Brain-derived neurotrophic factor
CAT	Catalase
COX2	Cyclooxygenase-2
CSF	Cerebrospinal fluid
DAMPs	Damage-associated molecular patterns
DHA	Docosahexaenoic acid, 22:6n-3
DMN	Default mode network
DNA	Deoxyribonucleic acid
DNMT1	DNA methyl transferases1
ECM	Extracellular matrix
EPA	Eicosapentaenoic acid, 20:5n-3
FAT	Fatty acid translocase
FATP-1	Fatty acid transport protein-1
FATP-4	Fatty acid transport protein-4
FC	Functional connectivity
GLA	Gamma linolenic acid
GSH	Glutathione
GSH-Px	Glutathione peroxidase
HD	Huntington's disease
IGF-1	Insulin-like growth-factor-1
IL-1β	Interleukin 1 beta
IL-6	Interleukin-6
JNK	C-Jun N-terminal kinase
LA	Linoleic acid, 18: 2n-6
LCPUFA	Long chain omega-3 polyunsaturated fatty acids
LOX	Lipoxygenase
LTP	Long-term potentiation
MAPK	Mitogen-activated protein kinase
MCI	Mild cognitive impairment
MIA	Maternal immune activation
miRNA	Micro RNAs
mPFC	Medial prefrontal cortex
MUFAs	Monounsaturated fatty acid

NADPH	Nicotinamide adenine dinucleotide phosphate
NO	Nitric oxide
NOS	Nitric oxide synthase
NOX	NADPH oxidase
Nrf2	Nuclear erythroid factor-2
PAMPs	Pathogen-associated molecular patterns
PCC	Posterior cingulate cortex
PC-DHA	Phosphatidylcholine-DHA
PD	Parkinson's disease
PE-DHA	Phosphatidylethanolamine-DHA
PFC	Prefrontal cortex
PLA2	Phosphatidylcholine 2-acylhydrolase
PRRs	Pattern recognition receptors
PUFA	Polyunsaturated fatty acids
RNS	Reactive nitrogen species
ROS	Reactive oxygen species
SERPINA5	Serpin Family A Member 5
SFA	Saturated fatty acid
TNF α	Tumour Necrosis Factor alpha
TrkB	Tropomyosin receptor kinase B
UPS	Ubiquitin proteasome system

6.1 Introduction

Ageing is a challenge to all living organisms. Ageing is considered the most significant risk for neurodegenerative disorders (Satoh et al. 2017). The progressive cellular damage, a gradual loss of functionality in tissues and organs, increases the vulnerability to diseases over time. Some declining processes such as defective repair mechanisms, aggregation of abnormal molecules and disturbed oxidative stress conditions lead to senescence (van Meer et al. 2008). Telomere shortening, mitochondrial dysfunction, genomic instability, DNA methylation, and dysregulated gene expression (Lee et al. 2017) are some of the hallmarks of the ageing process (Foster et al. 2019; Cole et al. 2019). It is essential to understand whether the cognitive decline during ageing is a normal consequence of ageing process or an indication of neurodegenerative diseases (Casaletto et al. 2019).

According to WHO, the global human life expectancy raised by 6 years from 66.8–73.4 years in the last 10 years. Asia is top in hosting a rapidly ageing population globally (Nations 2017). The average life expectancy in the Association of Southeast Asian Nations (ASEAN) is 71 years, and it rose to 75 years in Thailand, China and South Korea. The current Indian life expectancy is 70.19 years, showing a significant increase from the last few years (Lau et al. 2010). But with the increase in expectancy, a healthy life expectancy is not increasing at the same pace.

The brain, a complex human organ, comprises primarily two types of cells, i.e. neurons and glia. Glial cells provide structural and metabolic support, insulation, and coordination in development. Neuronal cells transmit signals over a long distance to specific targets. Mitochondrial dysfunction is a common pathology for brain ageing and neurodegenerative diseases in AD, PD, and Huntington's (HD). The lowered efficiency in mitochondrial energy coupling and function is correlated with alterations in the capacity of respiratory enzymes, mitochondrial content, or changes in enzyme activities. The impaired mitochondrial functions result in oxidative stress, exposure to mitochondrial permeability transition pores, and enhanced apoptosis of neuronal cells.

The brain represents 2% of body mass but utilises 20% of total oxygen demands making this organ susceptible to oxidative damage, which is predominant in the pathophysiology in the progression of several neurodegenerative disorders in ageing. Moreover, the brain contains high levels of lipids (60–65%), and modest antioxidant systems make it vulnerable to oxidative stress. Neurological oxidative stress has induced either failure of antioxidant protection or overproduction of reactive oxygen species (ROS) formed during mitochondrial dysfunction.

Brain membrane enriched with glycerophospholipid that contains saturated fatty acid (SFA) at the sn-1 position of glycerol moiety and PUFA (ARA or DHA) present at the sn-2 position. ARA, present in neuronal phospholipids, undergoes oxidation either by enzymatic or non-enzymatic pathways. ARA is released and oxidised by PLA2 and COX2, while non-enzymatic oxidation of ARA results in the production of ROS, pro-inflammatory cytokines, and elevated levels of n-6 fatty acids derived metabolites. The review will emphasise the latest data on brain dysfunctions during ageing and omega-3 fatty acids' roles in its protection.

6.2 Brain and Age-Related Disorders

6.2.1 Structure, Functions and Brain Maintenance

The brain develops in the third week of gestation and changes as life progresses. The human brain can be macro-anatomically divided into six lobes: frontal, parietal, temporal, occipital, limbic and insular. The structure and functions of the human brain exhibits a marked change with ageing. As age advances, the brain's volume and the cortices' thickness decrease (Raz et al. 2010). However, the shrinkage of the brain varies significantly among different individuals depending on different genetic and environmental factors. Even within a person, the shrinkage is not uniform throughout the brain. Some areas show more rapid shrinkage than other areas. During ageing, the cingulate gyrus area 24, and inferior temporal cortex area 20 are the most affected brain regions and they exhibit notable variations in fatty acid profiles with ageing (Mota-Martorell et al. 2022). During ageing, the forebrain is more susceptible to ageing complications, followed by the midbrain showing few changes in substantia nigra region. The hindbrain is unaffected by the ageing process. The

reason for some regions of the brain's high vulnerability to ageing is still unknown, and more studies are needed (Mota-Martorell et al. 2022). The 'last in, first out' theory of the brain proposes that the complex areas of the brain which take a longer period to develop are the regions which are more vulnerable to the ageing consequences and degenerate early. Neural stem cells proliferate continuously throughout life in the brain and are responsible for brain plasticity, memory and learning. But with mid-age onset, neural stem cell proliferation declines and neuronal output decreases (Apple et al. 2017). When the brain parts start shrinking with age, the nerve fibres they contain also start shrinking, which complicates the neurotransmitter system affecting the transport of signals from the brain to different parts of the body. Brain development occurs in a back-front pattern, leaving the prefrontal cortex's last part to develop. The prefrontal cortex, responsible for controlling cognitive functions and impulses and for creating and executing plans, is the one to develop last and is the most disrupted region of the brain during ageing. The degeneration of the prefrontal cortex may result in disturbing emotional responses such as more aggressive behaviour and difficulty in initiating new activities. With brain ages, the microglia are activated and primed to produce small impulses, which results in brain damage and neuronal death (Clegg et al. 2013).

The hippocampus is another region at risk of reduced volume and degeneration with ageing. Hippocampus formation is associated with memory consolidation, processing and regulating emotional behaviour. It is considered the critical mediator in the pathophysiology of cognitive impairment during ageing. With ageing, oxidative stress and neuroinflammation increase in the hippocampus. Hippocampus is also expected to be one of the early sites of neurofibrillary tangles development. The SERPINA5 gene is responsible for the hippocampal vulnerability in Alzheimer's disease (AD). SERPINA5 plays a role in blood coagulation and thrombosis. Recent studies disclosed that this gene plays a crucial role in AD pathogenesis and is also associated with neurofibrillary tangle pathology (Crist et al. 2021). Different parts of the brain regions and their degree of degeneration with ageing are depicted in Fig. 6.1.

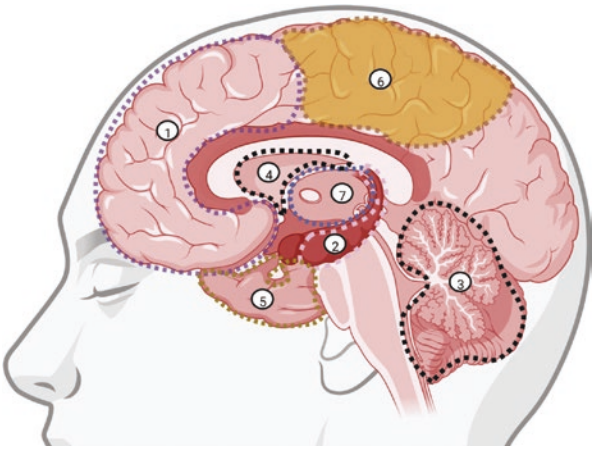

Fig. 6.1 Different parts of the brain regions are numbered in descending order to their degree of degeneration with ageing. 1. Prefrontal cortex; 2. Hippocampus; 3. Cerebellum; 4. Striatum; 5. Temporal lobe; 6. Parietal lobe; 7. Thalamus

6.2.2 Ageing and Brain Functions

Several brain functions, including circadian behaviour, cognition, autonomic function and emotion, diminish with age and affect the quality of life in social and cognitive aspects. The multiple processes associated with ageing can be divided into primary and secondary ageing. The inherent or the hereditary factors of decrement constitute primary ageing, and the defects acquired due to adverse conditions such as diseases and trauma collectively constitute secondary ageing factors (Hung et al. 2010). The difference between chronologic age and brain age is described as the 'brain age gap', which acts as the marker of brain health (Cole and Franke 2017). A higher brain age gap is associated with poor cognitive phenotypes and is raised in many brain disorders (Kaufmann et al. 2019). There are also credible associations between cardiometabolic risk factors such as phosphate, potassium, systolic and diastolic blood pressure, total cholesterol and age-associated neurodegenerative disorders (Beck et al. 2022).

During ageing, irreplaceable loss of cells occurs noticeably in the heart, brain and skeletal muscles. In the brain, loss of neurons, particularly in vulnerable regions such as the hypothalamus, may alter the metabolism and cause emotional and mental aberrations in the elderly. Antioxidant defence mechanisms decline during ageing, which may accumulate oxidative damage. In the early stages of life, more than a million neural connections are formed by the brain every second. But with the increasing age between 20–60 years, brain weight decreases by about 0.1% per year and the loss is more rapid after that. The reduction of volume is more dominant in the prefrontal cortex and hippocampus while least in the occipital cortex (Peters 2006). Hippocampus and frontal cortex perform cognitive functions and their shrinking affects cognitive abilities. The brain's outer layer, the cerebral cortex, also lessens with age. This low density of cortex results in fewer networks contributing to lowered cognitive processing. The space vacated by the reduced brain volume is filled with the expanding ventricular system and the CSF (cerebrospinal fluid) (Esiri 2007).

6.2.3 Brain Dysfunctions and Their Causalities

As proteins carry out biological activities of the cells, any imbalance in protein homeostasis affects the regular body functions (Xie et al. 2021). Errors in translational and post-translational processes lead to misfolding of more than 30% of newly synthesised proteins. These proteins are recognised by molecular chaperons and attempted to refold. When refolding of those proteins is not possible, ubiquitin proteasome system (UPS) and autophagy lysosomal pathway (ALP) are responsible for their cellular clearance (Schubert et al. 2000). If the misfolded proteins are left uncleared, they may alter the three-dimensional structures of proteins and impairs their biological functions. The autophagy-lysosomal pathway and the

ubiquitin-proteasome system, which are responsible for clearing misfolded proteins in the brain, may decline with age and this result in neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's and Huntington's disease (Loeffler 2019). With ageing, the regulation of gene expression and protein degradation is disrupted, and aggregated proteins' accretion is observed in all organisms. But in neurodegenerative diseases such as AD and Parkinson's, specific proteins such as amyloid-β and α-synuclein accumulation are amplified and observed as the hallmarks of those diseases (Kepchia et al. 2020).

Functional connectivity networks in the brain are crucial in maintaining interactions between different brain regions. The emergence of functional connectivity (FC) networks in the fetal brain starts during the third trimester and increases with age up to young adulthood (around 20 years). It stabilises during adulthood (around 30–40 years) and after 40 years, FC starts declining. This decline primarily involves the reduction in connections within the network connectivity, and it expands to reductions between the networks with progressing age (>60 years) (Edde et al. 2021). The interconnectivity networks supervise a range of diverse cognitive roles, and they are categorised as task-positive and task-negative networks (DeSerisy et al. 2021). Task positive network comprises frontoparietal, dorsal, ventral attention and cingulo-opercular networks. Their activity increases with an increase in task performance and cognitive demand. Contrary to them is DMN (Default Mode Network), whose activity increases when brain is not performing any specific task. One such network is DMN, in which mPFC (medial prefrontal cortex) is one of the central nodes (Jobson et al. 2021). With ageing, a consistent reduction in functional connectivity between mPFC-PCC (posterior cingulate cortex) regions are observed. Many pioneering studies have shown that with reduced functional connectivity between anterior mPFC and posterior DMN, the white and grey matter measures are decreased in cingulum tract and in brain regions with high vulnerability to age (Vidal-Piñeiro et al. 2014). Some studies showed that the reduction in connectivity strength is observed especially in ventral DMN, which includes the hippocampus. As hippocampus is the key memory region, this is assumed as one of the reasons for decreased memory in aged individuals (Huang et al. 2015). Any break in the balance between the integration of brain networks leads to reduced cognitive efficiency of the brain.

Several biological processes such as metabolic dysregulation, increased inflammation, immune reaction and oxidative stress, which are associated with depression, are also reported in ageing, proposing that major depression and accelerated ageing may be associated (M. Wolkowitz et al. 2011). Data supported the notion that distinctive microglial phenotypes are harboured by the aged human brain (Olah et al. 2018). The brain possesses an extracellular matrix (ECM) comprising perineuronal nets enveloping neurons, a basement membrane surrounding blood vessels and an interstitial matrix. The ECM regulates ion homeostasis, controls synaptic plasticity and has a role in regulating neuronal and glial functions. Ageing may alter the structural composition or stiffness of ECM, which may contribute to developing neurodegenerative diseases (Hall et al. 2021).

6.3 Oxidative Stress and Ageing Brain

Reactive oxygen species (ROS) are essential for normal physiological functions but turn toxic at higher concentrations (Ionescu-Tucker and Cotman 2021). In normal conditions, any adverse effects of ROS are neutralised by antioxidant defensive mechanisms. Any imbalance in this relationship due to excessive production of reactive oxygen (ROS) and nitrogen species (RNS) and an inefficacious scavenger system can result in oxidative stress (Song et al. 2020). Nucleic acids, proteins and lipids are damaged when reacted with excess ROS and accumulate in various organs resulting in their age-related functional decline. Oxidative stress also contributes to age-related conditions such as neurodegenerative diseases, chronic kidney and pulmonary diseases and cardiovascular diseases (Liguori et al. 2018).

6.3.1 Brain and Protection of Oxidative Stress

Oxidative stress is considered a self-propagating phenomenon as the macromolecules damaged by excessive ROS, may become or behave as ROS. Excessive ROS production in the brain causes immense protein oxidation and lipid peroxidation resulting in cellular degeneration and functional decline. ROS also alters brain morphology by increasing blood-brain barrier permeability leading to neuroinflammation and neuronal death (Salim 2017). Higher molecular mass antioxidant enzymes and low molecular mass antioxidants act as protective mechanisms that operate in the brain to challenge excessive ROS. Higher molecular mass antioxidant enzymes like superoxide dismutase coverts superoxide radicles to H_2O_2 by facilitating spontaneous dismutation and the formed H_2O_2 is further removed by glutathione peroxidase (GSH-Px) and catalase (CAT) enzymes (Salim 2017; Liguori et al. 2018). Glutathione, anthocyanins, carotenoids, vitamin A and C constitute lower molecular mass antioxidants (Garaschuk et al. 2018). Studies have reported that an elevated oxidative stress markers in the cerebral spinal fluid and brain tissue of mild cognitive impairment (MCI) and Alzheimer's disease (AD) patients indicating that oxidative stress may contribute to the pathology of AD (Di Domenico et al. 2016).

Nuclear erythroid factor-2 (Nrf2) is a stress-responsive transcription factor that regulates antioxidant gene expression through antioxidant response elements (AREs). Recent studies showed that omega-3 PUFAs can promote in raising Nrf2 expression and provide antioxidant defence. Particularly DHA alone or with vitamin E, is found to be capable of inhibiting oxidative damage and cell toxicity (Huang et al. 2019). Nrf2 and other antioxidants decrease in human brain with ageing, enhancing the risk factors such as oxidative stress, neuro inflammations and DNA damage (Zhang et al. 2015). A comparison of defensive and degenerative mechanisms in healthy vs. aged brain are illustrated in the Fig. 6.2.

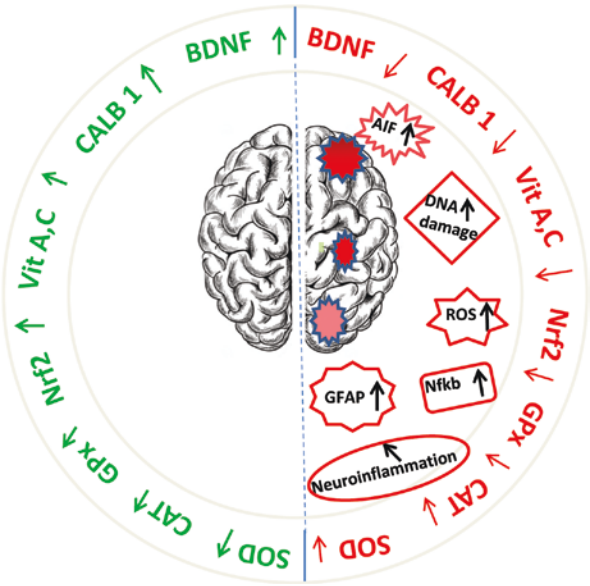

Fig. 6.2 Adequate levels of antioxidants (SOD, CAT, and GPx) and vitamins (A and C), activated transcription factors (Nrf2), calcium-binding protein (CALB1), growth factor (BDNF) maintain homeostasis in the healthy brain (left half) and these are diminished with ageing (right half). Green arrows indicate an increase, and red arrows indicate a decrease. *SOD* superoxide dismutase, *CAT* catalase, *GPx* glutathione peroxidases, *Nrf2* nuclear factor erythroid 2–related factor 2, *CALB1* calbindin 1, *BDNF* brain-derived neurotrophic factor, *GFAP* Glial fibrillary acidic protein, *AIF* Apoptosis-inducing factor, *ROS* reactive oxygen species, *NFkB* Nuclear factor kappa-light-chain-enhancer of activated B cells

6.3.2 *Factors Promoting Oxidative Stress in the Brain*

The brain's high oxygen consumption and higher lipid content make it more vulnerable to oxidative stress (Salim 2017). The high ATP requirement of the brain demands oxidation of lipids generating ROS. NADPH oxidase (NOX) is a cluster of enzymes that generate ROS in pro-inflammatory conditions, or during phagocytosis. In neuronal pathology, the expression of NOX1, NOX2, NOX3, and NOX4 is induced, mediating the oxidative burst releasing O_2^{-} and H_2O_2 (Simpson and Oliver 2020). One reason for the brain's susceptibility to oxidative stress is that the ROS produced by NOX2 or its isoforms are important in maintaining essential neural progenitors and regulating long-term hippocampal potentiation and NOX2 deletion leads to cognitive impairment in mice (Kishida et al. 2006). Ca^{+2} signalling in the brain may also contribute to oxidative stress as, in the presence of sufficient O_2 and NADPH. Ca^{+2} synthesises nitric oxide (NO^{-}) by nitric oxide synthase (NOS) (Cobley et al. 2018). Glutamate, which plays a role in learning and memory, is also a source of oxidative stress generation in brain. Excessive glutamate can inhibit system Xc- cystine/glutamate antiporter, which mediates the exchange of

intracellular glutamate and extracellular cystine. Cystine is reduced to cysteine and used for the de novo synthesis of glutathione (GSH) which is important in brain antioxidant defence mechanisms. Excess glutamate's interference in cystine intake depletes intracellular GSH and causes oxidative stress. Excess glucose uptake by the brain to maintain neuronal activities, and oxidative phosphorylation by mitochondria can be factors for generating oxidative stress. Redox-active transition metals, ample in the brain, can accumulate free radical generation by auto-oxidation of neurotransmitters like dopamine.

6.3.3 Mechanism of Oxidative Stress in Ageing Brain

Mitochondrial dysfunction and glucose hypometabolism are the initial symptoms of age-associated disorders in brain (Castelli et al. 2019). The brain continuously demands high glucose for maintaining synaptic ion gradients and for the resting potential of neurons. But during ageing, mitochondrial functional ability and glucose availability are altered, disturbing neuronal glucose uptake, increasing oxidant production and reducing electron ⁻ transport chain activity.

Elevated intracellular free radicals affect ageing, which can induce mitochondrial dysfunction, leading to altered cellular functions and impairing neuronal metabolism. Mitochondria and NOX systems are considered prime factors involved in the excessive generation of cellular oxidative stress (Leyane et al. 2022). Elevated NOX expression is reported in chronic degenerative diseases (Egea et al. 2017). Oxidative imbalance is thought to induce the development and advancement of Alzheimer's disease. When neuronal mitochondrial metabolism is impaired, it reduces ATP generation raising oxygen free radicles and accumulating the Aβ (amyloid-beta) fragments (Menzies et al. 2017). This Aβ accumulation and hyperphosphorylation of tau proteins stimulates c-Jun N-terminal kinase (JNK)/p38 MAPK signalling cascades and elevates ROS generation (Leyane et al. 2022). Nrf2, which upregulates antioxidant defences during oxidative stress, is functionally impaired in AD. Although the mechanism of how ROS damages the cerebral tissue is not clear, it activates different molecular signalling pathways like neuroinflammation and causes neuronal death. Neurons exhibit differential susceptibility to oxidative stress, and the hippocampus, amygdala, and cerebellar granule cells are the most affected (Castelli et al. 2019).

6.4 Lipids and Their Importance in the Brain

The importance of lipids in the human body is supported by the fact that 5% of all the genes in the human body are dedicated to lipid synthesis (van Meer et al. 2008). More than 1000 different species of lipids can be found in any eukaryotic cell with variations in aliphatic chains and head groups (van Meer et al. 2008). After adipose

tissue, brain is the organ in the human body with higher lipid content constituting half of its dry weight (Bourre 2009) and 10–12% of fresh weight (Jové et al. 2019). In the central nervous system, oligodendrocytes form a myelin sheath with 40 or more compactly wrapped lipid bilayers lining the neurons. The composition of myelin is 70–85% of lipids and 15–30% of proteins (Poitelon et al. 2020). The main lipid species present in human brain are fatty acids, glycerolipids, glycerophospholipids, sphingolipids and sterol lipids (Jové et al. 2019).

Dysregulated lipid metabolism is also considered a factor that contributes to neurological disorders or central nervous system damage (Shamim et al. 2018). The changes in global lipid concentrations are observed in human brain ageing and in cognitive diseases such as Schizophrenia, Down syndrome and Autism Spectrum Disorder (ASD) (Yu et al. 2020). Cholesterol plays a vital role in aetiology of Alzheimer's (AD) disease, which is a form of dementia. In brain, cholesterol is carried by 'Apolipoprotein E' and the gene encoding for ApoE4 is identified as a crucial risk factor for AD, indicating the role of cholesterol in the pathology of AD.

6.4.1 Fatty Acids and Their Requirement in the Brain Structure

Dietary fats influence brain health and constitute an essential part of human nutrition. Fatty acids are the building blocks of lipids and play a major role in the structure and function of the brain (Mallick et al. 2021). In addition to metabolic energy contributors, brain fatty acids or their metabolites exhibit neuroprotective and anti-inflammatory roles (Romano et al. 2017). Free fatty acids in adipocytes and circulating triacylglycerols undergo lipolysis and release long chain fatty acids (LCFAs), which bind to plasma albumin. Although diffusion of LCFAs across the membrane occurs according to the concentration gradient, this passive uptake is too low to satisfy the tissue's fatty acid demand. So active cellular uptake of LCFAs involves multiple chaperon proteins such as fatty acid translocase (FAT), plasma membrane fatty acid binding protein, and six fatty acid transport proteins (Mallick et al. 2021). While the brain can synthesise saturated and monounsaturated fatty acids (MUFAs), polyunsaturated fatty acids (PUFAs) need to be supplied by the blood. The transport of fatty acids across the blood-brain barrier (BBB) is an intricate process (Duttaroy 2009). It is mediated by protein-mediated transporters, primarily by fatty acid transport protein-1 (FATP-1) and fatty acid transport protein-4 (FATP-4) (Romano et al. 2017). The involvement of BBB in fatty acid transport becomes crucial during infancy and in ageing as these two stages are associated with immature BBB and structurally altered BBB, respectively.

PUFAs plays a vital role as nutrients for alleviating diseases. Omega-3 and omega-6 PUFAs maintain structure and function of cell membranes in the brain (Mallick et al. 2019). Among PUFAs, omega-3 and omega-6 fatty acids are considered as essential as they cannot be produced in the human body and should be

consumed through diet. Human body can use the 18-carbon ω-3 fatty acid, as the precursor and undergo elongation, desaturation and β-oxidation processes to synthesise eicosapentaenoic acid (EPA), a 20-carbon unsaturated ω-3 fatty acid and then synthesise docosahexaenoic acid (22; 6n-3) from EPA. But the ability of the human body to elongate and desaturase the short chain fatty acids is limited. So, it is essential to acquire ω-3 fatty acids from dietary sources. ω-3 fatty acids are obtained from dark vegetables, plant oils, marine fish and their oils. In the bloodstream, EPA and DHA can be present in non-esterified form bound to albumin or esterified into triacylglycerol, phospholipids and as cholesteryl esters as components of lipoproteins. EPA and DHA may be circulating in the bloodstream, or stored in adipose tissue or membrane bound.

Linoleic acid (LA, 18; 2n-6) and arachidonic acid (ARA) are the main omega-6 fatty acids while linolenic acid (ALA, 18; 3 n-3) is the precursor of long chain omega-3 fatty acids. Vegetable oils like sunflower and soybean contain higher quantity of omega-6 fatty acids and lower quantities of omega-3 fatty acids. LCPUFAs such as ARA, DHA and EPA have the capability to alter cell membrane composition and regulate the transcription and cell signalling. Particularly, long chain omega-3 polyunsaturated fatty acids (omega-3 LCPUFA acquired increasing interest as they are credited with neuroprotective and health-promoting properties (Zirpoli et al. 2020). EPA and DHA are the precursors of Resolvin E and Resolvin D which acts as anti-inflammatory lipid mediators. In humans and rats, Lysophosphatidylcholine-DHA is a circulating form of DHA (Hachem et al. 2020). Generally, DHA is present in higher concentrations than EPA, but in specific regions of brain and eye, the contribution of DHA is significantly high and EPA is almost absent (Duttaroy 2016).

6.4.2 Omega-3 and Omega-6 Fatty Acids and Brain Development

Omega-3 and omega-6 are the two families of PUFAs, constitute 30–35% of brain's fatty acid content (Wood et al. 2022). The beneficial effect of omega-3 fatty acids in improving cognitive functions in age-related mild cognitive impairment (MCI) or cognitive decline is supported by several studies (Bowman et al. 2019). From the gut, dietary PUFAs absorbed into bloodstream, can either be converted into LCPUFAs or may undergo β-oxidation for energy production. There is a competition between omega-3 and omega-6 PUFA as they share the same metabolic pathways and enzymes to synthesise long chain PUFAs (Layé et al. 2018). In the brain, omega-3 and omega-6 fatty acids undergo esterification at the sn-2 position into phospholipids, which are essential to maintain cell membrane structure and functions (Layé et al. 2018). DHA is essential for eye, and brain development, and it impacts on neuro development and mental health from the fetal development to adulthood (Basak et al. 2021; Basak et al. 2020a). In humans, DHA accumulation occurs primarily during the third trimester and 6–10 months after birth. When

infectious stimuli trigger maternal immune activation (MIA), a cascade of cytokines and altered immune cells are transmitted to the fetus via placenta, amniotic fluid and maternal serum (Minakova and Warner 2018). The fetal and maternal inflammatory responses to MIA can cause later life defects in hippocampal connectivity networks affecting memory behaviour in the offspring (Labrousse et al. 2018) and may increase the possibility of neurodevelopmental disorders such as autism and schizophrenia (Han et al. 2021). DHA targets the microglia, the primary innate immune cells in brain, and lowers the production of proinflammatory cytokines, TNFα, IL-6, IL-1β (Labrousse et al. 2018), protecting MIA. It is suggested that a balanced intake of omega-3 fatty acids such as ALA, EPA, DHA and omega-6 fatty acids such as linoleic acid (LA), gamma linolenic acid (GLA), ARA may contribute to a reduction in inflammation and oxidative stress in aged individuals (Simonetto et al. 2019).

Ageing corresponds to lowered antioxidants in the body, a rise in inflammatory reactions and abnormal redox homeostasis (Dolopikou et al. 2020). A recent cohort study on cognitive abilities and dementia has also shown that blood DHA levels positively impact cognitive functions and can lower the risk of Alzheimer's disease and dementia (van der Lee et al. 2018). Many neurophysiological functions such as cell survival, cellular signalling, neuroinflammation, and protection of BBB integrity are attributed to DHA (Basak and Mallick 2020). Because of its crucial role, any alteration to DHA metabolism affects neurological and psychiatric conditions.

6.4.3 Omega-3 Deficiency and Brain Development

Recently, it has been revealed that microglia are associated with brain maturation and immunogenic functions (Bilbo et al. 2018). In regular conditions, microglia function activity-dependently and guide axons, phagocytes, and apoptotic neurons (Shigemoto-Mogami et al. 2014). But any imbalance in nutritional intake of fatty acids, MIA obstruct these processes and results in behavioural defects (Madore et al. 2020). N-3 PUFA deficiency exacerbates the consequences of MIA on microglia and alters the oligodendrocyte expression in the developing brain (Leyrolle et al. 2021).

Brain-derived neurotrophic factor (BDNF) is a growth factor essential for brain functions and maintaining plasticity all through the lifespan. BDNF is expressed in the mammalian brain by binding to its receptor TrkB (tropomyosin receptor kinase B) (Bhatia et al. 2011). Any deviations in BDNF signalling and activity of TrkB receptor might result in anxiety and depression-like conditions (Castrén et al. 2007). It is evident that, deficiency of DHA during gestation, lactation and infancy enhances the risk of anxiety-like behaviour in later life. And brain DHA levels proportionally influenced BDNF signalling through TrkB. DHA deficiency caused a reduction in BDNF-related synaptic plasticity in frontal cortex, hypothalamus and hippocampus. This implies that DHA consumption during early life can influence mental health in adulthood (Bhatia et al. 2011). Long-term potentiation (LTP), which is the process of strengthening the synaptic connections between the neurons, is reduced in ageing

brain. The NR2B subunit of N-methyl-D-aspartate (NMDA) glutamate receptor is significantly involved in synaptic mechanisms of spatial memory such as LTP. Diets rich in DHA and EPA have the potential to reverse the damage of NR2B with ageing (Cutuli 2017).

6.5 Omega-3 Fatty Acids, Neuroinflammation and Ageing Brain

In older adults >65 years, 15–20% are affected by age-associated cognitive decline. Although the exact mechanisms deviating the healthy ageing process are not completely known, inflammation is proven to be notably involved.

6.5.1 Ageing and Brain Inflammation

With brain ageing, the central nervous system suffers chronic low-grade inflammation, which alters the morphology and functions of many neuronal cells, including microglia. With the help of pattern recognition receptors (PRRs), microglial cells recognise pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) and initiate immune responses. Aged microglia get primed and overproduces the inflammatory markers, lowering its homeostasis capacity. This rise in age-related immune responses develops cognitive deficits, and diminished synaptic plasticity (Joffre et al. 2020) and loss of homeostasis, leading to unhealthy brain ageing. Many studies reveal that inflammation during ageing marked by microglial priming and pro-inflammatory cytokine production contributes to age-associated cognitive decline.

6.5.2 Neuroinflammation and Brain Disorders

Neuroinflammation is initiated in response to infections, stress or neurodegenerative disorders. Although the purpose of this neuroinflammatory response is to exhibit protection from stimuli, it may turn detrimental and spread widely, bypassing the altered blood-brain barrier in any infection condition or with ageing. Inflammation-mediated immune mechanisms are risk factor for psychiatric diseases such as schizophrenia. Increased inflammation is also associated with reduced connectivity in reward-related brain regions in unmedicated depression patients. Reduced connectivity between dorsal, ventral striatum and ventromedial prefrontal cortex results in psychomotor slowing and anhedonia (Thibaut 2017). The continuous inflammatory mechanism in AD brains causes neuronal loss and alterations in astrocytes, cytokines, microglia and mitochondria. These alterations represent early

onset symptoms of neurodegeneration (Skaper et al. 2018). The elevated serum pro-inflammatory cytokine levels in AD patients and post-mortem brains indicate the central role of neuroinflammation in AD aetiology.

6.5.3 Omega-3 and Neuroinflammation

Omega-3 fatty acids and their derivatives, eicosanoids and docosanoids, affect the inflammatory pathways by down regulating pro-inflammatory gene expression and prevent or delay age-related neuroinflammation (Zirpoli et al. 2020). DHA, the main n-3 LC-PUFA in the brain, constitutes 12–14% of brain's total fatty acid content. EPA, the other important n-3 LC-PUFA is available in lesser quantities as it undergoes beta-oxidation. Unavailability or altered metabolism of n-3 LCPUFA in brain causes neuroinflammation leading to neurodegenerative disorders. n-3 long chain PUFA sequentially synthesises eicosanoids involved in regulating inflammation and specialised pro-resolving mediators (SPMs) in the resolution of inflammation. SPMs induce homeostasis by down regulating pro-inflammatory cytokines and upregulating anti-inflammatory cytokines. They also compete and limit the pro-inflammatory oxylipins synthesised by n-6 PUFA. In the brain, several enzymes such as phospholipases A2 (PLA2), cyclooxygenase 2 (COX2), cytochrome P450 monooxygenases (CYP450) and lipoxygenase (LOX) are responsible for releasing fatty acids from membranes and converting them into bioactive lipids (Joffre et al. 2020). A study reported that DHA lipoxygenase, can control white blood cell infiltration and pro-inflammatory gene expression, delaying the brain damage (Marcheselli et al. 2003).

With ageing, the intestinal absorption capacity of essential fatty acids decreases, along with minimised conversion of precursors into LCPUFA. Thus, brain experiences a decrease in n-3 LC-PUFAs predominantly in the cortex, hippocampus and cerebellum. Studies in mice showed that n-3 PUFA deficiency during adulthood worsened the inflammatory effects on spatial memory (Delpech et al. 2015). On the contrary, exposing the aged mice to n-3 PUFA supplemented diet for 2 months reversed the spatial memory deficits induced by ageing (Labrousse et al. 2012). Few studies in humans reported that fish oil consumption improved cognitive abilities in elderly people with cognitive impairments (McNamara et al. 2018) (Danthiir et al. 2011).

6.6 Epigenetics, Omega-3 Fatty Acids and Ageing Brain

As the human brain continuously responds to nutritional and environmental factors, a controlled interaction between genetic and environmental factors ensures efficient functioning. A balanced nutrition positively impacts age-related cognitive decline. Diet modulates synaptic plasticity, neuroinflammation, neurogenesis and

neuroprotection during early embryonic development via epigenetic changes and extends throughout adulthood (Polverino et al. 2021). Although ageing is a universal phenomenon, the rate of ageing differs between individuals. If the biomarkers of ageing in different individuals can be measured, it helps predicts age-associated diseases even before the onset of symptoms. The aim of developing therapeutics targets the delaying of ageing complications (Cole et al. 2018). Leucocyte telomere length (Vaiserman and Krasnienkov 2021), DNA methylation at CpG islands across the genome and N-glycan profiling (Paton and Suarez 2021) are some of the ageing biomarkers which correspond to chronologic age in healthy individuals (Cole et al. 2018).

6.6.1 MicroRNA and Brain Functions

MicroRNAs (miRNA) are short, non-coding RNAs that play a crucial role in post-transcriptional gene regulation. They target specific genes involved in oxidative stress and mitochondrial dysfunction and inhibit their translation by binding to 3′ untranslated regions of the mRNA. miRNA is associated with argonaut protein which involves in RNA-mediated gene silencing. Depending on the miRNA binding strength, argonaut is induced to cleave target mRNA and silence the genes. miRNA's ability to get packed into exosomes allows it to be transported into extracellular space by crossing membranes like the blood-brain barrier. This facilitates easy and inexpensive plasma biomarker analysis for ageing and disease. Brain miRNAs cross blood-brain barrier using exosomes and enter plasma, offering insights into the causes of diminishing cognitive function.

miRNAs are also known as modulators of longevity and regulate ageing process. miRNAs can directly influence lifespan by involving different ageing pathways such as insulin-like growth-factor (IGF-1) signalling, mitochondrial/ROS signalling and DNA damage response. These pathways function as adaptive mechanisms for maintaining the organism's homeostasis in adverse physiological stress, conditions and molecular damage. A single miRNA can target several genes simultaneously and can regulate their functions.

Different varieties of miRNA in the brain play functional roles in various brain activities. The regulation of miRNA profile in the mammalian brain varies with different brain regions, and the profile alters with ageing. Studying miRNAs' role helps understand age-associated neuropathology (Catanesi et al. 2020). miR-34c, miR-34a, miR-181-a-1 and miR-30e are age-regulated micro RNAs extensively studied in mammalian brains. miR-34c is upregulated in humans with AD, contributes to cognitive decline with brain ageing and decreases the expression of sirtuin 1(*sirt 1*), a transcription factor that regulates the lifespan. miR-34a is upregulated in brain and blood samples of aged mouse and down regulates *sirt 1*. Expression of miR-34a/*sirt 1* in blood and brain may be used as brain ageing biomarkers (Kinser and Pincus 2020). Although less data are available with brain

miRNA profiling of ageing, it is agreed that dysregulation of miRNAs could result in neuroinflammation, diminished cognition and neurodegenerative diseases (Barter and Foster 2018).

6.6.2 DNA Methylation and Ageing

Previously, telomere length was correlated with ageing outcomes because of their changes in epigenetic alterations and cellular senescence during ageing. However, recent research suggests that the correlation between ageing outcomes and telomere length is not accurate, alternate biomarkers are explored. Epigenetics is useful tool in this aspect which can be considered in association with ageing process.

Epigenetics refers to an alteration of gene activity without changing genomic sequence. Epigenetic modifications such as DNA methylation or histone modifications can alter the availability of DNA for binding sites and can upregulate or downregulate the gene transcription. Although all the cytosines of DNA can get methylated, 5-methyl cytosines being the hotspots of CpG dinucleotides, have distinctive methylation ability on both strands of DNA copied from parent to daughter strand during cell replication. DNA methyl transferases like DNMT1, DNMT3a and DNMT3b target five carbon of cytosine and add a methyl group to it, forming 5-methylcytosine (5mC). Methylated DNA blocks the binding of transcription factors, inhibits gene expression, and gives access to methyl binding proteins that may involve in gene silencing. DNMT1 maintains genomic stability by confining to established CpG methylation, while DNMT3a and DNMT3b involve increased methylation of non-CpGs with ageing (Barter and Foster 2018). A global shift in DNA methylation transmits epigenetic instability in developing fetuses due to n-3 PUFA deficiency (Basak and Duttaroy 2022).

Global DNA methylation does not change appreciatively during ageing, but a shift in the CpG methylation pattern is observed. Generally, CpG islands are hypomethylated in all tissues in developmental stages. But during ageing and nutritional deficiency, DNA hypermethylation is observed at many genomic loci in the cerebral cortex. This variation in methylation pattern during different developmental stages indicates dynamic control of methylation in differentiated neurons. The fate of gene expression during DNA methylation depends on the location of CpG islands. Methylation in the promoter region is negatively associated with gene expression, while methylation in the gene body positively affects gene expression (Prasad and Jho 2019). CpG methylation analysis in the human prefrontal cortex (PFC) showed that age and sex play dominant roles in DNA methylation in CpG islands. The expression of neuronatin (NNAT), a human brain developmental gene in the prefrontal cortex, decreases with age, while DNA methylation shows the opposite pattern. Genes like DRD2, NOS1, NRXN1, and SOX10 related to schizophrenia and autism also exhibited methylation variations with ageing. DNA methylation

analysis at sites like PIPOX, RHBDD1, DPP8, PTGER3 and FLJ21839 genes showed clear association with chronological age (Numata et al. 2012). The DNA methylation capacity reduces with age and hypermethylation occurs in most of the CpG islands with age. Identifying methylation changes in different cellular signalling pathways in the brain can help in assessing the development and progression of neurodegenerative diseases.

As chronic inflammation is a significant yet undetected contributor to cognitive ageing, epigenetic analysis of inflammatory markers like CRP helps to understand cognitive ageing mechanisms. Increased DNAm CRP is associated with brain cortical volume reductions in frontal, medial temporal and anterior lateral lobes and is proportional to cognitive decline. Variations in the distribution of proinflammatory receptors in different brain regions may be the explanation for the higher vulnerability of some regions for inflammation than others (Conole et al. 2021).

6.6.3 Omega-3 Fatty Acid and Its Epigenetic Regulation in the Brain

Alterations in one-carbon metabolism and omega-3 fatty acid deficiency can affect epigenetic modifications, producing long-term brain defects in learning, memory, cognition and behaviour. It can also cause brain disorders such as depression, schizophrenia, autism and bipolar disorder. S-adenosyl methionine (SAM) is a methyl group donor formed in one-carbon metabolism which provides methyl group for conversion of phosphatidylethanolamine-DHA (PE-DHA) to phosphatidylcholine-DHA (PC-DHA), which is essential for the transport of DHA from the liver to brain. When DHA levels are low, methyl groups are unused from SAM, and this excess methyl group availability may involve DNA methylation. Again, the impacts of long-term omega-3 PUFA deficiency on gene expression and epigenetic changes in the fetus could result in a change in cognitive function later in life (Basak et al. 2020b).

Studies have indicated that adequate omega-3 fatty acid can restore the global hypomethylation to control levels suggesting the important role of omega-3 fatty acid, especially DHA, in determining methylation patterns in the placenta (Srinivas et al. 2021). DNA methylation can control the expression of BDNF gene during forebrain development in mice. Any epigenetic changes during the developmental stages may continue throughout life and affect later life quality. Recently evidence has been reported that prenatal omega-3 supplementation may reverse methylation trends improving cognition and neuroprotection. In a study where pregnant women were given omega-3 supplementation (800 mg DHA) from 20 weeks of gestation till delivery, differences were observed in differentially methylated regions like TRAK1, LPHN3, SLC12A6, and RFPL2, which affects brain function (van Dijk et al. 2016). n-3 PUFA deficiency during neurodevelopmental stages may be

responsible for epigenetic silencing of the nuclear receptor genes *Rxr* and *Ppar*, resulting in schizophrenia (Maekawa et al. 2017).

6.7 Conclusion

The rapid dietary transition is associated with decreased accessibility to marine omega-3 products and the increased intake of LA in the diet globally. Omega-3 fatty acid (ALA) sourced from various plant oils, and seeds convert only 40–50% to their longer chain fatty acids such as EPA and DHA due to limited endogenous conversion, especially when LA is high in the diet. Again, higher LA in the diet competes with the enzymes for its conversion to ARA, which leads to the excess synthesis of leukotrienes and prostaglandins, mediators of neuroinflammation. The sources of ROS in the brain are often derived from uncontrollable ARA-cascade, defects in mitochondrial respiration, activation of NADPH oxidase and others. High ROS generation activates redox-sensitive NF-kB, resulting in downstream propagation of inflammatory cascades. Advanced glycation products also promote the production of ROS due to uncontrollable hyperglycaemia or increased nitric oxides associated with free radicals due to dysregulated mitochondrial dysfunction. Thus, lowering LA in diet may protect the brain from oxidative damage triggered by neuroinflammation.

Mitochondrial dysfunction and dysregulated NOX system are primarily responsible for the excessive generation of cellular oxidative stress. ROS-mediated damage in cerebral tissue triggers different molecular signalling pathways, including neuroinflammation that leads to neuronal death. Ageing shifts the balance of pro-inflammatory and anti-inflammatory cytokines in the brain towards the pro-inflammatory state, which makes the brain more vulnerable to stress, infections and the onset of neurodegenerative diseases (Gorlé et al. 2016).

DHA is obligatory for human brain development and performs essential roles in neurotransmission, neurogenesis, and protection from oxidative stress throughout life. It protects the brain from age-related decline in performance and activities (Troesch et al. 2020). Although animal studies promise a significant benefit of DHA in protecting age-related cognitive pathology, additional controlled clinical trials are required for its clinical use. In vivo *and* ex vivo data using ageing models of AD, PD, and HD showed enhancement in mitochondrial function after treatment with n-3 PUFAs, especially with DHA (Eckert et al. 2013; Lee et al. 2013).

Although the omega-3 supplementation benefits in AD, PD and MCI are not established, many clinical trials have proved the positive effects. Few clinical trials of omega-3 supplementation and the effects on neurodegenerative diseases are listed (Table 6.1). The high half-life of DHA in the human brain warrants life course intervention with a longer duration, much earlier than the start of healthy ageing. Nevertheless, it is safely recommended as a prophylactic measure in maintaining brain health and its delay in ageing.

Table 6.1 Effects of Omega-3 fatty acid supplementation in age-related neurodegenerative diseases: clinical trials

Trial	Fatty acid intervention	The major outcome with reference
1	DHA 1200 mg/d, EPA 300 mg/d, along with other nutrients (in Souvenaid form) for 12 wks to AD patients (n = 225)	Multi-nutrient supply to mild AD patients improved the memory (in verbal recall score) (Scheltens et al. 2010)
2	DHA 1.7 g/d, EPA 0.6 g/d for 6 mo, followed by omega-3 supplementation for another 6 mo to AD patients (n = 204)	Omega-3 supplementation increased plasma TTR, protecting from amyloid beta plaques (Irving et al. 2013)
3	DHA 1.7 g/d, EPA 0.6 g/d for 6 mo to AD patients (n = 171)	Omega-3 supplementation benefits in mild to moderate AD patients, influenced by the baseline tHcy levels of patients (Jernerén et al. 2019)
4	125 mL of Souvenaid (with specified nutrients) daily once for 24 weeks to patients with mild AD (n = 259)	Mild AD patients who received Souvenaid intervention showed better integrity and functioning of the brain network organisation in EEG analysis (de Waal et al. 2014)
5	DHA 1.72 g/d, EPA 0.6 g/d for 6 mo and further 6 mo. Omega-3 supplementation for all groups to AD patients (n = 174)	Supplementation increased plasma omega-3 and showed protection from declined cognitive performance measured by ADAS-cog scores (Eriksdotter et al. 2015)
6	Omega-3 fatty acids (flax seed oil) 1000 mg/d, Vit E supplements 400 IU/d for 12 wks to PD patients (n = 60)	In PD patients, supplementation showed favourable impact on UPDRS score (Taghizadeh et al. 2017)
7	EPA 2 g/d, Vit E 364 mg/d, Vit C 1000 mg/d for 16 wks in addition to antipsychotic drugs to schizophrenia patients (n = 99)	In schizophrenia patients, adding ethyl-EPA and vitamins to antipsychotic drugs impaired psychosis (Bentsen et al. 2013)
8	DHA-2 g/d for 12 mo to MCI patients (n = 240)	Supplementing DHA for 12 months delayed hippocampal degeneration and improved cognition in MCI patients (Zhang et al. 2017)
9	DHA 880 mg/d, EPA 1320 mg/d for 26 weeks (n = 121) to healthy aged adults	Betterment in brain grey matter volume, white matter integrity and cognitive abilities was observed after omega-3 intervention in elderly individuals between 50–75 years (Witte et al. 2013)
10	125 mL Souvenaid with specified nutrients (DHA 1200 mg/d, EPA 300 mg/day) for 24 mo (n = 311) to AD patients	Multi nutrient supplementation showed benefits on CDR-SB and brain degeneration in AD patients (Soininen et al. 2017)
11	DHA group (0.7 g/d), EPA group (1.6 g/d), EPA + DHA group (DHA 0.35 g/d + EPA 0.8 g/d) for 24 mo. To AD or MCI patients (n = 163)	In AD and MCI patients, although omega-3 supplementation did not lower adverse cognitive outcomes, positive impact was seen on oral language ability and constructional praxis scores (Lin et al. 2022)

Abbreviations: *Wk* week, *mo* month, *d* day, *AD* Alzheimer's disease, *TTR* Transthyretin, *tHcy* homocysteine, *EEG* Electroencephalogram, *ADAS-cog* Alzheimer's disease assessment scale-cognition sub scale, *PD* Parkinson's disease, *UPDRS* unified Parkinson's disease rating scale, *MCI* Mild cognitive impairment, *CDR-SB* Clinical dementia rating-sum of boxes

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Chapter 7
Traditional Foods and Ageing

Damal Chandrasekar Mathangi and Arambakkam Janardhanam Hemamalini

Abstract With increase in lifespan, aged population is on the rise across the globe. This underscores the need to explore avenues for healthy ageing and prevention of age related diseases. This chapter explores the traditional foods across the globe towards healthy ageing and thus creating a possibility to design integrated diet.

Keywords Ayurveda · Mediterranean diet · Okinawa

Gerontologists are of the view that the physiological impairing processes of ageing and senescence manifest primarily during the lifetime beyond the natural lifespan of a species, termed as the essential lifespan. A greater life expectancy, in fact, leads us to reconsider not only the condition of the elderly, but also what kind of implications ageing will have in our lifetime. The fundamental reason for ageing and age-related diseases such as the Alzheimer's, Parkinson's, cancer and others is the imperfect processes of life beyond this essential lifespan. Hence, the approach we follow for infectious and other disease successfully, i.e. 'one target, one shot' biomedical treatments does not work successfully on age-related disease (Rattan 2015).

The human lifespan has substantially extended since the 1900s, due largely to interventions that have reduced infant and childhood mortality, coupled with medical-surgical advances that have had a particular impact on older people (Wickramasinghe et al. 2020). While the biological process of ageing is irreversible

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and inevitable, it is mouldable with various easily adaptable techniques. One such easy adaptable technique is changing one's life style, i.e. diet and physical activity which are most important and allows increasing the quality of life of an individual. A low-cost solution for unmet health needs across all socio-economic states and ethnicity is food, as it is the daily input consumed to sustain human life from eons. However, food and drinking water are the most neglected basic human need-based resources from the respective of health sciences. Food also represents the tradition and cultural values of the region. Several studies examining the degree of food variety in different populations have found that those with the highest intake of variety tend to live the longest. Interestingly, the Japanese have the longest life expectancy in the world, and promote dietary guidelines that suggest 30 or more different kinds of food should be eaten daily. Food variety has been shown to correlate (positively) with nutritional quality, and this probably contributes, at least in part, to health and longevity.

A good nutrition and a well-planned balanced menu with all essential nutrients in adequate proportion, enhances the body's resilient flexibility and plasticity, in mitigating the ill effects of various metabolic storms. Healthy ageing by a healthy diet can be influenced by a number of ways including:

- Enhancing bone health by improving its mobility and prevention of muscle mass loss, which is more common during elderly stage of life.
- Improving vision by maintaining optical density and preventing macular degeneration.
- Maintaining a healthy heart by avoiding hyper or dyslipidemias and maintaining normal blood pressure.
- Effective glycemic control.
- Improved cognition and prevention of cognitive impairment.

The derangement in the above-mentioned activities, culminates in poor quality of life and an unhealthy ageing, where many fall a victim to various diseases during their course of life. Therefore, it is essential that an adequate nutrition is maintained, which could properly enforce the anti and healthy ageing mechanisms, towards an improved quality of life. Intervention studies that have taken a food-based approach (with variety) have also shown favourable outcomes in terms of health and survival. In the Dietary Approaches to Stop Hypertension study, the group that added low-fat dairy products to a diet that was high in fruit and vegetables showed greater improvements in blood pressure than the group that emphasised only the fruit and vegetable aspect of the overall diet. The Lyon Heart study, another food-based intervention study, found patients surviving a myocardial infarct were at lower risk of subsequent mortality if they followed a Mediterranean-type diet compared with a diet that presumably followed a more 'prudent' western format. Certain dietary patterns are associated with an increased risk of coronary heart disease and the development of certain cancers (Savige 2002). Hence, it is important to watch the food we eat not just when we are old but all through our life.

The Hippocrates saying 'Let food be thy medicine' applies aptly to the traditional Indian foods, with its diverse food ingredients, carefully chosen and combined to give maximum health benefits. Traditional nutritional knowledge is a wealth which has now been researched with the modern evidence methodology. With the innate judicious combination of whole grains, vegetables, spices, fruits and vegetables in addition to probiotics from fermented foods, the traditional foods not only ensure an optimal physiological function, but also improves gut health, enhance immune function, avoid unnecessary weight gain and fat accumulation, drive away extra lipids, reduce oxidative stress, neurodegenaration and inflammatory responses. Through these innumerable functions, the traditional food combination enhances the optimal resilience and metabolic flexibility, which is the pivot of healthy ageing.

Indian traditional foods history dates back to 3000 years back, with influences from Aryan, Harappan and Vedic civilisations and it has found a prominent position in the culture and life of the people. According to Ayurveda (a natural system of medicine, with origin in India 3000 years ago), food is one of the tripods of life to maintain and promote physical and psychological health of an individual. We should take food that is compatible to our body, minimal or the right proportion and should be appropriate to the season. Only such food increase the immunity of an individual and make them free from diseases both mentally and physically. As per Charaka Samhita, text book of traditional Indian system of medicine, 'one should eat according to their Prakruti'. According to this, there are certain foods that suit our nature and certain food are not suitable. The recent research has linked our genes to the prakruti (or our body constitution). This means our food needs to be customised, a wholesome meal for one may be incomplete for another. In addition, the diversification of our geography, food habits and culture need to be considered when studying the impact of food on ageing. Hence, as per Ayurveda, there are multiple factors taken into consideration while prescribing diet which includes the season, tastes and their constitution. Based on these the cereals and grains, pulses, vegetables, tubers, fruits, oil seeds, spices, milk and milk products, sugar items, non-vegetarian, water and even wine are identified (ref). In addition, Ayurveda follows restricted diet, specific diets as per rituals, fasting and cleansing regimen too as part of the lifestyle (Sukesh Suni et al. 2021). All these are in practice now in various modern terminologies including calorie restriction, fasting to increase autophagy, etc.

A sloka in Ayurveda states that 'If food is right, medicine is not needed and if food is not right, no medicine will work'. So the food one takes is personalised based on the individuals Prakruti (body composition), dosha (health types as per Ayurveda), special needs, age and practices in the context of seasons and daily cycles. Thus, it provides a holistic practical food personalisation. Hollistic, as it weaves together 'ahara (diet) and vihara (lifestyle)' continuum and a practical system. This is important, because while our genome or the prakruti, that we are born with can be modulated by multiple inputs, one of which is food. In addition, the six ritus (seasons) have been detailed, and specific dietary and lifestyle regimens are also well explained in Ayurveda. There

is a great interconnection between ahara, the gut microbiome and seasons (Rastogi 2014).

Food and Nutrition of India, over the years have been enriched through food combinations from primary easily locally available food ingredients, thereby complementing and supplementing each other. This further enhanced the digestibility, bioavailability which ultimately helps in health protection, disease prevention, resistance and improve longevity. Indian food traditions emerged from various cultures in addition to Aryans and Harappans. The Mughal invasion, British colonisation have all contributed highly to the then prevailing food habits and enabled meaningful interactions. Indian cultures gradually enriched them through long empirical experience using combinations of a variety of primary food materials, especially the locally available food grains and vegetables that nutritionally complemented and supplemented each other. This has contributed to better health protection, improvement of digestibility, resistance to health disorders, and increased human longevity.

Indian traditional foods are largely cereals, rice and wheat-based, with a variety of meal adjuncts, milk and milk-based beverages, sweets, steamed foods with ghee or vegetable oil as the medium of cooking. This versatile combination and composition enable the Indian traditional food to be rich in dietary fibre, antioxidants, phytochemicals, optimal carbohydrate sources and being low or moderate in fat. Almost all of these being closely resembling the current days, RDAs, developed based on evidence-based research.

The traditional Indian foods has been reviewed extensively and compiled by Srinivasan K., (Srinivasan 2010), where reportedly over 5000 traditional food recipes/combinations have been identified from across 50 cultural cuisines of India. It would be beyond the scope this chapter to cover all the reported foods. However, the wide classification under which these different foods are presented with highlighting their potential health benefits. Functional ingredients of traditions Indian foods have also been detailed well. Dietary fibers are abundant in whole grains (cereals and legumes), vegetables, fruits and certain spices. Whole grains, vegetables and fruits are rich sources of polyphenols and phytochemicals. Amla, amchur, tamarind are major source of acidulants. Fermented milk products are rich in probiotics (6). Using these raw materials, several traditional foods are prepared which are widely consumed on a regular basis.

The basic ingredient of many traditional Indian foods are cereals, millets such as sorghum, finger millet in combination with a variety of pulses. This type of combinations makes up for the limiting amino acids such as methionine and lysine in cereals and pulses and together exert the beneficial effect. Additionally, they also provide good soluble and insoluble fibre from their germ and bran portions.

The most commonly used pulses and lentils are black gram, green gram, red gram and Bengal gram. They are used in the roasted, powdered, sprouted and boiled forms in gravies, chutneys, snacks, soups, etc., which enhances the taste of the foods. These pulses form the major source of proteins in the traditional Indian

cuisine. Certain recipes made with cereal pulse combinations after fermentation namely idly, dosa and dhokla improve the digestibility, exclude unhealthy phytates and improve gut health through their microbial content.

7.1 Traditional Milk-Based Foods

Dahi (curd) and ghee are the two milk-based foods, traditionally forming the most important component of the diet. Dahi (fermented milk—curd) with its rich probiotic milieu offers a number of health benefits, such as reducing the cholesterol and triacylglycerols, protection against gastroenteritis, and strengthening of the immune system promotes optimal resilience against the ageing process. Ghee, although wrongly considered to be the causative factor for heart ailments, actually renders a cardio-protective function through its appropriate fatty acid composition and fat-soluble vitamin profile.

Traditional Indian food main courses are made much healthier and tastier through a variety of adjunct foods such as papads, wadis, chutneys, pickles, sauces, extracts (jal jeera made with cumin seeds), etc. The advantages of these adjuncts are that they make the food easily acceptable to any age of individual, and offer a variety of micronutrients. The practice of incorporating these adjuncts ensures the availability of fruits, vegetables and pulses during their lean period also.

Some of the commonly used dietary adjuncts are papads, chutneys, chutney powders, pickles, spiced and sun dried dumplings and spicy masalas. These are commonly prepared traditionally at house hold level by using pulse flours, left over rice, millets, legumes, oil seeds like peanuts, sesame, coconuts, leafy vegetables, seasonal fruits, seasonal acidic fruits and so on. These adjuncts, not only make the food tasty and acceptable for any age group, but also offer the benefit of being nutritious, healthy and make seasonal foods available at off seasons too.

The traditional Indian food uses a number of other foods such as amla, kokum (Garcinia indica), tamarind, etc., all of which are known to exert innumerable health benefits in promoting gut health and anti-ageing process.

The cooking medium of various healthy recipes are predominantly mustard and sesame oil. These vegetable oils are an excellent source of vitamin E, magnesium, calcium, copper, iron, zinc and vitamin B6. This profile of the oils renders them safer to use and effective in controlling high blood pressure, improving bone health and various other functions toward modulating the metabolic age of the human body and hence can be considered to help in graceful ageing.

Over and above these constituents, Indian cuisine is envied for its another very unique and important component the Spices. Every spice has been documented for its unique properties (6). Table 7.1, adopted from Srinivasan highlights the significant beneficial role played by these various spices in the traditional foods.

Table 7.1 XXX

Spice	Medicinal Properties
Turmeric (*Curcuma longa*)	Anti-inflammatory, diuretic, laxative, good for affections of the liver, jaundice, diseases of blood
Red pepper (*Capsicum annuum*)	Anti-inflammatory, for pain relief (rheumatism/neuralgia); useful in indigestion, rubefacient
Garlic (*Allium sativum*)	Antidyspeptic, antiflatulent, for ear infection, duodenal ulcers, as rubefacient in skin diseases
Onion (*Allium cepa*)	Diuretic, emmenagogue, expectorant, for bleeding piles
Fenugreek (*Trigonella Foenum-graecum*)	Diuretic, emmenagogue, emollient, useful in heart diseases
Cumin (*Cuminum cyminum*)	Antispasmodic, carminative, digestive stimulant
Coriander (*Coriandrum sativum*)	Antidyspeptic

The Mediterranean diet (MD) is characterised by a high intake of foods of plant origin (fruit, vegetables, breads, other cereals, potatoes, beans, nuts, and seeds) and fresh fruit. Olive oil, namely extra-virgin olive oil, is the main source of fat. Dairy products (mainly light cheeses and yogurt), fish and poultry are consumed in medium-low quantities; particularly, fish is an excellent source of polyunsaturated fatty acids (PUFAs), particularly omega-3 fatty acids; egg consumption is limited to a maximum of four per week; red meat is consumed sporadically and in small quantities, however, no more than once a week. MD has a very low saturated fat content, which represents no more than 8–10% of the total caloric intake. Caloric intake from lipids is not more than 30% of total caloric intake. Wine is usually consumed with meals, but always in moderate doses (1–2 glasses) (Willett et al. 1995). It has been shown that adherence to the MD significantly reduced the total mortality thus having a positive effects on the lifespan in the elderly. A greater adherence to the MD was negatively associated with a risk of death of 17% for an increase in one unit and over 50% for an increase of four units (Trichopoulou 2003).

Much of the longevity advantage in Okinawa is attributed to their healthy lifestyle; this includes the traditional diet, which is low in calories, yet nutritionally dense, particularly with regard to vitamins, minerals, and phytonutrients, several of which have neutraceutical potential. The traditional Okinawan cuisine centers on the staple sweet potato, green-leafy or yellow-root vegetables, and soy (e.g. miso soup, tofu or other incarnations of this legume) which accompanied almost every meal. Smaller servings of fish, noodles, or lean meats flavoured with herbs, spices, and cooking oil often accompanied these staples (Willcox et al. 2014). Similar to the Ayurvedic diet, dietary pattern in Okinawa is characterised with low caloric intake, high consumption of vegetables (particularly root and green-yellow vegetables), legumes (mostly soybean in origin), moderate consumption of fish products (more in coastal areas) and low consumption of meat products (mostly lean pork), dairy products, fat intake (high mono and polyunsaturated-to-saturated-fat ratio;

low omega 6:3 ratio). Their emphasis is on low-GI carbohydrates with high fibre intake and moderate alcohol consumption (Willcox et al. 2007).

In India, food is medicine or a 'food-first' approach is used to integrate realities of today with our culture. This forms the crux of all the traditional diets. Integrating modern science with traditional knowledge thus has a potential to provide 'adoptable' simple solutions to our present and future health and wellness challenges including ageing.

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Chapter 8
Macronutrients and Their Roles in Aging

Ahamed Basha Abdul Bari and Prince Johnson Samuel

Abstract Macronutrients are the essential nutrients that are needed in high amounts for healthy aging. Several acute and chronic illnesses such as diabetes, hypertension, atherosclerosis, other cardio-vascular disorders, dementia, bone morphological disorders, etc. are strongly linked to aging. Further, age-related morphological and functional changes are observed in every cell/organ in almost all living organisms. To cope with age-related illnesses, macronutrients such as carbohydrate, protein, and fat have to be supplemented in an ideal manner. Macronutrient supplementation must be planned as per age group, sex, ethnicity, country of origin, etc. to achieve successful aging. The various diet patterns, like the Mediterranean diet, the Japanese diet, the Okinawa diet, etc., strongly suggest that they contain different ratios of macronutrients. Thus, supplementation with the proper ratio of macronutrients in association with other strategies is the best way to achieve healthy aging.

Keywords Macronutrients · Carbohydrates · Proteins · Lipids and aging

8.1 Introduction

Macronutrients are nutrients required in large quantities for our well-being. They provide energy (calories) to maintain normal growth and metabolism and to carry out day-to-day activities. They are the building blocks of our body and are generally

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classified as carbohydrates, proteins, and lipids (Venn 2020). Most of the carbohydrates that we consume through our diet get digested and simple sugars like glucose are formed as end products, which act as a primary energy source for our body. Proteins are made up of amino acid residues and perform a wide range of functions in our bodies, including cell structure formation and key transporters in the metabolic process. Fats act as an important storage form of food and aid in the maintenance of body structure. These macronutrients must be consumed in adequate and balanced amounts in our diet to maintain good health. Human communities have traditionally lived on diets with widely different ratios. Several studies are still being conducted around the world to determine an ideal macronutrient ratio for the global population to live a healthy life. According to WHO, the recommended percentage of calories in a diet for protein is 10–15%, for fat is 15–30%, and for carbohydrates is 55–75% for young adults (Venn 2020). However, the acceptable macronutrient distribution ranges for carbohydrates, protein, and fat remain constant from middle age to old age. For the elderly, the recommended macronutrients for protein are 15–20%, fat is 20–35%, and carbohydrates are 45–60% (Kehoe et al. 2019). Among the macronutrients, unrefined carbohydrates, such as whole grains and brown rice, are especially important in preventing constipation and other gastrointestinal disorders, and may also lower the risk of colon cancer in older adults. A protein diet should be lean, and fats such as unsaturated and omega-3 fatty acids should be included in a healthy diet. Thus, every macronutrient has to be a part of the diet on a daily basis. Making each meal a combination of protein, complex carbohydrates, and healthy fats will make this easier. However, it might be challenging to determine the precise macro-balance that works for you. If there is a deficiency of carbohydrates in the diet, then it may lead to several disorders such as hypoglycemia, diabetic ketoacidosis, and hyperosmolar coma (Kalscheuer et al. 2017; Scott et al. 2019). Similarly, protein deficiency leads to protein energy malnutrition disorders in different age groups (Leij-Halfwerk et al. 2019), while altered levels of fat may lead to several cardio-vascular disorders, such as stroke, renal diseases, obesity, and metabolic syndrome (Carson et al. 2020). Thus, macronutrients play a significant role in healthy living (Nassar 2019). The diet that we eat as a child has an impact on our health as we grow older. A good, healthy macronutrient diet and regular physical activity can help us live a longer and healthier life. On the other hand, Irregular bowel habits with a lack of nutrition and exercise, might hasten the aging process and cause several pathological disorders. The appropriate macronutrients give several benefits at each and every stage of our lives. They help a new-born grow, a teenager develops mentally and physically, a young adult reaches his or her physical peak, and an older adult has to cope with aging and its related issues. At any age, nutritious meals are the foundation of a healthy lifestyle. Thus, macronutrients can address the majority of the nutritional issues that many older people confront. Furthermore, there are special nutritional issues that impact individuals in their process of aging. They include medical issues such as disability and disease, which might have an impact on macro diet and physical and mental activity levels. For example, as a person becomes old, dental disorders can cause mastication and swallowing difficulties, making it difficult to maintain a healthy macronutrient diet

(Peyron et al. 2017). Nutritional issues in the elderly can lead to a variety of consequences, including decreased energy levels and chronic health issues such as type 2 diabetes, high blood pressure, heart disease, stroke, and osteoporosis (Jaul and Barron 2017).

Aging is a normal physiological process that occurs for every living organism, including humans. The aging process starts in early adulthood and starts to deteriorate several body functions as age advances. Over the decades, the life expectancy of humans has increased to a greater extent, but it does not mean that as age increases, all humans are living a healthy life. Aging is a complex process with interconnected aspects at the molecular, macro-cellular, and functional levels that eventually results in chronic illnesses/disorders (Fig. 8.1). Thus, a healthy diet with ideal macronutrients is essential for a normal, healthy life. Furthermore, when compared to micronutrients, macronutrients are more essential. Without macronutrients, the risk factors associated with aging will be dominant and it will affect the quality of life to a greater extent as age advances. Clinicians and scientists have documented several biochemical changes or external factors that are linked with aging (Engelfriet et al. 2013). Further, a necessary dietary pattern can be regularized so that it can promote healthy aging. However, the main "gap" concerning the types of macronutrients that could actually improve healthy aging has to be documented. Additionally, it is thought that these crucial elements may be seen from a life-course perspective since altering these macronutrient routines might affect human cells or organs' aging, postpone the start of chronic illnesses, and enhance mobility, mental function, and general wellness (Stepaniak et al. 2022). Recent research work has used a nutritional geometric method known as the Geometric Framework to assess

Fig. 8.1 Common age-related chronic disorders

how aging is affected across a landscape of diets that differ orthogonally in macronutrient and total energy content (Simpson et al. 2017a). This chapter is restricted to only the importance of macronutrients and their influence on the aging process.

8.2 Macro Nutritional Requirement and Aging Process

The United States Department of Agriculture Food Patterns recommends different macronutrient goals for each age and gender group when evaluating requirements at different calorie levels (Krebs-Smith et al. 2018). For an infant to a child, and an adult to old age, it drastically varies to meet the macronutrient demands. Further, due to variations in body regulatory mechanisms, hormonal section, gastro intestinal related reflex, macronutrient absorption and metabolic rate, desire to eat, etc., influences the amount of intake of macronutrients to a greater extent. Moreover, plenty of researchers have documented in support of the above that in the aging process, the nutritional pattern varies. For example, during the growing period, a more carbohydrate and protein-based diet is advised, and in old age, as physical activity decreases with age, it is important to limit carbohydrates and fats. However, there is muscle loss and bone fragility, which is prevalent; as a result, protein is needed to make up for the loss and to promote cell development.

All of the physiological changes mentioned above are strongly influenced by macronutrients. The slowdown of the digestive functional capacity, along with other alterations, has the most direct impact on macronutrients and the aging phenomenon. Digestive secretions significantly decrease, although enzymes are still sufficient. Additionally, constipation is more common in older people than in younger adults. Normal bowl function, macronutrient digestion and absorption with adequate dietary fiber, exercise, and hydration consumption, on the other hand, can reduce age-related physiological and pathological changes (Soenen et al. 2016). Changes also occur in the kidneys, lungs, and liver, which has the ability to generate new protein tissue (Sheedfar et al. 2013; Glassock and Rule 2016; Maeso-Díaz and Gracia-Sancho 2020). In addition, aging can slow the immune system's response to making antibodies (Sadighi Akha 2018). Beyond this macronutrient oxidation, obesity in many individuals also contributes to the damaging effects of aging (Santos and Sinha 2021). Apart from macronutrients, micronutrients, gender, race, ethnicity, demography, physical activity, lifestyle, etc. are also strongly associated with the aging process (Emerson and Gay 2017).

8.3 Dietary Carbohydrates and Aging

Eating carbohydrate-rich foods such as rice, wheat, bread, potatoes, sugar-based sweets, etc. may increase the body weight and alter the glucose homeostasis. A carbohydrate diet with a high glycemic index increases blood sugar levels.

Furthermore, numerous studies have found that consuming an excessive amount of carbohydrates has a negative impact on an individual's life span (Seidelmann et al. 2018). The reason behind the decrease in life cycle span is its influence on various cellular signaling pathways. The common end product of carbohydrate metabolism is glucose, which acts as a king maker in the process of aging.

One of the best researched carbohydrates that impacts aging is glucose, which serves as the main energy source for most living things. In various model species, such as yeast, increased glucose consumption promotes aging. One of the possible reasons could be due to the downregulation of life enzymes like AMP-activated protein kinase, which function as energy sensors in the regulation of metabolism and the life cycle (Lee et al. 2017). Forkhead/winged helix box gene transcription factor is another growth inhibitory genetic factor that decreases its functional capacity in response to glucose intake via the insulin-like growth hormone-I signaling pathway (Morris 2005). Furthermore, its low level causes the aquaporin-1/glycerol channel to be downregulated and modifies the glycerol to tune the life existence (Lee et al. 2009). Additionally, intake of a diet rich in glucose leads to the formation of methylglyoxal, one of the end products of glucose metabolism that reduces the life span of the living organism (Xue et al. 2011). Another group of studies suggested that an increase in glucose level causes changes in glucose transporters and proapoptotic genes, growth-promoting signaling proteins such as Sch9, Tor1, glucose-sensing G-protein-coupled receptor Git3p, and proteins involved in the Ras pathways, resulting in a shorter life cycle (Versele et al. 2001; Wei et al. 2009). Adding to this, an increase in glucose concentration leads to modification of SIRT3/Sirtuin 3 (a nicotinamide adenine dinucleotide (NAD)-dependent protein deacetylase) expression is also negatively correlated with aging (Chen et al. 2017). Thus, to conclude, an increase in glucose intake reduces and restricts the same, which accelerates aging. In contrast to the pro-aging effects of carbohydrates, several other carbohydrate metabolites, such as trehalose, act as antistress sugars, increasing the life span of a group of organisms by upgrading endoplasmic reticulum proteins. Similarly, other carbohydrates such as pyruvate, malate, fumarate, and *N*-acetylglucosamine help in preventing the deteriorating effects of aging in many species.

Human studies related to aging and carbohydrates are still not conclusive. Successful aging means high physical, mental, and social functioning in old age without major diseases. The quantity of macronutrients consumed for successful aging in humans is primarily determined by the quantity of carbohydrate-based diets consumed. A few studies have found that eating a low carbohydrate diet reduces cardiovascular risk and keeps blood sugar levels stable, which is beneficial in the aging process (O'Neill 2020). Another group of research articles confirmed that a higher carbohydrate diet leads to obesity and a shorter lifespan (Sartorius et al. 2018). Further, intake of carbohydrates as a dietary fiber impacted the chance of effective aging throughout a 10-year period independently, and the data supported that a fiber-rich diet might be an effective strategy for living a disease-free and quality life (Park et al. 2011). In another study, a unique relationship was discovered between high cereal fiber consumption and a lower incidence of mild

chronic kidney disease, which was corroborated by a cross-sectional correlation with dietary glycemic index. In contrast, the same study also confirms that consuming a more energy-dense, nutrient-poor carbohydrate diet may compromise renal function, presumably through transient hyperglycemia (Mirmiran et al. 2018). Supplementing this, In an older Australian population, dietary glycemic index, dietary fiber, and carbohydrate-containing food categories were linked to death due to non-cardiovascular, noncancer inflammatory illness, and aging (Gopinath et al. 2011). Extending to this, carbohydrate dietary supplementation was assessed for depression score using Mental Health Index scale and the epidemiologic studies depression-10 scale, which documents that nutrition factors such as carbohydrate dietary fiber were shown to have a modest correlation with the occurrence of depressive symptoms (Gopinath et al. 2016). Additionally, plenty of studies proved that a carbohydrate nutrient diet affects age-related changes in almost all organ systems (Seidelmann et al. 2018).

Several scientists have studied the relationship between cardiac health and carbohydrate diets for many years, initially believing that processed carbohydrates in a diet lacking fiber were significant risk factors for cardiac health and influenced the aging process (Duan et al. 2022). However, carbohydrates with a low-carbohydrate diet were in turn found to have cardioprotective and antiaging effects (Farhadnejad et al. 2020). Another common age-related disorder is osteoporosis, which occurs when a high carbohydrate diet affects bone health during the aging process, reflecting its ability to alter calcium metabolism and skeletal homeostasis (Hashemi et al. 2015; Montalvany-Antonucci et al. 2018). In line with this, a low carbohydrate diet with rich fiber has an inverse relationship with kidney diseases. Furthermore, during the course of another age-related disorder, dementia, more than 35% of dementia patients consume more food than they did before the disease (Gentreau et al. 2020). Over half of patients with dementia are reported by their caregivers to have a significant shift in food preferences, specifically an increased preference for sugary foods and carbohydrate-rich diets. A study, on the other hand, discovered that increasing carbohydrate-based diet has a beneficial effect on dementia. Further, carbohydrate-rich diets in the process of aging also influence the majority of body functions such as decreased vital capacity, gastritis, dermatological disorders, etc. Further, higher carbohydrate intake, glycemic index, and glycemic load are found to cause metabolic dysregulation of the glucose-insulin axis and adiposity-related processes, which in turn make the body more prone to the development of various cancers as age advances (Jung and Choi 2017).

In conclusion about carbohydrates: whether carbohydrates really play a damaging role in the aging process. The solution is a little difficult because carbohydrates and aging include a wide range of physiological parameters. The availability of excellent literature supports that taking a carbohydrate-based diet during the different stages of aging when paired with an active lifestyle, can really postpone aging through reduced insulinogenic response. For example, when sports people like athletes take high amounts of carbohydrates, their overall life span is greatly prolonged when compared to non-sports people. Contradictory to this, intake of more carbohydrates makes our body more prone to inflammation due to the spikes in insulin

secretion and the formation of more glycation end products, which decreases the life span. Additionally, taking too many carbohydrates coupled with a sedentary lifestyle decreases life span. On the other hand, at any stage of the aging process, the recommended amount of carbohydrates in the diet along with a healthy (physical and mental) lifestyle like exercise, adequate sleep, etc. actually extends the life span. If a high carbohydrate diet is taken, then calorie levels have to be checked, because even a high carbohydrate diet with low calories also prolongs the life span. Thus, to extend the life span or to achieve healthy aging, way of physical and mental living (healthy lifestyle) and diet (ideal macronutrients – carbohydrates along with protein, fat, and other micronutrient diet patterns) is recommended.

8.4 Role of Protein Diet in Aging

Proteins and amino acids are one of the key biological macromolecules that function as structural components, enzymatic reaction catalysts, and act as an energy source. Numerous studies have shown that dietary proteins are factors that influence longevity. For example, deficiency of some critical amino acids increases the longevity of various model organisms (Kitada et al. 2019). Available literature exhibits a strong negative correlation between protein intake and aging (Simpson et al. 2017b). Furthermore, several nutrition-related studies on proteins and carbohydrate diets were conducted to determine whether the age-related changes were caused by the protein or carbohydrate diet. In a study done on experimental organisms, it was found that longevity is connected with a low-protein/high-carbohydrate diet; however, overall calorie intake had no influence on longevity (Foscolou et al. 2019). Furthermore, insulin-like peptides have been found to modulate the effects of protein and carbohydrate on the life span of an organism by modulating a brain insulin target that encodes an a-glucosidase. Decreased protein consumption also appears to increase longevity by suppressing the insulin/insulin-like growth factor-1 or target of rapamycin signaling pathways (van Heemst 2010). Dietary amino acid content influences longevity by influencing multiple nutrient-sensing signaling pathways. Adding to this, a human epidemiological statistic also found an association between the quality and quantity of dietary proteins and long-term health (Pan and Finkel 2017) and involvement of complex nutrient-sensing networks which fine-tune the metabolic responses to dietary proteins in a highly conserved manner. These metabolic reactions, in turn, can influence the emergence of insulin resistance, obesity, neurodegenerative illness, and other age-related disorders. In yeast, it was found that EIF2A eukaryotic translation initiation factor 2A kinase and general control nonderepressible 2, which directly bind to uncharged cognate transfer RNAs and target of rapamycin signaling pathway components that operate as cellular amino acid sensors to promote lifespan (Pan and Finkel 2017; Anderson et al. 2021). It further reduces overall protein translation while increasing translation of particular proteins implicated in longevity. Furthermore, dietary tryptophan limitation protects laboratory animals against renal and hepatic

ischemia damage and decreases inflammation in connection with lower serum insulin-like growth factor, which also limits the damaging effects of aging (Wu et al. 2022).

A protein-based diet comes from two different sources, i.e., animal and plant-derived protein diets. The effects of plant and animal protein on aging are not the same. A senior population research study found that people aged 50–65 years who ingested a lot of protein had a 75% increase in overall mortality and a fourfold increase in their chance of dying from cancer (Levine et al. 2014). Age-related illnesses such as excess weight gain are found to be less common in populations taking plant protein than animal protein. The probable reason could be that plant proteins have far less methionine than animal proteins, and this low methionine level may explain why dietary plant proteins are advantageous in physiologic aging (Foscolou et al. 2021). In contrast, there are reports that plant-based protein is not sufficient enough to cope with daily dietary requirements, so animal protein has to be supplemented to meet the age-related protein demand. Thus, evaluating the effect of lower protein consumption on longevity may appear to be a simple research subject. However, nutritional geometry has demonstrated that assessing the influence of protein limitation on longevity cannot be determined by merely lowering the protein content of meals (Simpson et al. 2017b).

Among the various bodily changes during the aging process, skeletal muscle mass and strength deteriorate to a greater extent. A study reported that age-related changes in sarcopenia can be attenuated by dietary protein and exercise in the older population. Several nitrogen balance studies in people ranging in age from 56 to 80 years old have revealed that greater protein consumption (1.4–1.6 g/kg/day) might be beneficial for older people. Individuals who consume more protein lose less lean mass as they age (Naseeb and Volpe 2017). In contrast, a health, aging, and body composition study found that dietary protein consumption was not linked with a 5-year change in mid-thigh muscle cross-sectional area measured by computed tomography in older people (Tuttiett et al. 2021). Thus, the effect of a protein diet on skeletal muscle in the elderly population is still debatable. Apart from protein intake, timing of protein intake also affects the aging process, especially in relation to sarcoplasmic reticulum synthesis and turnover in older adults. Another study correlated the impact of dietary protein on lifespan and metabolic health, i.e., amino acids, methionine, and branched-chain amino acids, have been linked to the control of lifespan and metabolism by influencing glucose and lipid metabolism, improving antioxidant status, etc. (Kitada et al. 2019). Although long-term protein intake is associated with aging effects, one study reported that protein supplementation for a shorter duration of time does not increase the feeling of food carving and appetite in middle-aged adult populations. Apart from this, anabolic resistance has been shown in older individuals, where higher quantities of protein are required to drive muscle protein synthesis and the response is varied. As a result, the recommended daily protein intake for elderly people is higher. Many of the proposed pathways for anabolic resistance include the gut flora, either directly or indirectly. The gut microbiota changes with age and is greatly impacted by the amount of protein consumed, which in turn is reflected in the functional role of skeletal muscle during the various

stages of the aging process (Ni Lochlainn et al. 2018). Expanding on this, load-dependent gut hormone plasma cholecystokinin and gastric inhibitory polypeptide responses to orally consumed whey protein were larger in older people than in younger adults (Tuttiett et al. 2021). In addition to this, the cardio vascular response to the dietary protein intake showed a fall in blood pressure despite an increase in heart rate (Giezenaar et al. 2021). Alternative research reported that the fractional synthesis rate of albumin, which plays a variety of roles in living organisms, responded well to the aging process of older people (Thalacker-Mercer et al. 2007). Further, another concept of nutritional approach, protein pulse feeding – a combination of protein-rich and low-diet in the elderly population, showed positive effects like optimizing anabolic density, exhibiting positive nitrogen balance (Dickerson 2016), etc. in the elderly population. To summarize the effects of protein diet on aging, we can say that we are still learning about the potential benefits and challenges of optimizing dietary protein intake in older people. Eating enough high-quality protein at each meal, combined with physical activity, may delay the onset of damaging aging effects.

8.5 Contribution of Fat (Lipids) on Aging

The major structures in biological membranes are dietary lipid components such as fatty acids, phospholipids, cholesterol, and triglycerides. Aging is greatly impacted by dietary lipids. Generally, a high-fat diet regardless of age affects the various organ systems, especially arthrosclerosis, hypertension, and other cardio-vascular diseases. Further, diabetes has a strong link with dietary lipids, which in turn affects the mortality rate from adulthood to old age (Kurozumi et al. 2016). At the same time, there are dietary lipids which are beneficial to health. Hence, dietary lipids have a dual role of both protective and damaging effects in the physiological process of aging. Sirtuin1, a NAD-dependent protein deacetylase, peroxisome proliferator-activated receptors, sterol regulatory element-binding protein 1, carbohydrate-responsive element-binding protein, superoxide dismutase 3, caspase-1, etc. are the common genetic factors that regulate high-fat diet-induced pathology in the aging process. Among the above, Sirtuin 1 was found to be a key factor which controls the changes associated with aging (Gao et al. 2020). In experimental study, a high-fat diet induces a spike in fat mass and worsens the age-linked damage to muscular performance. The probable reason could be due to the quicker build-up of intramyocellular lipids and the initiation of muscle dysfunction in older people than in young adult organisms (Degens et al. 2021). Adding to this, rats fed with high fat diets exhibit structural modification in the pancreas, which causes inflammation and accelerates oxidative damage and aging (Kvitnitskaya-Ryzhova et al. 2021). In the same manner, age-related changes were observed in non-alcoholic steatohepatitis. A non-alcoholic fatty liver disease experimental study suggested that animals fed a high-fat diet cause lipid accumulation in the liver and promote liver aging (Gao et al. 2020).

Dietary lipids have a direct effect on blood cholesterol level, as the cholesterol level increases, it causes damage to various vital functions and accelerates aging. It also leads to the development of various acute and chronic illnesses and may end up with the faster death of an individual. Dietary trans fats increase the blood level of low-density lipoproteins (bad cholesterol) and reduce the high-density lipoproteins (good cholesterol), which directly affects aging and shortens the life span of an individual. If the diet contains more natural unsaturated fatty acids, then it decreases age-related illness and lowers the mortality rate (DiNicolantonio and O'Keefe 2018). Significant evidence supports the idea that systemic insulin-like growth factor-I activity dictates the rate of aging. A study reported that a low-fat diet in addition to other strategies down regulates the insulin-like growth factor-I and ends up with the slowness of the aging process (McCarty 2003). In another study, omega-3 polyunsaturated fatty acids, particularly those found in fish, are well acknowledged to have anti-inflammatory qualities that aid in the prevention of degenerative diseases linked with aging (Troesch et al. 2020). According to another study, a diet high in n-6 poly unsaturated fatty acids and low in n-3 poly unsaturated fatty acids promotes low grade chronic inflammation, resulting in dysregulation of the mesenchymal stem-cell lineage, obesity, and osteoporosis, which is interlinked with aging (Liput et al. 2021). According to the above study, fatty acids also increase cognitive function in people with mild cognitive impairment. Thus, to conclude, in the diet pattern specific to the elderly population, it must contain more low-density lipoprotein and less trans fats to maintain healthy and successful aging.

8.6 Caloric Restriction and Macronutrients vs. Aging

Calorie restriction is a diet pattern that limits food intake without causing malnutrition. A person's calorie intake is reduced voluntarily to lose weight. It is indicated as a viable regimen for body weight control by US dietary standards and scientific bodies. Reduction of 1/3 of caloric intake without affecting nutrient requirements has been found to alleviate aging diseases such as cancer, cardiovascular disease, dementia, and diabetes in humans (Kökten et al. 2021). Further, it also causes weight loss of up to 8 kg. However, further research is necessary with a wide variety of populations across the world. The term caloric restriction is a contentious term that refers to either a total calorie restriction or a reduction in specific macronutrients such as carbohydrate, protein, or fat (or a combination of the two). Because conventional caloric restriction entails a reduction in total food availability, which leads to a reduction in all macronutrients, plenty of research articles have proved that protein and particularly amino acid restriction are the reasons behind the health benefits of caloric restriction. Studies in experimental organisms' report that restriction of certain amino acids leads to the activation of genes that are responsible for stress, which leads to anti-aging effects and an extension of life span (Le Couteur et al. 2020). In another comparative study in a fly, it was observed that when the protein:

carbohydrate dietary ratio was increased from 1:4 to 1:6, it caused an increase in the life expectancy of the fly (Fanson and Taylor 2012). Extending from this, protein restriction in their routine has been shown to extend life and reduce disease risk in study animals. The reason for much of the beneficial effects due to calorie restriction is the alteration in functional capacity of several nutrient-sensing pathways. Many experimental approaches have been documented to understand the mechanistic action of nutrient-sensing pathways that mediate the effects of macronutrients and aging. The significant contributors to the nutrient sensing pathways are (as mentioned earlier) mammalian target of rapamycin protein, AMP-activated protein kinase, insulin/Insulin-like growth factor-1, and Sirtuin (Efeyan et al. 2015). These regulators interact with one another and share many downstream targets that regulate aging-related cellular activities like mitochondrial production, cellular metabolic activity, autophagy, genetic expression, and protein translation and delay aging (Fig. 8.2). Furthermore, recently, a bunch of research has been initiated to address the interactions between macronutrients and explain the importance of macronutrient balance on health and aging. The Geometric Framework for Nutrition was used to generate details related to such macronutrient interactions. In this, nutrition is defined in an *n*-dimensional space, where n represents macronutrient components. Lifespan can be demonstrated in this *n*-dimensional space, providing a detailed picture of the effects of nutrition. Using this framework allows the use of nutritional geometry to simultaneously interpret the effects of energy, individual macronutrients, and the interactions within and between nutrients. This framework has helped to resolve conflicting ideas about the nutritional determinants of health and aging and to reconcile views on resource-mediated trade-offs between reproduction and longevity. This *n*-dimensional space can be used to explain the lifespan, with a clear idea of the effect of macronutrients' functional effects on aging (Efeyan et al. 2015).

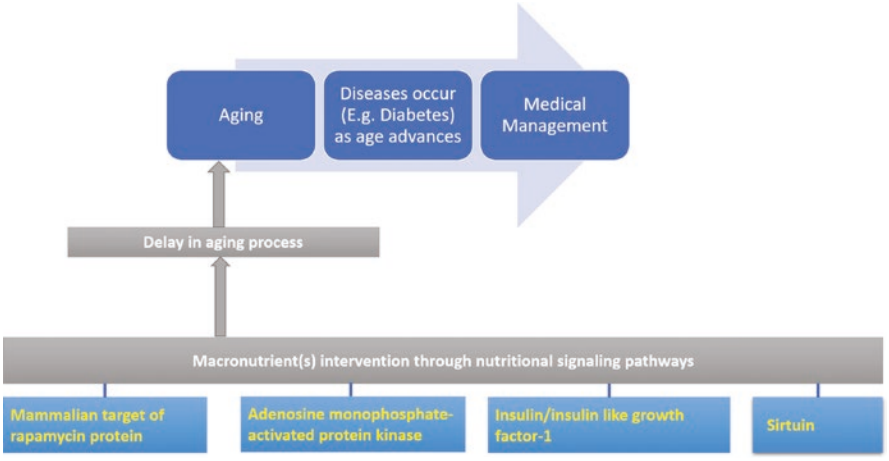

Fig. 8.2 Macronutrients intervention and aging

8.7 Macronutrient Components for Longevity

With the growth of macronutrient-based diets, from low-fat to low-carbohydrate, discussion of the three basic macronutrients – carbohydrate, proteins, and fats has become routine when discussing ideal diets. Researchers have begun comparing various "macronutrient management"-style diets to see which is the most successful. Older people have fewer appetites and a lower caloric need, so they may require more nutrients than they did previously. Their living patterns differ as well, which might influence the meals they consume. Fewer macronutrients are absorbed because of decreased physical activity and calorie intake, leading to the development of certain nutritional deficiencies. The chance of getting osteoporosis, heart disease, and other chronic conditions rises with age. Further, clinical malnutrition in aging is caused by an imbalance between macronutrient intake and need, resulting in a detectable decrease in tissue and, eventually, weight. As a result, enough calorie intake and greater protein consumption are required as people grow. Proper protein consumption is critical to preventing malnutrition. Protein consumption recommendations are mostly based on the idea of anabolic resistance, which describes the muscle's diminished ability to respond to anabolic stimuli as we age. However, protein consumption in older people has been observed to be regularly substantially below recommended intake, which is associated with a higher risk of malnutrition development. Protein catabolism can be severe as well, depending on the type of malnutrition and underlying condition. Protein needs are greatly increased in malnourished or diseased elderly individuals. Based on the literature search, it was found that a high-protein, low-calorie diet can help obese older people lose more weight while retaining muscle mass and enhancing bone density. The findings of the other three studies imply that a macronutrient-based dietary strategy may have some advantages, but research also reveals that although one macronutrient diet may result in weight loss for one person, it may not be beneficial for another owing to individual variances in genes and lifestyle. Another study reported that a low carbohydrate diet is highly beneficial for elderly people. Expanding on this low carbohydrate diet, a low-fat diet is also beneficial in the geriatric population. As a result, a low carbohydrate, high protein, low fat diet with a low-calorie count may be an ideal macronutrient component for aging. Still, a few authors suggest that there is no such thing as the "ideal" one-size-fits-all diet in the aging process. Hence, further macronutrient-based research studies must be done in a larger population at the molecular level to confirm the findings.

The longevity diet is a complex phenomenon involving genetics, the living environment, behaviour, and eating habits. The assumption that eating habits have a significant impact on longevity has shifted the focus to nutrition for longevity. The most popular diets associated with longevity aging are Japanese (Abe et al. 2020), fast-mimicking (Brandhorst and Longo 2019), Okinawa (Gavrilova and Gavrilov 2012), Mediterranean (Trichopoulou et al. 2003), and vegan diets (Norman and

Table 8.1 Macronutrient composition of various antiaging diet

S. No	Diet type	Carbohydrate	Protein (%)	Fat (%)
1	Japanese diet	65%	10	25
2	Okinawa diet	85%	9	6
3	Fasting-mimicking diet	Day 1: 34%	10	56
		Days 2–5: 47%	9	44
4	Mediterranean diet	50%	15	35
5	Vegan diet	30%	40	30

The values for carbohydrate, protein and fat are given in percentage of total energy. The standard deviation range for the above-mentioned diet is ±5%

Klaus 2020). Table 8.1 shows the macronutrient composition of the aforementioned diets. Japanese diet is an anti-aging diet that has been extensively explored since the Japanese population's life expectancy has steadily increased. Rice, noodles, fish, eggs, soy products, seaweed, seasonal vegetables, and green tea are traditional long-term health foods in the Japanese diet. Fasting-mimicking diet is a 5-day dietary programme that provides vital nutrients while being modest in total calories, protein, and sugar. It is believed that it regulates calorie restriction. However, it is not designed to be a long-term diet plan. Hence, it can be followed intermittently throughout the year for healthy aging. The traditional Okinawan diet is heavy in carbohydrates and low in calories and fat. It emphasises veggies and soy products, with minor portions of noodles, rice, pork, and fish. Mediterranean diet is built on plant-based foods such as whole grains, vegetables, legumes, fruits, nuts, seeds, herbs, and spices. The major source of additional fat is olive oil. In moderation, fish, seafood, dairy, and chicken are allowed. Red meat and sweets are only consumed on rare occasions. Vegan or plant-based diet which does not include any animal products, such as meat, dairy, or eggs. A vegan diet, when followed correctly, may be very nutritious, minimise the risk of chronic illnesses, and assist in weight loss.

8.8 Conclusion

Macro nutritional requirements fluctuate as people become older and it widely affects aging process. To meet the dietary and nutritional demands of senior persons, dietary recommendations should be differentiated by age. Energy demands drops down when metabolism slows, but because gastro intestinal absorption becomes less effective, there is a greater need for nutrient-dense meals, which often include more macronutrients nutrients (particularly carbohydrate, protein and fat). To achieve a healthy aging, the recommended micronutrients must be supplemented as per country specific guidelines. Further, age, sex, race, ethnicity, physical activity must be taken into consideration for successful aging.

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Chapter 9
Micronutrient Status Among Adults in the Asia Pacific and Potential Impact on Age-Related Diseases

Stephen French, Taichi Inui, and Akiko Kuwabara

Abstract Improving micronutrient status of populations provides a cost-effective mechanism to help improve health status. The Asia-Pacific region is home to some of the world's most rapidly ageing populations, and many of the non-communicable diseases associated with older age can be positively impacted by adequate and optimal micronutrient status.

Multiple factors can impact the ease of achieving optimal dietary micronutrient intakes, including socio-economic and cultural factors. Ageing, associated diseases, and certain medications can also impact the ability to achieve micronutrient intakes. Therefore dietary, fortification and supplementation interventions should be considered to help attain optimal micronutrient intakes.

However, targeting micronutrient interventions can be hampered by inadequate dietary intake data from national surveys.

In this chapter, we review the health issues associated with ageing and the role that micronutrients can play in helping to reduce risk. Based on the existing intake data, there was a high prevalence of insufficiency of vitamins A, D, E, C, B-6, B-12, folate, and for zinc in many countries. We also present analysis to suggest that, in the absence of raw data from dietary surveys, the use of mean and standard deviation (SD) is the best data to use when estimating micronutrient status among populations.

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Keywords Micronutrient intake · Age-related disease · Micronutrient insufficiency · Dietary survey · Micronutrient intervention

9.1 Introduction

The Asia-Pacific (APAC) region has a rapidly ageing population and is home to some of the most aged nations in the world (United Nations 2017). APAC countries, alongside other areas of the world, have been impacted by the double burden of malnutrition, characterised by the coexistence of undernutrition along with overweight, obesity and diet-related noncommunicable diseases (NCDs) (WHO 2017). This double burden can be observed at an individual, household, or population level and has multiple drivers of dietary shifts, relative affordability and availability of different foods, urbanisation and mechanisation, and demographic shifts to an ageing population.

Life expectancies are increasing and birth rates decreasing, leading to the overall demographic shifts to an ageing population and increasing burdens of health and social care for elderly populations (Inui et al. 2021). These effects are further exacerbated by NCD impacting health status of older individuals and the increasing time span requiring health interventions. Nutrition and lifestyle are two factors that are modifiable and can have significant impacts on health throughout life and particularly in later life.

Currently, global food systems in many low- and middle-income countries (LMICs) are not delivering nutritionally adequate diets across all populations, resulting in deficiencies in essential micronutrients (Mkambula et al. 2020). Micronutrients play an important role in maintaining health, including key health conditions at a later stage of life (Péter et al. 2015). The impacts of micronutrient deficiencies on the development of specific diseases have been well understood and investigated for many decades. We are now beginning to understand the importance of micronutrients in long term health maintenance and optimal health, with increasing evidence to support the role of specific micronutrients to contribute to health throughout the lifespan. However, the specific impacts of individual micronutrients and causal relationships between micronutrients and disease end-state are often lacking. This is further impacted by inconsistent, and sometimes lacking, national reporting of diet and micronutrient status across populations.

In this chapter, we provide a brief overview of the role of micronutrients in NCDs most prevalent in ageing populations, which include vision, cardiovascular health, cognitive functions, mobility and immunity. To assess micronutrient intakes, we also provide analysis of the data from national nutrition intake surveys and peer reviewed journal assessments of the micronutrient gap against the Dietary Reference Intakes (DRIs) of the national RDIs, and assess different methods of summarising population data for accuracy when compared with raw data. We also briefly review the challenges to meeting dietary recommendations for micronutrient intake and the roles that fortification and supplementation can play in helping to meet these recommendations.

9.2 Diet, Health and Ageing in the Asia-Pacific Region

The Asia-Pacific region is home to many of the most rapidly ageing populations in the world. 12% of the Asian population was above 60 years in 2017, and this is projected to reach 24% by 2050. The average life expectancy in the Association of Southeast Asian Nations (ASEAN) countries is 71 years, which reaches 75 years in Thailand, Vietnam and Malaysia, and just under 83 years in Singapore (United Nations 2017).

Ageing, alongside poor diets and lifestyles is leading to rising levels of NCDs which impact healthy life expectancy and the time of onset of deterioration in health as a function of total life expectancy. Therefore, although people are living longer, they are spending a greater period of later life in poor health (WHO 2020a). This does not only impact the individual; diseases such as type II diabetes, cardiovascular disease (CVD) and dementia significantly impact quality of life and place significant burdens on healthcare and social systems. The impacts of ageing and poor health on healthcare and social systems are compounded as birth rates across the region are below those needed for population replacement (United Nations 2017; Inui et al. 2021), and hence greater reliance outside of the immediate family to support individuals is needed.

One measure of the health quality in later life is the measure of disability-adjusted life years (DALYs); one DALY represents the loss of the equivalent of 1 year of full health. DALYs for a disease or health condition are the sum of the years of life lost (YLLs) due to premature mortality and the years lived with a disability (YLDs) due to prevalent cases of the disease or health condition in a population (WHO 2020b).

Figure 9.1 shows the gap between total life expectancy and healthy life expectancy, and hence the potential impact on the individual and burden on health and social care systems. The gap can be as great as 10 years in certain populations. Therefore, any interventions that can improve health through the lifespan can bring potentially significant benefits.

The leading causes of DALY In the Asia-Pacific region per age group include CVD (primarily ischemic heart disease and stroke); malignant neoplasms (cancers); neurological diseases (including depression and anxiety, Alzheimer's disease and other dementia particularly in older age groups); respiratory diseases, and falls/frailty (WHO 2019). Figure 9.2 shows the major health issues across the Asia Pacific region.

It can be seen from this data that the major non-communicable diseases are present, and increasing in prevalence, throughout adulthood into older age.

Data is expressed as Disability Adjusted Life Year per 1000 population. Each color-coded band is expressed as the percentage of the health condition in total DALY for the age group. Asia-Pacific data was calculated on weighted arithmetic means by population between data from the South-East Asia Region and the Western Pacific Region.

Multiple factors contribute to health throughout the lifespan. In addition to energy intake and physical activity, micronutrients play an important role in

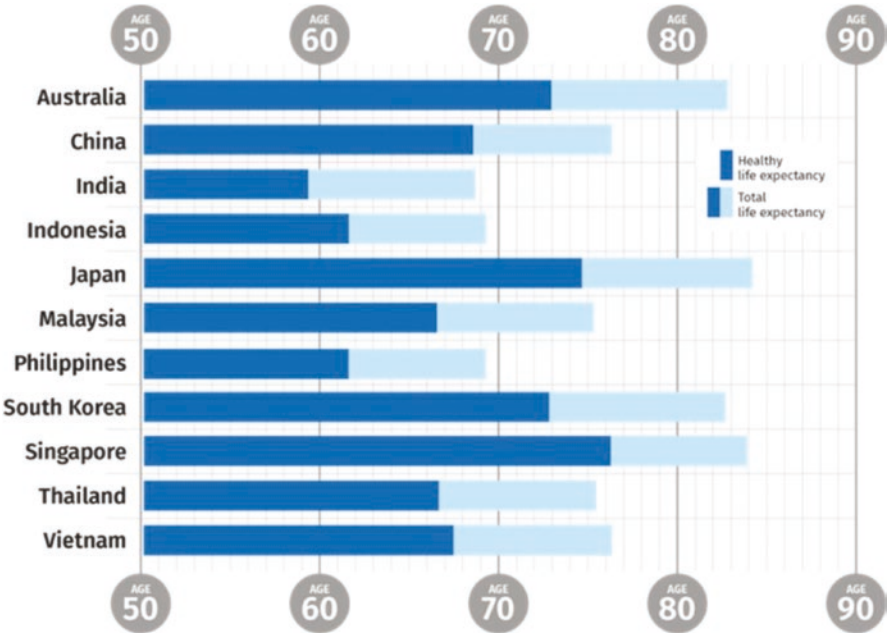

Fig. 9.1 The gap between total life expectancy (TLE) and healthy life expectancy (HLE) among selected APAC countries (data for both sexes) (WHO 2020a; Inui et al. 2021)

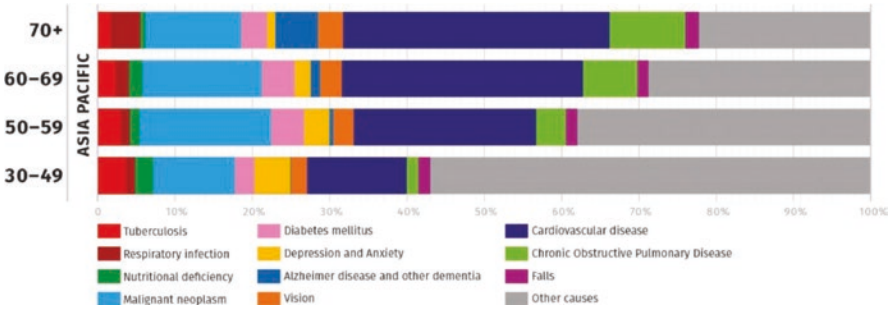

Fig. 9.2 Key health issues in the APAC region per age group (Inui et al. 2021)

maintaining health throughout life, including key health conditions in later stages of life. The impact of micronutrient deficiencies on disease occurrence has been widely investigated for many decades, with well recognised relationships between specific micronutrient deficiencies and disease states (Marriott et al. 2020). Whereas

much investigation has taken place relating to the effects of deficiencies of micronutrients leading to disease states, the concept of optimal health has risen in recent years, and we are beginning to understand that achieving optimal levels of micronutrients in the diet can support health throughout life. Optimal nutrition throughout life can support healthy ageing and can contribute to delaying or avoiding the onset of NCDs impacting DALYs. As mentioned previously, research into the role of optimal nutrition supporting health has received less attention until relatively recently.

9.3 Nutrition Gap Analysis

Understanding the micronutrient status at a population level across Asia-Pacific countries is important to assess the potential impacts on overall nutrition and health status, and to identify nutritional gaps especially for the micronutrients that have been reported to impact on the progression and onset of age-associated health conditions. However, the reporting format of national nutrition surveys differs between countries and access to the raw data is often restricted. This makes analysis and comparison between countries complex. Hence, we have recently determined which representative values are required to estimate the distribution of nutrition intake without raw data. To validate the estimation method of the nutritional intake distribution by a representative value obtained from national health surveys, the raw data of National Health and Nutrition Survey 2017 (NHNS 2017) in Japan was obtained from the Ministry of Health, Labour and Welfare (MHLW) of Japan, and used for analyses. The raw NHNS data were utilised after approval by the MHLW through official application procedures under Article 33 of the Statistics Act.

The methodology and data are summarised in the Supplemental Data section to this chapter. Briefly, the estimated average intake (EAR) cut-point method was used to estimate the prevalence of inadequate micronutrient intakes (Beaton 1994; WHO 2006). The probability density at the point of EAR of DRIs for Japanese was calculated by log-normal distribution (Johnson et al. 1994) using the 'μ and σ^2' calculated by three parameter combinations as the estimated prevalence of %below EAR. The three parameter combinations were:

1. the value of mean and standard deviation
2. the value of mean and median
3. the value of median and interquartile range (IQR)

The observed prevalence of %below EAR was also calculated from the raw NHNS data. To validate the estimation methods of nutritional intake distribution, a comparison of prevalence of %below EAR between estimated and

observed was made by one-sample *t*-test. The observed value, which is derived from the raw NHNS data is considered the most accurate value. Estimated values among three parameter combinations showed a range of values with as much as 10% differences from the raw NHNS data for %below EAR prevalence (Supplemental Table 9.1). The results suggested that the prevalence of %below EAR was most proximate to the raw NHNS data when it was derived from the combination of mean and SD. Validation of the estimated values derived from mean and SD were tested for the other micronutrients included in the analysis. The results showed the estimated log-normal distributions calculated by the combination of mean and SD were not significantly different from the value derived from the raw NHNS data across gender and age groups (Supplemental Table 9.2). Finally, the estimated prevalence of inadequate micronutrient intake for each nutrient was validated using the percentage of subjects with inadequate nutrient intake, calculated either by the cut-point method using the raw NHNS data (reference method) or from the sex- and age-specific mean and SD from NHNS 2017 for all the micronutrients analysed except of niacin and vitamin D. Niacin was excluded because the raw NHNS data did not provide the proportion of niacin equivalent derived from tryptophan (Supplemental Table 9.3). The results described that the ranking of nutrients according to the proportion of subjects with inadequate intakes was in general agreement with the observed data in both gender and age. Therefore, estimates can be made using only mean and SD and would have practical value in assessing the prevalence of inadequate micronutrient intake.

Table 9.1 Intakes for men and women aged 50 years and over in each country were obtained from national survey data. Data with mean and SD values were preferentially referred to, and incases where SD values were not given, the mean and median values were used to calculate the proportion of those whose intake was below the EAR

	Australia		India		Indonesia		Japan		Korea		Malaysia		New Zealand		Philippines	
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
Vitamin A	3%	3%	54%	54%	12%	15%	74%	67%	81%	81%	75%	81%	36%	13%	68%	70%
Vitamin D	18%	18%	76%	76%	73%	73%	54%	54%	50%	68%	100%	100%	26%	26%	NA	NA
Vitamin E	68%	56%	66%	66%	97%	97%	54%	48%	36%	30%	NA	NA	42%	17%	99%	100%
Vitamin B1	NA	NA	73%	73%	98%	90%	69%	64%	42%	39%	76%	82%	19%	32%	NA	NA
Vitamin B2	43%	43%	97%	97%	97%	94%	50%	40%	52%	55%	4%	4%	11%	8%	84%	NA
Niacin	6%	9%	73%	73%	5%	5%	0%	0%	49%	44%	NA	NA	0%	0%	8%	36%
Vitamin B6	66%	72%	NA	NA	94%	95%	39%	42%	6%	12%	NA	NA	34%	42%	51%	66%
Folate	25%	36%	91%	91%	71%	70%	16%	20%	0%	7%	71%	71%	29%	38%	88%	90%
Vitamin B12	46%	42%	100%	100%	28%	35%	13%	17%	12%	12%	4%	4%	12%	16%	5%	19%
Vitamin C	30%	31%	55%	55%	90%	88%	42%	40%	77%	75%	67%	74%	15%	1%	95%	96%
Calcium	76%	83%	45%	45%	99%	77%	67%	62%	67%	75%	96%	95%	70%	92%	97%	98%
Iron	22%	24%	90%	90%	62%	66%	28%	21%	20%	35%	72%	72%	1%	1%	76%	80%
Zinc	68%	45%	100%	100%	98%	100%	56%	47%	63%	55%	NA	NA	73%	18%	49%	NA

%below EAR >75% | %below EAR 50-75 | %below EAR 25-50 | %below EAR 2.5-25 | %below EAR <2.5% | NA

9.4 Assessment of Nutritional Gap in Asia-Pacific Countries

Using the methodology described above, national data from countries across the Asia Pacific region were analysed for a range of micronutrients (see Table 9.1 for full list of micronutrients and countries assessed). As can be seen, data are missing in certain countries for some micronutrients. Data are presented as percentage of the population who are below the Estimated Average Requirement (EAR) for that micronutrient against EAR set in national RDI. Where national RDI did not state EAR, we used EAR by US IOM.

The insufficiency of calcium was highly prevalent in all countries among senior adults. There was also a high prevalence of insufficiency of vitamins A, D, E, C, B-6, B-12, folate, and for zinc in many countries (Table 9.1). Generally, higher socio-economic countries in the region tend to have lower overall levels of micronutrient insufficiency (Australia, New Zealand South Korea, Japan, Malaysia and Thailand), however all countries have more than 50% of the population below the EAR for at least 1 micronutrient. These data correspond with previous studies, which have been summarised recently (Inui et al. 2021).

9.5 The Role of Nutrition in Health Ageing in Asia

Examples of the importance of achieving optimal micronutrient status during earlier life stages to improving health in later life include:

9.5.1 Osteoporosis

Osteoporosis is a bone disease that develops when bone mineral density and bone mass decreases, or when the quality or structure of bone changes. This can lead to a decrease in bone strength that can increase the risk of fractures. Osteoporosis tends to be asymptomatic until the point that a fracture occurs. Osteoporosis is the major cause of fractures in postmenopausal women and in older men and tends to be a greater issue for women than men.

Bone mass increases during early life and reaches a peak in women in early adulthood, levels tend to remain stable until menopause and then sees a rapid decline in the first years post menopause which slows but continues to decline through the remainder of life. Several dietary factors, alongside weight bearing exercise are important in achieving peak bone mass; these include protein, vitamin D and calcium intake (Lewis et al. 2021). Calcium and vitamin D intakes during teenage and early adulthood improve bone density and peak bone mass; this can significantly improve later life development of osteoporosis and slow the development of the multiple causes of frailty in the elderly. It is important to note that weight bearing exercise and protein intakes are important to maintain bone mass.

9.5.2 Cardiovascular Disease

Coronary heart disease and stroke are the most common causes of mortality and morbidity globally for people over the age of 60 (GBD 2016). Cessation of tobacco use, reduction of salt in the diet, eating more fruit and vegetables, regular physical activity and avoiding harmful use of alcohol have been shown to reduce the risk of cardiovascular disease (WHO 2021a). Additionally, replacing saturated fat with mono- and polyunsaturated fatty acids, such as omega-3 long chain polyunsaturated fatty acids (EPA and DHA) have been recognised by authoritative bodies such as The European Food Safety Authority (EFSA) in maintaining healthy cardiac function (EFSA 2022).

Two major studies have investigated the effects of vitamin D and omega-3 long chain polyunsaturated fatty acids (LC-PUFAs). The VITAL study showed LC-PUFA did reduce risk of these events by 19% in people with low fish intake although but not in the overall study population. LC-PUFA also reduced risk of heart attack by 28%, when considered separately from other cardiovascular events (Manson et al. 2019). Vitamin D supplementation did not reduce risk of major cardiovascular events, however the study found that participants already had vitamin D levels in the optimal range at the beginning of the study. The REDUCE-IT trial found a 25% reduction in risk in the primary endpoints of cardiovascular death, myocardial infarction and stroke, as well as improvement in secondary endpoints including blood pressure and plasma cholesterol levels (Bhatt et al. 2019). In a recent meta-analysis, although no effect was seen for the commonly used multivitamins, vitamin D, calcium, and vitamin C, folic acid and B-complex vitamins had a significant effect for stroke reduction (Jenkins et al. 2021).

9.5.3 Dementia

Cognitive decline is a major issue in ageing. From the age of around 60 the brain begins to shrink at a rate of approximately 0.5% per year, and for people with mild cognitive impairment, this accelerates to approximately 3% a year (Jernerén et al. 2015). Atrophy in the cerebral cortex and the hippocampus have been associated with elevated homocysteine levels. A recent consensus statement concluded that elevated plasma total homocysteine is a modifiable risk factor for development of cognitive decline, dementia and Alzheimer's disease in older people (Smith et al. 2018). B-vitamins have been shown to reduce levels of serum total homocysteine (tHcy), as vitamin B-6, folate and vitamin B-12 are co-factors in the conversion of homocysteine to methionine. Atrophy rates were reduced in subjects taking dietary supplements containing vitamin B-6, folic acid, and vitamin B-12 and who had sufficient omega-3 LC-PUFA status (Jernerén et al. 2015).

9.5.4 Immunity

Immune functions generally decline with age, increasing susceptibility to infectious diseases and leading to poorer responses to vaccination (Castelo-Branco and Soveral 2013). Many vitamins and trace elements have been shown to play an important role in supporting cells and tissues of the immune system (Calder et al. 2020). Of these, the best available evidence has been shown for vitamins C and D, and the trace element zinc (Gombart et al. 2020; Abioye et al. 2021). A meta-analysis of data for almost 11,000 people reported that overall taking vitamin D supplement reduced the risk of having at least one upper respiratory tract infection (Martineau et al. 2017; Jolliffe et al. 2021).

9.5.5 Vision

The prevalence of visual impairment increases markedly in later life. The main factors associated with visual impairment in the elderly are amyotrophy, cataracts and acute macular degeneration (AMD) (WHO 2021b). Oxidative stress is one of the main causes of lens opacification and therefore antioxidant nutrients have been investigated for effects on reducing the risk of development of cataracts. One meta-analysis concluded that supplementation of vitamin A, vitamin E, vitamin C, beta-carotene, lutein and zeaxanthin was associated with a reduced risk of age-related cataracts (Jiang et al. 2019). Two further large studies in humans (AREDS 1 and 2) demonstrated that ingestion of dietary supplements containing vitamin C, vitamin E, zinc, iron and the carotenoids lutein and zeaxanthin reduced the risk of the progression of advanced AMD, with individuals taking lutein and zeaxanthin, alone or in combination with DHA and EPA, having a 10% reduction in the risk of developing advanced AMD (National Eye Institute 2022). The roles of omega-3 LC-PUFAs (DHA), vitamin A and zinc in maintaining normal vision are acknowledged by EFSA (EFSA 2022).

9.5.6 Cancer

Several studies have shown associations between markers of micronutrient status for various micronutrients and cancer prevalence. Many of these findings may represent micronutrients as markers of overall dietary quality (fruit, vegetable, or fibre consumption for example), and causality between specific micronutrient interventions and outcome cannot be determined from these studies (Aune et al. 2018; Dong et al. 2017; Chowdhury et al. 2014; Maalmi et al. 2018; Schwingshackl et al. 2017; Bjelakovic et al. 2012). Furthermore, care is needed as several associations between

specific micronutrient supplements and increased cancer risk have been identified. To better understand the complex role of micronutrients per se and specific cancer disease outcomes, more randomised control intervention trials are needed.

It is not within the scope of this chapter to review all the relationships and strength of evidence supporting the role of micronutrients to the main health issues related to ageing. These have been extensively reviewed recently (Inui et al. 2021).

The Global Burden of Disease study showed that in 2017, 11 million deaths and 255 million DALYs were attributable to dietary risk factors (GBD 2017). The major NCDs impacting DALYs can be significantly impacted by diet and lifestyle. There is also increasing evidence to show that micronutrient intakes throughout life can impact the onset and development of NCDs in later life. This report also identified micronutrient interventions as the best return on investment. Additionally, three of the top five challenges to improve global welfare outlined in the 2008 Copenhagen Consensus are related to improving micronutrient status (Copenhagen Consensus Centre 2008).

9.6 Challenges to Achieving Optimal Micronutrient Intakes

As described earlier, there is increasing evidence that achieving an optimal micronutrient intake throughout life stages is important to support health into ageing. Furthermore, multiple micronutrients play a role in overall health, and it is likely that complex interactions between micronutrients and other dietary factors exist. Existing randomised controlled studies suggest the intervention may be more impactful when applied to those with insufficient baseline intake. Currently available national data concerning intake of certain micronutrients is incomplete which makes it challenging. Multiple elements exist in impacting the micronutrient intake. Two drivers that increase the risk of micronutrient insufficiency among elderly are drug-nutrient interactions and decreased food intake.

9.6.1 Drug Interactions

Drug interactions can affect the absorption and/or metabolism of vitamins, contributing to malnutrition. Additionally certain medical treatments, including cancer chemotherapy can suppress appetite. Acid suppressing drugs and proton pump inhibitors, anti-hypertensives and diuretics, and medicines to treat diabetes can all affect micronutrient status (Onoue et al. 2018; Mohn et al. 2018; König et al. 2017). These treatments can make achieving adequate micronutrient intakes more challenging. The term polypharmacy has been defined as the use of 5 or more oral prescription medications per month (Onoue et al. 2018). Polypharmacy and hyperpolypharmacy (more than ten medicines) increase the risk of unwanted drug interactions, and a wide range of prescription medications can increase the risk of

nutritional inadequacy (Mohn et al. 2018). The prevalence of polypharmacy varies amongst populations in Asia, and more research is required to define any specific problems and relevant nutritional interventions.

9.6.2 Decreased Food Intake

Ageing itself presents problems in meeting adequate nutritional status. Energy metabolism and lean body mass decrease as people age, leading to a decreasing need for energy, reduced appetite, and lower intake. Despite this decrease energy need, micronutrient requirements remain and need to be met. This has led to the concept of hidden hunger in the elderly and can be further compounded for micronutrients in which metabolism and absorption are impaired with age, such as vitamins B-12 and D (Eggersdorfer et al. 2018). Oral disease and decrease in oral function can lead to difficulties in swallowing (dysphagia) which can in turn affect food intake leading to undernutrition; the prevalence of periodontal disease in a Center for Disease Control Study (CDC) from 2012 reported that 47.2% of adults over the age of 30 in US had some form of periodontal disease, and this increases to 70.1% for people over the age of 65 (Eke et al. 2012).

The difficulty in achieving adequate micronutrient intakes can be further compounded under certain dietary patterns. Certain micronutrients are found in higher density in foods of animal origin. Vitamin B12 deficiency has been found to be more prevalent amongst groups for whom a high intake of animal products is not possible for economic, cultural or religious reasons (Allen 2009). Anti-nutritional factors are compounds which reduce the nutrient utilisation and/or nutrient intake from plants or plant products used as human foods. For example, phytates and oxalates can inhibit the absorption of calcium and iron, and phenol compounds can inhibit the absorption of certain minerals (especially zinc). It is not within the scope of this chapter to review this area in detail; however, these have been recently reviewed elsewhere (Thakur et al. 2019).

Nutrient density is defined as the ratio of nutrient to energy, and therefore in situations where energy intakes or dietary choices are limited achieving the recommended micronutrient intakes becomes more challenging and the nutrient density of the foods consumed becomes more critical.

9.7 Potential Approaches to Optimise Nutrient Intakes

Because the barriers to achieving optimal micronutrient intakes are multifactorial, cross-disciplinary collaboration and approaches are needed to promote food intake with high micronutrient density. These can include consumer education, setting appropriate RDA, food labelling, and personalised nutritional advice. However as highlighted earlier in this chapter achieving optimal micronutrient levels is

challenging, and fortification and supplementation should be considered as safe and effective methods to deliver nutrients and meet recommendations for dietary intakes. Some countries are beginning to adapt dietary guidelines for the elderly focusing on, for example, nutrient dense foods, adapting diets to account for lower energy intakes (e.g. inclusion of snacks), particularly focusing on protein and calcium (See Inui et al. 2021 for further references).

9.7.1 Supplementation

Supplementation can be a useful adjunct to food-based approaches to improve micronutrient status. However, long-term compliance with supplementation programs has been suggested to be challenging to maintain, although this has been more successful in certain situations where the need for additional micronutrient intake is for a relatively short period of time (such as supplementation of pregnant and lactating women, or children in school) (Allen 2008). Folic acid supplementation during pregnancy and preconception has long been recommended by authoritative bodies such as US CDC and UK NHS (CDC 2022; NHS 2022). In 2021, multiple micronutrient supplements (MMS), containing 10 vitamins and 5 minerals, was added to the World Health Organization (WHO) model Essential Medicines List (EML) as an antenatal supplement for pregnant women (WHO 2021c).

9.7.2 Fortification Programmes

Several countries have implemented fortification of certain food categories, these have been demonstrated to be safe and effective. Some of these programmes are voluntary, whilst others have been implemented as mandatory fortification of certain foods.

One of the widest fortification programmes has been the fortification of salt with iodine. Iodine deficiency is a major cause of preventable mental retardation, and UNICEF estimate that worldwide, 89% of people consume iodised salt (UNICEF 2021).

Systematic vitamin D food fortification is an effective approach to improve vitamin D status in the general population and this has already been introduced by countries such as the US, Canada, India and Finland. Recent advances in our knowledge on the safety of vitamin D treatment, the dose-response relationship of vitamin D intake and 25(OH)D levels, as well as data on the effectiveness of vitamin D fortification in countries such as Finland provide a solid basis to introduce and modify vitamin D food fortification to improve public health with this likewise cost-effective approach.

Fortification of milk and dairy products with vitamin D in Finland has resulted in an increase to 91% of the population reaching the recommended levels of serum vitamin D biomarker concentrations (Jääskeläinen et al. 2017).

Many countries have regulations permitting voluntary fortification of calcium, and UK has mandatory fortification of flour (235–390 mg calcium carbonate per 100 g flour) (Cormick et al. 2020). An analysis in the UK assessed that if calcium fortification prevented 2% of fractures annually, stopping mandatory calcium fortification would increase social care costs by £3.06 million per year and by £22.39 million per year in the National Health Service (UK Government 1998). Sandman, in 2015, estimated that the annual costs for 200 mg calcium per day was EUR 0.22 per person in 2014 and that the implementation of a vitamin D plus calcium fortification program in Germany would cost EUR 41 million per year while saving EUR 315 million per year because of reduced fracture costs (Sandmann et al. 2015).

Mandatory folic acid fortification programs in the USA, Canada, Costa Rica, Chile, and South Africa are associated with significant increases in blood folate concentrations and declines of 25–50% in the prevalence of neural tube defect (NTD) affected pregnancies (Murphy and Westmark 2020). Reported NTDs in the USA decreased from 10.8/10,000 births in 1995–1996 to 6.9/10,000 births in 2006 (CDC 2010). A systematic review (179 studies) and meta-analysis (123 studies) covering the prevalence of spina bifida in response to folic acid fortification status, geographic region and study population indicate a lower prevalence of spina bifida in geographic regions with mandatory folic acid fortification (33.86 per 100,000 live births) versus voluntary fortification (48.35 per 100,000 live births) (Atta et al. 2016; March of Dimes 2006).

Fortified foods are also useful for sustainability. Food production has a significant impact on greenhouse gas emissions (Poore and Nemecek 2018), and meeting sustainability challenges will therefore also require shifts in dietary habits. Some governments have already included sustainability into national dietary guidelines (Lang 2017). Recently Bruins and Létinois (2021) modelled the dietary shifts needed to achieve vitamin D intakes whilst aiming to achieve limits to the carbon footprint expressed as kg CO_2 equivalents. This study showed that achieving adequate vitamin D intakes through diet alone was not possible without greatly increasing CO_2 equivalents or energy intakes above recommended levels. Inclusion of vitamin D fortified bread, milk and oil into the diet, alongside dietary shifts towards fish and plant based nutrient dense foods, did allow vitamin D intakes to be achieved within a 2000 kcal diet and without a significantly increased carbon emission. Whilst this study only assessed one micronutrient, and vitamin D status varies due to exposure to sunlight, it does highlight the complex interactions between diet, nutrient status and sustainability. Fortification itself had only minimal impacts on carbon footprint.

9.8 Discussion

As populations continue to age, and birth rates remain low, the focus on health through ageing is critical to ensure that the years of life lost to disability can be minimised. We have highlighted in this chapter some of the key nutrient interventions that can be effective to support health throughout the lifespan and particularly into older age. Key micronutrients that should be considered as insufficient are vitamin A

(under supervision), vitamin D, vitamin E, vitamin C, B vitamins, zinc, and Omega-3 LC PUFAs. There was also a high prevalence of insufficiency of vitamins A, D, E, C, B-6, B-12, folate, and for zinc in many countries. Multiple socio-economic factors and constraints on food systems impact on the ability of populations to meet adequate and optimal nutrient intakes. Having a clear understanding of these requirements are necessary to target appropriate interventions to address these nutritional gaps.

To analyse nutritional status at a population level effective monitoring is required. We have shown the importance of consistent reporting and analysis of population nutrition status to allow meaningful comparison and to support effective targeting of nutrition interventions. Currently national data are collected using a variety of methodologies and summary data are produced using different statistical methods making this comparison difficult. The data and analysis presented as supplemental data shows that, in the absence of raw data, the best proximate method for comparison is to use mean and SD.

Reviewing the available data from national nutrition surveys across APAC countries identifies a wide range of sub-optimal micronutrient levels in adulthood, and particularly in the over-50 age group. Several of the most common age related non-communicable diseases prevalent across the region can be positively impacted by nutritional status. As shown in Fig. 9.2, the progression of non-communicable diseases tends to develop over years or decades, with the majority of diseases present throughout adulthood. Many NCDs begin in middle age before any clinical signs of the disease are recognisable, and these early phases of the progression of the diseases are often modifiable, and potentially reversable through dietary and lifestyle interventions. Therefore, nutritional sufficiency along with other lifestyle factors should be considered throughout the life course to have the greatest impact in reducing health impacts in later life. This can be most clearly seen for osteoporosis, a leading cause of frailty in later life. Osteoporosis is a progressive decline in bone mass and structure throughout adulthood, and peak bone mass which occurs around the age of 30 is an important protective factor. Therefore, optimal nutritional status alongside physical activity is critical during adolescence and early adulthood to support peak bone mass development.

Therefore, the optimal nutritional interventions to support health in later life may require long-term intake of micronutrients in addition to an overall healthy diet and lifestyle. It is important to meet the RDI through various means for these micronutrients to help impact on NCDs. However, beyond our knowledge of the impacts of nutritional deficits on disease status, our current understanding of the optimal nutritional status and the effectiveness of specific interventions to reduce the risk of disease in later life is still relatively low and requires further research to be unequivocally elucidated. Many of the studies highlighted in this chapter rely on associative data linking micronutrient status to health outcomes. In addition, it can be seen in several studies that micronutrients were only effective in a subset of the population group where baseline data indicated that there was a micronutrient deficiency. Hence, studies measuring baseline status and targeting groups with low or marginal nutritional status would be helpful to better understand the impact of specific interventions on health outcomes. This may be especially relevant for populations in the Asia-Pacific as we have seen a broad range of micronutrient insufficiencies across

all countries in the region. Finally, designing randomised controlled intervention studies would be important to further understand the potential role of specific micronutrients to support long-term health.

Multiple factors need to be considered in terms of estimating micronutrient sufficiency. However, in this chapter we have highlighted the importance of considering absolute energy intakes and nutrient densities, and also the impacts of meeting sustainability goals whilst achieving micronutrient sufficiency. Absolute intakes of micronutrients over a period of time from dietary sources will be determined by overall energy intake and nutrient density of foods consumed. Recently researchers of the United Nations Food Systems Summit 2021 Scientific Group prepared a Summit Brief on the role of Science, Technology, and Innovation for Transforming Food Systems in Asia. This report highlights outputs of the DELTA model (SNi 2022) that has recently been developed and calculates nutrient availability to consumers from differing global food production scenarios. The model predicts that the current food system would provide sufficient energy and protein for the forecast 2030 global population of 8.6 billion, however, it would fail in supplying several micronutrients (calcium, iron, potassium, zinc, and vitamins A, E, B-2 and B-12) (UN FSS 2021).

9.9 Conclusions

Within this chapter we have reviewed data that demonstrates that multiple micronutrients play important roles in maintaining health throughout adulthood and can help to delay the onset of age-related non-communicable diseases prevalent in ageing. To better target nutrition-based interventions, high quality and consistent information is required from national dietary surveys to assess the most effective nutritional strategies. Based on the existing intake data, there was a high prevalence of insufficiency of vitamins A, D, E, C, B-6, B-12, folate, and for zinc in many countries. These micronutrients are known to play key roles in maintaining health in ageing, especially for the health conditions that pose high burden among the ageing population in the Asia-Pacific. Currently, the data is collected and reported in heterogeneous ways; our data suggest that, in the absence of access to raw data, values derived from mean and SD provide the most accurate approximation to the original data.

Access to data in a more consistent manner would allow a better evidence base to further elucidate optimal as opposed to adequate nutrition requirements. Meeting the RDI should be a first target to support health through adulthood into ageing using a variety of methods – diet shifts through national programs, setting RDA, consumer education, food labelling, fortification and supplementation.

Additionally, better information concerning the dietary status of populations and specific demographic groups would provide a base to develop intervention studies to help establish causal effects of nutrients in preventing diseases of ageing. Better data is also needed to define the optimal intake levels of micronutrients to support health into ageing.

These strategies would help to build further on the already recognised cost-effectiveness of nutrition strategies to address life-long health, and as a result reduce healthcare costs and medical treatments.

Supplemental Data

The Method for Estimating sDistribution of Nutrient Intake

The mean, median and standard deviation of each nutrient intake reported in the National Health Nutrition Survey 2017 in Japan (NHNS 2017) were used to estimate the distribution of nutrient intake from the following equation.

- Parameter combination 1. the value of mean and standard deviation

$$\mu = \ln\left(X(\quad)\bar{X} / \left(1+\sigma^2 / X(\quad)\bar{X}^2\right)^{(1/2)}\right)$$

$$\sigma^2 = \ln\left(1+\sigma^2 / X(\quad)\bar{X}^2\right)$$

- Parameter combination 2. the value of mean and median

$$\mu = \ln(\text{median})$$

$$\sigma^2 = 2^* \ln\left(X(\quad)\bar{X} / \text{median}\right)$$

- Parameter combination 3. the value of median and interquartile range (IQR)

$$z = (X - \mu) / \sigma$$

$$z = \left(X_i - X_m\right) / \text{NIQR}$$

(NIQR = IQR/1.3489 = IQR*0.7413)

Validation of the Estimated Distribution in Each Nutrient from the National Health Nutrition Survey 2017 in Japan (Supplemental Tables 9.1 and 9.2)

To validate the estimation methods of nutritional intake distribution, a comparison of prevalence of %below EAR between estimated and observed was made by one-sample *t*-test. The estimated and observed prevalence of inadequate micronutrient intake (vitamin A, D, E, C) were shown in Supplemental Table 9.1. The estimated values calculated by parameter combination 3 (median and interquartile range, hereafter IQR) tended to be high compared with those observed. One-sample *t*-test showed no significant differences in any vitamins except vitamin D which had a

high skewness between estimated and observed prevalence used parameter combination 1 (mean and standard deviation, hereafter SD). These results suggested that the prevalence of %below EAR was most proximate to the raw NHNS data when it was derived from the combination of mean and SD.

For a more detailed examination of the estimated distributions using the mean and SD, we compared each percentile value of the raw data with the percentile values obtained from the estimated equation. The results showed that there were no significant differences between the measured and estimated values for all nutrients for any age and gender (Supplemental Table 9.2). The intake of niacin equivalent is used for the assessment of inadequacy intake of niacin. Since the NHNS 2017 does not list niacin equivalents, it was excluded from the analysis due to a lack of comparability. As shown in Supplemental Table 9.2, there was no significant difference between the estimated and observed percentile values for any gender and age group in the Student's *t*-test, suggesting that there is a certain validity in the estimation of the intake distribution.

Supplemental Table 9.1 The prevalence of %below EAR estimated by three patterns

Age categories	Parameters		Vitamin A	Vitamin D	Vitamin E	Vitamin C
18–30 years	AV & SD	Male	76.4	86.9	93.1	65.8
	AV & Median		74.9	86.8	94.1	66.6
	Median & IQR		82.4	96.1	97.2	66.1
	The observed prevalence (%)		78.4	83.9	92.1	62.3
	AV & SD	Female	70.0	89.7	95.0	53.3
	AV & Median		69.3	89.2	95.6	54.3
	Median & IQR		75.9	99.2	99.8	53.5
	The observed prevalence (%)		72.8	87.8	95.3	52.8
31–50 years	AV & SD	Male	78.2	83.6	93.2	66.5
	AV & Median		76.6	84.2	94.8	66.7
	Median & IQR		86.4	91.6	97.5	67.7
	The observed prevalence (%)		80.6	79.3	93.1	65.7
	AV & SD	Female	72.5	86.9	93.6	51.7
	AV & Median		68.5	86.8	95.1	52.7
	Median & IQR		74.5	96.6	98.7	52.5
	The observed prevalence (%)		71.9	83.8	94.9	53.1

(continued)

Supplemental Table 9.1 (continued)

Age categories	Parameters		Vitamin A	Vitamin D	Vitamin E	Vitamin C
51–70 years	AV & SD	Male	72.3	73.6	90.2	46.0
	AV & Median		71.3	75.6	92.2	40.7
	Median & IQR		76.6	76.8	94.0	43.2
	The observed prevalence (%)		72.9	70.0	90.3	43.2
	AV & SD	Female	61.1	78.3	91.3	25.1
	AV & Median		59.4	79.1	92.9	20.7
	Median & IQR		60.2	81.9	97.5	30.1
	The observed prevalence (%)		59.0	73.6	92.8	28.2
71 years	AV & SD	Male	72.9	70.6	91.1	28.8
	AV & Median		67.7	71.5	93.9	25.6
	Median & IQR		72.1	70.5	96.3	34.1
	The observed prevalence (%)		71.1	65.9	91.9	31.8
	AV & SD	Female	64.9	73.6	92.9	17.8
	AV & Median		57.0	73.9	94.2	14.3
	Median & IQR		57.4	72.6	97.9	26.2
	The observed prevalence (%)		58.1	67.7	93.0	20.8
The ratio of predicted %below for observed (95%CI)						
AV & SD			−0.032 to 0.053 ($p = 0.576$)	0.035–0.071 ($p < 0.001$)	−0.011 to 0.004 ($p = 0.285$)	−0.095 to 0.037 ($p = 0.333$)
AV & Median			−0.051 to −0.017 ($p = 0.002$)	0.037–0.083 ($p < 0.001$)	0.003–0.195 ($p = 0.015$)	−0.213 to 0.031 ($p = 0.122$)
Median & IQR			0.012–0.056 ($p = 0.008$)	0.088–0.146 ($p < 0.001$)	0.043–0.054 ($p < 0.001$)	−0.010 to 0.134 ($p = 0.082$)

The ratio of predicted %below for observed one was calculated as below; The predicted prevalence of %below EAR/the observed prevalence of %below EAR
AV & SD; %below EAR estimated from AV & SD, AV & Median; %below EAR estimated from AV & Median, Median & IQR; %below EAR estimated from Median & IQR
One-sample *t*-test (The observed prevalence of %below EAR was used for reference (=1))
Analysis was conducted for all age groups and all genders combined

Supplemental Table 9.2 Validation of the estimated distribution in each nutrient from the National Health Nutrition Survey 2017 in Japan

Male 19–49 years	*n* = 689 EAR/AI		P 2.5	P 5.0	P 10	P 25	P 50	P75	P 90	P 95	P 97.5	*p* value
Calcium (mg)	650/600	Actual	134	160	191	275	390	563	747	881	1079	0.969
		Estimated	153	178	212	284	393	543	727	866	1007	
Iron[a] (mg)	6.5	Actual	3.2	3.6	4.3	5.6	7.2	8.9	11.1	12.4	14.1	0.933
		Estimated	3.4	3.8	4.4	5.5	7.0	9.0	11.3	12.9	14.5	
Zinc (mg)	9	Actual	4.3	4.9	5.7	7.1	8.8	10.8	13.2	15.1	16.3	0.869
		Estimated	4.3	4.8	5.5	6.9	8.8	11.3	14.1	16.1	18.0	
Vit. A (μgRAE)	600/650	Actual	63	99	136	218	362	565	857	1221	1496	0.819
		Estimated	58	76	104	175	315	576	1004	1407	1893	
Vit. D[b] (μg)	8.5	Actual	0.3	0.4	0.7	1.4	2.9	7.7	15.5	22.7	26.7	0.834
		Estimated	0.6	0.8	1.1	1.9	3.7	7.0	12.6	17.9	24.2	
Vit. E[b] (mg)	6.0	Actual	2.4	2.7	3.3	4.5	6.2	8.5	11.3	12.6	14.3	0.985
		Estimated	2.5	2.8	3.4	4.4	6.1	8.3	10.9	12.9	14.9	
Vit. B_1 (mg)	1.2	Actual	0.39	0.44	0.47	0.63	0.85	1.17	1.55	1.85	2.09	0.839
		Estimated	0.38	0.44	0.51	0.68	0.92	1.25	1.65	1.95	2.25	
Vit. B_2 (mg)	1.3	Actual	0.42	0.50	0.60	0.79	1.03	1.36	1.79	2.12	2.44	0.913
		Estimated	0.44	0.51	0.59	0.76	1.01	1.34	1.73	2.02	2.31	
Vit. B_6 (mg)	1.1	Actual	0.5	0.5	0.6	0.8	1.1	1.4	1.7	1.9	2.2	0.812
		Estimated	0.5	0.6	0.7	0.8	1.1	1.4	1.8	2.1	2.4	
Vit. B_{12} (μg)	2.0	Actual	0.6	0.8	1.3	1.9	3.3	6.7	12.1	17.9	23.6	0.892
		Estimated	0.7	1.0	1.3	2.2	3.9	6.9	11.5	15.7	20.4	
Folate (μg)	200	Actual	84	103	129	168	236	309	408	463	575	0.931
		Estimated	89	103	123	165	228	316	424	505	589	
Vit. C (mg)	85	Actual	9	14	22	35	57	92	139	173	201	0.921
		Estimated	16	19	25	37	58	91	137	175	216	

Female 19–49 years	*n* = 705 EAR/AI		P 2.5	P 5.0	P 10	P 25	P 50	P 75	P 90	P 95	P 97.5	*p* value
Calcium (mg)	550	Actual	138	168	202	286	403	558	747	848	973	0.914
		Estimated	146	170	203	272	376	520	697	830	966	
Iron[a] (mg)	8.5/9.0	Actual	3.2	3.5	4.0	5.0	6.1	8.1	9.8	11.1	12.5	0.916
		Estimated	2.7	3.1	3.6	4.6	6.1	8.1	10.5	12.3	14.0	
Zinc (mg)	7	Actual	3.5	4.1	4.6	5.6	7.0	8.6	10.2	11.2	13.0	0.800
		Estimated	3.6	4.0	4.5	5.6	7.1	9.0	11.1	12.7	14.1	
Vit. A (μgRAE)	450/500	Actual	81	110	158	235	365	540	790	1047	1511	0.371
		Estimated	60	74	94	141	223	355	555	739	966	
Vit. D[b] (μg)	8.5	Actual	0.3	0.5	0.9	1.5	2.6	6.8	14.2	20.6	24.8	0.787
		Estimated	0.5	0.7	1.0	1.7	3.3	6.3	11.2	15.9	21.6	
Vit. E[b] (mg)	5.0/5.5	Actual	2.0	2.5	3.0	4.1	5.7	7.7	10.3	11.9	14.2	0.941
		Estimated	2.0	2.4	2.8	3.8	5.3	7.5	10.1	12.0	14.0	
Vit. B_1 (mg)	0.9	Actual	0.32	0.37	0.43	0.54	0.70	0.96	1.25	1.46	1.63	0.825
		Estimated	0.32	0.37	0.43	0.56	0.76	1.02	1.33	1.57	1.80	

(continued)

Supplemental Table 9.2 (continued)

Female 19–49 years	*n* = 705 EAR/AI		P 2.5	P 5.0	P 10	P 25	P 50	P 75	P 90	P 95	P 97.5	*p* value
Vit. $B_{2\,(mg)}$	1.0	Actual	0.40	0.46	0.59	0.74	0.98	1.33	1.67	2.03	2.47	0.742
		Estimated	0.43	0.49	0.57	0.72	0.93	1.22	1.55	1.79	2.02	
Vit. $B_{6\,(mg)}$	1.0	Actual	0.4	0.5	0.5	0.7	0.9	1.2	1.5	1.7	1.9	0.946
		Estimated	0.4	0.5	0.5	0.7	0.9	1.2	1.5	1.8	2.0	
Vit. $B_{12\,(\mu g)}$	2.0	Actual	0.5	0.8	1.0	1.6	2.8	5.5	9.4	13.4	18.7	0.922
		Estimated	0.6	0.7	1.0	1.7	3.0	5.5	9.3	12.7	16.7	
Folate (μg)	200	Actual	92	110	128	169	222	290	384	440	508	0.950
		Estimated	86	100	118	155	211	287	379	448	517	
Vit. C (mg)	85	Actual	12	17	22	36	57	97	142	179	206	0.982
		Estimated	16	20	25	37	59	92	137	174	215	

Male ≥50 years	*n* = 1370 EAR/AI		P 2.5	P 5.0	P 10	P 25	P 50	P75	P 90	P 95	P 97.5	*p* value
Calcium (mg)	600	Actual	182	211	259	356	513	695	891	1048	1222	0.970
		Estimated	202	233	274	361	489	664	874	1030	1188	
Iron[a] (mg)	6.5/6.0	Actual	3.9	4.4	5.1	6.5	8.3	10.3	12.5	14.1	15.9	0.946
		Estimated	3.9	4.4	5.0	6.3	8.1	10.3	12.9	14.8	16.6	
Zinc (mg)	9	Actual	4.5	5.0	5.6	7.0	8.6	10.4	12.3	13.9	15.6	0.863
		Estimated	4.4	4.9	5.6	6.8	8.6	10.8	13.3	15.0	16.7	
Vit. A (μgRAE)	600/650	Actual	89	119	161	269	426	659	1032	1251	1574	0.643
		Estimated	44	60	87	163	329	668	1270	1870	2618	
Vit. D[b] (μg)	8.5	Actual	0.2	0.7	1.3	2.4	5.4	12.2	20.3	25.5	31.4	0.874
		Estimated	1.0	1.3	1.8	3.0	5.4	9.8	16.6	22.8	30.0	
Vit. E[b] (mg)	7.0/6.5	Actual	2.2	2.8	3.3	4.7	6.7	9.0	11.5	13.6	16.0	0.848
		Estimated	2.6	3.0	3.6	4.8	6.6	9.2	12.4	14.8	17.2	
Vit. $B_{1\,(mg)}$	1.1/1.0	Actual	0.37	0.44	0.51	0.66	0.87	1.16	1.52	1.75	1.96	0.919
		Estimated	0.38	0.44	0.51	0.67	0.89	1.19	1.55	1.81	2.07	
Vit. $B_{2\,(mg)}$	1.2/1.1	Actual	0.54	0.62	0.73	0.94	1.21	1.55	1.93	2.21	2.53	0.962
		Estimated	0.56	0.63	0.73	0.92	1.20	1.56	1.97	2.27	2.57	
Vit. $B_{6\,(mg)}$	1.1	Actual	0.5	0.6	0.7	1.0	1.3	1.6	1.9	2.2	2.5	0.869
		Estimated	0.6	0.6	0.7	0.9	1.2	1.6	2.1	2.4	2.7	
Vit. $B_{12\,(\mu g)}$	2.0	Actual	0.8	1.1	1.5	2.5	4.9	8.8	15.7	19.4	23.6	0.868
		Estimated	1.0	1.3	1.8	3.0	5.2	9.2	15.3	20.8	27.1	
Folate (μg)	200	Actual	119	142	171	232	309	400	507	560	627	0.916
		Estimated	128	146	171	222	296	395	513	600	687	
Vit. C (mg)	85/80	Actual	14	21	31	56	94	149	221	265	324	0.978
		Estimated	31	37	46	65	97	144	206	255	307	

Female ≥50 years	*n* = 1664 EAR/AI		P 2.5	P 5.0	P 10	P 25	P 50	P75	P 90	P 95	P 97.5	*p* value
Calcium (mg)	550/500	Actual	184	217	267	359	500	697	883	1024	1144	0.955
		Estimated	196	226	266	351	477	648	854	1007	1163	

Female ≥50 years	*n* = 1664 EAR/AI		P 2.5	P 5.0	P 10	P 25	P 50	P75	P 90	P 95	P 97.5	*p* value
Iron[a] (mg)	9.0/5.5/5.0	Actual	3.5	4.2	4.8	5.9	7.5	9.5	11.6	12.9	14.7	0.970
		Estimated	3.7	4.2	4.7	5.8	7.3	9.3	11.4	13.0	14.5	
Zinc (mg)	7.0/6.0	Actual	3.7	4.2	4.8	5.9	7.2	8.8	10.1	11.6	12.8	0.872
		Estimated	3.7	4.1	4.7	5.7	7.2	9.0	11.0	12.4	13.8	
Vit. A (μgRAE)	500/450	Actual	87	117	175	281	430	662	953	1209	1524	0.624
		Estimated	38	53	78	150	310	645	1254	1872	2654	
Vit. D[b] (μg)	8.5	Actual	0.3	0.7	1.1	2.2	5.0	11.2	18.7	24.3	28.7	0.890
		Estimated	0.8	1.1	1.5	2.7	4.9	9.0	15.5	21.6	28.7	
Vit. E[b] (mg)	6.0/6.5	Actual	2.2	2.6	3.2	4.5	6.2	8.4	10.8	12.6	14.9	0.885
		Estimated	2.4	2.8	3.4	4.5	6.2	8.5	11.4	13.5	15.7	
Vit. B_1 (mg)	0.9/0.8	Actual	0.32	0.39	0.45	0.58	0.77	1.02	1.28	1.50	1.71	0.964
		Estimated	0.35	0.40	0.46	0.59	0.77	1.02	1.30	1.51	1.72	
Vit. B_2 (mg)	1.0/0.9	Actual	0.47	0.56	0.68	0.87	1.14	1.47	1.80	2.05	2.29	0.994
		Estimated	0.52	0.59	0.68	0.85	1.10	1.42	1.79	2.05	2.31	
Vit. B_6 (mg)	1	Actual	0.5	0.5	0.6	0.8	1.1	1.4	1.7	1.9	2.1	0.862
		Estimated	0.5	0.6	0.7	0.8	1.1	1.4	1.8	2.0	2.3	
Vit. B_{12} (μg)	2	Actual	0.6	0.9	1.2	2.1	4.1	7.2	12.8	16.8	20.9	0.875
		Estimated	0.9	1.2	1.6	2.6	4.5	7.9	13.0	17.5	22.7	
Folate (μg)	200	Actual	122	142	172	223	296	383	487	548	628	0.836
		Estimated	106	122	143	189	257	351	466	553	642	
Vit. C (mg)	85/80	Actual	18	26	36	61	102	162	225	266	318	0.976
		Estimated	31	38	47	67	100	149	213	265	319	

Student *t*-test

[a]The reference value of iron in female = EAR of female without menstruation

[b]Vitamin D and Vitamin E intake were assessed by % above AI

Validation of the Estimated Prevalence of Inadequate Micronutrient Intake in Each Nutrient from the National Health Nutrition Survey 2017 in Japan (Supplemental Table 9.3)

NHNS 2017 data including 4428 subjects (males/females: 2059/2369), aged 19 years and older, excluding pregnant and lactating women, were analysed with stratification by gender and age (younger; 19–49 years vs., older; 50 years and older) for micronutrients intake status, including calcium, iron, zinc, vitamin A, vitamin B-1, vitamin B-2, vitamin B-6, vitamin B-12, folate, and vitamin C. Percentage of subjects with inadequate nutrients intake was calculated either by the cut-point method using the raw NHNS data (Observed) or from the sex- and age-specific mean and SD (Estimated) from NHNS 2017. The ranking of nutrients according to the proportion of subjects with inadequate intakes was in general agreement with the observed data in both gender and age. Differences [observed value-estimated value)/observed value*100%] were relatively smaller (would be good to define the threshold, i.e. less than 10%) in calcium, vitamin A, and vitamin B-1, and larger (more than 20%) in iron, vitamin B-6, and folate. These results indicated that an estimate can be made with mean and SD alone would be of practical value in assessing the prevalence of inadequate micronutrient intake.

Supplemental Table 9.3 Validation of the estimated prevalence of insufficient intake in each nutrient from the National Health Nutrition Survey 2017 in Japan

Gender	Age group	% of population with intakes below the EAR or above AI										
		Calcium	Iron[a]	Zinc	Vit.A	Vit. E[b]	Vit.B_1	Vit. B_2	Vit.B_6	Vit.B_{12}	Folic acid	Vit.C
	19–49 years											
Male	Observed proportion	**79.6**	**39.1**	**52.9**	**80**	**54.5**	**75.9**	**70.6**	**42.7**	**28**	**34.8**	**71.2**
	Estimated proportion	81.8	44.6	57.8	77.5	50.6	77.3	70.8	56.8	26.6	39.2	73.2
	Difference (Observed-estimated)	−2.2	−5.5	−4.9	2.5	3.9	−1.4	−0.2	−14.1	1.4	−4.4	−2.0
	Difference (Observed-estimated)/ observed*100	−2.8	−14.1	−9.3	3.1	7.2	−1.8	−0.3	−33.0	5.00	−12.6	−2.8
Female	Observed proportion	**73.9**	**36.3**	**49.8**	**69.9**	**54.5**	**70.5**	**51.9**	**60**	**35**	**41.3**	**68.5**
	Estimated proportion	77.1	40.5	53.6	70.1	49.8	72.5	55.5	64	33.7	45.3	73.4
	Difference (Observed-estimated)	−3.2	−4.2	−3.8	−0.2	4.7	−2.0	−3.6	−4.0	1.3	−4.0	−4.9
	Difference (Observed-estimated)/ observed*100	−4.3	−11.6	−7.6	−0.3	8.6	−2.8	−6.9	−6.7	3.7	−9.7	−7.2
	≥50 years											
Male	Observed proportion	**63**	**21.9**	**55.6**	**70.9**	**48.2**	**68.2**	**45.5**	**35.7**	**17.4**	**16.5**	**42**
	Estimated proportion	66.2	28.1	58.5	73.7	57.4	71.6	51.6	40.3	14.4	14.2	46.2
	Difference (Observed-estimated)	−3.2	−6.2	−2.9	−2.8	−9.2	−3.4	−6.1	−4.6	3.0	2.3	−4.2
	Difference (Observed-estimated)/ observed*100	−5.1	−28.3	−5.2	−4.0	−19.1	−5.0	−13.4	−12.9	17.2	13.9	−10.0

(continued)

Supplemental Table 9.3 (continued)

Female	Observed proportion	**55.3**	**14.7**	**40.4**	**57.5**	**49.3**	**62.5**	**33.5**	**41.4**	**23.2**	**17.3**	**38.3**
	Estimated proportion	60.7	22.4	48.7	63.2	50.7	65.8	40	45.4	20.7	21.2	43.2
	Difference (Observed-estimated)	−5.4	−7.7	−8.3	−5.7	−1.4	−3.3	−6.5	−4.0	2.5	−3.9	−4.9
	Difference (Observed-estimated)/ observed*100	−9.7	−52.4	−20.5	−9.9	−2.8	−5.3	−19.4	−9.7	10.8	−22.5	−12.8

Observed proportion: %below EAR or % above AI from National Health and Nutrition Survey 2017 in Japan
Estimated proportion: %below EAR or % above AI from Top-up Nutrition APAC Data calculated by parameter combination
Niacin was excluded because the raw NHNS data did not provide the proportion of niacin equivalent derived from tryptophan
[a] The reference value of iron in female= EAR of female without menstruation
[b] Vitamin E intake were assessed by % above AI

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Chapter 10
Gut Microbiome and Its Metabolites in Ageing

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Abstract Ageing is a complex biological process which has significant effects on host physiology. It is associated with an altered gut microbiome structure and function characterised by a lower diversity, stability, increase in pathogenic microorganisms (such as *Clostridium*, *Escherichia*, *Staphylococcus*, *Streptococcus, Proteobacteria,* etc.) and a decrease in beneficial microbes (such as *Actinobacteria*). Age-associated impairment of the gut mucosal barrier (also known as 'leaky gut') allows such pathogenic microbes and microbial components to enter the circulation, causing hyperinflammatory responses and inflammageing leading to several diseases. Gut microbes utilise different dietary components to produce a wide range of metabolites, such as short chain fatty acids (e.g. acetate, propionate, butyrate), aryl hydrocarbon receptor ligands (e.g. metabolites of tryptophan), polyamines (e.g. putrescine, spermidine, spermine), etc., thereby exerting local effects and mediating cross-talks between the gut and other organs such as the brain, liver, kidney, heart, eye, bone, muscle, adipose tissue, etc. Age-related gut dysbiosis is associated with the production of harmful metabolites which impair health outcomes. Specific gut

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microbial metabolites, such as trimethylamine (TMA), *p*-cresol, and indole, are related to clinical conditions such as cardiovascular diseases, renal diseases, liver diseases, respiratory diseases, diabetes, etc. Supplementation with probiotics, prebiotics, synbiotics, and dietary and lifestyle modifications may be helpful to improve and maintain gut eubiosis, although results are still inconclusive. In this chapter, we will highlight the age-associated changes in gut microbiome composition and associated metabolite profile, along with its involvement with commonly encountered age-associated conditions.

Keywords Elderly · Ageing · Gut microbiome · Inflammation · SCFA · TMAO

10.1 Introduction

The human gastrointestinal tract is home to trillions of microorganisms, including bacteria, fungi, protozoa, archaea, eukarya and viruses (Matijašić et al. 2020). The terms 'Microbiome' and 'Microbiota' are often used interchangeably to refer to the sum of all genomes present in these microorganisms and specific microorganisms present in the body. The gastrointestinal tract of humans provides an ideal infrastructure for the host, microbes and the environment to interact, thereby regulating host physiology. The human gut microbiome (GM) is highly diverse. It may include around 1000 bacterial species with about 2000 genes per species, which accounts for an aggregate of 2,000,000 bacterial genes, which is about a hundred times greater than 20,000 human genes (Gilbert et al. 2018). For millions of years, we have coevolved with this wide variety of microorganisms to share a symbiotic relationship. The relationship between the host and microbes inhabiting it constitutes a 'Superorganism' which can be considered a step of integration in evolution (Salvucci 2019). The gut microbiota undergoes extensive changes throughout the lifespan. GM colonisation may begin *in utero* by the placental and amniotic microbial communities characterised by low diversity and predominance of Proteobacteria (Collado et al. 2016). During birth, the baby comes in direct contact with the environment, for example, the vaginal fluid and skin microbiota of the mother, which shapes the microbiome makeup of the neonate (Hasan and Yang 2019). Up to 2 years of age, the human GM remains highly susceptible to environmental alterations that determine the individual's future health status. The community of microbes gradually mature and becomes quite stable in adulthood, especially at the phylum level. Firmicutes, Bacteroidetes, Actinobacteria, Proteobacteria, Fusobacteria and Verrucomicrobia are the predominant intestinal microbial phyla, with the two phyla Firmicutes and Bacteroidetes accounting for 90% of gut microbiota (Rinninella et al. 2019). Firmicutes to Bacteroidetes (F/B ratio) is an essential index for GM composition and health. An increase in the F/B ratio may be observed in obesity and metabolic disorders, whereas a decreased ratio may be observed in inflammatory conditions (like inflammatory bowel disease) (Stojanov et al. 2020).

Acute perturbations do not usually alter the composition of host GM, and slight changes, if any, will return to the initial composition rapidly. But continuous exposure to various environmental hazards, stress factors and modern lifestyle factors may lead to 'dysbiosis', which exerts deleterious effects on the health. These gut microbes are found to produce a plethora of metabolites from dietary components which in turn exert numerous biological effects locally as well as in other target organs. For instance, Short Chain Fatty Acids (SCFAs) such as acetate, propionate and butyrate are produced from undigestible dietary carbohydrates by the gut microbes which help in maintaining intestinal barrier integrity, prevent inflammatory damages, maintain immune homeostasis, establish link between gut and other organs such as the brain, lung, liver, pancreas, bone marrow, adipose tissue (Tan et al. 2014). Similarly, other metabolites such as aryl hydrocarbon receptor (AHR) ligands (for example, metabolites of tryptophan) (Dong and Perdew 2020), polyamines (such as putrescine, spermidine, spermine) (Tofalo et al. 2019) produced by the gut microbes have numerous physiological functions. A dysbiotic gut may produce potentially harmful metabolites and/or cause an imbalance of beneficial metabolites.

Ageing is a complex biological process determined by several host and environmental factors.

It affects various genomic, physiological, biochemical, metabolic and immunological functions. Age-associated changes in physiological processes influence gut microbiome composition and vice-versa (Ragonnaud and Biragyn 2021). Increasing evidence suggest the intricate involvement of gut dysbiosis in various age-associated diseases. A major converging point for most mechanistic pathways underlying ageing and age-related disorders is inflammation. Chronic, sterile, low-grade inflammation is a vital contributor to ageing, also known as inflammageing (Xia et al. 2016). The gut microbiota and their metabolites directly interact with the gut mucosal cells and immune system, thereby regulating several complex pathways involved in inflammageing. As seen in centenarians, healthy ageing is characterised by a eubiotic GM composition that does not activate inflammatory pathways. Thus, it is essential to understand the role of GM and their metabolites in ageing to target the specific factors which can result in successful ageing. In this chapter, we aim to highlight the age-associated changes in GM composition, its involvement with common age-associated disorders and the molecular mechanisms underlying these processes.

10.2 Gut Microbiome Composition and Ageing

The ageing process has significant effects on the host physiology and microbiome composition, thereby influencing their interactions. It is often difficult to comprehend whether alterations of gut microbiome composition are cause or consequence of ageing. As people age, the overall stability and diversity of gut microbiota are found to be reduced (Nagpal et al. 2018). At the phylum level, an

increase in inflammation-related proteobacteria and a reduction in beneficial actinobacteria may be observed. The relative abundance of commensals such as bifidobacteria, lactobacilli, bacteroides are decreased and opportunistic pathogens such as *Clostridium perfringens*, *Clostridium difficle*, and *Enterobacteria* are found to increase (Nagpal et al. 2018). However, the average and successfully ageing individuals have higher alpha diversity (species diversity within a single host/ local environment), functional pathways and metabolites, especially among the oldest-old individuals (Badal et al. 2020). Beta diversity (species diversity between different environments/ communities) is found to differ significantly between younger-old and oldest-old adults. Interestingly, the oldest-old individuals are found to have a higher predominance of beneficial taxa and SCFA production, which help them maintain an anti-inflammatory condition leading to successful ageing (Badal et al. 2020). The gut microbiome composition may vary among elderly individuals in different geographical locations. Disruption of gut microbial eubiosis, diversity and functionality in old age has numerous adverse consequences. Dysbiosis, along with reduced gut microbial metabolic capacities in elderly individuals, such as a reduction in SCFA production, are associated with age-related frailty, weight loss, appetite reduction, sarcopenia, arthritis, cognitive decline, and other non-communicable diseases. As mentioned before, altered gut microbiome metabolism and functionality may change the levels of several microbial metabolites directly related to human health. Studies on animal models have shown an age-dependent increase in Proteobacteria and a decrease in Firmicutes along with alteration of tryptophan, purine, nicotinamide and amino acid metabolisms (Wu et al. 2021). Notably, primary ageing in mice was found to be associated with a decrease in circulating levels of gut microbial metabolites indole and indole-3-lactic acid, which may result in compromised barrier function and a pro-inflammatory state. Additionally, an increase in kynurenine and a decrease in nicotinamide may be observed which are associated with physiological ageing (Wu et al. 2021). Similarly, significant increase in metabolites involved in inflammatory and cytotoxic pathways can be observed in non-human primate models (Pallikkuth et al. 2021). However, clinical studies on these parameters are relatively scanty. The commonly encountered reasons behind these age-related changes in gut microbiome profile are changed lifestyle, dietary habits, reduced mobility, altered intestinal functionality, gut morphology, immunosenescence, recurrent infections, hospitalisations, use of medications and so on. Some overlooked factors such as romantic relationship dissolution (for example, death of a beloved person), commonly faced by the elderly individuals, may also alter gut microbiome composition due to social isolation, depression and changes in food habits (Chuang 2021). The underlying physiological and molecular mechanisms involved in age-related disorders and GM composition are highly complex, which are discussed in the next section.

10.3 Mechanisms Involved in Gut Dysbiosis and Ageing: Role of Gut Microbial Metabolites

As we discussed earlier, gut dysbiosis and ageing have a two-way connection. Ageing is associated with certain physiological and environmental changes which may be detrimental to gut eubiosis. For instance, decreased gut motility and increased gut permeability are frequently encountered in elderly people (Nagpal et al. 2018). As per existing evidence, gut microbial changes in old age may be associated with increased TNF levels αIL-6 and IL-8, although it is unclear whether such associations are direct or indirect. The intestinal epithelial cells secrete a mucinous component which, along with intercellular junctions (like tight junctions) form the gut barrier and separate the systemic compartment from the external environment. Under healthy eubiotic conditions, gut microbes produce SCFAs that help maintain gut barrier integrity. At the same time, gut microbes regulate antimicrobial peptide (AMP) production from the epithelial cells and influence mucus production (Nagpal et al. 2018). Secreted IgA (sIgA), produced by plasma cells, binds to certain microbes and soluble antigens in the lumen, thereby preventing their adherence to the epithelium and invasion through the gut barrier. If this homeostasis is disturbed, several harmful conditions may set in, including inflammatory damage and gastrointestinal disorders. A 'leaky gut' allows pathogens, bacterial components (lipopolysaccharides, flagellins, nucleic acids), mucus, histamine, etc. to enter the lamina propria, increasing antigenic load and triggering hyper-inflammatory responses (Nagpal et al. 2018). These processes may ultimately increase the susceptibility of the hosts to various systemic and gut-related disorders by perturbating the gut-brain axis, gut-liver axis, gut-lung axis, etc.

Apart from SCFAs, other gut microbial metabolites may also significantly affect host ageing. For instance, gut microbes use certain amino acid decarboxylase enzymes to produce polyamines (e.g. spermidine, spermine, putrescine), which have a wide range of biological activities (Tofalo et al. 2019). Preclinical studies have shown that the supplementation of probiotics leads to an increase in gut polyamine concentration, inhibiting cellular senescence and promoting longevity. Mice supplemented with arginine, and *Bifidobacterium* LKM512 exhibited increased putrescine concentration in the colon and higher levels of spermidine and spermine in the blood (Kibe et al. 2014). Such changes were associated with suppressed inflammation, reduced age-related cognitive impairment and increased longevity, thereby preventing the age-associated decline in quality of life. In humans, higher consumption of dietary spermidine is found to be associated with reduced age-associated conditions such as cardiovascular disorders and lower mortality (Madeo et al. 2018).

Similarly, in a study on geriatric human subjects with elderly-type gut microbiome composition, an increase in specific metabolites (such as trimethylamine, choline, N8-acetylspermidine) was observed to be linked with age-associated with conditions like arteriosclerosis and colorectal cancer (Yoshimoto et al. 2021). These changes may serve as effective points for targeted interventions to promote longevity and healthy ageing (Fig. 10.1).

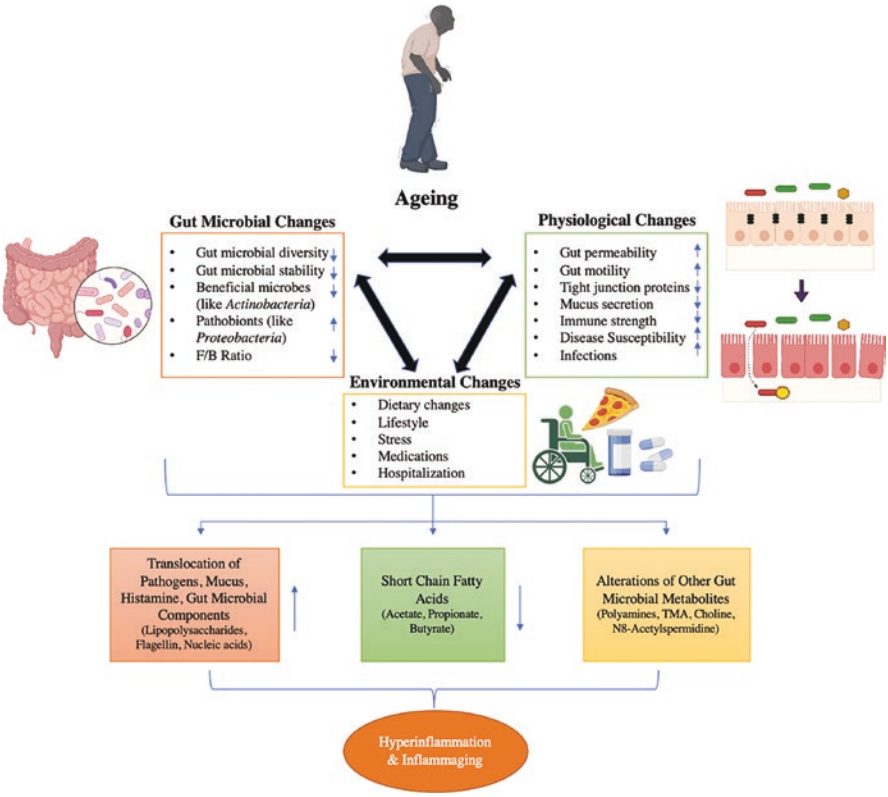

Fig. 10.1 Ageing-associated gut microbial, physiological and environmental changes and their consequences

10.4 Changes in Gut Microbiome and Its Metabolites in Common Age-Associated Conditions

As we have already discussed, age-associated changes in gut microbial composition and metabolite profile significantly impact host physiology. Dysbiosis promotes systemic inflammation and immune-senescence, which are associated with poor prognosis of several communicable and non-communicable diseases in aged individuals. In the following sections, we will highlight the changes observed in gut microbiome composition under certain age-dependent clinical conditions.

10.4.1 Cardiovascular Diseases

Ageing is a non-modifiable risk factor for cardiovascular morbidities. The imbalance of gut microbes, commonly associated with ageing, is an important contributor to cardiovascular diseases (CVDs) (Masenga et al. 2022). Studies have shown that

CVDs are associated with an abundance of *Escherichia, Shigella, Streptococcus, and Enterococcus* species along with a decrease in *Faecalibacterium*, *Roseburia, Bacteroides fragilis, Subdoligranulum and Eubacterium rectale,* the latter group having anti-inflammatory effects (Masenga et al. 2022). Dietary components such as choline, phosphatidylcholine, and carnitine, primarily found in animal products, are converted into trimethylamine (TMA) by certain gut microbes, which is further oxidised in the liver to produce trimethylamine oxide (TMAO). TMAO has atherogenic properties, promotes inflammation, impairs reverse cholesterol transport and increases platelet hyper-responsiveness (Zhu et al. 2016; Masenga et al. 2022). In mice, ageing is associated with dysbiosis and an increase in plasma TMAO, thereby increasing the risk of arterial dysfunction and CVDs (Brunt et al. 2019). Apart from this, SCFAs produced by gut microbes are found to regulate blood pressure through distinct G-protein coupled receptors (GPCRs) (Masenga et al. 2022). Certain SCFAs, like acetate and propionate, exert antihypertensive effects by reducing systemic inflammation and atherosclerosis development. Other SCFAs like butyrate and lactate may also regulate blood pressure by modulating vasoconstriction and vasodilation (Razavi et al. 2019). Depletion of SCFA-producing microbes, as observed in ageing, may lead to hypertension. The composition of GM may also influence bile acid homeostasis, which in turn is associated with lipid metabolism, glucose metabolism and inflammation. Complex interactions among diet, gut microbes and bile acids contribute to several cardiometabolic phenotypes. Dysregulated bile acid homeostasis may lead to CVD development which is common among elderly individuals. Such effects are mediated mainly by specific GPCRs like Takeda G-protein–coupled receptor 5 (TGR5) and specific nuclear receptors such as Farnesoid Xenobiotic Receptor (FXR), Liver Xenobiotic Receptor (LXR) and Pregnane Xenobiotic Receptor (PXR) (Callender et al. 2022).

10.4.2 Diabetes

Diabetes mellitus (DM) is a metabolic condition characterised by higher than normal blood glucose levels. The three major classes of DM are Type 1 DM/T1DM (characterised by autoimmune destruction of insulin-producing pancreatic beta cells), Type 2 DM/T2DM (characterised by insulin resistance) and Gestational DM/GDM (diagnosed first time during pregnancy). Among these three types, T2DM is adult-onset and commonly observed in the geriatric population (Bradley and Hsueh 2016). The gut microbes are found to exert significant effects on host glucose metabolism. They interact with dietary components, alter inflammatory responses, regulate gut permeability and modulate insulin sensitivity. Therefore, perturbation of GM composition may be a risk factor for T2DM development in elderly individuals. Studies have shown that the abundance of *Bifidobacterium*, *Faecalibacterium*, *Akkermansia*, *Roseburia*, and *Bacteroides* is negatively associated with T2DM, whereas *Ruminococcus*, *Blautia* and *Fusobacterium* have positive associations (Gurung et al. 2020). An increase in inflammatory and a decrease in anti-inflammatory cytokines and chemokines can be commonly observed in

T2DM. Certain species of *Akkermansia*, *Lactobacillus*, and *Roseburia* induce anti-inflammatory IL-10 formation, which helps protect against an age-related decrease in muscle insulin sensitivity (Gurung et al. 2020). Similarly, *Roseburia intestinalis* may induce anti-inflammatory IL-22 formation, which helps to restore insulin sensitivity. On the contrary, the predominance of certain pathobionts such as *Ruminococcus gnavus* and *Fusobacterium nucleatum* trigger pro-inflammatory responses (Gurung et al. 2020). Increased gut permeability, commonly associated with T2DM, results in metabolic endotoxemia and hyperinflammatory responses, as discussed earlier. Such responses further complicate disease prognosis. Certain probiotic species (such as *Bifidobacterium lactis*) downregulate hepatic gluconeogenesis-related genes, increase glycogen synthesis, and promote translocation of GLUT4 and insulin-dependent glucose uptake (Kim et al. 2014; Gurung et al. 2020). Treatment with probiotics and maintenance of eubiosis may be an effective way to protect against T2DM in the elderly population.

10.4.3 Neurodegenerative Diseases and Cognitive Impairment

Ageing-associated dysbiosis is essential to age-related neuro-inflammation, neurodegeneration and cognitive impairments. Dysbiosis leads to the aggregation of stress proteins in the healthy brain resulting in neuroinflammation, neuronal apoptosis and astrocyte activation (Alsegiani and Shah 2022). Lower GM diversity can be observed among elderly individuals with memory impairments compared to healthy subjects. Age-associated decrease in GM diversity and dysbiosis reduce the synthesis and secretion of specific neurotrophic factors such as Brain-Derived Neurotrophic Factor (BDNF), Gamma Amino Butyric Acid (GABA), *N*-methyl-D-aspartate (NMDA) receptor, etc. (Askarova et al. 2020). Certain gut microbes such as *Bacillus subtilis*, *Escherichia coli* are found to be associated with amyloid fibre production which has the potential to cross the intestinal and Blood-Brain Barrier (BBB). This may result in amyloid-β protein formation and accumulation in the brain leading to Alzheimer's Disease (AD) pathogenesis (Askarova et al. 2020). Patients newly diagnosed with AD or Mild Cognitive Impairment (MCI) are found to have a GM with a decrease in protective *Bacteroides* and an increase in inflammation-promoting *Prevotella*. The Apolipoprotein E (*APOE*) genotype, one of the strongest risk factors for AD, is also associated with a particular GM composition. The *APOE4* genotype which carries the highest risk of AD is associated with a decrease in SCFA and butyrate-producing microbes which may regulate neuropathology (Tran et al. 2019). A reduction in SCFA-producing microbes is also consistently observed among patients having Parkinson's Disease (PD) (Romano et al. 2021). Huntington's Disease reported lower diversity, richness, evenness and dysbiosis (Wasser et al.

2020). Similarly, many studies have found significant associations between gut dysbiosis and Lateral Sclerosis (Boddy et al. 2021), Depression (Limbana et al. 2020), Vascular cognitive impairment (Li et al. 2018), etc. Such effects mostly result from prolonged exposure of the brain to different deleterious gut microbial metabolites and pro-inflammatory cytokines.

10.4.4 Kidney Diseases

Gut dysbiosis in ageing is associated with multiple renal diseases and pathologies. A "leaky gut", as discussed before, allows pathogens to enter the circulation, activating the immune system. Such activated immune cells may penetrate the kidney and initiate inflammatory reactions. The GM of CKD patients can be characterised by a reduction in *Lactobacillaceae* and *Prevotellaceae* (normal colonic microbiota) and a relative increase in *Enterobacteria* and *Enterococci* (usually pathogenic) (Ramezani and Raj 2014). Patients undergoing haemodialysis have a lower level of *Bifidobacterium* and a higher level of *Clostridium perfringens*. Patients with End Stage Renal Disease (ESRD) are at increased risk of having *Clostridium difficle-associated* diarrhoea. Dysbiosis in Chronic Kidney Disease (CKD) patients leads to the retention of uremic toxins, which in turn contributes to the progression of CKD (Ramezani and Raj 2014). Specific gut microbial metabolites such as *p*-cresol and indole are found to predict CKD progression and reduction in glomerular filtration rate (GFR). These metabolites are produced by the fermentation of tyrosine and tryptophan by the gut microbes, respectively. After absorption, these are converted to *p*-cresyl sulfate and *p*-indoxyl sulfate in the liver. Levels of these two compounds are negatively associated with kidney function (Lin et al. 2011). Higher *p*-cresol levels are associated with an increased risk of death in ESRD (Ramezani and Raj 2014). TMAO, produced by gut microbes, is also found to be elevated in patients with CKD and is associated with 2.8 folds higher risk of all-cause mortality (Tang et al. 2015). Kidney diseases are found to be associated with increased use of antibiotics, metabolic acidosis, slow colonic transit, intestinal wall congestion, oral iron intake and low dietary fibre intake (al Khodor and Shatat 2017). Such factors may perturbate gut microbial homeostasis, increase pathogenic growth, reduce intestinal tight junctions and increase gut permeability, thereby triggering immune responses. CKD is also associated with increased secretion of urea in the gastrointestinal tract, which is broken down by gut microbes to produce large quantities of ammonia. This may alter the gut microbial balance and affect the growth of commensals.

10.4.5 Liver Diseases

The gut microbes and their metabolites can significantly alter hepatic health as they can enter the liver through the portal circulation. Under normal conditions, small amounts of microbial products go into the liver, which is eliminated by the Kupffer cells with minimal activation. But, due to dysbiosis, intestinal barrier disruption and other related conditions, higher amounts of microbes and microbial products go to the liver, activating Kupffer cells and hepatic stellate cells (Minemura and Shimizu 2015). For instance, pathogen-derived lipopolysaccharides may bind to the Toll-like Receptor 4 (TLR4) in these cells, thereby activating them. Such activation may lead to increased production of pro-inflammatory cytokines and associated inflammatory damages. Other microbial components such as flagellin, nucleic acids, and formyl-peptides are also detected by certain Pattern Recognition Receptors (PRRs), thereby initiating adverse responses in the liver. Liver diseases are associated with dysbiosis and bacterial overgrowth in the intestine. It may disrupt bile acid metabolism, which alters hepatic metabolism through transcription factors such as LXR, FXR, and TGR5 (Li et al. 2021). Alcohol consumption is associated with gut mucosal barrier disruption, which increases microbial translocation into the portal vein. Dietary and microbiota-derived ethanol can damage the hepatocytes by generating reactive oxygen species (ROS) (Li et al. 2021). Choline utilised by the gut microbes to produce TMA may result in a choline-deficient state. Choline deficiency may lead to reduced Very Low-Density Lipoprotein (VLDL) excretion from the liver, which may cause triglyceride accumulation (Mehedint and Zeisel 2013). TMAO may also exert significant adverse effects on the liver and is associated with non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) (Li et al. 2021). Gut dysbiosis may affect other tissues (such as adipose tissue) and alter local and systemic immune systems, which may indirectly affect liver health.

10.4.6 Cancer

The incidence of cancer increases substantially with an increase in age. Ageing decreases GM diversity and the levels of beneficial microbes in the gut, which are involved in the control of pathogens and maintenance of the gut mucosal barrier. Age-associated dysbiosis may exert adverse effects on the host immune system which may impair mutant and senescent cell removal, thereby facilitating tumour outgrowth and cancer development (Biragyn and Ferrucci 2018). Gut dysbiosis in ageing provides a selective benefit to oncogene-expressing and malignant cells. Dysbiosis impairs the ability of plasmacytoid dendritic cells to induce adaptive immune responses against neoantigens and decreases phagocytosis of monocytes, neutrophils and macrophages (Biragyn and Ferrucci 2018). Thus, deficient immune surveillance and inflammageing may promote carcinogenesis. Inflammageing is promoted by gut dysbiosis, which

is associated with an increase in various pro-inflammatory pathways, thereby sustaining the production of various pro-inflammatory cytokines from monocytes and macrophages such as Interleukin-1α/β (IL-1α/β), Interleukin-6 (IL-6) and Tumour Necrosis Factor-α (TNF-α) (Biragyn and Ferrucci 2018). Higher concentration of TNF-α is found to be proapoptotic and pronecrotic, whereas chronic low concentrations of TNF-αare tumourigenic. Higher TNF-α is also found to impair the fitness of hematopoietic stem cells in ageing bone marrow, thereby promoting leukaemogenesis and acute myeloid leukaemia (Biragyn and Ferrucci 2018).

10.4.7 Respiratory Diseases

GM dysbiosis, decreased GM diversity, and increased gastrointestinal permeability are associated with respiratory health issues. Increased levels of gut microbe-associated TMAO are found to be associated with mortality in Chronic Obstructive Pulmonary Disorder (COPD) patients (Enaud et al. 2020). Cystic fibrosis (CF) patients with intestinal inflammation have a higher abundance of *Streptococcus, Staphylococcus and Escherichia coli* in the gut. Similarly, associations can be found between dysbiosis, asthma and acute lung infections (Enaud et al. 2020). Specific perturbations in GM composition may also affect the lung microbiome. For instance, a decrease in gut *Parabacteroides* may cause an increase in lung *P. aeruginosa* (associated with infections). Gut microbes may also significantly affect the lung immune system via CD8+ T cells, T helper 17 cells (T_H-17), prostaglandin E2, IL-25, IL-13 and NF-kB pathways (Enaud et al. 2020).

10.4.8 Impaired Musculoskeletal Health

GM composition significantly affects bone and muscle health among elderly individuals. Gut dysbiosis and leaky gut are associated with an inflammatory phenotype. This leads to an increase in IL-17-producing T_H-17 cells, which is related to a reduction in bone mass by stimulating osteoclast differentiation (Cooney et al. 2021). GM composition's perturbation is correlated with conditions such as osteoporosis and osteopenia.

On the contrary, gut eubiosis leads to better nutrient absorption (such as Calcium, Magnesium, Phosphorus, Vitamin B, and Vitamin K), produces beneficial SCFAs, promotes bile acid metabolism and maintains the balance between regulatory T cell (Treg) and T_H-17 cells which are associated with an increase in bone formation and decrease in bone resorption (Ding et al. 2020). Butyrate produced by the beneficial gut microbes stimulates the differentiation of Treg cells, promoting bone formation.

Treg cells stimulate CD8+ T cells, which release Wnt10b, promoting osteoblast differentiation (Cooney et al. 2021). Gut microbes may also promote bone health by producing serotonin (5-HT). Similarly, perturbed GM may be associated with sarcopenia. A reduction in GM diversity and butyrate producers (such as *Lachnospira*, *Roseburia*, *Eubacterium,* etc.) can be observed in patients having sarcopenia. An increase in LPS biosynthesis and a decrease in phenylalanine, tryptophan and tyrosine biosynthesis may also be observed (Kang et al. 2021).

10.4.9 Poor Ocular Health

GM composition may influence ocular health, which suggests the existence of a Gut-Eye axis. Dysbiosis may be an important contributor to the development of ocular diseases such as uveitis, dry eye, macular degeneration and glaucoma. Dysbiosis impairs intestinal homeostasis and the gut mucosal barrier, which allows microbial products and activated immune cells to reach the eye. This may induce ocular inflammation through direct effects on the eyes (Napolitano et al. 2021). Eyes are usually prone to develop inflammatory diseases, even in the absence of an infectious component, which can be attributed to a dysbiotic GM. Prominent associations can be found between intestinal inflammatory diseases and ocular diseases. For instance, ten per cent of subjects suffering from inflammatory bowel diseases (IBD) may suffer from various ocular diseases (Scuderi et al. 2022). Associations have been found between GM composition and autoimmune uveitis, age-related macular degeneration (ARMD), glaucoma, chalazion, etc. Age-related gut dysbiosis may lead to premature senescence of retinal cells. This results in the release of pro-inflammatory cytokines and angiogenic factors, which in turn causes neovascularisation and disruption of vascular repair (Napolitano et al. 2021; Scuderi et al. 2022). Dysbiosis may lead to diabetes development through several physiological pathways. Dysbiosis-associated retinal inflammation, disruption of the blood-retinal barrier, apoptosis and neovascularisation may lead to the progression of diabetic retinopathy. Zinkernagel et al. have shown that ARMD can be characterised by a predominance of *Anaerotruncus*, *Oscillibacter, Ruminococcus torques* and *Eubacterium ventriosum.* This composition is associated with glutamate degradation and upregulation of arginine biosynthetic pathways (Zinkernagel et al. 2017). The reduction of glutamate leads to deficient neurotransmission in the retina, whereas an increased level of arginine is associated with chorioretinal atrophy and retinal degeneration. There was also a decrease in bacteria responsible for fatty acid elongation pathways. On the contrary, subjects without ARMD were found to have a higher level of *Bacteroides eggerthii,* which may exert protective effects through SCFAs production (Zinkernagel et al. 2017). Such evidence suggest a crucial link between gut microbes, their metabolites and ocular health in ageing (Fig. 10.2).

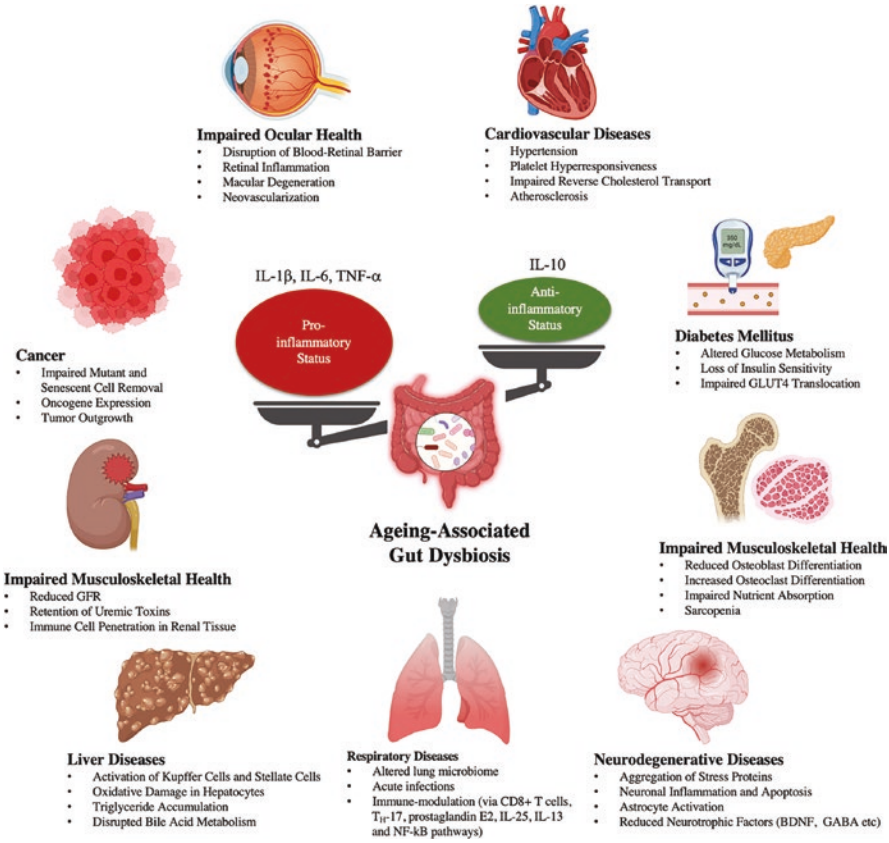

Fig. 10.2 Association of ageing-associated gut dysbiosis with common age-associated conditions. *BDNF* brain-derived neurotrophic factor, *CD8+ T Cells* cluster of differentiation 8 T cells, *GABA* gamma amino butyric acid, *GFR* glomerular filtration rate, *GLUT4* glucose transporter 4, *IL-1β/6/10/13/25* interleukin-1β/6/10/13/25, *NF-kB* nuclear factor kappa B, T_H*-17* T helper 17 cell, *TNF-α* tumour necrosis factor-α

10.5 Targeting Gut Microbiome for Healthy Ageing

From the above-mentioned evidence, it can be clearly understood that the composition of GM and the wide range of metabolites produced by them have significant effects on host physiology. Ageing-associated gut dysbiosis, disruption of the gut mucosal barrier, loss of tight junctions and entry of microbial components through the leaky gut lead to hyperinflammatory responses resulting in several age-associated diseases. At the same time, maintenance of gut eubiosis may lead to healthy ageing and better quality of life. Thus, GM is a vital intervention site to prevent age-associated diseases. Following strategies may be suitable to maintain a healthy GM composition in ageing,

10.5.1 Probiotics

Probiotics are live microorganisms which exert beneficial effects when consumed in adequate amounts. Certain factors such as strains, dosage and duration are essential regarding probiotic supplementation. Probiotics are beneficial for modifying GM composition in healthy elderly individuals and exert modest effects on immune functions. In a meta-analysis, short-term probiotic supplementation was found to improve polymorphonuclear phagocytic activity and Natural Killer (NK) cell tumouricidal activity among elderly individuals (Miller et al. 2019). Probiotics are found to reduce chronic inflammatory status, as seen in ageing. Certain probiotic strains such as *Bifidobacterium* and lactic acid bacteria may exert immunomodulatory effects. They are found to produce specific bioactive metabolites from various dietary components. For instance, dietary isoflavones, lignans and ellagitannins can be metabolised to produce equol, enterolignans and urolithin respectively, which are more bioavailable and exert anti-inflammatory, anti-oxidant and anti-carcinogenic effects (Landete et al. 2017). A recent meta-analysis suggests that probiotics may improve cognitive and gastrointestinal symptoms in patients having AD, PD and MCI, by reducing inflammatory responses and improving lipid metabolism (Xiang et al. 2022). Although, the effects of probiotics on other physiological functions are still inconclusive, often showing conflicting results.

10.5.2 Prebiotics

Prebiotics are edible substances which selectively promote the growth and activity of beneficial microorganisms in the gut. The most widely consumed prebiotics include fructo-oligosaccharides, galacto-oligosaccharides and inulin. Prebiotics may be useful for maintaining gut eubiosis in elderly individuals. Usually, the major targets of these prebiotics are *Bifidobacterium* and *Lactobacillus* in the gut (Jayanama and Theou 2020). Several clinical studies have been conducted on the effectiveness of prebiotics in reversing age-related changes. Prebiotic supplementation is found to improve frailty parameters (exhaustion and hand grip strength) among elderly individuals (Jayanama and Theou 2020). Supplementation with a commercial resistant starch may increase the predominance of Bifidobacteria and Bacteroides in the gut of elderly subjects (Alfa et al. 2018). Galacto-oligosaccharide administration may stimulate Bifidobacteria growth and exert immunomodulatory effects by increasing phagocytosis, NK cell activity, anti-inflammatory cytokines (such as IL-10) and reducing pro-inflammatory cytokines (such as IL-1β, IL-6, TNF-α) (Vulevic et al. 2008 2015). Administration of enteral formula with

prebiotics may improve *Bifidobacterium* count and lead to better influenza vaccine response (Akatsu et al. 2016). Although, in free-living elderly subjects no significant effects of prebiotic supplementation are found on influenza vaccine response.

10.5.3 Synbiotics

Synbiotics are combinations of prebiotics and probiotics which act in synergism. Studies have shown that synbiotics may be beneficial for improving GM composition in elderly individuals. Synbiotics may promote the growth of bifidobacteria and lactobacilli in the gut (Ale and Binetti 2021). They may improve stool frequency, and gut mucosal health, enhance SCFA (like butyrate) production and lipid metabolism and diminish pro-inflammatory responses. Synbiotics are also found to improve the markers of metabolic health, cardiovascular health and decreased insulin resistance in elderly subjects. Synbiotics may reduce total serum cholesterol, triglycerides, and fasting glycaemia and increase HDL cholesterol (Ale and Binetti 2021). Sometimes, certain synbiotic combinations work more effectively than individual prebiotics or probiotic. For instance, a combined regimen of live binary Bacillus subtilis and lactulose worked better than individual components for treating constipation. Synbiotic therapy is also associated with increased *Actinobacteria* and *Firmicutes* and a reduction in *Proteobacteria* (Ale and Binetti 2021).

10.5.4 Other Strategies

Several strategies may be used to promote GM composition in elderly individuals other than probiotic, prebiotic and synbiotic supplementation. For instance, dietary modifications play an essential role in promoting gut eubiosis. Western dietary patterns, characterised by calorie-dense food items, high fat, high sugar, high salt, refined carbohydrates, processed meat, saturated fats, and additives, lead to a dysbiotic condition (Shi 2019). A healthy, balanced diet, characterised by whole grains, fresh vegetables, fruits, nuts, herbs and fish consumption, promotes GM diversity and maintains eubiosis. A Mediterranean dietary pattern is associated with an increase in beneficial microbes and a decrease in opportunistic pathogens (Nagpal et al. 2019). Supplementation with gut microbial metabolites (such as SCFAs) may have a promising role in reversing age-associated health impairments. Novel therapies such as Fecal Microbiota Transplantation (FMT) may also be beneficial in future. Some latest innovative interventions to modify GM composition in elderly individuals are listed in Table 10.1.

Table 10.1 Innovative intervention strategies to modify gut microbiome in elderly individuals

Strategy	Study subjects	Intervention/duration	Major outcomes	References
Dietary modifications	Influenza vaccinated free-living elderly subjects (age 60–80 years) 25 subjects in the intervention group vs. 25 subjects in the placebo group	Probiotic Food Supplement (*Lactobacillus plantarum*, *Bifidobacterium animalis*, *Bifidobacterium longum* subsp. *infantis*, *Bifidobacterium longum* subsp. *longum*.)/28 days	Reduced number of subjects with symptoms of common infectious diseases and reduced duration of symptoms in the intervention group. Improved total anti-oxidant capacity and β-defensin 2 levels. Increased abundance of beneficial gut microbes associated with SCFA production	Sandionigi et al. (2022)
	Elderly individuals (age ≥60 years) 51 subjects in the intervention group	Polyphenol Rich Diet (3 servings of polyphenol rich food per day)/8 weeks	Positive association with butyrate producing bacteria and negative association with zonulin (marker of 'leaky gut')	Peron et al. (2021)
	Healthy Caucasian seniors (age 55–80 years) 13 subjects in the intervention group vs. 13 controls	Chicory Long-Chain Inulin/2 months	Higher gut microbial diversity with an abundance of *Bifidobacterium* in the intervention group. Immune responses were unchanged	Kiewiet et al. (2021)
	Non-frail or prefrail elderly subjects (age 65–79 years) across five European countries 324 cases vs. 289 controls	Mediterranean Diet/12 months	Increased abundance of specific taxa is associated with lower frailty, reduced inflammation and improved cognition. Increased production of SCFAs and decreased production of secondary bile acids, ethanol, *p*-cresol and carbon dioxide	Ghosh et al. (2020)
	Elderly individuals (age >75 years) 45 subjects in the intervention group vs. 34 subjects in the placebo group	Biscuits containing Probiotics (mix of *Bifidobacterium longum* Bar33 and *Lactobacillus helveticus* Bar13, 1:1)/30 days	Improved innate and adaptive immune function. Increase in naïve and activated memory T cells, regulatory T cells, B cells, Natural Killer activity and modulation of cytokine activity	Finamore et al. (2019)
	Elderly individuals (age 70–96 years) 22 subjects in intervention group vs. 22 subjects in placebo group	Potato Resistant Starch/3 months	Reduction in Proteobacteria and increase in *Bifidobacterium*. Increase in faecal SCFA levels	Alfa et al. (2018)

Table 10.1 (continued)

Lifestyle modifications	Elderly Chinese individuals (age 60–85 years) diagnosed with mild cognitive impairment 46 cases vs. 77 controls	Mindfulness Awareness Practice/9 months	Improvement of cognitive function associated with specific changes in gut bacterial profile. Abundance of *Ruminococcus* was associated with four cognitive functions.	Khine et al. (2020)
	Elderly Japanese subjects (age 62–76 years) 33 subjects in randomised crossover trial	Endurance Exercise Programme/5 weeks	Decrease in *Clostridium difficle* and increase in beneficial *Oscillospira*. Gut microbial changes in the intervention group were correlated with improvement in cardiometabolic risk factors	Taniguchi et al. (2018)
Dietary and lifestyle modifications	Healthy adult males (age 50–72 years) 22 subjects in intervention group vs. 22 controls	Diet and Lifestyle Intervention (sleep, exercise, relaxation guidance, probiotics and phytonutrient supplements)/8 weeks	Reduction in DNA methylation age (epigenetic age) by 3.23 years in intervention group as compared to controls	Fitzgerald et al. (2021)

10.6 Conclusion and Future Perspectives

Ageing is an obvious and non-reversible biological process. However, age-associated changes in physiological processes, which often lead to several complications, maybe reversible. From the above-mentioned evidences, it can be clearly understood that GM composition changes significantly with chronological age and correlates with altered physiological processes. Both, structural and functional attributes of GM are altered with age, resulting in dysbiosis and systemic inflammation. The metabolites produced by the gut microbes (such as SCFAs, polyamines, AHR ligands, etc.) are mostly involved in the cross-talk between gut and other organs such as the heart, kidney, liver, brain, bone, muscles, pancreas, etc. Healthy ageing, on the other hand, is associated with better GM composition and gut metabolite profile. Thus, maintenance of eubiosis should be an essential component of geriatric health interventions. Strategies such as probiotics, prebiotics, synbiotic supplementation, dietary and lifestyle modifications maybe helpful to improve health outcomes and quality of life. However, further research is required to have a better understanding of the molecular mechanisms underlying GM alteration, inflammation and ageing to identify suitable targets for intervention. Deciphering the GM-induced epigenetic changes, such as DNA methylation, histone modifications and regulation of non-coding RNAs, may give us thorough understanding of the pathogenesis of several metabolic diseases as seen in ageing. In this regard, transfer of gut microbes from healthy and diseased elderly individuals to germ free animal models may give us stronger evidences. Although, it is quite difficult to define a healthy baseline GM, since the composition is highly variable based on different host-associated and environmental factors, making it difficult to get comparison groups. Thus, unfolding the dynamic changes in age-related GM composition and associated metabolome, through large scale community sequencing studies are in demand. Solving these queries are urgently required to support healthy ageing and reduce healthcare burden.

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Chapter 11
Importance of Functional Foods Against Aging of Adult Stem Cells

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Abstract Functional foods offer vital nutrients that can protect against different diseases in humans. These functional foods are exclusively full of antioxidants that can remove many detrimental compounds including free radicals (ROS/RNS) to protect from adult stem cell damage to different diseases including cancer, diabetes, chronic obstructive pulmonary disease (COPD), and cardiovascular lesions, namely, fibrous obliterative pericarditis and rheumatoid granulomas, vasculitis, valvulitis, and nonspecific myocarditis. Functional foods are ingredients that give health benefits beyond the nutritional value. Some types of functional foods contain supplements or additional ingredients intended to recover health. Recently, scientific studies showed that functional foods rich in fruits and vegetables are important having anticancer effects of phytochemicals which are also focused to aim cancer stem cells (CSCs). Several preclinical and clinical investigations are still ongoing

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on the effects of dietary phytochemicals on adult stem cells and the prevention of aging and against CSCs of different cancers. The population of adult stem cells (ASCs) is reduced, unable to regenerate and reprogram, and showed the failure of tissue homeostasis during aging. The developing therapeutic methods with functional foods could modulate the major signaling pathways of losing adult stem cell populations, as well as could sustain healthy stem cell pool reprogramming to increase human lifespan.

Keywords Antioxidants · Phytochemicals · Adult stem cells · Aging

11.1 Introduction

Upon hearing the term "functional food," the vast majority will be puzzled, despite them already knowing the meaning. Doubts may clear after hearing some examples of commercialized products with the word "fortified" or "enriched." Functional foods are those nutritional products with an additional purpose besides providing the consumer with nourishment. These products seek to help lower the risk of disease and contribute to health and well-being. Examples of these foods can be found naturally, such as some fruits or vegetables, although there are also minimally processed functional foods such as grains and legumes. Another puzzling yet famous term to most is "stem cell." This is yet another word multiple people hear daily, but do not know its exact meaning. In biology, stem cells are those bases from which a cell with specialized function derivates. A stem cell doesn't have a specific function, but grows, develops, and differentiates to create the different cells in our body, such as skin, bone, blood, and muscle cells. There are different types of stem cells. For instance, embryonic stem cells aid in embryonic growth and development, to create a functional human that will develop to become a baby in the womb. These cells have the ability to differentiate into any type of cell. In contrast, there are also adult stem cells. These are present in adults in a moderate quantity and aid in cell replacement, as opposed to growth and development. When the old cells in the body age, stem cells help grow new ones to replace those which are now deteriorated. Additionally, adult stem cells have a limited ability to differentiate, in comparison with embryonic stem cells. As humans age, stem cells follow. When stem cells age, they also slowly deteriorate, which affects their ability to differentiate and replace old cells. Some reasons why stem cells age include cell cycle regulators, shortening of chromosomes' telomeres, DNA damage, signaling pathways, and other gene-related factors. The aging of adult stem cells plays a role in many disorders related to age. This has led many to inquire if there is anything that could be done to prevent the aging of adult stem cells. Many believe functional foods could play a role in the prevention of this issue. Scientific studies showed that aging is a risk factor for chronic disease in humans and intercessions with functional food could reduce the occurrence and harshness of many chronic diseases which should outcome in healthy aging or "successful aging" (Franceschi et al. 2018a, b). Therefore,

nutrition/functional food would pay significantly to improved human lifespan and/or healthspan (Baghdadi et al. 2022). The ASCs showed an important part in sustaining good health and have the ability to regenerate tissues and organs during the lifespan. The onset and progression of chronic disease in humans showed reduced sensory ability, response-ability, and pliability, along with increased organ system haphazardness related to the post-maturation aging process (Tierney et al. 2018; Lee and Kimmel 2020; Levy et al. 2020).

11.2 Different Functional Foods and Adult Stem Cell Aging

There are many different types of functional foods. Each has different characteristics and molecules that act through different mechanisms and are important to prevent aging in adult stem cells. Throughout this chapter, the effect of various functional foods in regard to adult stem cell aging will be discussed to highlight the importance of fortified foods and a good diet on longevity and aging prevention.

11.2.1 Fruits

A common type of food consumed by many daily is fruit. Many know fruits are healthy, but fail to understand how fruits contribute to health and wellness.

Fruits are the fleshy products of plants that contain seeds. For years, humans have used fruits as means of nourishment. Fruits contain various nutrients essential for life and cell maintenance, such as vitamins, potassium, dietary fiber, and folate. In the adult stem cell context, many may have heard that fruits contain antioxidants that help reduce aging. But what are antioxidants?

Antioxidants are stable molecules that bind to free radicals in the body. Free radicals are molecules with unpaired electrons produced in the body due to metabolic processes such as respiration and phagocytosis or caused by external factors such as pollutants and radiation. Since free radicals have unpaired electrons, most are unstable and highly reactive. In biology, they can serve as powerful oxidants or reductants. When an imbalance of free radicals occurs in the body, free radicals can damage DNA, throw off homeostasis, and negatively affect the macromolecules necessary for cell survival. For a while, they have also been linked to cancer.

The condition caused by poor free radical balance is called oxidative stress. Oxidative stress damages cells by deteriorating their membranes since they attack the macromolecules from which they are composed, and it affects stem cells by altering their differentiation and regenerative capabilities, leading to aging.

Antioxidants donate their electrons to the aggressive free radicals and neutralize their negative effect on cells by breaking the chain of reaction, which prevents further cell damage and hence reduces aging. If a sufficient amount of fruit is

consumed daily, the antioxidants present in them will keep a healthy balance of free radicals in the body, preventing aging by giving stem cells the optimal biological conditions required for proliferation (Lobo et al. 2010).

11.2.2 Vegetables

Another functional food group famously associated with optimal health is the vegetable group. A vegetable is a part of a plant, such as the roots or leaves, used for nutrition. There are many reasons why vegetables are considered ideal for daily consumption. Vegetables are low in calories and contain essential nutrients such as potassium, folate, dietary fiber, and vitamins A and C. In addition, vegetables contain another molecule that is not as well-known as the previously mentioned. Sulforaphane, or SFN, is an organosulfur and isothiocyanate which is abundantly present in cruciferous vegetables, such as kale, cabbage, cauliflower, bok choy, broccoli, and Brussels sprouts. It is the product of the hydrolysis of glucoraphanin. SFN is known for having anti-inflammatory and antioxidant properties. These properties exhibited in SFN target the issues that lead to adult stem cell aging, such as poor homeostasis, inflammation, and mitochondrial and genetic modification.

For instance, during aging, proteasome activity declines, which leads to cell stress due to an abnormal accumulation of damaged protein. However, SFN can reactivate proteasomal activity through the reactivation of the NRF1 (Das et al. 2018, 2022) and Nrf2 molecule (a regulator of cellular resistance to oxidative damage) through transcriptional regulation. Further research has also proven that moderate amounts of SFN can prevent aging by protecting stem cells from senescence and apoptosis. Plus, SFN is an antioxidant and hence protects DNA from oxidative damage and modulates epigenetic modifications such as DNA methylation and histone modification. It can also prevent skin aging by maintaining appropriate collagen levels and protecting the skin against UV-ray damage through mechanisms of action such as inhibition of AP-1 activation and expression of metalloproteinases (Santín-Márquez et al. 2019).

11.2.3 Nuts

Nuts are fruits protected by a tough shell with an edible kernel inside. They are rich in multiple oils, vitamins, and minerals the body needs to ensure proper physiological function. Of all these nutrients, an important one for adult stem cells is alpha lipoic acid, often abbreviated as ALA, an impactful molecule on human health.

Different organs in the body have various mechanisms of aging. When intestinal stem cells age, the performance of the endocytosis-autophagy network declines,

which negatively affects the process of human digestion. Despite this, a proven way to prevent these effects caused by aging is through the consumption of foods that are high in alpha lipoic acid (ALA). ALA is an antioxidant made in the body, which can also be present in enriched foods, especially nuts. It is an organosulfur deviated from caprylic acid, used to break down carbohydrates and convert them into energy used by the body. The importance of ALA for adult stem cells is that its oral administration has a positive effect on intestinal health by reversing age-associated hyperproliferation of stem cells. ALA does this by promoting the activation of the age-degraded endocytosis-autophagy network.

It is important to note that humans naturally produce ALA. However, as the human body ages, the production of ALA declines significantly. Hence, consuming plenty of functional foods which contain ALA is crucial to prevent age-related disorders and organic dysfunctions.

In addition to the benefits regarding intestinal health mentioned previously, ALA has also proved to reduce the loss of hematopoietic cells. Hematopoietic cells are those stem cells that differentiate into different types of blood cells, such as erythrocytes, leukocytes, and platelets. ALA lowers ROS, or oxygen-containing reactive species levels in the body, which affects apoptosis, and saves these cells (Du et al. 2020).

11.2.4 Seafood

Seafood is food such as fish and shellfish. Throughout the years, various cultures have used seafood and fish as their primary source of nourishment. Today, seafood has proved to be extremely important for human health, especially in adult stem cell aging. This is because seafood contains a type of fatty acid named omega-3, which many may have heard of and used as a supplement. Omega-3 helps regulate the growth of fat cells in the body.

Cells detect the omega-3 fatty acids through primary cilia, a type of organelle acquired from evolution. Once these fatty acids are detected and bound to the receptors on the cell, signaling encourages stem cell proliferation, which in return creates more fat cells. Having a significant number of fat cells is extremely important because when there are too few fat cells, as energy is stored in them, they get bigger. These large fat cells are far from the oxygen supply, have poor signaling, and are prone to bursting, which releases toxins in the body. Large fat cells are also associated with inflammation, insulin resistance, and diabetes.

Through seafood consumption, omega-3 fatty acids are acquired and healthy stem cell proliferation is ensured. In addition, research has also proven that consuming food rich in omega-3 can not only regulate fat stem cell proliferation but also contribute to healthy neural stem cells and reduce triglycerides to prevent issues in cardiac stem cell behavior (Birgisdottir and Johansen 2020).

11.2.5 Tea and Coffee

In various cultures worldwide, it is habitual to drink tea or coffee every day, especially in the mornings. Coffee is a beverage made from roasted and ground coffee beans, while tea is the water-based boiled product of dry and crushed leaves of specific plants. It has been argued in the scientific community that both beverages contain substances such as caffeine that could be detrimental to human health. However, the positive effects of consuming these drinks are often overlooked. In the case of tea, it is a source of antioxidants, which, as previously discussed, can slow down adult stem cell aging by preventing an excess of free radicals in the body, which would otherwise damage cells and DNA. When it comes to coffee, it has proven to prevent severe cardiovascular diseases and cognitive impairment that would otherwise come as a consequence of aging. Coffee is known to contain polyphenols which improve heart health and lower fat accumulation. In the case of stem cells, caffeine can increase the phagocytosis of neutrophils in mesenchymal stem cells, which can reduce the production of reactive oxygen substances. Caffeine can also prevent dermal stem cells from aging by activating A2AR/SIRT3/AMPK-mediated autophagy (a mechanism that protects stem cells from oxidative stress).

11.2.6 Fortified Dairy (Low Fat)

In addition to coffee, another drink that many consume daily during breakfast, sometimes even combined with coffee, is milk. Milk is a white fluid composed mainly of fat and protein secreted by mammal mothers to nourish their newborn offspring. Additionally, people may consume dairy products that are derived from milk, such as cheese, yogurt, or butter. Dairy products are known to provide essential amounts of calcium for optimal bone health and proper child growth and development. As a functional food, milk and dairy products have often added nutrients such as vitamin D, vitamin A, folic acid, iron, and zinc. Many are not aware of the significant benefit milk has when it comes to adult stem cell aging and its prevention. The various nutrients in dairy products have been demonstrated to target the main issue regarding aging, the shortening of the telomeres. As milk prevents this change in the DNA, the aging process slows down since cells will not lose physiological function caused by genetic material loss. Zinc, specifically, is required for cellular division and proliferation. Without a significant amount of zinc in the body, adipose-derived mesenchymal stem cells, or AD-MSCs, the type of stem cells which can differentiate into neurons, can be impaired. In addition, milk is critical for humans to keep good muscle health as the body ages. However, this only applies to low-fat and nonfat milk, as high-fat milk tends to induce aging instead of preventing it, since it can cause oxidative stress and inflammation. Moreover, vitamin D also plays a crucial role in adult stem cell aging, since it stimulates MSC osteogenic

differentiation, which can reduce aging by encouraging proliferation (Tucker 2019; Moon et al. 2018; Mares 2016; Fujita et al. 2021).

11.2.7 Eggs

Eggs are oval or round objects laid by birds, fish, or reptiles. They contain a developing embryo inside, surrounded by a shell or a membrane, depending on the species. Eggs are considered essential nutrients since they are a great source of protein, selenium, phosphorus, choline, and vitamins. Eggs also can lower triglycerides since they contain high-density lipoprotein, or HDL, a healthy type of cholesterol essential for good heart health. When it comes to impeding damage to adult stem cells to help prevent aging, eggs have vitamins like D, E, and A, which work as antioxidants to combat free radical imbalance in the body to inhibit damage caused by oxidative stress. This process has been demonstrated to prevent skin wrinkles in adults. Additionally, eggs contain lutein and zeaxanthin, two naturally occurring xanthophylls (oxygen-containing carotenoids). These carotenoids can also protect the body from oxidative stress and contribute to optimal eye health by preventing vision damage caused by aging, as they absorb damaging light.

Eggs also contain choline, a water-soluble and vitamin-like cation. It has been demonstrated choline plays a critical role in neural stem cells by increasing proliferation, differentiation, and maturation. This is because they are crucial for cellular membrane synthesis and can regulate epigenetic pathways. For instance, they can regulate DNA methylation, a process that plays a role in the differentiation of neural stem cells by adding methyl groups to DNA (Soto et al. 2020).

11.3 Different Compounds of Functional Foods to Prevent Adult Stem Cell Aging

11.3.1 Carotenoids

Plant-derived carotenoid—**β-carotene**—has been known to have ROS-quenching ability and hence has been used to treat erythropoietic protoporphyria (EPP) (rare inherited metabolic disorder) (Krinsky 1989). Interestingly, in a study conducted by Cho et al., β-carotene increased type 1 collagen mRNA levels, thereby improving facial wrinkles and rigidity in photoaged female subjects. However, due to its capacity to decrease minimal erythema dose (MED), β-carotene made the skin more predisposed to UV-induced erythema. A key factor is the dosage, as low doses (30 mg/day) seem to be more beneficial in cutaneous photoaging compared to higher doses (90 mg/day), where oxidative DNA damage is not significantly affected (Cho et al. 2010). Differentiation studies conducted by Mahtab et al. showed significantly higher potential for differentiation if mouse ciliary epithelium-derived MSCs into retinal cells (Haghighat et al. 2021).

11.3.2 Astaxanthin

Astaxanthin, a xanthophyll carotenoid found in bacteria, microalgae, and yeasts, is an antioxidant with anti-inflammatory properties (Higuera-Ciapara et al. 2006). Cho et al. found that astaxanthin along with collagen improves facial skin elasticity and decreases MMP-1 and MMP-12 mRNA expression in human subjects (Cho 2014). Interestingly, it has been reported to induce proliferation of neural progenitor cells (NPCs) via upregulation of stemness acting signals (OCT4, SOX2, Nanog, and KLF4) (Kim et al. 2010a). Astaxanthin has also been reported to induce adipose-derived mesenchymal stem cells potency (Choi et al. 2019). Astaxanthin has been reported to improve motor impairments and activate mitochondrial biogenesis in spinal cord injury (Mohaghegh Shalmani et al. 2020).

11.3.3 Polyphenols and Isoflavones

11.3.3.1 Resveratrol

Resveratrol is a polyphenol found in fruits and mainly in red wine with the ability to possess anti-inflammatory properties and anticancer properties (Frombaum et al. 2012). Interestingly, resveratrol improves the functionality and facilitates the regeneration of autologous MSCs (Wang et al. 2018). Resveratrol a sirtuin 1 (SIRT1) activator has also been reported to play a significant role in neuronal differentiation with slightly increased calcium intensity (Songsaad et al. 2020). Resveratrol has also been extensively reviewed to ameliorate oxidative stress and inflammation and improve mitochondrial bioenergetics (Zhou et al. 2021).

11.3.3.2 Apigenin

Apigenin is a naturally occurring polyphenol with beneficial effects in diabetes, Alzheimer's disease, cancer, etc. (Salehi et al. 2019). Apigenin was also able to successfully reduce Ca^{2+} signals and caspase-3/7-mediated apoptosis in iPSC-derived Alzheimer's disease neurons (Balez et al. 2016).

11.3.3.3 Luteolin

Luteolin is a flavonoid with anti-oxidative, anti-tumor, and anti-inflammatory properties (Luo et al. 2017). Luteolin has been reported to promote proliferation of skin epidermal stem cells through increased expression of β-catenin, c-Myc, and cyclin expression (Wan et al. 2019). Luteolin has also been reported to modulate neural stem cell fate determination, thus placing itself as an astrocytogenic potential (Achour et al. 2021). In PC12 cells, luteolin increased heme oxygenase-1 (HO-1) mRNA and protein levels, thus enhancing the cholinergic activity

(Lin et al. 2010). Interestingly, luteolin has been reported to eliminate p53-dependent hPSCs and not smooth muscle cells or perivascular progenitor cells (Go et al. 2020).

11.3.3.4 Quercetin

Quercetin is a naturally occurring flavonol known for its anti-inflammatory and wound-healing abilities (Salehi et al. 2020). Quercetin has also been reported to affect adipose tissue aging by reducing senescence and oxidative stress and down-regulates miRNA-155-5p, through the NF-κB and SIRT-1 (Zoico et al. 2021). Another interesting observation was the ability of quercetin to rejuvenate senescent fibroblasts (Chondrogianni et al. 2010). Quercetin can also induce dental pulp stem cells upregulating stemness-associated genes (OCT4, NANOG, SOX2, and cMyc) (Fageeh et al. 2021). Interestingly, quercetin stimulates bone marrow mesenchymal stem cell differentiation enhancing BMP2, Smad1, Smad4, and other osteogenic differentiation markers like RUNX2, OSX, and OPN (Pang et al. 2018).

11.3.3.5 Hesperidin

Hesperidin, a flavanone, is known to be a neuroprotective agent (Hajialyani et al. 2019). Hesperetin, a known metabolite of hesperidin, is also known to induce osteogenesis of human mesenchymal stem cells (Xue et al. 2017). Additionally, hesperetin has also been reported to alleviate signals that suppress osteogenic differentiation in periodontal ligament stem cells by regulating ROS levels and cell proliferation signaling pathways (Kim et al. 2013).

11.3.3.6 Taxifolin

Taxifolin is a strong antioxidant flavonoid known to improve skin viscoelasticity (Micek et al. 2021). Interestingly, taxifolin also has been reported to protect dental pulp stem cells under hypoxia and inflammatory conditions (Fu et al. 2021). Osteogenic differentiation of human bone marrow mesenchymal stem cells has also been reported by taxifolin via NF-κB pathway (Wang et al. 2017). As far as aging, taxifolin reduces oxidative stress, thereby ameliorating D-galactose-induced aging process through inhibiting Nrf2 (Liu et al. 2021).

11.3.3.7 Catechin

Catechin is a flavanol known to target neurodegeneration through antioxidant pathways (Farzaei et al. 2019). Epigallocatechin gallate (EGCG) a monomer is known to have antiaging activities while exhibiting significantly higher EGFR proteins (Chen et al. 2017).

11.3.3.8 Genistein

Genistein an isoflavone induces adipogenic differentiation from mesenchymal stem cells by upregulating PPAR γ. It also significantly inhibited Runx2 and type 1 collagen which are involved in osteogenic differentiation (Zhang et al. 2016). Genistein could also be a promising anti-aging agent for the skin suggesting it prevents skin aging after menopause for topical use.

11.3.3.9 Daidzein

Daidzein, an isoflavone, has been known to repress adipogenic differentiation of human adipose tissue-derived mesenchymal stem cells through the stimulation of lipolysis using Wnt/β-catenin signaling (Kim et al. 2010b).

11.3.3.10 Anthocyanins

Anthocyanins are water-soluble flavonoids, known to reduce aging-induced oxidative stress and further induced autophagy via the AMPK pathway (Mattioli et al. 2020; Li et al. 2019). Anthocyanin has also been reported to accelerate NSC proliferation while decreasing NSC senescence markers via downregulation of TNF-α protein levels (Gao et al. 2020).

11.4 Molecular Biomarkers, Adult Stem Cell (ASC) Aging Process, and Functional Foods

The ASC aging process is related with seven different mechanisms, namely, stem cell enervation, reduced adaptation to stress, metabolic disquiet, damage of proteostasis, epigenetic alterations, macromolecular injury, and inflammation (Stover et al. 2022; Kim et al. 2010a; Kennedy et al. 2014). Therefore abovementioned seven different mechanisms, associated biomolecular markers, as well as clinical actions are also prognostic and typical of chronic disease illness and death (Arbeev et al. 2016). There are several changes observed due to the onset and progression of aging and chronic diseases, and those are mainly blood lipid levels, cardiovascular performance indices (blood pressure as well as pulse rate), body mass index, hypothalamic-pituitary-adrenal (HPA) axis activation, and inflammation, as well as markers of organ system function (such as the kidney, nervous system) (Arbeev et al. 2016; Partridge et al. 2018). Therefore, the identification of the causal and predictive biomarkers of molecular stem cell signaling pathways is necessary to prevent chronic disease and aging process and to initiate the development of effective lifestyle and/or pharmaceutical interventions by functional foods (Balez et al. 2016; Jia et al. 2017) (Fig. 11.1).

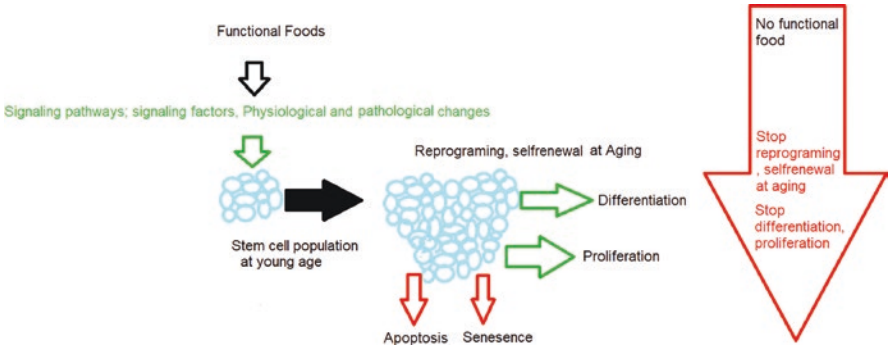

Fig. 11.1 ASC signaling with or without functional food during aging

The biomarkers for "biological age" have been demarcated with specific norms by the American Federation for Aging Research as follows: (a) record the phases of aging and expect mortality more consistently than linear age; (b) describe about the output of a range of organ; and (c) authorize following changes over time (Balez et al. 2016). The genes or metabolic pathways in the organ systems are altered during aging process that should be explored more (Wagner et al. 2016). Therefore, biomarkers will demonstrate the molecular mechanism of the damaging effects of different risk exposures and will specify the efficiency of antiaging interventions with functional foods to stop physiological deterioration and inability to reprogramming of ASCs during aging. Finding and confirming specific ASC biomarkers of aging through interposition investigations will augment the lifespan andwill avoid diseases that are preferably aimed at younger persons specified that age-associated chronic diseases consequence from any lifetime of exposures. Recently, the most scientific studies of aging are completed within elder population who have previously established age-associated chronic diseases and therefore did not explain the lifelong exposures that move the aging. One scientific study highlighted the relationship of disease biomarkers to biological age in the Dunedin cohort (the 38-year-old birth cohort; New Zealand; 1972–1973) (Belsky et al. 2015). Belsky et al. explained both the static "biological age" of the individuals in cohort and the more dynamic "pace of aging," or the rate of biological age changes. These determinations showed different biomarkers of organ system function, cardiovascular health, metabolism, inflammation, and DNA damage. The "multibiomarker algorithm," associated with the biological age of cohort individuals at the single time point by joining all measurements from ten individual biomarkers, has been shown in the data of National Health and Nutrition Survey (NHANES) (Belsky et al. 2015; Levine 2013). The individuals in the cohort, restrained at age 38 years, were mostly free of any chronic disease, and the mean biological age in the cohort was similar as their chronological age. However, the distribution of biological age was calculated from the multibiomarker algorithm range (21–61 years). The Dunedin cohort "pace of aging" was shown in individuals over 12 years with additional period of the

study. The score of 18 biomarkers was observed on distinct elements of cardiovascular, immune, organ, and metabolic function. The robust relationship between the biological age and the pace of aging was found among the participants of chronical age 26–38 years and showed the marked variation of the biological aging rate among individuals in the cohort. The significant connections were reported between the pace of aging and functional measures of successful aging, namely, cognitive function and physical strength (Belsky et al. 2015). Therefore, the measures with functional food consumption, status, and function are also judgmentally wanted.

Scientific studies also showed that the aging of human intestinal stem cells (ISCs) stem cell biomarker, schlafen-3involved in to rise in colorectal cancer occurrence with age (Schultz and Sinclair 2016; Patel et al. 2009a, b), but this remains hypothetical because it not yet identified how cells expressing mammalian ISC stem cell markers alteration in occurrence and role with age. There are two interconvertible populations of ISCs observed, namely, proliferative Lgr5-expressing cells in the base of the crypt as well as quiescent label-retaining cells above the crypt base (Takeda et al. 2011). Before these molecular biomarkers were found, irradiation experiments recommended that the intestine was more delicate to damage with age as the total number of clone-forming units or cancer stem cell numbers increase (Martin et al. 1998).

The characteristic of hematopoietic stem cells (HSCs) aging showed twisted differentiation latent. The aged HSCs have more tendency to differentiate as the myeloid lineage (Rossi et al. 2005). This founding is fully reliable with the reflection that the adaptive immune system drops with age (Linton and Dorshkind 2004) and also reported that acute lymphoblastic leukemia, the primarily juvenile disease, drops with age, whereas the acute myeloid leukemia rises with age (Lichtman and Rowe 2004). The aging of HSCs might subsidize to moderate anemia found among elderly population (Guralnik et al. 2004). Therefore, more scientific investigations are needed to find the intervention of differentiation both ISCs and HSCs by functional foods during aging process (Table 11.1).

The DNA methylation, a repressive epigenetic biomarker of HSCs, declines in aging, and the hypomethylation is linked to the proliferation of HSCs, indicating why they are programmed to persist as quiescent (Beerman et al. 2013). The H3K4me3, an epigenetic modulator (Ortega et al. 2020; Das et al. 2021a, b), is

Table 11.1 The changes of different types of stem cell population with aging

Names of stem cell population	Population changes with aging; causes	References
Germline stem cells (GSCs)	Reduction; reduced differentiation	Ryu et al. (2006)
Melanocyte stem cells	Reduction; reduced differentiation	Inomata et al. (2009)
Neuronal stem cells (NSCs)	Reduction; reduced differentiation	Ahlenius et al. (2009)
Hematopoietic stem cells (HSCs)	Rising, differentiation	Beerman et al. (2010)
Intestinal stem cells (ISCs)	Rising, differentiation to cancer stem cells	Patel et al. (2009a, b)

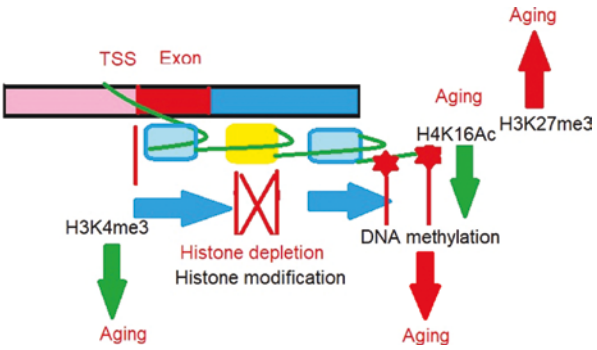

Fig. 11.2 Changes of epigenetic biomarkers (DNA methylation, H4K16Ac, H3K4me3, and H3K27me3) in ASCs during aging

highly expressed with age at loci that reprogrammed HSC self-regeneration, potentially underlying the upregulation of HSCs found with aging (Sun et al. 2014). The reduction of H4K16Ac was found with aging in HSCs, and the inhibition of CDC42 returns the H4K16Ac levels to reprogrammed new population of HSCs that converses the phenotypes of HSC aging in the transplantation studies (Florian et al. 2012). The H3K4me3 levels modestly reduce with age, whereas the levels of the repressive alteration of H3K27me3 rise with age, and it has also been found that the expression of histones themselves reduces with age (Liu et al. 2013) (Fig. 11.2).

11.5 Conclusions

The role of functional food in diet can be shown in the inhibition, management, and the reverse of chronic diseases during aging. The recommended daily intake of nutrients or nutrient reference values (NRVs) is offered to individuals and populations on intake levels of essential vitamins and minerals needed to avoid any nutrient deficiencies. The United States National Academy of Sciences, Engineering and Medicine established the framework entitled "Guiding Principles for Developing Dietary Reference Intakes Based on Chronic Disease" in 2017. This framework offers an approach for establishing nutrient intake recommendations based on chronic disease reduction. The role of functional food needs in ASCs of tissues for renewal as well as regeneration is developing as vital consideration in starting nutrition necessities in chronic, acute disease and trauma recovery and during aging. Therefore, the full potential for founding nutrient references for chronic disease decrease will need the main developments in our empathetic of the biological pathways and mechanisms of aging, ASCs, as well as chronic disease. Hence, the functional food is essential in reducing the rates of aging.

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Chapter 12
Advantages of Functional Foods in Supporting and Maintaining Hair and Skin Health

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Abstract The skin, the body's largest and most visible organ, is crucial in shielding us from many external factors. Alterations in diet and current lifestyle exponentially affect the organ's degeneration. While many synthetic skincare products are available, their prolonged use can cause skin irritation, redness, peeling, the "bleach panda" effect, blister formation, dark pigmentation, and more. Consequently, the only cure is to utilize natural products and adopt a healthy diet. Degeneration is one of the leading causes of skin and hair disorders and aging, which is affected by the effect of both internal and external factors. So the mere intake of food is not sufficient, but the intake of a nutritive and organized diet is necessary to trigger regeneration and growth of the integumentary system. The term "functional foods" is used to describe those that provide health benefits beyond those provided by their nutritional value. Using them is a great way to treat health problems naturally. Wrinkles and the aging process can be slowed or stopped using various nutraceuticals rich in collagen, lipids, proteins, vitamins, and minerals. Plants like *Hibiscus rosa*, ginger, grape (*Vitis vinifera*), etc. can delay aging and cease hair loss. The use of marine goods such as seaweed, microalgae, corals, shelled organisms, etc. is very effective in treating skin problems. Several of these have been shown to be effective in reducing hair loss. They promote hair development by activating potassium-ATP channels, decreasing 3-oxo-5-alpha-steroid 4-dehydrogenase activity, and increasing Wnt/beta-catenin and extracellular signal-regulated kinase (ERK) activity. Collagen, polyphenols, polysaccharides, lipids, vitamins, and minerals are some active ele-

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ments in functional meals that maintain the physique of skin and hair. Ayurveda and regional foods and medicines have also been used to prevent skin and hair damage. Having access to nutritious foods and ensuring timely consumption are fundamental to maintaining a healthy lifestyle.

Keywords Nutraceuticals · Antioxidants · Regional food · Microbiome · Ethnic food · Antiaging · Collagen synthesis

12.1 Introduction

The skin keeps the body safe from heat, light, cuts, and diseases. It is part of the same system as the hair, nails, nerves, and glands. This system acts as a barrier between us and the outside world (Yousef et al. 2017). Apart from the latter, it also helps to regulate the body temperature, store water and fats, and prevent water loss and the entry of microorganisms and produces vitamin D with exposure to the sun. Human skin shows topographic differences in structure, i.e., a structural variation from part to part. For example, the skin structure on the forehead and cheek differs from that of the lips and their borders. There is seldom visible hair on the forehead and cheek, whereas in the lips and its borders, hair is absent. In males, thick hair growth is seen in the jaw regions when compared to low or no hair growth of females (Montagna et al. 2021).

The layers of human skin can be into the epidermis, dermis, and hypodermis (Prost-Squarcioni et al. 2008). The significant role of the epidermis is to produce new skin cells; melanin, which defines the skin's color; and protect the body from the external environment. The epidermis primarily consists of keratinocytes which act as a physical barrier against invading microorganisms, heat, UV radiations, and water loss. It contains another type of cell called melanocytes which gives pigmentation to the skin and also guards the skin against UV rays. The epidermis is devoid of blood vessels. The epidermis consists of five strata: stratum corneum, lucidum, granulosum, spinosum, and germinativum. Stratum germinativum or stratum basale forms the epidermis' innermost layer, and the basement membrane (basal lamina) separates it from the dermis. Hemidesmosomes attach the stratum basale to the basement membrane. Stratum basale includes cuboidal to columnar-shaped cells, producing keratinocytes through continuous mitosis. Stratum basale also has melanocytes.

The next layer forms the stratum spinosum, which contains spines and dendritic cells, which are cytoplasmic processes and are made of polyhedral cells. These spines extend toward the neighboring cells forming desmosomes. The third layer of the epidermis, stratum granulosum, includes diamond-shaped cells with lamellar granules and keratohyalin granules and contains glycolipids and the precursor molecules of keratin. Stratum lucidum is present only in regions where the skin is thick, like in the palms and soles. This layer produces the transformation product of keratohyalin, eleidin. The stratum corneum's topmost layer is highly keratinized as it is

made of horny scales of dead keratinocytes. The dead keratinocytes, also called the anucleate squamous cells, secrete defensins that act as a first-line immune defense (Yousef et al. 2017).

The dermis makes up the majority of the skin and serves as a barrier between the body and the outside world (Montagna et al. 2021). The dermis is a layer of amorphous and fibrous connective tissue that has blood vessels, nerves, appendages from the top layer of skin, fibroblasts, macrophages, and mastocytes. The most common types of fibrous connective tissue are elastic and collagen tissue. The elastic connective tissue is made up of premature elaunin fibers, oxytalan fibers, and mature elastic fibers that form a continuous network. Oxytalan fibers exclusively possess microfibrils, whereas fully grown elastic fibers and elaunin possess both the components of the microfibrillar and amorphous matrix (Prost-Squarcioni et al. 2008). The dermis encompasses collagen and glycosaminoglycans, which can store a lot of water and keep the skin turgid. The dermis is highly packed with blood vessels, and the epidermis gets the nutrients through diffusion from the dermis. Nerves and sensory organs are also found in the dermis at various levels (Montagna et al. 2021).

The hypodermis forms the thickest and innermost sheet of the skin which connects the dermis to the muscles and the bones and is also known as the subcutaneous fascia (Yousef et al. 2017). Fibroblasts, fat cells, connective tissue, bigger nerves, blood vessels, and macrophages are found in the hypodermis, which supports the immune system and protects against invaders. It contains fatty lobules and skin accessory organs such as hair follicles, sensory neurons, and blood vessels (Yousef et al. 2017). They store energy in the adipose tissue and regulate the body temperature by protecting against heat (by sweating) and cold (by insulating).

12.1.1 Skin: Accessory Organs

The skin's accessory organs—hair, nails, sebaceous glands, and sweat glands—embryologically develop from the epidermis, which is referred to as an "appendage" because it can extend downward through the dermis into the hypodermis (Gawkrodger and Ardern-Jones 2016). The skin appendages are a collection of ectodermal origin appendages that include apocrine and eccrine glands, pilosebaceous units, nails, and ducts that are formed as epidermal down-growths during the development. When an appendage is abrated, keratinocytes can move from the appendage epithelium to the epidermal surface and reepithelialize it. Because the face and scalp have more pilosebaceous units than the torso and limbs, which has fewer appendageal structures, they reepithelialize faster (James et al. 2006).

Eccrine sweat glands are seen more on the feet soles and less on the back as they regulate heat (Sato and Dobson 1970; Murphy 1997). Sweat glands are developed from the epithelial cell layers that are extended downward from the dermal ridges (Mauro and Goldsmith 2008). During development, this tubuliform structure is transformed to produce the three combined sections of the eccrine sweat unit: intraepidermal spiral tube, straight dermal part, and twined secretory duct. The

spiral duct is made up of dermal duct cells that have ascended and opened onto the skin's surface. Cornification occurs within the duct, and thus produced corneocytes eventually form part of the cornified layer (James et al. 2006; Mauro and Goldsmith 2008). Eccrine glands are mainly responsible for heat regulation, whereas apocrine glands are responsible for body odor. Apocrine sweat glands are mostly seen in the axillae and perineum of humans. Like apoeccrine-eccrine glands, apocrine glands are not exposed straight to the dermal surface. Instead, the intraepithelial duct goes into the infundibulum above the sebaceous duct and opens into pilosebaceous follicles (Murphy 1997). The AEG, apocrine sweat gland, originates from eccrine-like precursors throughout puberty and opens straightly to the dermal surface. The apoeccrine sweat gland was detected in the adult axillae while isolating the human axillary sweat from patients with axillary hyperhidrosis. Axillary hyperhidrosis is a condition in which the patient experiences a rapid increase in the perspiration rate. The frequency of it varies from individual to individual. The AEG, as eccrine glands, opens straight to the dermal surface. Because the apoeccrine sweat gland secretes tenfold more than the eccrine gland, it is believed to endow axillary hyperhidrosis (Mauro and Goldsmith 2008).

The pilosebaceous unit is made up of the follicle, sebaceous gland, shaft, and arrector pili muscle (Agarwal et al. 2000). The hair follicle is epidermal in origin and lengthens deep into the dermis and rarely into the subcutis for follicles that produce terminal hairs. Meanwhile, vellus hair follicles only extend to the top reticular dermis. The isthmus, infundibulum, and lower follicle are three major hair follicle segments present on the head (Poblet et al. 2002). The infundibulum fragment starts from the epidermis' surface, which forms the top piece of the follicle and lengthens to the sebaceous duct's orifice. The isthmus is the space amidst the opening of the sebaceous duct and the bulge. Finally, the inferior section of the hair follicle extends from the bulge to the base. The bulb is included in this segment. It contains the follicular matrix surrounding the dermal papilla's sides and top. In the dermal papilla, you can find capillaries. The matrix and the papilla work together, and the papilla has the highest rate of cell division of any organ. The hair shaft is made when matrix keratinocytes multiply in a hair that is growing. Melanocytes are mixed with matrix cells to give the hair shaft its color (Glover et al. 2017; Tapia-Paniagua et al. 2018).

The medulla is the innermost layer of the hair shaft. The cortex, the bulk of the hair, encloses it. Shaft cuticle cells form a layer of cellular activity. Three layers of cuticle are wrapped around the shaft to form the inner root sheath. After the hair follicle emerges from the matrix, the inner sheath becomes a critical structural component of the hair shaft. Keratinization of the inner sheath occurs inward and ends at the follicle's isthmus. Finally, the outer root sheath completely encases the hair follicle. Trichilemmal keratinization occurs in this layer at the isthmus (Poblet et al. 2002; Tapia-Paniagua et al. 2018).

Sebaceous glands are holocrine glands that are seen with hair follicle and are prominently found on the face and scalp. These gland cells are rich in lipid droplets called sebum and are organized in lobules. These lipid-filled cells are produced by basaloid germinative cells surrounding the lobule, and they are ejected toward the

infundibular region of the hair follicle along the sebaceous duct (Thiboutot 2004; Danby 2005).

The arrector pili muscles attach to the papillary layer of the dermis and insert at the level of the bulge. Sympathetic activation makes these muscles shrink in cold weather. This lifts the skin's level slightly and causes hair to stand erect, giving the appearance of "goose bumps" (Poblet et al. 2002).

12.2 Degeneration and Regeneration of Skin

Degeneration is the thinning and deterioration of the skin and hair cells due to intrinsic and extrinsic factors. The skin's growth and development can cause the skin's expansion both intrinsically and extrinsically as the cells should expand themselves to cover the skeleton and the tissues, which is undergrowth, and it has to overcome the mechanical forces produced by the external environment. The degeneration of the skin occurs with aging. Aging is the major factor that contributes to the degeneration process. During the process, the epidermal layers deteriorate, thereby causing skin layer thinning. Degeneration leads to the early occurrence of wrinkles, chronic wounds, loss of elasticity and plasticity, dryness, etc. Rather than the skin, the hair follicle also undergoes degeneration once in 7–8 years. The hair cycle includes anagen (growth phase), catagen (degenerative phase), telogen (resting phase), and exogen (shedding phase). When the hair follicles are retained in the catagen phase, the hair growth rate retards, leading to degenerative diseases like alopecia. Hair degeneration in alopecia is characterized by the apoptosis of keratinocytes, melanocytes, dermal papilla, and Langerhans cells. In androgenetic alopecia, hair shaft thins, and the hair follicle undergoes degeneration leading to constant hair fall. This is mainly due to the physiological changes caused by the binding of androgens like dihydroxy testosterone to the androgen receptors. Degeneration can also be due to the intake of an unhealthy diet that includes a high glycemic index, processed foods, alcohol, fatty meats, and dairy products. To avoid degeneration, the cells should be rejuvenated and should undergo regeneration (Meydani 2000; Kartikey et al. 2019).

Regeneration is the process of restoration and replacement of lost or damaged cells and their organization to retain its function. Regeneration is mainly studied for treating injuries and diseases, thereby resulting in a new field of science called regenerative medicine. Every organism has the ability to regenerate to maintain its tissue organization and structure. Through regeneration, the injuries and the amputated body parts are repaired or regrown. The degree of regeneration decreases with the increase in the complexity of the organisms. In higher organisms like mammals, the regeneration is restricted to tissue repairing, wound healing, and the regrowth of the skin and hair cells. They increase remodeling of the skin and the tissues which promote wound healing. In hair, regeneration occurs when the hair follicle re-enters the anagen phase after the telogen resting phase. Here the hair follicle stem cells maintained in the bulge undergo continuous division to produce new hair. Skin cells

undergo rejuvenation every 27 days to properly maintain the skin structure. Recent studies on skin regeneration have shown that 40–56 days is the average time taken for the epidermis turnover. The period of epidermal turnover increases with age. As age increases, the regenerative capacity of the individual decreases (Yu et al. 2008).

Stem cells play a significant role in tissue regeneration. The basal layers of the epidermis contain stem cells that undergo rapid division to produce new cells which differentiate to form various types of skin cells. The degree of keratinization and the morphological and biochemical changes in such cells determine various layers of the skin. So, skin cells are made at the base of the epidermis and moved to different layers through a process called "differentiation." This process ends with apoptosis in the skin's outermost layer. Collagen is a crucial part of tissue repair, so skin cells should have it in adequate amount for wound healing. Regeneration takes place through a cascade of processes that includes inflammation of the skin cells, proliferation, and remodeling. Throughout these phases, collagen plays a crucial role in tissue repair; in case of any deficiency, it can lead to chronic wounds (Mahjour et al. 2012).

Food does play an important role in regulating the degeneration and regeneration of skin and hair. Unhealthy diet can cause inflammation and premature aging of the skin. Eating healthy can supply nutrients and minerals necessary for adequately maintaining the skin and hair. It is necessary to have an adequate supply of nutrients like vitamins C, B, and D, iron, zinc, and proteins to rejuvenate the skin and hair cells. Proteins from fish, legumes, beans, low-fat meats, and dairy products can help provide supplements necessary for regeneration (Takeo et al. 2015).

12.2.1 Human Skin Cell Aging: An Overview

Healthy skin is something that society strives for, and some people go to great extents to attain it. As opposed to real age, the mere appearance of age predicts crucial aspects of health and well-being (Porcheron et al. 2013). Skin beauty has always been a significant indicator of one's health that has existed in the course of history and cultures. Furthermore, healthy skin influences social characteristics such as self-confidence, charisma, and etiquette (Jones et al. 2016). The look of youth and beauty can positively influence people's social behavior and fecundity (Blanpain and Fuchs 2006). Different elements, like skin disorders, individual characteristics, and internal and external elements, influence skin aging (Tan et al. 2018).

12.2.1.1 Cutaneous Aging

The histological, morphological, and physiological skin changes caused by chronological and environmental factors can be defined as a skin cell or cutaneous aging. It is the accumulation of various harmful changes in cells and tissues with increased aging, leading to an increased risk of disease and death (Harman 2000). Cutaneous

aging results from a combination of biological aging and external aging influenced by elements like UV radiation, smoking, pollution, and inflammation (Cho 2014). Wrinkling, loss of elasticity, laxity, and a rough-textured look are all signs of skin aging. The aging process causes phenotypic differences in skin cells and structural and functional alterations in extracellular matrix elements, including collagen and elastin (Zhang and Duan 2018). Cutaneous aging is caused by intrinsic and extrinsic factors (Krutmann et al. 2017). Intrinsic aging is a natural physiological process that makes the skin thin, dry, and prone to tiny wrinkles and dermal degeneration over time. On the other hand, extrinsic aging is caused by factors like air pollution, smoking, a unbalanced diet, and sun exposure, making the skin look rough, saggy, and wrinkled (Huertas et al. 2016). Diet is an essential fact in the process of aging. A poor and unhealthy diet can cause premature aging. It is important to have a nutrient-rich and balanced diet for healthy aging. Healthy habits bring about healthy aging. Using tobacco and alcohol can affect the lipid concentration of the skin and increase skin necrosis and pigmentation and proliferation of keratinocytes (Cao et al. 2020).

Intrinsic Aging

Intrinsic skin aging is a physiological alteration that occurs throughout time. Photoprotected areas, such as the palm, age mainly due to genetic or metabolic causes, whereas exposed skin ages due to exogenous factors, particularly solar UV radiation (Mancini et al. 2014). The most noticeable histological alterations in such aged skin happen in the basal cell layer. According to studies, the proliferation of cells in the basal layer decreases as people age (Makrantonaki and Zouboulis 2007). The epidermis thins, and the surface area of touch between the corium and the epidermis shrinks, giving a decreased area for exchanging the nutrition delivery to the epidermis and deteriorated basal cell growth (Moragas et al. 1993). Cellular senescence is the process of cells such as keratinocytes, fibroblasts, and melanocytes losing their ability to proliferate. There was a rise in the expression of the age marker-galactosidase with age in dermal fibroblasts and epidermal keratinocytes in skin samples from human donors of various ages, demonstrating that aged skin includes more senescent cells (Dimri et al. 1995).

Extrinsic Aging

Extrinsic aging is mainly caused due to external factors like sun exposure, air pollution, smoking, poor diet, and other factors like the impact of stress and sleep deprivation (Wong and Chew 2021). External variables will have a long-term impact on skin physiology (Tobin 2017). Excessive and unprotected sun exposure is the primary cause of extrinsic aging (also known as photoaging), which is mainly restricted to the face, neck, and hands, with the lower arms and legs less affected. Low-grade chronic UVR exposure is responsible for over 80% of facial skin aging. However, it induces sunburn, skin coloration, inflammation, immune suppression,

and harm to skin connective tissue (Leyden 1990; Young 2006). Coarse wrinkling, rough texture, sallow complexion with uneven coloration, and loss of skin elasticity are extrinsically aged skin characteristics mainly caused by UVR (Seité et al. 2006). In pale-skinned Caucasians' initial sign of extrinsic aging (on exposed sites) can be observed during the early age of 15 years, although alterations to nonexposed areas do not appear until the age of 30 (Grove 1989). Unfortunately, the great value placed on the golden tan in Western culture is linked to the increased rates of skin cancer and premature aging (Seité et al. 2006). Photoaged skin is characterized by deep wrinkles, looseness, roughness, a sallow or yellow tone, increased fragility, the development of purpura, mottled pigmentary changes, telangiectasia, slow wound healing, and benign and malignant growths. The severity of these alterations is determined by the amount of sun exposure accumulated over time. The second major cause of extrinsic aging is cigarette smoking (Yin et al. 2000, 2001).

Wrinkles, laxity, and pigmentary abnormalities are some of the most noticeable symptoms of aging on the skin (Halder and Ara 2003). Extrinsic and intrinsic factors can accelerate aging (Perner et al. 2011). The deterioration and fragmentation of the dermal collagen matrix is a significant feature of aging skin (Fligiel et al. 2003). In aged skin, the destruction of the extracellular matrix guides to the destruction of fibroblasts in the dermis, as these cells no longer receive mechanical signals. Collagen production is reduced as a result, and collagen-degrading enzymes (matrix metalloproteinases) are increased (Varani et al. 2001, 2006).

It is challenging to design a diet to maintain young and healthy skin. Premature aging is mainly caused due to the intake of unhealthy food along the diet. Healthy skin can be maintained with the help of a proper diet. Maintaining antioxidant activity, tissue stability, regeneration, and the synthesis of various metabolites is necessary to maintain healthy skin. Drinking water can maintain internal balance and tissue functioning. Taking proteinaceous food along the diet can improve tissue repair, protein synthesis, and physiological functions of the skin. Trace elements like zinc, selenium, copper, and iron are essential for the synthesis of protein and keratinocytes and the activity of the antioxidant enzymes of the skin. Vitamin-rich diet is helpful for reducing lipid peroxidation, excreting reactive oxygen species, collagen synthesis, and so on. An organized diet can prevent aging caused by external factors with necessary supplements.

12.3 Nutraceuticals, Functional Foods, and Healthy Aging

Due to constant desquamation, which starts with the division of multiplying cells in the inner layer to make keratinocytes that change as they are pushed outward by cell divisions, the skin needs to be constantly renewed (Fuchs and Raghavan 2002; Milstone 2004). The continuous renewal of the skin cells has functioned with the help of various components that can be supplied through a healthy and nutritious diet. The components like water, proteins, nutrients, and vitamins are necessary for maintaining the proper health of the skin, which can be attained from various plants and animals through diet, which is otherwise referred to as functional foods (Cao

et al. 2020). Nutraceuticals, another term for functional foods, offer a wide variety of bioactive compounds that go beyond the nutritional benefits of individual foods.

Maintaining the skin's internal balance and ensuring proper tissue functions are crucial in the face of aging and inflammation, and water intake plays a vital role in both (Palma et al. 2012, 2015). Proteins are the body's metabolic, physiological, and repair workers. Copper, zinc, iron, and selenium are some essential trace elements for healthy skin. Copper aids in the synthesis and stabilization of extracellular matrix and angiogenesis-related skin proteins (Borkow 2014). Epidermal keratinocytes rely on zinc for proper differentiation and cell growth (Ogawa et al. 2016, 2018). In the skin, iron plays a significant role in how effective the enzymes are at neutralizing free radicals (Reelfs et al. 2010). The antioxidant enzyme activity of keratinocytes and their development are both aided by selenium (Sengupta et al. 2010). Vitamins A, B, C, D, and E are just as important for skin health as trace elements.

Along with these valuable components, other components negatively impact the skin functions, thereby damaging the skin. The components like fats, tobacco, alcohol, sugar, and baked goods are all harmful to the skin (Cao et al. 2020). Essential fatty acids like linoleic acid, omega-3 fatty acids, and omega-6 fatty acids are involved in lipid synthesis in the skin and metabolism. However, high-fat diet content can lead to skin inflammation (Balić et al. 2020; Zhang et al. 2015). Consumption of tobacco can alter the thickness of the cuticle and increase skin pigmentation and necrosis (Dupati et al. 2014). Alcohol promotes the proliferation of the keratinocytes and changes skin permeability. It destroys the skin's barrier function and affects the skin's lipid composition (Park and Kim 2012). Sugar products and baked foods are associated with the alteration of the skin thickness, AGEs, autophagy, and inflammation of the skin (Nguyen and Katta 2015; Wu et al. 2019).

The free-radical theory states that DNA damage, inflammation, and lipid peroxidation are the fundamental reasons for skin aging, disease, and malfunction. As a result, a medical insurrection was centered on antioxidants and free-radical scavengers for avoiding skin aging and treatment (Ratnam et al. 2006; Callaghan and Wilhelm 2008). Oxygen-free radicals are present throughout the cellular processes. They can react with DNA, proteins, and polyunsaturated fatty acids in the body, resulting in DNA fragmenting, oxidative damage, protein-protein cross-linking, protein-DNA cross-linking, and lipid metabolism oxidation. Reactive oxygen species have been related to a variety of diseases like cardiovascular disorders, malignancies, and the aging process. *In vivo* oxidation leads to organism's aging. Therefore, extracellular antioxidant supplements, with food as a significant source, have become a research issue (Kandola et al. 2015). The following shows the influence of natural antioxidants (such as collagen peptides, polyphenols, vitamins, polysaccharides, and fatty acids that are extracted from food products) on skin aging (Cao et al. 2020).

Collagen is a long cylindrical polymeric protein seen as mammals' wealthiest and most readily scattered functional protein. Collagen is the main component of the animal extracellular matrix (ECM) and has unique physiological functions. It accounts for about 25–30% of total protein in mammals, whereas, in some

organisms, it can be up to 80% or more collagen. It is broadly used in tissue engineering, medicine, cosmetics, food, and other fields (Nagai and Suzuki 2000). Collagen peptides and other protein peptides may help to slow down the aging process in three ways. After digestion and absorption, the protein or peptide enters the bloodstream and subsequently acts as a precursor to collagen formation in the skin fibroblasts, preserving the aged skin. Subsequently, when collagen peptides reach skin cells, they have anti-senescent benefits by eliminating reactive oxygen species (ROS), maintaining the cell's inherent antioxidant defense system, and lowering oxidative damage and inflammatory responses. Peptides that cross the cell membrane have been shown to have multiple effects on the skin, including the promotion of collagen and hyaluronic acid production, the suppression of inflammation through the regulation of cytokines and the activation of TGF/SMAD or other signaling pathways, and the prevention of collagen degradation through the suppression of the expression of proteases such as nuclear transcription-activating protein-1 (AP-1), MMP-1, and MMP-3 (Cao et al. 2020).

Polyphenols are plant secondary metabolites found in various foods, including vegetables, fruits, tea, and other plants. Polyphenols have been one of the chief substances utilized in cosmetics and nutritional cosmetology to counteract skin aging due to their noticeable antioxidant effects. In recent years, flavonoids, tea polyphenols, curcumin, grape resveratrol, and silymarin have been the much investigated antiaging polyphenols. Polyphenols have antioxidant and anti-inflammatory properties that reduce oxidative damage and inflammation in the skin, primarily by inhibiting collagen degradation, inhibiting inflammation, and increasing collagen synthesis, including the regulation of cytokines, signaling pathways, and matrix metalloproteinases (e.g., Nrf2, NF-B, MAPK, and others) (Chuang et al. 2017; Davinelli et al. 2018).

Many vitamins are known for their antioxidant properties. They can minimize ROS in aging skin cells to low-activity molecules and thereby reduce the oxidative damage to critical constituents of skin cells. Coenzyme Q10, lipoic acid, and vitamins A, B (B3 and B12), D, C, and E have all been the subject of several scientific investigations. The most popular antiaging medications that treat and slow skin photoaging include retinoids (such as retinoic acid, which stops skin aging by modifying genes and MMPs) (Fuchs and Green 1981; Fisher et al. 1999). B vitamins have been demonstrated to slow down skin aging by reducing inflammation and pigmentation (Brescoll and Daveluy 2015). Vitamin C is a potent antioxidant, and its content in the skin is linked to biological processes of the skin. It is frequently employed as a positive control in skin aging tests. It works as an enzymatic factor and as an antioxidant to increase collagen synthesis and eliminate cellular ROS, which helps to retard the aging activity of the skin (Pullar et al. 2017). As light helps in the synthesis of vitamin D, it also promotes skin aging. The conclusion that vitamin D can cure skin photoaging appears to be paradoxical. On the other hand, vitamin D has been shown to protect the skin by reducing DNA damage, inflammation, and photocarcinogenesis produced by UV rays (Gordon-Thomson et al. 2014). Vitamin E protects the skin against chemical stressors and UV-induced irritation and damage by blocking lipid peroxidation in the skin, which can be activated by combining

vitamins E and C (Schempp et al. 2012; Wu et al. 2013). Coenzyme Q10 is a vitamin-like molecule in meat diets with antiaging properties (Suganuma et al. 2012). Vitamins are frequently combined with other antioxidant compounds (such as collagen, astaxanthin, carotenoids, and others) to boost their anti-senescent properties due to their instability, limited water solubility, and low usage during storage (Cao et al. 2020).

Polysaccharides are polymer carbohydrates made up of several monosaccharides that have been dehydrated and condensed. Polysaccharides' pharmacological properties, such as improved immune function, tumor and viral inhibition, glucose and oxidant neutralization, blood cholesterol lowering, and low cytotoxicity, make them a useful active component in functional foods and medicines (He et al. 2012). One of the features of polysaccharides is antioxidant activity, which is beneficial for skin aging. Lycium polysaccharides, agaric polysaccharides, lingzhi polysaccharides, mushroom polysaccharides, and algal polysaccharides have been stated to decelerate the aging process of the skin. Dietary polysaccharides help to enhance the appearance of aged skin. Oral polysaccharides work by increasing the activity of skin antioxidant enzymes, removing reactive oxygen species (ROS), and reducing oxidative damage. They prevent apoptosis and modulate the production of Bcl-2, Bax, and caspase-3 through triggering Nrf2/ARE and other pathways. Finally, polysaccharides prevent collagen deterioration by suppressing the development of enzymes like MMP-1 and MMP-9, allowing for a constant collagen ratio, skin healing, and moisture retention (Wen et al. 2016; Ye et al. 2018).

Lipids are an essential component of the skin's epidermal barrier function, the structure of the membrane, internal environment balance, and damage repair. Aging is associated with a decrease in fat content, primarily because of the loss in the ability of skin cells to generate and produce fat (Pappas et al. 2013). Furthermore, dietary fat consumption is linked to the composition of lipids in the body and skin tissues. A deficiency in necessary fatty acids or aberrant fat metabolism can result in significant skin disorders (Horrobin 1989). Polyunsaturated fatty acids like omega-3 fatty acids and omega-6 fatty acids are very important in human skin barrier function, as well as preventing and treating skin inflammation (Balić et al. 2020). In mice, orally administered olive oil inhibits skin aging caused by persistent psychological stress via acting on the NF-B NRF2 pathway (Romana-Souza and Monte-Alto-Costa 2019). In mice, oral 7-MEGA™ 500 (fish oil supplement with 50% palmitoleic acid, omega-7) was demonstrated to reduce UV-B and H_2O_2-induced skin oxidative stress, inflammation, and aging and promote skin regeneration (Song et al. 2018; Park et al. 2019). The anti-inflammatory effects of fatty acids derived from *W. somnifera* seeds are enhanced on psoriasis by lowering the production of pro-inflammatory factors (TNF- and IL-6) (Balkrishna et al. 2020). By decreasing the activity of PM2.5-induced reactive oxygen species and matrix metalloproteinases and by stopping the mitogen-activated protein kinase/activator protein 1 (MAPK/AP-1) pathway, fermented fish oil protects skin against aging (Hyun et al. 2019).

Apart from those mentioned above, certain foodborne antioxidants and the combinational usage of several antioxidants have been reported to be effective against skin aging. Recent studies have proved the usage of dietary probiotics and their

products against skin aging. Probiotic fermentation is an example in which it can boost *Agastache rugosa* leaves' anti-photoaging activity. In some, probiotic extracts are used to treat early aging of the skin (Tsuji et al. 2018; Shin et al. 2018). Rather than the contents mentioned above, there are furthermore plants and animal products that are functional foods used against skin aging.

Some active ingredients and their functions

Active ingredients	Property of the compound	Functional food
Carotenoids, lycopene	Antioxidant; anticarcinogenic; anti-inflammatory; inhibits LDL oxidation	*Solanum lycopersicum* (tomato), *Daucus carota* (carrot), *Capsicum annuum* (bell pepper), green leafy vegetable, fruits, palm oil
Curcuminoids, bis-*p*-hydroxy-cinnamoyl methane, diferuloylmethane, *p*-hydroxycinnamoyl methane	Decrease lipid oxidation	*Curcuma longa* (turmeric)
Anthocyanin, catechin, cyanidin, flavanols, myricetin, and quercetin	Antioxidant activity; inhibits LDL oxidation, superoxide scavenger	Peels, juice and wine of *Vitis vinifera* (red grapes), berries like *Vaccinium sect. Cyanococcus* (blueberry), *Rubus subg. Rubus* (blackberry)
Fiber phytochemicals	Reduces total and LDL cholesterol	Oat cereals, fortified juices, *Chondrus crispus* (Irish moss)
Flavonoids (flavanols, flavanones, flavanes, flavan-3-ol)	Antioxidant; antiproliferative; antihypertensive; anticarcinogenic; antithrombic; inhibition of LDL cholesterol	*Apium graveolens* (celery), *Petroselinum crispum* (parsley), citrus fruits, *Allium cepa* (onion), *Camellia sinensis* (tea), *Phaseolus vulgaris* (green beans), *Theobroma cacao* (cocoa), *Solanum lycopersium* (tomato), *Malus domestica* (apple), berries like *Vaccinium sect. Cyanococcus* (blueberry), *Rubus subg. Rubus* (blackberry), certain beans, and chocolates
Phenolic acids and monosaturated fatty acids	Anti-inflammatory	*Coffea arabica* (coffee), cereal brans, fruits, black tea and green tea (*Camellia sinensis*), and extra virgin olive oil
Sesaminol	Inhibits LDL oxidation; decreases cancer risk; stimulates growth	Rice and rice oil (*Oryza sativa*), seeds and oils of sesame (*Sesamum indicum*)
Stilbenes	Antioxidant; protects from cardiovascular problems	*Vitis vinifera* (grapes), *Arachis hypogaea* (peanuts)
Tocopherols, ubiquinol, tocotrienols, ω-3 fatty acids, phytosterols	Decrease blood cholesterol; inhibit lipid peroxidation	*Prunus dulcis* (almond), nuts, flax seeds, fish oil, olive oil, and fat

Source: Plaza et al. (2008), Siró et al. (2008), Gry et al. (2007), Shahidi and Ambigaipalan (2015), Patil et al. (2009)

12.4 Functional Foods and Their Active Ingredients with Antiaging Properties

The dietary fiber content of berries like raspberries and blackberries is high, and they also contain essential micronutrients like vitamins C and K and the minerals manganese and copper. It contains a wide variety of bioactive compounds, including glycosides, steroids, terpenes, and phytochemicals. The skin benefits from these substances' anti-inflammatory, antioxidant, and antiaging properties. They cause more dermal follicular cells to proliferate, as well as more collagen fibers and growth factors to be produced (Zambrano et al. 2018).

Rice bran is high in macronutrients such as dietary fiber, proteins, and lipids. Rice bran contains a wide range of bioactive chemicals, including antioxidants such as ubiquinones, tocopherols, tocotrienols, and oryzanol. The nutraceuticals derived from rice bran have anticancer, anti-inflammatory, and antidiabetic properties in addition to antioxidant activity. They help enhance hair growth and prevent hair loss by promoting the release of growth factors like VEGF, TGF, etc. (Danilenko et al. 1996; Sharif et al. 2014).

Ginseng is a *Panax* genus plant that has been used in traditional herbal treatment for centuries. The primary bioactive components of ginseng include saponins like ginsenosides. They are highly beneficial for body functions, including anticancer, anti-fatigue, anti-obesity, anti-oxidative, antimicrobial, anti-inflammatory, antidiabetic, and defensive effects on the immune system, respiratory system, neurologic system, and cardiac system (Baek et al. 2016).

Stem cells extracted from plants are also extensively used in reducing aging. The stem cells extracted from plants like *Malus domestica*, *Vitis vinifera*, and *Saponaria pumila* were shown to have antiaging properties as they reduced wrinkle formation and improved the activity of the epidermal stem cells. The extracts from ginger leaf cells (*Zingiber officinale*) have glycerin extracts from other plants like *Iris pallida*, *Olea europaea*, *Hibiscus rosa*, and *Camellia sinensis* that can also be used to prevent aging (Miastkowska and Sikora 2018).

Marine products like seaweeds, shelled organisms, microalgae, corals, fishes, eggs, etc. are highly useful in treating skin disorders. Various compounds derived from the animals are known to prevent hair loss and aging. They help reduce 5-alpha-reductase activity, activate the ATP-potassium channels, and upregulate ERK and Wnt/β-catenin pathways, promoting hair growth.

Because of its antioxidant capabilities, β-carotene has been shown to play a significant role in the hindrance of inflammation and oxidative stress through its ability to suppress the activities of singlet oxygen, oxidize, and scavenge free radicals. Reactive oxygen species (ROS), such as organic peroxides, hydrogen peroxide, superoxides, singlet oxygen, hydroxyl radicals, and peroxyl and alkoxyl radicals, play a role in skin physiology. Nutritional supplementation or a diet rich in β-carotene has been found to prevent early skin aging, skin cancer, and cellular damage. β-Carotene is a 40-C chain (most of it has a straight-chain structure). β-Carotene cannot be synthesized by the human body and should be obtained from

food sources. Pumpkin, sweet potato, spinach, carrots and carrot juice, turnip greens, cantaloupe, and squash have all been found to contain β-carotene (Vollmer et al. 2018).

Astaxanthin is a keto-carotenoid with a structure similar to -carotene. While there are multiple astaxanthin stereoisomers in nature, the all-*trans* 3S,3S′astaxanthin appear to be the most common molecular organisms in everyday foods, nutritional supplements, cosmetics, and food industries. *Haematococcus pluvialis* (chlorophyte algae) is known to have a high quantity of astaxanthin, which can be used for its production. By conducting electrons down the length of the molecule, 3S-3S′ astaxanthin orientation of the transverse cell membrane provides anti-inflammatory or reduced oxidative stress. Plants, animals, and algae are all sources of astaxanthin. Astaxanthin can be seen in a diversity of seafood, such as *Salmo salar*, *Oncorhynchus mykiss*, *Caridea*, and *Homarus americanus*. There have also been reports of antiaging effects in animal and human studies, including anti-inflammatory, antidiabetic, anticancer, gastro-protective, ethyl alcohol and drug-protective, free-radical scavenger, hepato-protective, skin-protective, eye (ocular)-protective, and skin-protective effects (Vollmer et al. 2018).

12.5 Functional Food for Skin and Hair Regeneration

Regeneration is essential for the maintenance of healthy skin. It can be carried out with the help of functional foods containing vitamin C, vitamin B, vitamin E, vitamin A, alpha-lipoic acid, hyaluronic acid, and retinoic acid. Vitamin C or L-ascorbic acid is highly seen in citrus fruits, cruciferous vegetables, *Capsicum annuum* (bell pepper), *Fragaria ananassa* (strawberry), *Solanum lycopersium* (tomato), *Solanum tuberosum* (potatoes), etc. Vitamin C during the inflammatory phase aids neutrophils' death and subsequent clearance. Furthermore, it is essential for the synthesis of collagen. Thiamine, riboflavin, niacin, pantothenic acid, pyridoxine, biotin, folate, and cobalamin are all part of the vitamin B complex. They are rich in foods like *Salmo salar* (salmon); *Oncorhynchus mykiss* (trout); leafy green vegetables like *Spinacia oleracea* (spinach); *Brassica oleracea var. viridis* (collard); *Brassica rapa* (turnip greens); *Lactuca sativa var. longifolia* (romaine lettuce); Leguminosae family (legumes); liver and meat of animals like beef, chicken, lamb, and pork; milk and milk products; oysters, clams, and mussels; egg; yogurt; fortified cereals; and sunflower seeds. Vitamin B helps cell proliferation and decreases inflammation, dryness, and acne formation. Vitamin E is seen in seeds of *Helianthus annuus* (sunflower) and *Prunus dulcis* (almond), *Spinacia oleracea* (spinach), *Beta vulgaris var. cicla* (Swiss chard), *Capsicum annuum* (bell pepper), and *Asparagus officinalis* (asparagus). Vitamin E is known to help moisturize the skin and also helps in modulating cell signaling during wound healing. Vitamin A is seen mainly in vegetables like *Daucus carota* (carrot), *Ipomoea batatas* (sweet potato), *Cucurbita maxima* (winter squash), *Cucumis melo var. cantalupensis* (cantaloupe), *Prunus ameniaca* (apricots), *Brassica oleracea var. sabellica* (kale), *Brassica oleracea var. viridis*

(collard greens), and *Spinacia oleracea* (spinach). Compounds like alpha-lipoic acid, retinoic acid, and hyaluronic acids are also necessary to rejuvenate the skin (Takeo et al. 2015; Yamada et al. 2021).

12.6 Regional Food and Skin Health

The digestive system plays a crucial role in skin health. Skin health can be maintained through proper nutrition, diet, and digestion. Gut, liver, stomach, and proper bowel movement are necessary for glowing skin. People from different regions add a range of dishes—known for their nutrient richness—to their diets for better digestion and health.

The Mediterranean diet (a dietary pattern) is gaining favor as a way to prevent, cure, and manage several health problems. The diet includes mainly a glass of red wine per day; a high intake of fruits, vegetables, and virgin olive oil; a high intake of fruits, vegetables, and virgin olive oil; and a limited intake of fish and meat. The Mediterranean diet mainly includes virgin olive oil as it has a high level of beneficial phenolic compounds. The high quantities of resveratrol and lycopene in red wine and tomatoes are also important. People who ate a Mediterranean-style diet rich in vegetables and herbs had a 56–57% lower risk of getting androgenetic alopecia. In a C57BL/6 mouse model, hair growth can be promoted using *Lycopersicon esculentum* extracts. The administration of *Lycopersicon esculentum* extracts resulted in enhanced VEGF, KGF, and IGF, leading to enhanced hair growth both histologically and via gene expression. Red oranges, an essential part of the Mediterranean diet, have been proven to impact keratinocyte populations in the epidermis favorably. The red-orange extract treatment in human keratinocyte cell lines helped to decrease the inflammatory activity, as mentioned by inflammatory markers (Fortes 2018).

Indian diet is rich in minerals and nutrients that are highly useful for skin health. The Indian diet includes quality food like yogurt, turmeric, fruits, leafy vegetables, green tea, cucumber, fish, and meat. Yogurt is rich in probiotics that enrich the gut microbiome, which helps appropriately digest food. Usually, every Indian meal contains yogurt as a dish. It helps in preventing the dryness of the skin, and it enhances the radiance of the skin. Green leafy vegetables like *Spinacia oleracea* (spinach), *Coriander sativum* (coriander), *Murraya koenigii* (curry leaves), and *Brassica oleracea var. italic* (broccoli) are rich in vitamins and minerals. Indian dishes like palak paneer, thaali meals, or Sadhya are rich in leafy vegetables, fruits, and Indian spices that are known for their antioxidant properties. Fruits like *Citrus sinensis* (orange), *Citrus limon* (lemon), *Vitis vinifera* (grapes), etc. are rich in vitamin C. *Malus domestica* (apple), *Actinidia deliciosa* (kiwi), and berries are good for clear and radiant skin. Dishes are primarily prepared with turmeric. Turmeric is known for its antibacterial, antifungal, and anti-inflammatory properties and helps in clear and radiant skin. The skin benefits from the inclusion of *Camellia sinensis* (green tea), *Cucumis sativus* (cucumber), and *Aloe vera* in the diet since these foods

contain vitamins A, K, and C and help to prevent skin issues including wrinkles, acne, dark spots, and wrinkle formation (Kaur and Kapoor 2003; Krishnaswamy 2008; Mukherjea et al. 2013).

Like homeopathy, Chinese medicine, and western medicine, Ayurveda is a medical practice that has a natural solution for most skin and hair issues without causing many side effects. Ayurveda classifies individuals into three main doshas: *Vata*, *Pitta*, and *Kapha*. These three doshas determine the type of the individual and the treatment in Ayurveda is carried out based on these doshas. According to these doshas, the characteristics of the skin and hair of the person can differ from dry and rough to oily and cold. Basically, every skin type should be nourished with appropriate nutrients, as eating healthy can make the skin healthy. The diet should include components with anti-inflammatory, antiaging, and rejuvenating properties that keep the integumentary system intact. Natural products like turmeric, saffron, tulsi, sweet potatoes, and bell peppers are rich in nutrients that efficiently rejuvenate the skin and reduce pigmentation, acne formation, and blemishes. Fruits and vegetables rich in vitamins A and C and those that can help in collagen and protein synthesis can keep the skin and hair healthy. Fishes like salmon, mackerel, and herring are known for the presence of the omega-3 fatty acids that are necessary for skin and hair regeneration (Hazra and Panda 2013).

12.7 Gut Microbiome Modulations and Skin

Gut microbiomes play a significant role in skin health. The trillions of microorganisms that make up the gut and skin microbiota come in hundreds of diverse strains and coexist in a complex ecological ecosystem. These microbiotas, as well as their metabolic waste products and interactions with the host, directly influence healthy physiology and disease. Skin illnesses such as atopic dermatitis, psoriasis, acne vulgaris, dandruff, and even skin cancer are promoted by dysbiosis in the skin and/or gut microbiome, which is linked to an altered immune response. The makeup and metabolic processes of the gut microbiome are greatly influenced by diet and probiotics, which influence the skin. The bacteria in a person's gut—*Bacteroidetes*, *Firmicutes*, *Actinobacteria*, and *Proteobacteria*—can change over time, but adults typically have a diverse mix of these four types. Some believe that the gut and the skin are connected in a two-way communication pathway that allows for a variety of neurological and immunological responses to shifts in the microbiota (O'Neill et al. 2016). The mechanisms by which the gut flora may affect the skin include neurotransmission, anti-inflammatory effect, and increased intestinal permeability. To a person's general and intestinal immune systems, the gut microbiome's function in regulating epithelial cell renewal and intestinal integrity is critical. So, the gut microbiome is essential in maintaining skin and hair health. Food products containing dietary fibers, a protein-rich diet, probiotics, and prebiotics help in the maintenance of healthy and valuable microbiomes in the gut (Yan et al. 2017; Lunjani et al. 2019).

12.8 Nanonutraceuticals and Good Health

Marrying nutraceuticals to nanotechnology, we get the alluring field of nanonutraceuticals. The term "nutraceutical" refers to bioactive ingredients that provide health benefits above and beyond their nutritive value. However, they fall short as far as the bioavailability of these compounds is concerned. Nanotechnology helps us effectively encapsulate these bioactive ingredients in nanocarriers that winnow the challenges. Such thoughtful techniques bring about effective delivery of the concerned compound alongside enhanced bioavailability (Shende and Mallick 2020).

12.8.1 Ethnic Foods to Combat Skin Aging

Ethnic communities around the globe have, in their culinary repository, a concatenation of recipes for what has now been called "ethnic foods." Such foods, originating from the rich cultural past, have many lesser-known ingredients, some of which could potentially cure chronic human diseases. Ethnic cuisines predate our current understanding of ingredients, and an extensive study of the same could open a window to cure many dreaded lifestyle diseases (Kwon 2015; Shukla 2021).

12.9 Rasayana Therapy and Healthy Aging

The Rasayana therapy is a rejuvenating Ayurvedic therapy to slow down the multifaceted aging process using a combinatorial formulation of *Rasa*, the essence of nutrition, and *Ayana*, the channel or tracts of the body. Such therapies are promising in the face of accelerated aging and deteriorating skin vitality. Rasayana therapy aims at holistic mind-body recuperation by targeting the system as one comprehensive entity. All this and more, the future of Rasayana therapy looks bright enough (Singh and Rastogi 2011).

12.10 Conclusion

Healthy skin is something that society strives for, and some people go to great extents to attain it. Furthermore, it influences social characteristics such as self-esteem, attractiveness, and behavior. To produce healthy skin, cosmetic companies produce products made of synthetic compounds like hydroquinone, ascorbic acid, and retinoic acid, which may have harmful effects on the skin. On continuous use, these synthetic compounds cause skin irritation, redness, excess skin peeling, bleach panda effect, blister formation, dark coloration, etc. The natural compounds are

highly useful in preserving healthy skin and hair. The utilization of functional foods which contain high nutritional value is very much valuable for maintaining healthy skin and hair. The plant-derived compounds from rice bran, Mediterranean diet, berries, ginger, and aloe vera are rich in collagen, elastin, polyphenols, and vitamins, which can increase collagen production. Marine organisms are also rich in compounds that improve skin health. So, it is always better to switch to functional foods as they are perfect for healthy skin and hair. They trigger the regrowth of the skin and hair cells with the help of the corresponding stem cells within the organ. Ayurveda is another medical care that can implement skin and hair care via natural products. So, the proper rejuvenation of the integumentary system at regular intervals is necessary which can be attained by having a nutritive and healthy diet as they can provide the necessary supplements in the most efficient way than any skin care product.

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Chapter 13
Delineating the Role of Phytochemicals in Targeting Age-Related Cardiovascular Diseases Through the Lens of Network Medicine

Monojit Kamilya, Asim K. Duttaroy, and Subhajit Dutta

Abstract The most significant risk factor for cardiovascular disease is, sadly, aging, which is an unavoidable aspect of life. There are still many open concerns regarding how the genetic processes governing aging in model species affect cardiovascular aging, even though countless studies in the cardiovascular area have taken into account both young and old humans. Similar to this, there isn't much research that comprehensively evaluates how these longevity pathways affect cardiovascular health in the field of the molecular biology of aging. Thankfully, this chasm is starting to close, and these two fields are combining. We present an overview of some of

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the central genes involved in regulating longevity pathways, including insulin-like growth factor 1, AMP-activated protein kinase, forkhead transcription factors, sirtuins, and mammalian target of rapamycin, as well as their implications in cardiovascular health. In addition, we provide insight into network medicine-based approaches to identify additional genes connected with longevity genes within an interactome space that are involved in regulating the age-related cardiovascular signaling axes. In this context, we addressed many in vitro, in vivo, and human clinical trial studies to better appreciate how essential phytochemicals can be in the fight against age-related cardiovascular disorders.

Keywords Aging · Cardiovascular disease · Longevity genes · Network medicine Phytochemicals

13.1 Introduction

Over the years, one of the primary causes of mortality and morbidity around the globe has been cardiovascular diseases (CVDs). The World Health Organization (WHO) estimated that approximately 18 million deaths which account for more than 31% of all deaths worldwide were caused by CVD in 2019, and every year the numbers are rising steadily (WHO 2021). Cardiovascular diseases are more prevalent in elderly people than in younger ones across all sex (Our World in Data 2022). A study from Global Burden of Disease (Roth et al. 2020) reported that the number of prevalent cases of CVD has nearly doubled from 271 million cases to 523 million cases, with around 12.1 million to 18.6 million global deaths in 1990 and 2019, respectively, the rate of which is climbing substantially every year (Fig. 13.1). Almost all nations outside of high-income countries continue to see an increase in the burden of CVD, and alarmingly, the age-dependent rate of CVD has started to rise in some places where it was previously declining in high-income nations (Roth et al. 2020).

Additionally, the cost of treating cardiovascular disease will soon soar to unprecedented heights (North and Sinclair 2012). Therefore, we must still comprehend why aging is such a crucial factor in the etiology of CVD. But until recently, studying the biology of aging and the pathophysiology of cardiovascular diseases remained largely separate fields. The majority of rodent studies on atherosclerosis or cardiomyopathies were conducted in young mice, whereas genetic studies on increasing longevity rarely assessed whether CVD or heart function is improved. Nevertheless, current findings linking cardiovascular disease to aging are springing up. In this book chapter, we understand the interrelation between aging and cardiovascular diseases using concepts of biological network theory, discuss a few essential longevity genes that have controlling action on both lifespan and cardioprotective properties, and introduce the role of phytochemicals in treating age-related cardiovascular disease signaling axes.

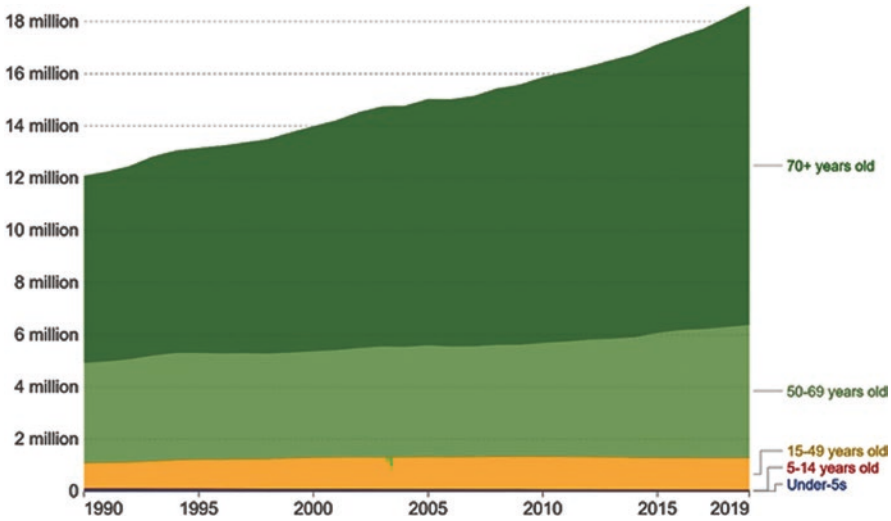

Fig. 13.1 Age-related global deaths from cardiovascular diseases (in millions) from 1990 to 2019. (Adapted from IHME, Global Burden of Disease, 2019)

13.2 The Link Between Aging and CVD

With advancing age, several physiological processes degrade, eventually culminating in illness and severe health issues. In the process, the cardiovascular systems are significantly impacted, increasing the risk of cardiovascular diseases like atherosclerosis, hypertension, myocardial infarction, and stroke (Lakatta and Levy 2003). Aging causes a decrease in cardiac output, which causes the myocardium to be stimulated to grow muscle by undergoing cardiac hypertrophy. Although this may momentarily increase cardiac output, the long-term effects of hypertrophy weaken the heart's capacity to pump blood effectively (Levy et al. 1988). Contrarily, with growing age, vascular dysfunction triggers diverse pathological manifestations, such as inadequate tissue perfusion and vascular development leading to ischemia and hypertension, respectively. Following tissue damage, the endothelial cells cease to multiply and migrate (Wessells et al. 2004). Furthermore, nitric oxide synthase (eNOS) activity in endothelial cells also decreases with cellular aging, resulting in less NO, a vasodilator involved in various pathological manifestations like abnormal cellular proliferation, thrombotic events, etc. (Collins and Tzima 2011).

The cardiac system faces complicated alterations that influence its cellular makeup as it ages. In the process, the increase in apoptotic and necrotic events causes a decrease in cardiomyocytes, which are also vulnerable to oxidative stress. In older adults, oxidative stress is generally higher, leading to the formation of reactive oxygen species (ROS), which kills cardiomyocytes and mediates significant changes in cardiomyocyte functions. However, a recent study shows that eliminating senescent cardiomyocytes may not be the only way to correct heart

abnormalities in some aging models (Chimenti et al. 2003). Understanding the relationship between aging and CVD (AGE-CVD) will require measuring cardiac-specific senescence, DNA damage, levels of apoptosis, and necrosis, along with fibrosis assessments in aging animal models. Senescence is accompanied by the expression of essential genes, including p53, p21, p16, and senescence-associated-galactosidase activity, which immunoblotting or histological techniques detect.

Although being assumed to be post-mitotic, cardiomyocytes divide and regenerate, and studies have revealed cardiac regeneration as one of the critical mechanisms for sustaining cardiovascular health. However, in the elderly, the regeneration rate may not be sufficient to maintain cardiomyocyte numbers in response to cardiomyocyte loss (Anversa et al. 2006). A small pool of cardiac stem cells and a minority of tiny, incompletely differentiated cardiomyocytes that can reenter the cell cycle are thought to be involved in heart tissue regeneration.

It is widely acknowledged in aging and cardiovascular disease that a low-calorie diet and regular exercise will lengthen mammals' healthy lives. But obesity and a sedentary lifestyle have the reverse impact. The conventional understanding holds that CVD is triggered by an accumulation of cholesterol and fatty acids in tissues which impairs tissue function and stimulates the generation of inflammatory cytokines and ROS. However, a diet high in calories without exercise may be harmful because it suppresses the expression of "longevity genes," which support cellular defenses against aging and age-related cardiovascular diseases (Sinclair 2005).

13.3 Involvement of Longevity Genes and CVD

A variety of longevity genes have been found in model species apart from humans, which includes the yeast *Saccharomyces cerevisiae*, the nematode *Caenorhabditis elegans*, and the fly *Drosophila melanogaster*. Many of these genes and the linked pathways have since been investigated for their function in controlling mouse lifespan and to start investigating their involvement in cardiovascular disease (CVD).

13.3.1 IGF-1

IGF-1 was one of the first genes identified as a longevity gene, with knockout resulting in an increase in lifespan in *C. elegans* (Kenyon et al. 1993). Furthermore, it was discovered that genes associated with the IGF-1 pathway are associated with longevity signaling axes and functions by upregulating mTOR activity (Fig. 13.2a, b) via the regulation of Akt activity. A pleiotropic role of IGF-1 was observed where its overexpression in the mice heart reduced ventricular dilation, hypertrophy, and diabetic cardiomyopathy while also preventing myocardial cell death after infarction (Li et al. 2007). On the other hand, a study reported that overexpression of the same gene resulted in ventricular hypertrophy, failure, and delayed recovery of

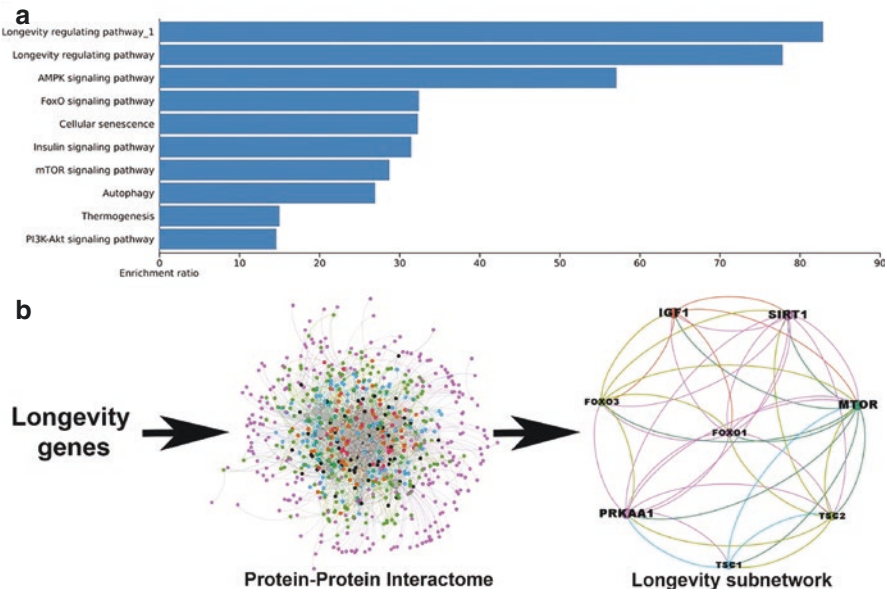

Fig. 13.2 (**a**) Pathway enrichment analysis of longevity genes associated with cardiovascular diseases. We generated the enrichment plot using the web tool Web-Gestalt (http://www.webgestalt.org/) accessing KEGG pathways, and pathways having FDR q-value < 0.05 were considered significant. (**b**) Construction of a longevity subnetwork. Longevity genes involved in lifespan and related cardiovascular diseases were mapped to protein-protein interactome (PPI) to generate a subnetwork that shows interconnections among sirtuins, AMPK (PRKAA1), IGF1, FOXO, and mTOR. We retrieved the interactome from the String database (13,478 nodes and 647,548 edges) and implemented the subnetwork using Gephi software

heart function following an acute ischemia challenge (Prele et al. 2012). The deletion of the IGF-1 homologue (InR) in *Drosophila* sp., which has a primitive cardiovascular system, delayed the effects of aging on the fly cardiovascular system (Wessells et al. 2004). Even though it has been demonstrated that the IGF-1 pathway is crucial for controlling cardiovascular health, more investigation is needed to fully comprehend the mechanism and explain the discrepancies that have been observed.

13.3.2 AMPK

Several studies suggest the involvement of AMP-activated protein kinase in different signaling pathways associated with longevity, autophagy (Fig. 13.2a), lipid and glucose metabolism, gene expression, cellular polarity, and cell growth. AMPK promotes mitophagy and the formation of new mitochondria via activating mitochondrial biogenesis (Hardie 2011). By assessing the relative AMP:ATP ratio, AMPK (PRKAA1) serves as a metabolic sensor within the longevity subnetwork. It controls

mTOR by phosphorylating the TSC1/2 complex directly (Fig.13.2b). AMPK has a regulatory effect on the IGF-1 pathway through the extracellular signal-regulated kinase (Erk) cascade, and by adjusting the levels of NAD and nicotinamide phosphoribosyltransferase, it regulates sirtuins activity. AMPK protects the heart from damage during ischemia and reperfusion. Myocardial infarction aggravated in mouse models with dominant-negative AMPK (Russell et al. 2004). It has been observed that metformin which activates AMPK minimizes pressure overload-induced ventricular hypertrophy in mice (Zhang et al. 2011). Mutations in the regulatory two subunits of AMPK (PRKAA1/PRKAA2) cause a hereditary disease with hypertrophic cardiomyopathy and ventricular pre-excitation (Blair et al. 2001).

13.3.3 Forkhead Transcription Factors (FOXOs)

FOXOs are one of the major transcription factors associated with the expression of the genes involved in cell growth, proliferation, differentiation, and lifespan (Fig. 13.2a). FOXOs are also downstream effectors of the IGF-1 signaling cascade and are controlled by sirtuins-mediated deacetylation (Fig. 13.2b). FOXO1 deletion causes embryonic fatality in mice, resulting in poor vascular and cardiac growth, including an underdeveloped dorsal aorta and defective cardiac looping (Furuyama et al. 2004). A cardiac-specific overexpression of FOXO1 results in embryonic lethality, reduced myocardium thickness, heart size, and heart failure. In mouse hearts, FOXO3a expression decreased cardiomyocyte size and suggested the role of FOXO in preventing cardiac hypertrophy (Potente et al. 2005). More investigation is required to fully comprehend the function of these transcription factors in regulating cardiovascular development, process, and disease and to clarify how FOXO factors interact with other downstream members within the longevity subnetwork in cardiovascular tissues.

13.3.4 SIR2

Sirtuins are NAD-dependent deacetylases and ribosyltransferases that remain conserved throughout evolution. Seven sirtuins (SIRT1–7) are found in mammals that govern a wide range of cellular processes, including DNA damage repair, cell cycle, metabolic response to nutrition availability, defense against neurological deterioration, and, most importantly, longevity (Fig. 13.2a). From yeast to mammals, sirtuins have been demonstrated to control aging. Nevertheless, several studies have confirmed that sirtuins are essential to the longevity subnetwork (Fig. 13.2b). Through deacetylation of the liver kinase B1, SIRT1 has been shown to regulate the AMPK pathway (Zu et al. 2010). SIRT1 modulates the IGF-1 pathway via regulating UCP2 levels and directly influencing the IGF-1 signaling pathway. Additionally, SIRT1 interacts with TSC1/2 by reducing mTOR activity. SIRT1 knockout mice exhibit

increased injury in response to ischemia-reperfusion studies, whereas SIRT1 transgenic mice exhibit reduced harm with regard to cardiovascular illness development. Mice that overexpress SIRT1 exhibit delayed age-dependent cardiomyopathies and reduced stress-induced apoptosis. However, a 20-fold increase in SIRT1 overexpression led to cardiomyopathy, oxidative stress, and apoptosis (Kawashima et al. 2011). Even SIRT1 has been found to control the development of blood vessels in zebrafish. By avoiding arterial calcification brought on by hyperphosphatemia, SIRT1 also regulates artery stiffness. SIRT3 is located in the mitochondria, and knockout mice show age-dependent as well as exercise/pressure overload-induced cardiac hypertrophy. On the other hand, SIRT7 knockout mice experience an upsurge in fibrosis, heart hypertrophy, and inflammatory cardiomyopathy. Cardiomyocytes exhibit increased apoptosis and lower oxidative stress tolerance in SIRT7 knockout mice. The molecular processes by which sirtuins regulate the heart and vasculature are still poorly understood, even though sirtuins have various effects on cardiovascular health.

13.3.5 Target of Rapamycin (TOR)

The bacterial product rapamycin inhibits the serine-threonine protein kinase known as target of rapamycin (TOR). The conserved gene TOR controls cell size, growth, proliferation, longevity (Fig. 13.2a), motility, protein synthesis, and transcription by integrating insulin, growth factor signaling, and intracellular amino acid level monitoring. It has been noted that rapamycin administration or TOR deletion can lengthen life in flies, yeast, worms, and mammals. mTOR typically functions as an effector of upstream sirtuin/AMPK/IGF-1 activity within the longevity network (Fig. 13.2b). Inhibiting mTOR signaling in the heart suppresses pressure-induced cardiac hypertrophy, possibly through limiting mTOR control of protein translation and cell growth. Furthermore, mTOR controls hypoxia-inducible factor-1 to mediate hypoxia-induced angiogenesis in tumors through its participation in the PI3K/AKT signaling pathway. When mTOR is inhibited, either by nutritional deprivation or by the drug rapamycin, autophagy is activated, allowing for the degradation of damaged molecules and organelles and enhancing the health of cardiovascular tissues (Halapas et al. 2008). The PI3K/AKT/mTOR pathway is at the confluence of many signaling pathways, making it an essential mediator of aging and the cardiovascular system.

These five genes and evidence from different studies also shed light on the involvement of *Pit1*, *Clock1*, *p66shc*, and *catalase* genes in AGE-CVD pathophysiology. Network-based strategies shall help identify other novel proteins (or genes) associated with essential longevity genes and predict possible metabolic reactions, protein-protein interactions, protein-transcription factor interactions, protein-protein co-expression, and disease-drug interactions with AGE-CVD signaling axes. The use of principles of network theory in understanding the causes and mechanisms of diseases has led to the emergence of a new avenue called “network medicine.”

13.4 Emerging Role of Network Medicine in the Treatment of Human Diseases: AGE-CVD

Barabási AL et al. (Barabási et al. 2011) developed and expanded the concept of network theory to explain how disease-relevant genes interact in an interactome. It relies, in essence, on the hypothesis that a disease phenotype results from a complicated network of genes interacting with one another. The players involved in the pathophysiology of a disease have a propensity to group together in this process in a nonrandom manner. We refer to these nonrandom clustered subnetworks as disease modules because they cooperate together to contribute to the phenotypic presentation of the disease. It has been discovered that within such networks, genes linked to the disease not only have a tendency to remain proximal but are also intricately interconnected with each other. The network theory also hypothesizes that a disease module may contain clusters of potential therapeutic targets linked to that disease module (Dutta et al. 2022). We may postulate that for phytochemicals to be effective against age-related cardiovascular diseases, they must target genes that are inside or proximal to the disease modules.

Systems-based techniques are likely to become more essential in revealing the higher-order interactions underlying features, including atherosclerosis, cardiac hypertrophy, cardiovascular system complexity, and cardiovascular system and cardiovascular illnesses. These methods must be useful in the real world because they provide a framework for designing therapeutic interventions and put the numerous genetic variants linked to disease in a biological context. In cardiovascular research, network medicine has several uses, such as identifying novel disease mechanisms, redefining complex clinical entities, predicting patient outcomes, finding novel biomarkers, and discovering and repurposing drugs. To dissect complex mechanisms in coronary artery disease and myocardial infarction (MI), for example, network construction and analysis using the existing inflammation- and MI-related PPIs revealed a few highly interconnected but distinct modules with unique biological properties and endophenotypes, such as coagulation, cell death, wound healing, and immune responses. On the other hand, pulmonary arterial hypertension (PAH) is now considered to be a complicated disease distinguished mostly by the interaction and cross-talk of numerous pathogenic signaling pathways. About 25% of patients with suspected idiopathic PAH will have an identified pathogenic variation (e.g., BMPR2, EIF2AK4, SOX17, others). Early studies on network medicine in pulmonary vascular disease addressed posttranscriptional events relating to BMPR-2 bioactivity and found that hypoxia, inflammation, or genetic BMPR-2 inhibition upregulates miR-21 in pulmonary artery endothelial cells (Parikh et al. 2012).

Considering the molecular relationships between the targets of polyphenols and the proteins linked to diseases, a network medicine-based framework has already been used to identify the mechanisms by which polyphenols improve health. The proximity of disease proteins to the polyphenol targets within a human interactome strongly indicates the molecule's potential therapeutic benefits. The study confirmed established relationships between epigallocatechin-3-*O*-gallate and type 2

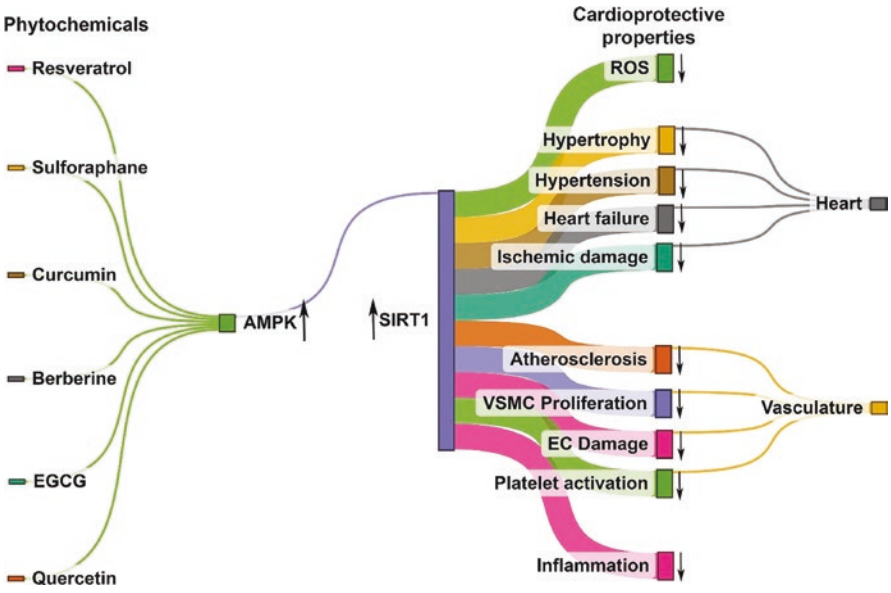

Fig. 13.3 Sankey diagram illustrates the positive benefits of potential phytochemicals on the age-related cardiovascular system mediated by the AMPK/SIRT1 signaling axes

diabetes and predicted that rosmarinic acid directly influences platelet function, offering a novel mechanism through which it may impact cardiovascular health (do Valle et al. 2021). These phytochemicals target the CVDs by modulating the longevity signaling axes (described in Sect. 13.5, Fig. 13.3), and it can be presumed that predicting phytochemicals through network medicine-based approaches will reveal the downstream gene associations, molecular mechanisms, and other underlying complexities associated with age-associated cardiovascular diseases.

13.5 Phytochemicals in the Treatment of AGE-CVD

Plants supply essential nutrients for life and additional bioactive phytochemicals that promote health and prevent diverse diseases. In the context of cardiovascular disease, dietary food supplements containing phytochemicals are doing a remarkable job as antioxidants by scavenging reactive oxygen species, which is detrimental for tissues in age-related cardiovascular disease and reduces the risk of it. The phytochemicals can reduce inflammation and modulate mitochondrial function in the human body. Various studies have proved that phytochemical plays a pivotal role in modulating cell signaling pathways. Resveratrol, curcumin, *Brassica oleracea* (BO), and berberine are engaged in various cardioprotective events (Table 13.1) and are the most studied phytochemicals in age-related cardiovascular diseases. Network medicine, which interprets diseases to be the result of perturbed interconnections

Table 13.1 Essential phytochemicals targeting age-related cardiovascular disorders

SR. no.	Phytochemicals	Source	Targets	Cardioprotective properties
1	Resveratrol	Peanuts, *Polygonum cuspidatum*, berries, grapes, and their processed products	SIRT1, AMPK	1. Shows antihypertensive properties where it impacts the sympathetic nervous system and causes blood pressure to fall
				2. Protects against ischemic heart disease, and a lower dose is effective against myocardial infarction, stable angina, and acute coronary syndromes
				3. Prevents heart hypertrophy and dysfunction
2	Sulforaphane and anthocyanins	*Brassica oleracea*	NF-κB, Nrf2, MAPK, JNK, AKT/PKB, and AMPK/SIRT1/ PPARA/UCP2	1. Consumption of dried broccoli sprouts significantly increases glutathione which activates the heart
				2. Anthocyanins support ideal platelet function and have antithrombotic properties
				3. 150 mL of kale juice per day for 12 weeks dramatically decreased the risk of coronary artery disease in hypercholesterolemic males
				4. Consumption of anthocyanins (8.4–23.6 mg/day) has been linked to decreased arterial stiffness and central blood pressure in females
3	Curcumin	*Curcuma longa*	p38MAPK, AMPK/UCP2, JAK2/STAT3, AKT/NRF2, ICAM-1, ERK, JNK, IL-8, and MCP-1	1. Smaller doses were linked to more significant reductions in total HDL and LDL cholesterol levels in acute coronary syndrome
				2. With a single dose of 15 mg/kg curcumin, superoxide anion, xanthine oxidase, myeloperoxidase, and lipid peroxides appear to be decreased
4	Berberine	*Hydrastis canadensis*	Nrf2, AMPK/ MAPK/SIRT1	1. Most of the 100 arrhythmic patients who received berberine treatment had their premature beating reduced by >89%
				2. Significant decrease in total cholesterol, triglycerides, and LDL cholesterol levels, as well as a small but significant increase in HDL cholesterol
				3. Berberine functions by reducing inflammation

(continued)

Table 13.1 (continued)

SR. no.	Phytochemicals	Source	Targets	Cardioprotective properties
5	Epigallocatechin gallate (EGCG)	*Camellia sinensis*	IκB kinase, cJUN, AP1, FAS receptor, STAT1, catalase, HO-I, and Nrf2	1. Older persons drinking five or more cups of green tea daily had a significantly lower mortality rate related to cardiovascular disease
				2. EGCG therapy affects VSMC migration and proliferation, which slows the development of atherosclerosis
				3. Slows down the heart's aging
6	Quercetin	Apples, grapes, citrus fruits, berries, onions, and others	AMPK/SIRT1	1. Quercetin consumption was found to be inversely related to hypertension in both animal models and humans
				2. Decreases ventricular hypertrophy by largely modulating angiotensin II
				3. Inhibits telomere shortening to lower cardiac myocyte apoptosis

LDL low-density lipoprotein, *HDL* high-density lipoprotein, *VSMC* vascular smooth muscle cells

across various interrelated biological components, is essential to understanding age-related clinical manifestations and cardioprotective effects of plant-derived phytochemicals.

13.5.1 Resveratrol

Resveratrol is one of the most extensively studied polyphenols in age-related cardiovascular research, commonly found in peanuts, *Polygonum cuspidatum*, berries, grapes, and their processed products. Resveratrol (3,5,4′-trihydroxy-*trans*-stilbene) appears with both *cis* and *trans* configurations, with *trans*-resveratrol being the most physiologically active. Resveratrol, present in red wine, was assumed to be one of the reasons for France's low CVD incidence, and the suggested amount of 20 mg/kg/day of resveratrol daily was thought to provide adequate protection. The SIRT1/AMPK pathway is the primary molecular mechanism mediating the biological effects of resveratrol (Fig. 13.3) (Cao et al. 2014). Resveratrol triggers SIRT1, but the underlying mechanism by which it does so is not well understood. Resveratrol's most significant health benefits are related to oxidative stress, vascular inflammation, and platelet aggregation. It upregulates the superoxide dismutase enzymes in endothelial cells (ECs) and cardiac myoblasts and downregulates ROS production. Resveratrol alters the activity of cyclooxygenase-2 (Cox-2) and phospholipase A2 and also inhibits inflammatory mediators like tumor necrosis factor-α

(TNF-α), nuclear factor-κB (NF-κB), interleukin-6 (IL-6), monocyte chemotactic protein-1 (MCP-1), and inducible nitric oxide synthase (iNOS) activity (Zarzuelo et al. 2013). Resveratrol alters ROS formation and platelet-mediated signaling by increasing nitric oxide production (Table 13.1). Several studies shed light on the downregulation of protein kinase C activation and intracellular calcium release, which results in the blockage of phosphoinositide metabolism.

13.5.1.1 Hypertension

Resveratrol shows antihypertensive properties by both endothelium-independent and endothelium-dependent mechanisms. It participates in VSMC (vascular smooth muscle cell) contractility inhibition via decreasing the expression of vasoconstrictor molecules like angiotensin-II and endothelin-1. It takes the route of the extracellular-signal-regulated kinase (ERK1/2 pathway) to suppress the endothelin-1 gene expression (Liu et al. 2003). This overall process impacts the sympathetic nervous system, which causes blood pressure to fall.

13.5.1.2 Atherosclerosis and Dyslipidemia

Resveratrol inhibits the expression of intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM1) on endothelium and increases the hepatic absorption of low-density lipoprotein (LDL) through an AMPK-independent mechanism in the very early stages of atherosclerosis. Additional in vitro investigations have shown that resveratrol inhibits the production of MCP-1 and chemokine receptor type 2 in monocytes, most likely through the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (PKB or Akt) pathway (Cullen et al. 2007). Resveratrol inhibits oxidized LDL uptake and increases cholesterol transporters' expression, which limits foam cell development. A conventional dose of resveratrol (20 mg/kg/day) has been demonstrated to have hypocholesterolemic effects in several in vivo investigations. The phytochemical boosted the expression of cholesterol-7-hydroxylase (CYP7A1) in the liver of high fat-fed rats, which resulted in increased bile acid production and secretion, decreasing plasma total and LDL cholesterol levels.

13.5.1.3 Ischemic Heart Disease

Preclinical studies shed light on multiple mechanisms that explain how resveratrol protects against ischemic heart disease. Nitric acid (NO) and antioxidant enzyme heme oxygenase-1 (HO-1) appear to be the primary mediators of the preconditioning effect of resveratrol. Through an increase in oxidative-stress-related proteins like Trx-1 and HO-1, resveratrol boosted VEGF expression in cardiomyocytes and endothelial cells (Wang et al. 2007). Resveratrol administration significantly

improved the altered microRNA expression in the ischemic heart. Few clinical trials with favorable outcomes examined the effectiveness of resveratrol at conventional and lower dosages in patients with prior myocardial infarction, stable angina, and acute coronary syndromes.

13.5.1.4 Hypertrophy and Heart Failure

There is evidence that resveratrol prevents heart hypertrophy and dysfunction. The underlying molecular mechanism relies on the reduced expression of the hypertrophic genes, and increased Ca^{2+} handling subsequently lowers the oxidative stress.

13.5.2 Sulforaphane and Anthocyanins

The active secondary metabolites sulforaphane and anthocyanins obtained from *Brassica oleracea* have an essential role in age-related cardiovascular disease. The NF-κB, Nrf2, MAPK, JNK, AKT/PKB, and AMPK/SIRT1/PPARA/UCP2 (uncoupling protein-2) are some of the molecular targets of phytochemicals of *Brassica oleracea*. These genes participate in different molecular signaling axes exhibiting antioxidant, anti-inflammatory, and antithrombotic properties (Table 13.1).

Sprouted broccoli possesses essential cardioprotective properties. The active constituent sulforaphane boosted the expression of many nuclear factors, including Nrf2, which is involved in ROS eradication (Fig. 13.3), and upregulation of detoxification enzymes, the so-called "ARE" (antioxidant response element) targets. The most common "ARE" targets are nicotinamide adenine dinucleotide (NADH), quinone reductase, HO-1, and glutathione transferase. Sulforaphane activated Nrf2, reducing the synthesis of VCAM-1, thereby preventing p38MAPK expression in endothelial cells. With the consumption of dried broccoli sprouts, a significant increase in glutathione content was observed along with increased glutathione reductase and peroxidase (GPx), which activates the heart. In 32 hypercholesterolemic males, 150 mL of kale juice per day for 12 weeks dramatically decreased plasma LDL cholesterol and elevated HDL cholesterol and GPx activity, decreasing the risk of coronary artery disease (CAD). On the other hand, anthocyanins support ideal platelet function and possess antithrombotic properties. They upregulate MCP-1 secretion in primary human endothelial cells and exhibit a protective effect against TNFα. Anthocyanins inhibited VEGF expression in vascular smooth muscle cells (VSMC) driven by PDGF-AB with p38MAPK and c-JNK suppression. Consumption of anthocyanins (8.4–23.6 mg/day) has recently been linked to decreased arterial stiffness and central blood pressure in females (Pagliaro et al. 2015). More studies on human subjects are required to understand the mechanism of action by which it controls AGE-CVD.

13.5.3 Curcumin

Diferuloylmethane, commonly known as curcumin, is a phenolic phytochemical extracted with yellow color from spice turmeric. This chemical has gained a lot of attention because of its diverse biological and immense pharmacological effects, particularly in inflammatory diseases. There is mounting evidence that curcumin may play a role in preventing many CVDs. The molecular targets of curcumin are p38MAPK, AMPK/UCP2, JAK2/STAT3, AKT/NRF2, ICAM-1, ERK, JNK, IL-8, and MCP-1 (Duan et al. 2012) (Table 13.1, Fig. 13.3), and these genes are involved in various antioxidant and anti-inflammatory signaling axes. With a single dose of 15 mg/kg curcumin, superoxide anion, xanthine oxidase, myeloperoxidase, and lipid peroxides appear to be decreased, whereas glutathione-*S*-transferase, catalase, SOD, and GPx appear to be enhanced. In acute coronary syndrome (ACS) patients, the impact of curcumin administration on lipid profile was assessed at ascending levels (low dose, three times 15 mg/day; moderate dose, three times 30 mg/day; high dose, three times 60 mg/day). This study unexpectedly demonstrated that smaller doses of curcumin were linked to more significant reductions in total HDL and LDL cholesterol levels. On the other hand, in a diverse population, a meta-analysis could not demonstrate the preventive benefits of curcumin on the levels of cholesterol and triglycerides. However, more investigation is required to understand the mode of action and the signaling axes through which curcumin targets AGE-CVD.

13.5.4 Berberine

Traditional Chinese treatment has an ancient legacy of using berberine, an alkaloid derived from *Hydrastis canadensis*, and many other plants belonging to the Berberidaceae and Ranunculaceae families. Several studies suggest that berberine is helpful in the treatment of hyperlipidemia and cardiac conditions. Upregulation of SOD and UCP2 and downregulation of NADPH oxidase expression, particularly about NADPH oxidase 2/4 subunits, appear to be the key molecular mechanisms mediating antioxidant effects (Table 13.1). The Nrf2 pathway, which is essential for antioxidant and anti-inflammatory activity, is activated by berberine treatment (Mo et al. 2014). By AMPK-dependently suppressing the MAPK pathway expression, berberine may reduce inflammation. The majority of the 100 arrhythmic patients who received berberine treatment had their premature beating reduced by >89%, while the remaining patients had their premature beating reduced by >50%. These outcomes were verified separately. There was a significant decrease in total cholesterol, triglycerides, and LDL cholesterol levels, as well as a small but significant increase in HDL cholesterol, according to a meta-analysis that included 11 randomized controlled studies and 874 Chinese participants with hyperlipidemia, type 2 diabetes, or both diseases. The network-based analysis will provide an in-depth idea of berberine targets-age-related cardiovascular disease relationship.

13.5.5 Epigallocatechin Gallate: EGCG

Epigallocatechin gallate is a phytochemical abundant in green tea, *Camellia sinensis*. A study reported that older persons who drank five or more cups of green tea daily had a significantly lower mortality rate related to cardiovascular disease. EGCG reduces inflammation by indirectly controlling NF-κB and angiotensin II. In addition, EGCG impacts endothelium and smooth muscle cells' IκB kinase, cJUN, AP1, FAS receptor, STAT1, catalase, HO-I, and Nrf2. Additionally, EGCG therapy affects VSMC migration and proliferation, which slows the development of atherosclerosis (Table 13.1, Fig. 13.3). It has been demonstrated that EGCG inhibits cyclins D1 and E, resulting in a G1 arrest. EGCG modulates platelet function by regulating PDGF, which subsequently regulates ERK1/2, cFOS, and EGR1 mitotic genes. EGCG activates ERK1/2, which downregulates IκBα, NF-κB, TNFα, IL-12p40, and p38MAPK pro-inflammatory genes and reduces inflammation (Stangl et al. 2012). The advantages of incorporating EGCG in a daily diet cannot be overstated because it is beyond question that it has a preventive impact against the development of cardiovascular disease and slows down the heart's aging.

13.5.6 Quercetin

Quercetin is a plant flavonol in various fruits and vegetables, such as apples, grapes, citrus fruits, berries, onions, and others. Plums, like broccoli and green and black tea, contain quercetin, the most prominent polyphenol accounting for almost two-thirds of the polyphenolic content. Quercetin is associated with decreased levels of plasma lipid peroxidation. Quercetin consumption was found to be inversely related to hypertension in both animal models and humans. It inhibits clotting by competitively binding plasminogen and modulating plasmin levels via urokinase plasminogen activator (uPA) regulation (Mozzicafreddo et al. 2008). The anti-proliferative impact of quercetin on VSMC is predominantly achieved through inhibiting the JNK and AP-1 signaling pathways (Table 13.1, Fig. 13.3). Additionally, it has been shown that quercetin decreases ventricular hypertrophy by largely modulating angiotensin II and inhibiting telomere shortening to lower cardiac myocyte apoptosis. However, more studies must be conducted to elucidate the mechanism of action of quercetin in AGE-CVD.

13.6 Conclusion

Despite being an inherent cardiovascular risk factor, aging may outweigh all other risk factors taken together. Therefore, gaining a better knowledge of the fundamental processes at a molecular level that control aging could result in considerable

improvements in both the preventative and therapeutic management of cardiovascular disease. In this book chapter, we shed light on the studies that possibly link aging to cardiovascular diseases and offer insight into novel and intriguing areas to research by combining these two closely related fields of study. Many mechanistic investigations and drug development efforts have recently relied heavily on gene associations predicted by various interactomes. We shed light on using the concepts of the network biology approach to identify the hidden complexities associated with AGE-CVD signaling axes. We presented different preclinical studies to understand the effect of the most essential phytochemicals, such as resveratrol, sulforaphane, curcumin, berberine, EGCG, and quercetin, on age-related cardiovascular diseases. The antioxidant, anti-inflammatory, and antithrombotic characteristics appeared to be the most important. Researchers and clinicians tested the effects of phytochemicals on humans as a result of the excellent outcomes of both in vitro and in vivo investigations. However, there is ongoing debate regarding the limited clinical trial data on the preventive effects of these substances in several CVDs. The critical drawback of current clinical trials is the variability and limited sample size of these studies. Therefore, there is a need for more extensive and well-controlled human clinical trials. Moreover, we may adopt different network medicine-based strategies and machine learning approaches in the future to predict potential phytochemicals that can target the deregulated signaling axes associated with age-related cardiovascular diseases.

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Chapter 14
Plant-Derived Natural Products Targeting Multiple Pathways as Potential Therapeutics in the Treatment of Parkinson's Disease

Amulya Vijay and Anandan Balakrishnan

Abstract Parkinson's disease (PD) is a chronic neurodegenerative disorder (ND) characterised by gradual degradation of dopaminergic neurons in the substantia nigra pars compacta (SNpc) area of the human midbrain, which results in a reduction in dopamine levels. After a certain age, neurodegeneration becomes an extremely important factor in human life. Given its high incidence rate, PD continues to be one of the NDs that represent a serious hazard to adults over 60. Neuroinflammation, oxidative stress, mitochondrial dysfunction, and apoptosis are all recognised as contributing factors to the pathophysiology of PD, despite the fact that the precise origin of the disease is still unknown. There is a need for a highly tailored therapy strategy for PD, as different pharmacological combinations are only available to manage the symptoms. This is where the use of plant-derived natural compounds as a neuroprotective agent has been in the spotlight. With their antioxidant properties, which are thought to help in repairing the damage caused by free radicals, as well as their antiapoptotic and anti-inflammatory properties, flavonoids are one of the main classes of phytochemicals that have demonstrated their effectiveness in acting as a neuroprotective agent for PD. These properties could activate pathways that target mitochondrial dysfunction and induce neurotrophic factors by exhibiting a neuroprotective effect. The scientific literature on the anti-neurodegenerative and neuroprotective functions of phytochemicals is reviewed in this chapter, with a particular emphasis on the potential of flavonoids as natural products for the prevention and treatment of PD.

Keywords Phytochemicals · Flavonoids · Parkinson's disease · Therapeutics

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Abbreviation

6-OHDA	6-Hydroxydopamine
α-Syn	Alpha-synuclein
AD	Alzheimer's disease
DA	Dopaminergic
MPTP	Methyl-4-phenyl-1,2,3,6-tetrahydropyridine
NDs	Neurodegenerative disorders
PD	Parkinson's disease
ROS	Reactive oxygen species
SNpc	*Substantia nigra pars compacta*

14.1 Introduction

Neurodegeneration is a pathological condition that affects the neurons in different regions of the brain. Several NDs have been discovered; among them, the most common are Alzheimer's disease (AD), PD, amyotrophic lateral sclerosis, and Huntington's disease (Young et al. 2018). The gradual loss of nerve cells is the common pathogenic process in all NDs. Since a considerable number of neurons have been lost (or a specific area of the central nervous system has been damaged), the process leading to the development of the initial symptoms starts significantly earlier and is asymptomatic for a very long period. Finally, a number of neurological injury symptoms have an impact on motor and cognitive abilities (Hajdusianek et al. 2021). Among several NDs, PD is the second-most prevalent degenerative condition after AD. PD affects the human central peripheral and enteric nervous systems which leads to a progressive loss in the dopaminergic neurons in the substantia nigra *pars compacta* (SNpc) part of the midbrain. Evidences also state that deregulation in the growth of neuronal processes affecting the neuronal cytoskeleton could also give rise to PD (Foley and Riederer 1999; Graybiel et al. 1990; Morrish et al. 1998). As per reports, the prevalence rate of PD has seen a hike from 2.5 million in 1990 to 6.1 million in 2016 making it the second most common neurodegenerative disease (Hajdusianek et al. 2021).

The neuropathology of PD is characterised by the degeneration of dopaminergic (DA) neurons in the SNpc region of the brain (Feraco et al. 2021). The DA neurons synapse with neurons in the striatum; thereby their loss leads to the depletion of striatal dopamine. PD is also characterised by the presence of Lewy bodies which are cytoplasmic protein aggregates found in the remaining DA neurons of the SNpc. The Lewy bodies are aggregated form of the protein alpha-synuclein (α-Syn). α-Syn plays a key role in the pathogenesis of Parkinson's disease (PD). These aggregated forms of α-Syn protein accumulate within the neurons which leads to impairment in the neuronal functioning. As a result of which, the neurons die. The motor symptoms associated with PD such as gait, resting tremor, and bradykinesia are the end result of the neuronal destruction in the substantia nigra (Alam et al. 2022).

There is currently no test to identify PD before the appearance of motor symptoms, and the present therapies only work to alleviate the symptoms rather than treating the underlying cause or slowing the disease's development. Importantly, striatal dopamine is lowered by 80% by the time the first symptoms arise, and 60% of the DA neurons of the SNpc would have entirely perished (Maher 2019). The need for enhancing and introducing new modalities for treating or managing PD has emerged as a result of the disease's high prevalence and adversity. Dopamine replacement therapy, using primarily levodopa (L-Dopa), in conjunction with dopamine receptor agonists, monoamine oxidase (MAO) inhibitors, or catechol-*O*-methyltransferase (COMT) inhibitors, is one among the very few and commonly used treatment options available that only focuses on extending control of symptoms in PD patients. The hunt for innovative therapeutic drugs with fewer side effects is crucial because there is currently no full cure that stops the pathogenic pathways that cause illness development (Vuletić et al. 2021). Growing interest has recently been shown in the therapeutic use of natural products for Parkinson's disease, particularly those derived from plants. Compared to synthetic medications, natural products are recognised to have fewer negative effects (Jung and Kim 2018). Experimental and epidemiological data have shown that flavonoid polyphenols, in particular, ameliorate neuronal loss and show neuroprotective properties in models of PD (Mandel et al. 2004).

Natural products continue to be a source of great chemical variety, biochemical specificity, and diverse molecular properties that make them excellent for modulating many signalling pathways/cascades in various clinical states including cancer and neurological illnesses (Hussain et al. 2018). This book chapter will give a general overview on the neuroprotective advantages of plant-derived flavonoids in PD. Flavonoids are phytonutrients which are found in practically all fruits and vegetables. The chapter will also focus on the mechanisms by which these flavonoids may prove beneficial for PD. Variety of flavonoids have been studied over the decade and are found to be promising candidates for the treatment of PD and other neurodegenerative diseases.

14.2 Parkinson's Disease

PD is an ND which is associated with severe disability leading to adverse effects on life quality. In PD, motor dysfunctions such as quiescence, muscle stiffness, and postural instability are commonly observed. PD is also associated with autonomic nervous dysfunction, sleep disorders, psychiatric symptoms, and other non-motor symptoms such as olfactory impairment, pain, autonomic dysfunction, impaired sleep, fatigue, and behavioural changes. Degeneration of dopaminergic neurons in the SNpc, Lewy body accumulation, and neuroinflammation are the main pathological features of PD. The death or dysfunction of dopaminergic neurons in the dense part of the substantia nigra leads to dopamine deficiency in the basal ganglia and motor dysfunction. The formation of the Lewy body is associated with the misfolding of α-Syn, which becomes insoluble and abnormally aggregated. The

pathogenesis of PD is believed to involve oxidative stress, disruption to mitochondria, alterations to the protein α-Syn, and neuroinflammatory processes (Aryal et al. 2020; Liu et al. 2021). Figure 14.1 depicts the different pathways involved in the pathophysiology of PD (Kanehisa and Goto 2000).

The primary cause of PD, a progressive neurological movement condition, is the loss of dopaminergic (DA) neurons in the substantia nigra pars compacta (SNpc). Environmental factors and mutations in genes linked to familial Parkinson's disease (PD), such as SNCA, parkin, DJ-1, PINK1, and LRRK2, are connected to the aetiology of PD. Due to oxidative stress, impaired intracellular Ca^{2+} homeostasis, mitochondrial dysfunctions, and altered protein handling, these pathogenic mutations and environmental variables are known to induce disease and compromise the function and survival of DA neurons as represented in Fig. 14.1. The loss of dopaminergic input to the striatum caused by the death of DA neurons in the SNpc is thought

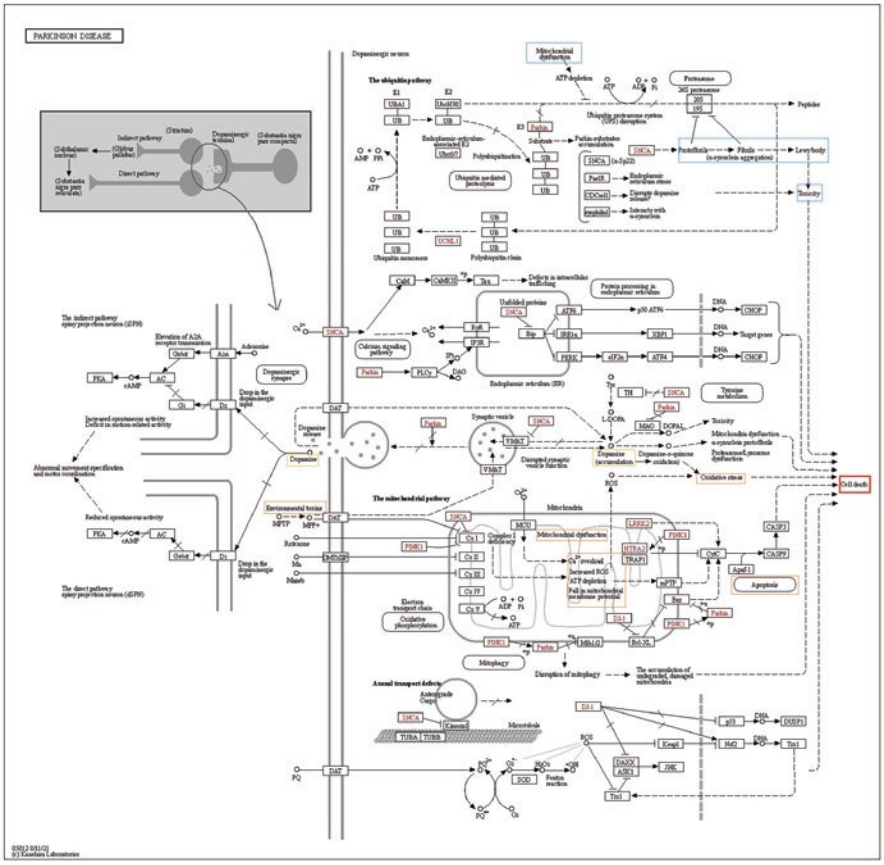


Fig. 14.1 Pathways involved in Parkinson's disease (pathway retrieved from KEGG (Kyoto Encyclopedia of Genes and Genomes)) (Kanehisa and Goto 2000)

to impair movement by causing hypo- and hyperactivity in striatal spiny projection neurons (SPNs) of the direct (dSPNs) and indirect (iSPNs) pathways in the basal ganglia, respectively (Kanehisa and Goto 2000).

14.3 Phytochemicals

Phytochemicals are compounds generated by plants. However, the word is commonly used to describe plant-derived compounds that may have an impact on health but are not required nutrients. While there are plenty of data to support the health advantages of diets high in fruits, vegetables, legumes, whole grains, and nuts, there is little evidence that these effects are attributable to specific nutrients or phytochemicals. Because plant-based diets are complex combinations of bioactive components, research on individual phytochemicals' potential health impacts is related to information on the health consequences of foods containing those phytochemicals. These secondary metabolites have shown significant biological and health-promoting effects (Sajad et al. 2022). Figure 14.2 depicts the different classes of phytochemicals and further elaborates the subclasses of polyphenols, which is one of the most abundant classes of phytochemical.

These plant-derived compounds, or phytochemicals, have long been employed as medicinal treatments. Traditionally, whole plant parts were utilised to cure a variety of ailments. Phytochemicals are now regularly collected from plant components and employed by the modern pharmaceutical industry to synthesise pharmaceuticals, including medications and bioenhancers for cancer chemotherapeutic therapy. The biggest, most diverse, and most researched class of phytochemicals is flavonoids. It has been reported that plant foods contain more than 6000 different flavonoids. Here, the chapter will focus on how flavonoids can be used as a neuroprotective agent for PD.

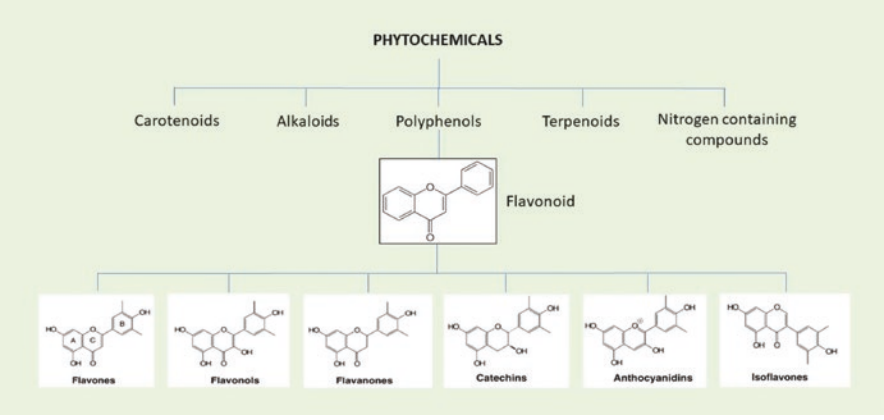


Fig. 14.2 Classification and structure of main classes of phytochemicals

14.4 Flavonoids

Phenolic molecules are one of the most significant types of secondary metabolites. They come in a variety of forms and are in charge of giving meals and drinks made from plants their fundamental organoleptic qualities, notably their colour and flavour. Additionally, they aid in the nutrient retention of fruits and vegetables. One of the most prevalent groups of phytochemical substances is flavonoids. A deeper knowledge of their processes and biological traits enables them to be employed as medicinal medications as well as monitor and control food quality due to their significance to food organoleptic features and human wellness (Tapas et al. 2008).

It is crucial to think about the therapy choices accessible for PD given the rise in the disease's incidence rate. Through several research, the natural chemicals known as flavonoids have demonstrated their effectiveness against neurological illnesses. Flavonoids have demonstrated positive benefits on the cellular stress response, making them potentially effective treatment choices for neurological diseases and NDs. In recent years, there has been a lot of interest in these compounds. Although their mode of action has to be further investigated, evidence suggests that flavonoids may be used to provide neuroprotection through a variety of mechanisms, including antioxidant, anti-inflammatory, and antiapoptotic capabilities. This book chapter sheds light on the possible contribution of flavonoids to PD neuroprotection (Devi et al. 2021).

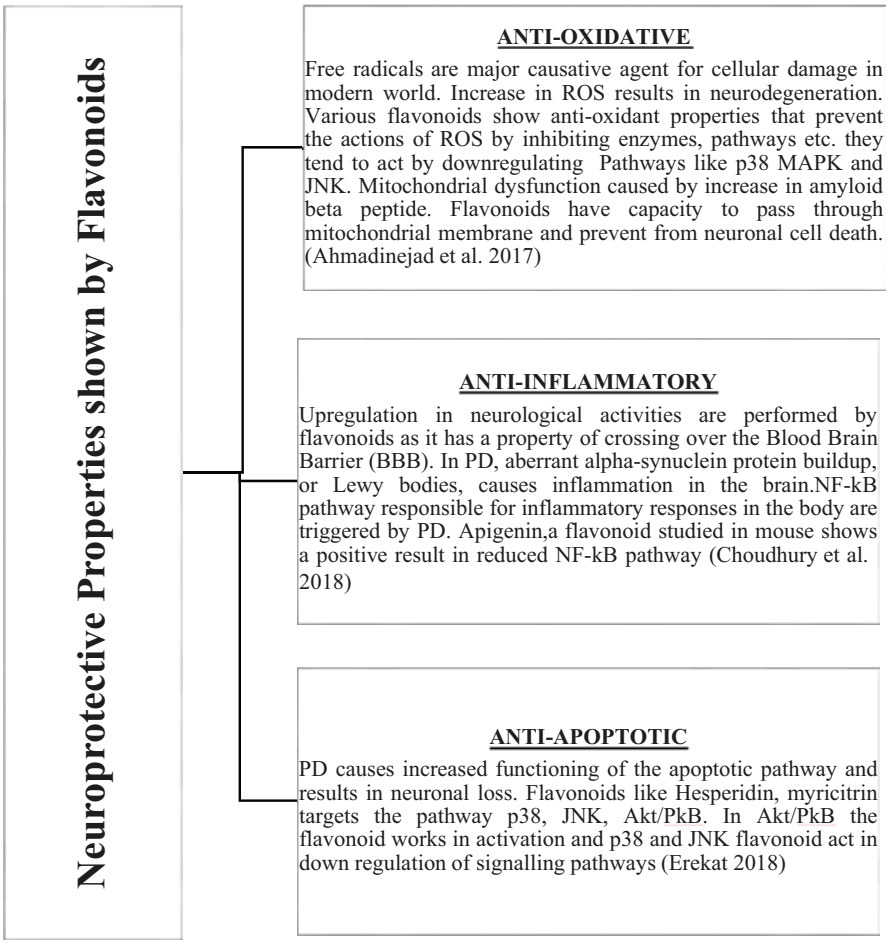
The neurodegeneration observed in PD appears to be caused by a number of mechanisms, including neuroinflammation, glutamatergic excitotoxicity, elevations in iron, depletion of endogenous antioxidants, and an increase in reactive oxygen species (ROS). According to a growing body of research, flavonoids may be able to lessen the neuronal damage that underlies a variety of diseases and hence shorten the duration of the sickness. Flavonoids have an impact on biochemical signalling pathways involved in neurodegeneration, neuroinflammation, learning, and memory. Their ability to interact with crucial brain neuronal signalling cascades, which in turn inhibits the apoptosis produced by neurotoxic species and instead promotes neuronal survival and differentiation, appears to be what underpins this variety of effects (Vazour et al. 2013).

14.4.1 Neuroprotective Effects of Flavonoids

Numerous research have focused on the underlying neuroprotective molecular mechanism of flavonoids and their metabolites during the last decade. Recent research has demonstrated the positive neuropharmacological effects of different flavonoids, including anti-inflammatory, antidepressant, anticonvulsant, antioxidant (Table 14.1), as well as memory and locomotor boosting properties (Hajialyani et al. 2019).

Several in vivo and in vitro models that are unique to neurodegenerative illnesses were used, as this chapter demonstrates, to assess the underlying

Table 14.1 Flowchart representing the modes by which flavonoids exert neuroprotection



Note: *p38 MAPK* mitogen-activated protein kinase, *JNK* Jun N-terminal kinase, *NF-κB* nuclear factor kappa B, *Akt/PkB* PI3K (phosphatidylinositol 3-kinase) and Akt (protein kinase B)

neuropharmacological processes of different flavonoids. The neuroprotective potential of flavonoid involves a variety of pharmacological targets, such as the enhancement of brain growth factors and endogenous antioxidant defence capabilities, which reduce neuro-inflammatory and apoptotic pathways and ROS pathways (Table 14.1).

14.4.1.1 Anti-inflammatory Properties

Numerous flavonoids have been proven to have anti-inflammatory activities in both in vitro and in vivo investigations. An important mechanism for anti-inflammatory action is inhibition of eicosanoid-producing enzymes like phospholipase A2,

cyclooxygenases, and lipoxygenases, which leads to lower levels of prostanoids (a subclass of eicosanoids) and leukotrienes (eicosanoid inflammatory mediators produced in leukocytes). Other methods include histamine release, phosphodiesterase inhibition, protein kinase inhibition, and transcriptase activation (Rathee et al. 2009). A coordinated collection of cell activation mechanisms, the majority of which are connected to prostanoid production through arachidonic acid digestion, are involved in an inflammatory reaction. Arachidonic acid is released from phospholipids by phospholipase A2, which is subsequently oxidised by cyclooxygenase (COX) or 5-lipoxygenase (LOX) into prostaglandins or thromboxanes, respectively. Numerous plant flavonoids are essential in inhibiting the formation of prostaglandins. Hesperidin and diosmin have been demonstrated to inhibit the formation of prostaglandins in vivo (Damon et al. 1987). A flavonoid called quercetin triggers the cyclooxygenase cascade. The enzymes COX-2 and 5-LOX, which are involved in the production of eicosanoids from arachidonic acid, are powerfully inhibited by the compound quercetin, which may be found in onions, fruit juices, and tea (Kimata et al. 2000). Flavonoids bind to platelet membranes in vitro, and reports claim that over time, they have an accumulative impact (Van Wauwe and Goossens 1983). According to study, flavones prevent lipopolysaccharide (LPS)-activated monocytes from transcriptionally activating cyclooxygenase (Kim et al. 1998). Apigenin inhibits a specific LPS-induced kinase, which may be why it reduces the LPS-induced activation of NF-kB transcriptional activity (Middleton Jr and Kandaswami 1992).

Studies have demonstrated that these natural compounds can delay the late stages of allergy responses by reducing histamine release. Histamine release during an allergic response is tightly controlled by leukotrienes generated by lipoxygenase-catalysed processes. While methoxylated flavones have a significantly lesser inhibitory impact than hydroxylated flavones, many hydroxylated flavones, or aglycones, block this mechanism (Petkov et al. 1981). Inhibiting phosphodiesterase is crucial in the management of allergy and chronic inflammation. A variety of medicinal plants naturally inhibit phosphodiesterase, and flavonoids have been linked to this inhibitory effect in many conventional drugs (Kusano et al. 1991). Four licorice flavonoids and biflavones from *Ginkgo biloba* were discovered to inhibit cAMP phosphodiesterase in vitro. In LPS-activated human monocytes, citrus flavones have been observed to suppress phosphodiesterase activity. In a number of studies, the competitive binding of flavonoids at nucleotide-binding sites has been connected to flavonoid inhibition of protein kinases (Ferriola et al. 1989). Due to their distinct method of action and high in vivo efficacy, flavonoids are regarded as intriguing candidates for new anti-inflammatory medicines. There is growing evidence that the events leading to progressive neuronal disruption in neurodegenerative illnesses including PD and AD may be triggered by inflammatory processes.

14.4.1.2 Antioxidant Properties

According to Halliwell and Gutteridge, the mechanism of antioxidant action includes (1) repressing ROS formation by inhibiting enzymes or chelating trace elements associated with free radical production, (2) scavenging reactive oxygen species, and (3)

upregulating or defending antioxidant capacity (Halliwell and Gutteridge 2015). Flavonoids have been reported to satisfy the aforementioned criteria. As a result, their impact has been multiplied by twofold. Flavonoids, such as xanthine oxidase and protein kinase C, inhibit superoxide anion-producing enzymes. Flavonoids have also been demonstrated to inhibit enzymes involved in the formation of reactive oxygen species, such as cyclooxygenase, mitochondrial succinoxidase, lipoxygenase, NADH oxidase, and glutathione *S*-transferase (Brown et al. 1998). Several flavonoids are effective in chelating trace metals that are necessary for oxygen metabolism. Dietary flavonoids are thought to give their initial antioxidant protection in the digestive system by limiting the generation and scavenging of reactive oxygen species. They continue to be antioxidants until they are absorbed, either as aglycones or glycosides (Pietta 2000).

The antioxidant activity of flavonoids was the first biological mechanism studied, particularly in terms of their protection against cardiovascular disease. Most oxidising chemicals, including singlet oxygen and numerous free radicals, are particularly effective flavonoid scavengers (Bravo 1998). The imbalance generated by oxidants, which form ROS, free radicals, and antioxidants, which eliminate free radicals, is referred to as oxidative stress. The levels of oxidants and antioxidants are nicely balanced in healthy people. However, excessive ROS generation and a deficiency in antioxidants lead to oxidative stress, which may be the reason for speeding up the onset of neurodegenerative disorders. This suggests that lowering oxidative stress and limiting ROS formation is essential for both the treatment and prevention of NDs, including Parkinson's disease (Kim 2021).

14.4.1.3 Antiapoptotic Properties

Apoptosis has been suggested as the primary cause of neuronal death in PD, as indicated by the discovery of DNA fragmentation and apoptotic chromatin alterations in PD patients' dopaminergic neurons. Apoptosis is mediated by a number of initiator and executioner caspases and can occur via either the intrinsic or extrinsic routes. The intrinsic route, also known as the mitochondria-mediated pathway, is mediated by activation of initiator caspase-9 (Erekat 2018). Cell damage caused by oxidative stress has long been linked to the process of ageing as well as a number of neurological illnesses such as PD. Numerous investigations have revealed that oxidative stress is a primary source of cellular damage in a variety of neurodegenerative illnesses. ROS such as hydrogen peroxide, superoxide anion, and hydroxyl radical easily damage biological molecules, and such damage can eventually lead to cellular apoptosis or necrosis. Removal of excess ROS or suppression of their generation by antioxidants could be how flavonoids can exert their importance and neuroprotective role in order to prevent oxidative cell injuries that cause apoptosis.

Treatment of dopaminergic cells (e.g., SH-SY5Y, PC12 cells) with neurotoxins like 6-hydroxydopamine (6-OHDA) or methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) elevated pro-apoptotic genes and other genes that induce cellular death, according to studies on the PD model. As a result, medicinal medicines targeting these genes may protect neurons from the apoptotic process and neuronal death (Magalingam et al. 2015).

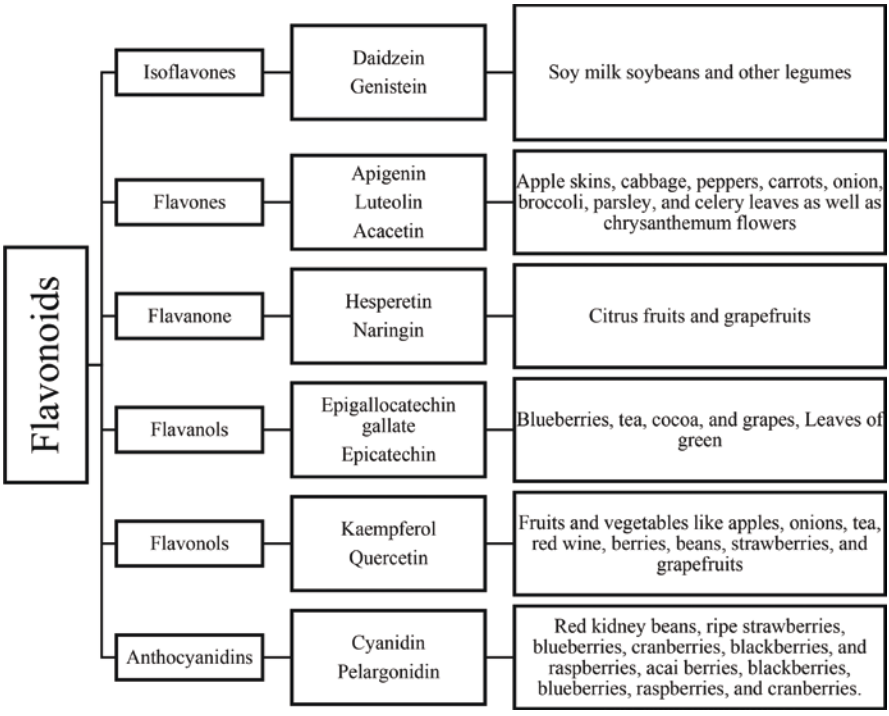
14.4.2 Neuroprotective Effects of Flavonoids on PD

Despite the fact that the underlying disease mechanisms of PD that lead to the degeneration of nigrostriatal DA neurons are still unknown, it is well-known from evidence-based information that the upregulation of risk factors is involved in the pathogenesis and progression of PD and that the following factors are particularly important for its onset: neuroinflammation, improper management of apoptosis and autophagy, genetic mutations, neurotrophic support failure, and oxidative stress. Among them, oxidative stress is regarded as a major contributor to the development of PD since it can lead to neuroinflammation, increased ROS generation from dopamine metabolism, mitochondrial malfunction, and iron deposition in the SNpc (Devi et al. 2021). Table 14.2 summarises main groups of flavonoids, some derived compounds with neuroprotective properties, and their food sources.

Introducing flavonoids might lessen the negative effects of cellular events brought on by stress. Therefore, by using these flavonoids, the harmful effects of environmental stress and cellular stress response might be reduced (Kim et al. 2020).

It is widely recognised that there is no effective treatment for PD, and the medications that are now available are primarily intended to treat its symptoms. When it comes to PD, flavonoids have demonstrated preventive properties such as the

Table 14.2 Flowchart representing the main groups of flavonoids, some derived compounds with neuroprotective properties, and their food sources



prevention of dopamine decrease, ROS production, TH protein loss, and mitochondrial complex 1 deficiencies. In addition, flavonoids boost cell survival, stop apoptosis, and lower pro-inflammatory cytokines (Aryal et al. 2020).

The treatment of an animal model of PD with a toxin, such as a pesticide or another hazardous substance that has been linked to PD in vivo, is typical. The two most popular models are 1-MPTP and 6-OHDA. PD has also been modelled using the pesticide rotenone and the herbicide paraquat (PQ). In contrast to the age-dependent progression of PD in actual patients, none of these models accurately simulates every component of human PD, and most have start times that are far faster. Despite the fact that animal models have been created in which one or more of the genes linked to familial PD are mutated, the majority of these genetic PD models do not exhibit nigrostriatal degeneration. Additionally, there is a problem with inconsistent phenotypes between different mouse lines carrying the same mutation. As a result, they have not been widely utilised to investigate putative medicinal substances (Maher 2019).

In both in vivo and in vitro PD toxin models, a sizable variety of flavonoids from most of the main classes have been investigated. Some of these have already been discussed, but the following table reviews and describes some of the outcomes (Table 14.3).

Table 14.3 Protective mechanism of various phytochemicals in Parkinson's disease

S. no.	Key findings	References
1.	By scavenging free radicals and maintaining the activity of several antioxidant enzymes, the natural flavonoid kaempferol (Ka) has neuroprotective properties that delay the onset and progression of neurodegenerative diseases	Siddique (2021)
	Kaempferol has several targets and can cross the BBB, making it a promising dietary supplement for the prevention and treatment of neurodegenerative disorders	
2.	*Citrus reticulata* (mandarin) flavonoids have neuroprotective properties. In 6-OHDA-induced SH-SY5Y human neuroblastoma cells, the neuroprotective effects of mandarin juice extract (MJe) were investigated. It demonstrated antioxidant effects by lowering the ROS and nitrogen species that 6-OHDA produced, as well as by restoring the potential of the mitochondrial membrane and preventing the oxidative DNA damage that 6-OHDA elicited	Cirmi et al. (2021)
	Additionally, MJe corrected the imbalance of PD-related genes (SNCA, LRRK2, PINK1, parkin, and DJ-1) affected by 6-OHDA oxidative stress, indicating that MJe protects SH-SY5Y cells from 6-OHDA-induced cell death through a combination of its antioxidant properties and specific interactions with intracellular pathways	
3.	A perennial plant in the Asteraceae family called *Coreopsis lanceolata* L. (CL) is noted for having flavonoids in its flowers that have a variety of bioactivities	Kim et al. (2021)
	By altering the expression of genes associated with apoptosis and further decreasing caspase-3 activation, CL has neuroprotective benefits against oxidative stress (OS)-induced apoptosis in PC12 cells in Parkinson's disease model mice. These findings suggest that CL may have therapeutic benefit in the management of neurodegenerative illnesses that worsen over time	

(continued)

Table 14.3 (continued)

S. no.	Key findings	References
4.	In pertinent cellular models, the dietary flavonoid fisetin was assessed against the primary PD markers	Rosado-Ramos et al. (2021)
	The findings demonstrated that fisetin performs modulatory actions against typical cellular diseases prevalent in PD; surprisingly, it controls α-Syn aggregation, supporting the notion that diets high in this substance may be advantageous	
5.	A flavonoid known as baicalein that is obtained from the plant *Scutellaria baicalensis* Georgi. displays anti-PD action by easing the disease's motor symptoms	Zhao et al. (2021)
	Repeated baicalein administration decreased α-Syn aggregation, prevented neuroinflammation, and preserved the equilibrium of neurotransmitters. Additionally, in the PD-related depression mouse model, baicalein therapy was observed to significantly preserve synaptic plasticity and activate the BDNF/TrkB/CREB pathway	
	Baicalin therapy enhanced the behaviour of an MPTP-induced Parkinson's disease mice model and decreased dopaminergic cell loss in the substantia nigra, which was linked to the inactivation of pro-inflammatory cytokines and oxidative stress. Thus, our investigation provided evidence that baicalin inhibited C/EBP via redox homeostasis, suggesting that it may be a useful therapeutic therapy for Parkinson's disease	Lei et al. (2020)
	In PD mouse models, baicalein treatment restored MPTP-induced motor impairment, dopaminergic neuron loss, and pro-inflammatory cytokine increase. Baicalein also reduced the activation of caspase-1 and NLRP3, as well as the gasdermin D (GSDMD)-dependent pyroptosis. The findings imply that baicalein can inhibit the NLRP3/caspase-1/GSDMD pathway to prevent mice from developing neuroinflammation brought on by MPTP	Rui et al. (2020)
6.	A unique *Ginkgo biloba* leaf extract supplement from China called the *Ginkgo biloba* dropping pill (GBDP) has the potential to be utilised as an alternative treatment for Parkinson's disease. It is anti-inflammatory and neuroprotective. According to in vitro research, the neuroprotective effects of GBDP may be mediated through the Akt/GSK3 pathway. These findings showed that GBDP could help control PD by providing neuroprotective advantages	Yu et al. (2021)
7.	Pomegranate seed extract (PSE) and juice (PJ) preadministration substantially decreased the PQ-induced oxidative stress by reducing the MDA level and raising the activities of antioxidant enzymes. PSE and PJ significantly reduced levels of pro-inflammatory cytokines, CD11b, and TGF-β while significantly increasing levels of interleukin-10 (IL-10), GDNF, and ATP in comparison to animals treated with PQ. They also greatly reduced the expression of the NF-κB gene in the striatum	Fathy et al. (2021)
8.	Another experiment using the flavonoid icaritin improved mitochondrial dysfunction by stabilising the levels of proteins essential for mitochondrial function, such as voltage-dependent anion channel (VDAC) and ATP synthase subunit beta, as well as molecules involved in energy metabolism, such as ATP and ADP (ATP5B). Using molecular docking, it was also shown that icaritin can interact with NLRP3, VDAC, ATP5B, and a variety of BBB-related proteins. These results highlight the fascinating therapeutic potential of icaritin in Parkinson's disease	Wu et al. (2021)

Table 14.3 (continued)

S. no.	Key findings	References
9.	Silibinin (silybin), a flavonoid isolated and extracted from the fruit of *S. marianum*, was examined to determine its potential in protecting against motor damage in PD model mice produced by MPTP	Liu et al. (2021)
	In addition to reducing mitochondrial damage by suppressing pro-inflammatory response and α-Syn aggregation, silibinin's neuroprotective action also involves enhancing the oxidative defence system. In particular, the enhancement of mitophagy, which results in the elimination of the toxic effects of damaged mitochondria, is responsible for the preservation of dopaminergic neurons. These results imply that silibinin has the potential to be explored further as a treatment option for Parkinson's disease	
10.	A flavanone called naringenin has been shown to inhibit the activation of microglia and to reduce the activity of the glial fibrillary acidic protein (GFAP)	Clairembault et al. (2014)
	When 6-OHDA is used to produce neurotoxicity in zebrafish larvae as a model for Parkinson's disease, naringenin lowers the levels of oxidative stress indicators and downregulates the PD genes	Kesh et al. (2021a)
11.	In the zebrafish model, flavanone hesperidin was observed to downregulate kinases such gsk-3 and lrrk2, suggesting a potential therapeutic candidate for the treatment of Parkinson's disease	Kesh et al. (2021b)
	In a study employing the 6-OHDA-induced animals PD model, hesperidin decreased the 6-OHDA-induced loss in glutathione peroxidase and catalase activity, total reactive antioxidant capacity, and levels of dopamine and its metabolites in the striatum of aged mice	Antunes et al. (2014)
	Chronic hesperidin treatment attenuated the effects of 6-OHDA on reactive oxygen species levels and glutathione reductase activity in the striatum	
12.	Valeric acid (Val), a naturally occurring straight-chain alkyl carboxylic acid found in the plant *Valeriana officinalis*, has been used to treat neurological illnesses. In rat models of Parkinson's disease, Val was found to protect against the rotenone-induced rise of pro-inflammatory cytokines, oxidative stress, and α-Syn expression, resulting in an increase in crucial antioxidant enzymes	Jayaraj et al. (2020)
13.	Parkinsonism cell model using rotenone-treated dopaminergic PC12 cells with the natural substance curcumin, recognised for its antioxidant qualities. It has been shown that rotenone treatment of PC12 cells results in significant protein damage, including the creation of carbonylated and nitrotyrosine-derived proteins, but co-exposure to curcumin has protective benefits by lowering the amounts of oxidised proteins. Additionally, curcumin encourages proteasome activity, which eliminates rotenone's inhibitory effects on this degradative pathway	Buratta et al. (2020)
14.	The most prevalent and strong green tea catechin, epigallocatechin-3-gallate (EGCG), has significant antioxidative, anti-inflammatory, and neuroprotective properties. The study looked at whether EGCG may protect rats from motor and neurochemical dysfunctions brought on by ROT. It was shown the antioxidative impact, prevention of mitochondrial dysfunction, protection of neurochemical insufficiency, anti-neuroinflammatory action, and antiapoptotic effect of EGCG against ROT-induced motor impairments	Tseng et al. (2020)

(continued)

Table 14.3 (continued)

S. no.	Key findings	References
15.	Procyanidin (PC), a bioflavonoid antioxidant with a unique molecular structure that is extensively present in plants like grapes and is capable of efficiently removing free radicals from the human body. In rats and PC12 cells, it was shown that PC had a protective effect against 6-OHDA-induced neurotoxicity. This effect may have been caused by activating the PI3K/Akt signalling pathway	Zhang et al. (2019)
16.	Proanthocyanidins (PA) are natural flavonoids that are abundantly found in many fruits, vegetables, nuts, and seeds, particularly grape seeds. Significantly reduced rotenone-induced activation of caspase-9, caspase-3, and cleavage of poly(ADP-ribose) polymerase (PARP), which are biochemical characteristics of apoptosis. Significantly improved cell survival against rotenone neurotoxicity. The outcomes showed that PA inhibited p38, JNK, and ERK signalling pathways to reduce rotenone-induced ROS formation and prevent apoptosis in SH-SY5Y cells	Ma et al. (2018)
17.	Chrysin is an active flavonoid with shown neuroprotective properties. In the rat PD model, chrysin-treated animals had a substantial decrease in the motor behavioural alterations, loss and degradation of nigrostriatal dopaminergic neurons, and enhanced positivity to anti-TH antibody. In the rat model of PD, it was found that chrysin confers neuroprotection	Ahmed et al. (2018)
18.	Rutin, a glycoside of the flavonoid quercetin, is found in a variety of plants and fruits, including buckwheat, apricots, cherries, grapes, grapefruit, plums, and oranges. Rutin has been found to have positive effects in a variety of illness states according to pharmacological investigations, and its therapeutic potential in a number of ND models has generated a lot of interest. Pro-inflammatory cytokines are decreased, antioxidant enzyme activity is increased, the mitogen-activated protein kinase cascade is activated, PD-linked and pro-apoptotic gene mRNA expression is downregulated, ion transport and antiapoptotic genes are upregulated, and mitochondrial complex enzyme activity is restored	Enogieru et al. (2018)
19.	Studies on the flavonol fisetin's beneficial effects in PD models found that by lowering inflammation, protein aggregation, and mitochondrial dysfunction, it may be able to lessen the impacts of PD on brain function	Maher (2017)
20.	A flavonoid called myricitrin that was discovered in the root bark of the plant *Myrica cerifera* has strong antioxidant capabilities. When SN4741 cells were incubated with myricitrin, the neurotoxin MPTP's ability to cause cell death was dramatically decreased. This was demonstrated by the protective effects of myricitrin against MPTP-induced mitochondrial dysfunction in SN4741 cells. Myricitrin may be a helpful treatment for age-related neurodegenerative disorders, notably Parkinson's disease, since it has been proposed that it reduces MPTP-induced mitochondrial dysfunction and boosts cell viability via DJ-1	Cai et al. (2015)

14.5 Summary and Conclusion

The development and application of flavonoids as neuroprotective medicines for the treatment of PD has emerged as one of the most significant goals of neuropathological research into this condition. Research to find natural substances capable of

stopping or reducing the progression of neurological degeneration has been sparked by the growing understanding of the molecular processes underlying the degenerative process of PD. Flavonoids are recognised as natural substances that are also well-known for having a variety of bioactivities that promote health, such as antioxidation, anti-inflammation, and antiapoptotic, as well as providing neuroprotective properties.

One of the most prevalent neurodegenerative illnesses, PD, causes a slow loss of dopamine neurons due to a rise in ROS levels and inflammation. Although the entire pathophysiology of the disease is still unknown, these elements are thought to be crucial in the development of the illness. The choices for treating Parkinson's disease are severely constrained to a few medications and pharmacological combinations that solely address the symptoms. Therefore, in terms of PD or any other NDs, the need for therapeutic alternatives is urgently needed. Numerous flavonoids with neuroprotective qualities have gained attention during the past decade.

This chapter provides a thorough summary of the neuroprotective properties of phytochemicals that have recently been researched, with a focus on their neurorescue/neurodegenerative activity in PD. This chapter explores the potential mechanisms through which flavonoids may provide positive outcomes when tested in a variety of in vivo and in vitro PD models. Many or most of the natural compounds reviewed in this chapter have shown promising neuroprotection which makes them potential drug candidates for treating NDs.

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Chapter 15
Aging in Indian Women: Health Status

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Abstract Young India will be greying in a decade or so. And there will also be an increase in older women than older men by 18.4 million by 2050. Most elderly persons are likely to suffer from one or the other morbidity conditions. This study assesses the acute and chronic morbidity conditions the elderly widows are suffering from and their principal determinants.

Keywords Elderly widows · Acute morbidity · Chronic morbidity · Puducherry · Determinants

15.1 Introduction

Globally aging is an inevitable phenomenon. India's aging is comparatively slow than other developing countries. By 2050 there will be nearly 320 million aged people. Young India will be graying in a decade or so because of the projected increase in the life expectancy of males at 71.8 years and females to 75.7 years by 2050. There will be an increase from 23 older people per 100 children in 2001 to 53 older people per 100 children in 2050. And there will also be an increase in older women than older men by 18.4 million. Health determines the quality of life of the elderly enabling them to be functional and participate in activities.

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Generally, people say that "aging is a synonym for ill health" as most elderly persons are likely to suffer from one or the other morbidity conditions. It is natural that as persons become older or age increases, the functions of human organs weaken; in addition to a decrease in their immunity, such conditions would lead to disease. Of course, such diseases may last long for a few days (like in the case of acute morbidity) if they take curative medicine on time and if their organs in the body respond promptly to those medicines. However, some diseases will be difficult to cure completely, and these diseases are likely to end up with partial/absolute disability (chronic morbidity). Another principal dimension of ill health among the elderly is psychological. Such adverse psychological conditions would likely take place mainly because being aged persons, the majority of them are likely to live alone and are considered a burden by their family members, in addition to the lack of physical and emotional care, and also most of them (especially elderly widows) primarily lack economic autonomy. All these situations would lead to loneliness, depression, and psychological distress. In addition to these, elderly persons would lose their headship status and decision-making capacity, besides respect at the family level. All these further deteriorate both their physical and psychological health.

15.2 Theoretical Consideration and Earlier Research

This research attempts to collect information from the respondents (elderly widows) about their physical and psychological health conditions with the above discussion. Based on this data, this chapter helps to understand to what extent they are suffering from acute and chronic morbidity conditions and also to know the magnitude of psychological stress and their state of subjective well-being (patterns). Further, the differentials in all these dimensions are examined across their selected background characteristics and attempted to determine the principal determinants of these four outcomes.

15.3 Materials and Methods

This paper is based on a community-based cross-sectional survey. Originally, the required sample size was estimated as 315 based on Daniel (1999) formula, sample size (n) = $Z2$ (1-P)P/$d2$ keeping the proportion of elderly widows (i.e., 60 years and above) as 0.051 (5.1%) and precision (d) as 0.5 × P (i.e., 0.255) with a confidence level (Z) as 95%. Adding 10% of the non-response rate and the design effect of 1.25, the sample size was increased to 390. These elderly widows (60+ years) were selected by giving due representation to rural and urban areas of Puducherry district, Puducherry Union Territory. To this end, at the first stage, 30 clusters were formed—20 rural primary sampling units (PSUs) (villages/parts of villages) and 10

PSUs from urban areas (wards/parts of streets)—and selected the same using a simple random sampling technique. At the next stage, from these 30 PSUs adopting the systematic sampling technique, the required sample size of 390 was selected by allocating a sample of 13 widows to each PSU (20 × 13 = 260 from rural areas and 10 × 13 = 130 from urban areas). However, while selecting the sample widows, the following inclusion criteria were used: (1) all those widows who completed 60 years of age, (2) those who gave informed consent, and (3) widows who are ill/bedridden at home with proxies. The exclusion criteria followed included (1) elderly widows who are in old age homes; (2) who are physically and mentally ill and, thereby, not able to speak; (3) who are absent (for a longer time) at their residence during the period of data collection in the respective clusters; and (4) those elderly who refused/not interested to participate. From the sample respondents, the required information was collected from January to May 2019 making use of a structured schedule assisted by a personal interview method.

Dependent Variable For the present paper, response on physical health is measured based on the respondents who have been asked to provide information about selected acute morbidity conditions from which they suffered **30** days before the survey date—analyzing this information in detail in this section of their patterns, differentials, and deter**minants.**

Information about several chronic morbidity conditions from which the elderly were suffering for more than 30 days was collected, and an analysis of such data has been carried out looking into their patterns, differentials across their socioeconomic characteristics, and the factors that influence the same.

Independent Variables Independent (Explanatory) Variables: About **13** selected background characteristics of the elderly widows have been taken into account as the independent variables, which are categorized in nature (**2–4** categories) and mostly self-explanatory (Table **15.2**), except **3** of the following, viz., the standard of living index, exposure to mass media (index), and self-reported health status. The standard of living index (SLI) of households is a good indicator to measure the economic status of the elderly widows indirectly. In the present study, the SLI of households has been computed based on (weighted) scores provided to the housing structure-related aspects and household amenities and possession of household goods. The analysis of data is carried out on the following lines. At first, the background characteristics of the elderly widows and "whether the elderly widows are suffering from psychological distress or not have been analysed through frequency tables. Then, the differentials in 'whether respondents suffering from psychological distress or not" are looked into across their background characteristics under consideration with the help of cross-tabular analysis and Chi-square test of significance. In the last stage, adopting the binary logistic regression analysis, the researcher examined to find out the principal factors that are likely to determine/influence the elderly widows suffering from psychological distress. All these analyses have been carried out with the assistance of IBM SPSS software (versio**n 20.0).**

15.3.1 Patterns in Acute Morbidity

Table 15.1 reveals that 14% of the sample elderly widows reported suffering from cold and cough, and another one-tenth of them (10%). On the other hand, few of the elderly stated to be suffering from leg problems (7.4%) and arthritis (5.6) followed by gastric problems (3.6%), headache (3.6%), and asthma/wheezing (2.8%), which are somewhat common among elderly (Fig. 15.1).

Table 15.1 Acute morbidities from which the elderly widows are suffering

Acute morbidities	Percentage	Frequency
Cough and cold	14.1	55
Fever	10.3	40
Leg problems	7.4	29
Arthritis	5.6	22
Gastric problems	3.6	14
Headache	3.6	14
Asthma/wheezing	2.8	11
Diabetes	1.3	5
Blood pressure	1.3	5
Malaria	1.0	4
Diarrhea	0.8	3
Suffering from any acute morbidity		
No Yes	66.4 33.6	259 131
Total	100.0	390

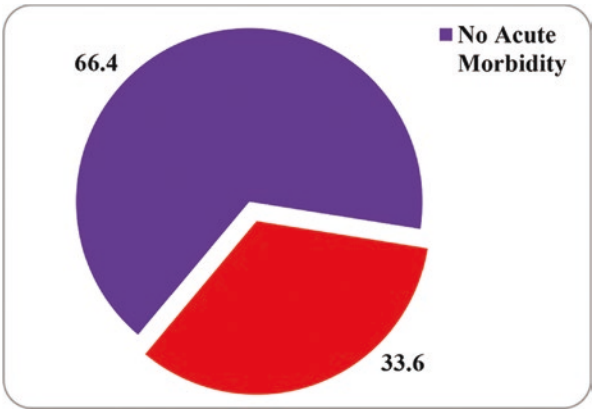

Fig. 15.1 Prevalence of acute morbidity among elderly widows

15.4 Background Characteristics of the Elderly Widows

Table 15.2 (columns 2–3) reveals that two-thirds of the elderly widows are residing in urban areas (66.7%). About two-fifths (41%) and one-third (32%) are in the age groups of 66–75 and 60–65 years, respectively. A sizeable percentage of the elderly widows (60%) are illiterates and one-fifth studied up to primary school (22%). One-third of the elderly widows (36%) belong to families that have low monthly income (₹3000 and less), whereas one-third (33.3%) belong to a fairly higher-income bracket (₹9001 and above). On the other hand, a little less than two-fifths {38%)

Table 15.2 Factors influencing elderly widows suffering from any acute morbidity (*results based on multivariate logistic regression analysis*) (*with* living arrangements)

Explanatory variables	β-Coefficient	Odds ratio	p-Level	95% CI for Exp(B) Lower/upper
Place of residence *(ref: rural)* Urban	–0.102	0.903	0.738	0.495–1.645
Current age *(ref: 60–65 years)* 66–75 76+	0.078 0.382	1.082 1.456	0.816 0.383	0.559–2.090 0.621–3.458
Educational level *(ref: illiterate)* Up to primary school Middle school and above	–0.446 –0.765	0.640 0.453	0.173 **0.05**	0.337–1.216 0.212–1.010
Monthly personal income (*ref: ≤ ₹2000)* 2001+	0.629	1.875	**0.05**	1.013–3.469
Monthly family income (*ref: ≤ ₹3000)* 3001–6000 6001+	–0.670 –1.609	0.512 0.182	0.120 **0.001**	0.220–1.191 0.075–0.440
Caste (*ref: scheduled castes/tribes)* Most backward castes Backward castes Forward castes	0.236 –1.609 –0.803	1.267 0.200 0.448	0.485 **0.001** 0.10	0.652–2.460 0.079–0.508 0.183–1.097
Economic dependency *(ref: not dependent)* Partially/fully dependent	0.734	2.082	**0.01**	1.190–3.643
Have debt *(ref: no)* Yes	0.483	1.620	0.190	0.787–3.334
Living arrangements (*ref: co-residence*) Living alone	–0.364	0.695	0.385	0.306–1.581
Physical disability status *(ref: no disability)* Have disability	0.519	1.680	0.10	0.949–2.971
Have any habits *(ref: no)* Yes	0.146	1.157	0.618	0.652–2.054
–2 log likelihood Chi-square; df; sig.; N Cox and Snell R square (in %) Nagelkerke R square (in %)	399.508 98.348; 16; 0.001; 390 22.3 30.9			

Elderly widows in the age group of above 76 suffered from more acute morbidities followed by those in the age group of 66–75. Elderly widows with middle school education suffered from more acute morbidity. Acute morbidity was less in elderly widows who had an income above 6000

belong to households with a middle-level standard of living (index), and one-third of them belong to a comparatively low standard of living (index). More than two-fifths of the elderly widows belong to the most backward castes (MBCs), while one-fifth (21%) belong to the backward castes (BCs), and about 17 and 18% belong to forwarding castes (FCs) and scheduled castes/tribes (highest and lowest standing in social strata), respectively. More than two-fifths of the elderly widows (44%) have ownership of a house, 58% are economically (partially/fully) dependent, and a greater percentage (79.5%) have a BPL ration card. Two-fifths of the elderly widows (41%) are having exposure to mass media to a moderate extent followed by a higher extent (36%). A large percentage of the elderly widows (66%) are suffering from one or the other physical disability, whereas 53% and 30%, respectively, are suffering from any one and two or more chronic morbidities. On the other hand, around 37% of each of them reported being "fair" and "good" in their health status, and the rest 26% reported their health status as "poor."

15.5 Factors Influencing Elderly Widows Suffering from Any Acute Morbidity

One of the study's specific objectives is to identify the principal factor that affects the magnitude of those suffering from any acute morbidity among elderly widows. To this end, this study attempts to use multivariate logistic regression analysis. For this, the dependent variable was measured as "those suffering from any acute morbidity" (coded as "1") and "not" (coded as "0"). However, two logit models have one without the inclusion of living arrangements and another with living arrangements. The latter model is essential as the present research work's chief aim is to understand the interrelationships between living arrangements, morbidities, and care-seeking behavior. Therefore, all those variables having theoretical importance and statistical significance (at least up to 10% level), except in living arrangements, with the dependent variable, have been included in the model. The following two variables, the standard of living index of households and exposure to mass media index, are not included in the model as they are highly correlated with other explanatory variables considered for the analysis. Results are based on the binary logistic regression analysis in Table 15.2.

Overall, results presented in Table 15.2 reveal that of the 11 variables included in the model, 6 variables and their categories have exhibited significant (at different levels of significance) net effects in influencing the extent of acute morbidity from which the elderly widows have suffered. Among all the variables, economic status-related factors appeared to be the most prominent ones affecting acute morbidity among the elderly, however in different directions. As expected, the probability of suffering from acute morbidity is strikingly lower in the elderly with reasonably higher monthly family income bracket, viz., ₹6001 and above (OR = 0.182; 95% CI, 0.075–0.440; $p < 0.001$), than in lower monthly family income bracket (₹3000 and less). Likewise, it is also pertinent to note that the likelihood of elderly widows who

suffered from any acute morbidity is lower among those who belonged to backward castes (OR = 0.200; 95% CI, 0.079–0.508; $p < 0.001$) and also to some extent among those in the forward castes (OR = 0.448; 95% CI, 0.183–1.097; $p < 0.10$). This finding supports the fact that elderly widows in higher social class (strata; BCs and FCs) have a lesser chance of suffering from any acute morbidity than their SC/ST counterparts (poor/lower in socioeconomic strata). It is pertinent that the odds of suffering from any acute morbidity are 2.1 times higher and also apparent among economically dependent on others (OR = 2.082; 95% CI, 1.190–3.643; $p < 0.01$). This finding specifies that those elderly widows who are either partially or fully dependent on others for financial-related matters have a higher tendency to suffer from acute morbidity than their counterparts. On the other hand, contrary to the expectation, elderly widows whose personal monthly income (through social pension) is comparatively higher have shown a higher tendency to suffer from acute morbidity than those whose personal income is less (OR = 1.875; 95% CI, 1.013–3.469; $p < 0.05$). One of the principal reasons for such a pattern is that these elderly widows are higher in age by which they use to get a higher amount of old-age pension.

Among the other variables under investigation, educational status has exhibited the expected net negative effect on acute morbidity. The result shows that the odds of elderly widows suffering from acute morbidity are strikingly lower among those who have completed middle school and above level of education (OR = 0.453; 95% CI, 0.212–1.010; $p < 0.05$) than their illiterate counterparts. Likewise, the odds of suffering from any acute morbidity are relatively higher by 1.7 times among those who have difficulty from one or the other physical disability than their matching ones, but the statistical significance in this regard is very weak (OR = 1.680; 95% CI, 0.949–2.971; $p < 0.10$).

15.6 Chronic Morbidity

The elderly suffer from one of the other chronic morbidities, and in fact, some of them are likely to suffer from multi-morbid conditions. Therefore, in this study, attempts are made to collect information about several chronic morbidity conditions from which the elderly were suffering for more than 30 days.

15.7 Patterns in Chronic Morbidity

Information provided in panel 1 Table 6.4 suggests that more than one-third of the sample elderly widows suffered from poor vision/cataract conditions (36%) followed by arthritis (31.5%), (high) blood pressure (30%), and diabetes (29%). As stated earlier, all these are mostly related to the lifestyles followed during adulthood. Next to these, back pain/slipped disk is the major chronic morbidity condition

(12%) followed by an ulcer or gastric problem and kidney trouble (8% each), osteoporosis (5%), lung problem/asthma (4.6%), and heart disease (4%). Other chronic morbidities under study exist among the sample elderly, between 0.3% (one person) and 1.8% (seven persons).

In Table 15.3 it is evident that slightly more than one-quarter of the elderly widows (27%) are believed to be suffering from two chronic morbidities under study, followed by any one chronic morbidity (26%). While a little over one-sixth and one-tenth of them, respectively, are suffering from three (17%) and four (11%) chronic morbidities, just about 2% of them are suffering from five or more chronic morbidities. Overall, a higher percentage of the sample elderly widows (83%) suffer from one or more chronic morbidities. On the other hand, about one-sixth (17%) of the elderly widows are not suffering from any morbidities enquired in this study (Fig. 15.2).

Table 15.3 Distribution of elderly widows by chronic morbidities from which they are suffering *(N = 390)*

Chronic morbidities	Percentage	Frequency
Poor vision/cataract	35.9	140
Arthritis	31.5	129
Blood pressure	30.3	118
Diabetes	28.7	112
Back pain/slipped disk	12.3	48
Ulcer or gastric problem	8.2	32
Kidney trouble	8.2	32
Osteoporosis	4.9	19
Lung problem/asthma	4.6	18
Heart disease	4.1	16
Renal disease	0.5	2
Skin diseases	1.8	7
Dental problems	1.8	7
Chronic lung disease	1.3	5
Cancer	1.3	5
Tuberculosis	0.3	1
No. of chronic morbidities among the elderly widows		
0	16.7	65
1	25.9	101
2	27.4	117
3	16.9	66
4	11.4	44
5	1.8	7
Total	100.0	390

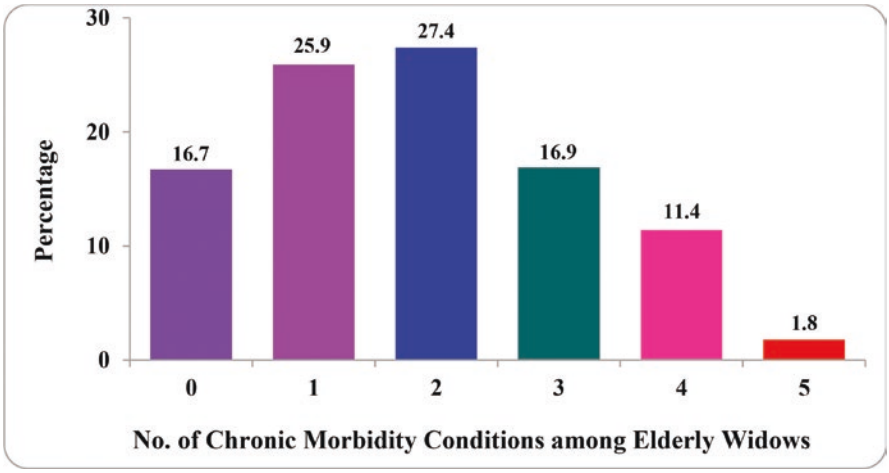

Fig. 15.2 Distribution of elderly widows who are suffering from chronic morbidity conditions

In Table 15.4, one can notice that the average number of chronic morbidities the elderly widows are suffering is a little bit higher among those in the category of higher standard of living (index) households (2.07) as compared to those in the categories of lower and moderate standard of living (index) households (1.73 and 1.81, respectively). However, the one-way ANOVA test results turned out as significant to a lesser extent ($p < 0.10$). Result related to the mean number of chronic morbidities across their living arrangements (panel 7 of Table 6.5) highlights that elderly widows living alone appear to be suffering from a fairly higher mean number of chronic diseases than those who are co-residing with children/others (2.03 vs. 1.75). The t-test result related to this finding has emerged as moderately significant ($p < 0.05$).

Table 15.4 suggests that the mean number of chronic morbidities from which the elderly widows were suffering was observed as higher among those who have exposure to mass media to a higher extent (2.09) as well as to a lower extent (1.92). In contrast, the similar figure is much lower (1.61) among those who have such exposure to a moderate extent. Nevertheless, the one-way ANOVA test results in this regard have emerged as highly significant ($p < 0.01$). Furthermore, as expected, from panels 9 and 11 of Table 6.5, it is clear that the mean number of chronic morbidities from which the elderly suffer is significantly higher among those who suffer from one or more physical disabilities as well as who have savings than their counterparts (2.10 and 2.41 vs. 1.39 and 1.77, respectively; $p < 0.001$ in each case). On the other hand, the mean number is moderately lower among those elderly widows who are economically dependent on others than those who are economically independent (panel 10; 1.75 vs. 2.01; $p < 0.05$).

Table 15.4 Mean no. of chronic morbidity conditions among elderly widows suffering across their background characteristics

Background characteristics of the elderly widows	Chronic morbidities		Total	t/F-value; sig. level
	Mean	S.D.		
1. Place of residence	1.33	1.19	130	6.023
Rural	2.12	1.28	260	**0.001**
Urban				
2. Current age (in years)	1.60	1.19	126	5.965
60–65	2.11	1.29	159	**0.01**
66–75	1.78	1.38	105	
76+				
3. Educational level	1.78	1.29	234	6.605
Illiterates	1.66	1.23	85	**0.001**
Up to primary school	2.34	1.32	71	
Middle school and above				
4. Monthly family income	1.91	1.16	141	3.547
3000 and less	1.61	1.27	119	**0.05**
3001–6000	2.03	1.44	130	
6001 and above				
5. Caste	1.53	1.22	68	8.820
Scheduled castes/tribes	1.66	1.29	172	**0.001**
Most backward castes	2.04	1.21	81	
Backward castes	2.46	1.29	69	
Forward castes				
6. Standard of living index	1.73	1.23	131	2.342
Low	1.81	1.22	149	0.10
Middle	2.07	1.47	110	
High				
7. Living arrangements	1.75	1.36	242	2.116
Co-residence with others	2.03	1.18	148	**0.05**
Living alone				
8. Exposure to mass media	1.92	1.22	92	5.406
Lower	1.61	1.34	159	**0.01**
Moderate	2.09	1.27	139	
Higher				
9. Physical disability	1.39	1.03	134	5.323
No	2.10	1.35	256	**0.001**
Yes				
10. Economic dependency	2.01	1.18	164	1.963
Not dependent	1.75	1.37	226	**0.05**
Partially/fully dependent				
11. Have savings	1.77	1.26	336	3.399
No	2.41	1.45	54	**0.001**
Yes				
Total	1.86	1.30	390	

Note: t-test of significance is computed for those variables which have two categories
F-test of significance is computed for those variables which have three to four categories
Elderly widows in the age group of above 76 suffered from more acute morbidities followed by those in the age group of 66–75. Elderly widows with middle school education suffered from more acute morbidity. Acute morbidity was less in elderly widows who had an income above 6000

15.8 Factors Influencing the Chronic Morbidity Conditions Among Elderly Widows

One of the key objectives of this research work is to find out the different factors that influence (or determinants of) the extent of elderly widows suffering from chronic morbidity conditions. Fulfilling this objective, multiple linear regression analysis is carried out as the dependent variable is the number of chronic morbidity conditions from which the elderly widows are suffering, which is discrete (ranges between "0" and "5"). All those variables which have theoretical importance and found to be having statistical significance (at least up to 10 percent level) with the dependent variable are included in the model, except the following two variables, *standard of living index of households* and *exposure to mass media index*, as they are highly correlated with other explanatory variables. For using multiple linear regression, the structure of explanatory (independent) variables is considered as given below.

Results are based on the multiple linear regression analysis presented in Table 15.5. On the whole, eight variables included in the regression model together have explained a 17.4% variation in the number of chronic morbidities from which the elderly widows are suffering at the time of the survey. As expected, among all the variables, those suffering from one of the other physical disabilities have shown a higher tendency to suffer from chronic morbidities to a greater extent than their counterparts ($\beta = 0.211$; $p < 0.001$). Next to this, the urban residence appears to be triggering the elderly widows to suffer from more chronic morbidities than those residing in rural areas ($\beta = 0.150$; $p < 0.01$). Following these, both caste background and years of schooling have exhibited positive net effects on the number of chronic morbidities. These results indicate that the chances of elderly widows suffering from more chronic morbidities are likely to be increasing with an increase in their caste (social strata) background ($\beta = 0.139$; $p < 0.01$) as well as with their educational level—years of schooling ($\beta = 0.137$; $p < 0.01$). Monthly family income has exhibited a net positive influence on the number of chronic morbidities, i.e., the extent of

Table 15.5 Factors influencing the number of chronic morbidities from which elderly widows are suffering (*results based on multiple linear regression analysis*)

Explanatory variables	β-Coefficient	t-value	p-Level
Constant	–	1.526	0.126
Place of residence (*urban)*	0.150	2.785	**0.01**
Current age (*in years*)	–0.033	–0.636	0.924
Educational level (*years of schooling*)	0.137	2.548	**0.01**
Monthly family income (*in* ₹)	0.105	2.167	**0.05**
Caste (*four categories*)	0.139	2.564	**0.01**
Living arrangements (*living alone*)	0.084	1.661	0.10
Economic dependency (*dependent*)	0.002	0.040	0.968
Physical disability status (*yes*)	0.211	4.149	**0.001**
R-Square (in %)	17.4		
N	390		

Elderly widows in the age group of above 76 suffered from more acute morbidities followed by those in the age group of 66–75. Elderly widows with middle school education suffered from more acute morbidity. Acute morbidity was less in elderly widows who had an income above 6000

suffering from more number of chronic morbidities among the elderly widows has shown a tendency to increase with an increase in their household/family monthly income (in) and statistically also significant at a moderate extent ($\beta = 0.105$; $p < 0.05$). Another pertinent finding here is that controlling for all the variables included in the model, elderly widows who are living alone have more susceptibility to suffering from more chronic morbidities than those who are co-residing with children/others, but statistically significant to a lesser extent only ($\beta = 0.084$; $p < 0.10$).

Of the remaining two variables, as expected, economic dependency's role is positive on the number of chronic morbidities from which the elderly widows are suffering; contrary to the expectation, current age has exhibited a negative net effect on chronic morbidities. However, statistically both these net effects are insignificant.

The point of interest in this research work is the role of living arrangements on acute morbidity. By and large, as expected, elderly widows who are living alone have shown a lesser likelihood of ever suffering from any acute morbidity than those who are living with children/others. Likewise, the sample elderly living in urban areas also displayed lower odds of ever suffering from acute morbidity than their rural counterparts. However, the Wald test findings are not significant. Conversely, the odds of ever suffering from any acute morbidity are higher among those elderly widows in higher age groups, viz., 66–75 and 76+ years, who have some form of debt and are habituated to adverse habits (that affect health) as against their respective counterparts. However, the Wald statistics related to these results were not significant even at the 10% level.

Overall, one-third of the respondents are suffering from any one or more acute morbidities. Bivariate analysis results showed that the percentage of elderly widows suffering from any acute morbidity is significantly higher in 76+ years old, having higher social pension income, economically dependent, debt, habituated to betel nut/tobacco, and presence of any physical disability than their respective counterparts. On the other hand, a similar percentage of suffering from any acute morbidity is noted as significantly (at different levels) lower among the urban residents, educated (primary/middle school+), belonged to moderate/higher family income and SIL of households, belonged to relatively higher social status communities (backward and forward castes), and have higher exposure to mass media than their respective counterparts. Furthermore, multivariate logistic regression analysis reiterated that the odds of elderly widows suffering from any acute morbidity are significantly lower in families of higher monthly income brackets, backward castes (to some extent forward castes also), and studied middle school and above than their corresponding others. In contrast, similar odds are modestly higher among the elderly widows who perceived themselves as economically independent, getting fairly higher social pension, and to a small extent among those with one or more physical disabilities than their respective counterparts.

Findings from some studies are analogous about the positive influence of current age, presence of disabilities, and economically dependent on acute/any morbidity/ailment, whereas a negative role in the case of the following: level of education,

urban residence, and household income/SLI/wealth quintiles (Ranjan and Muraleedharan 2020; Agrawal and Patel 2017; Afshar et al. 2015; Agrawal and Keshri 2014; Arokiasamy et al. 2015; Singh 2015; Wandera et al. 2015; Audinarayana 2005, 2017; Mini 2009; Rahman et al. 2007; Woo et al. 2007; Khan et al. 2005; Kumar et al. 2005; Zimmer and Kwong 2004). However, in a few studies from India, the prevalence of acute or any morbidity among the elderly is noted as higher among those who belonged to higher household income quintiles/higher SES and SC/ST/BC communities (Kaur et al. 2019; Agrawal and Patel 2017; Agrawal and Arokiasamy 2010).

The preceding analysis and interpretation bring out the following findings. As high as 83 percent of the sample elderly widows reported to be suffering from one or more chronic morbidities at the time of the survey, and on average, it comes out as 1.86 ± 1.30. Bivariate analysis results revealed that the mean number of chronic morbidities from which the elderly suffer is significantly (at different levels) higher among the urban residents, 66–75 age group, studied middle school and above, households of higher (family) income and SLI, belonged to backward and forward castes, living alone, having one or more physical disabilities, and have some savings than their respective counterparts. Conversely, a similar meaning is lower among those who are said to be economically dependent than independent. Further, most of these findings are also found to be intact in the case of multiple linear regression analysis. For example, the probability of suffering from one or more chronic morbidities has shown an increasing tendency with an increase in the sample widows' educational level ($p < 0.01$), social status (caste; $p < 0.01$), and monthly family income ($p < 0.05$). Equally, the tendency of suffering was observed to be higher among those who are experiencing one or more physical disabilities ($p < 0.001$), residing in urban areas ($p < 0.01$), and to a small extent living alone ($p < 0.10$). Overall, it appears that elderly widows from higher socio-economic status categories appeared to be suffering from more chronic morbidities. Few studies from India on any acute/chronic morbidity among the elderly have exhibited, more or less, a similar type of findings, especially in the case of urban areas, higher family income brackets, social status (caste), and also, to some extent, educated (Ranjan and Muraleedharan 2020; Kumar et al. 2017; Audinarayana 2005, 2017, 2018; Himanshu and Talukdar 2017; Agrawal and Keshri 2014; Agrawal and Arokiasamy 2010).

On the other hand, few studies from abroad and India have conclusively supported that the magnitude of chronic morbidity is higher among elderly in advanced age, economically dependent, living alone, and having a disability, whereas a similar magnitude is lower among those who belonged to lower SES categories (Ranjan and Muraleedharan 2020; Audinarayana 2017, Sudarshan and Chethan 2016; Ha et al. 2015; Nunes et al. 2015; Phaswana-Mafuya et al. 2013; Khanam et al. 2011; Marengoni et al. 2008; Jatrana and Chan 2007; Wandera et al. 2015; Banjare and Pradhan 2014; Audinarayana 2005, 2017; Mini 2009; Medhi et al. 2006; Kumar et al. 2005; Joshi et al. 2003).

15.9 Conclusion, Discussion, and Implication

This research measures physical morbidity in terms of acute morbidity (reference period is <30 days) and chronic morbidity (reference period is 30 days and above) conditions from which the elderly widows are suffering before the survey period. This research highlights that one-third of the sample of elderly widows (34%) stated to be suffering from one of the other acute morbidity conditions, which are cough and cold (14%) and fever (10%) higher followed by leg problems (7%) and arthritis (6%). While assessing the factors affecting (multivariate logistic regression), the following results have emerged. Similarly, elderly widows suffering from acute morbidity conditions are noted as high among families having a higher monthly income (₹6001 and above), backward and forward castes, and have education up to middle school and beyond than their counterparts. Conversely, the odds of suffering from acute morbidity conditions are higher among those perceived as economically (fully/partially) dependent, getting modest higher personal monthly income through a social pension (₹2001 and above), and experiencing one or more physical disabilities. Besides these, bivariate analysis results showed that the percentage suffering from one or more acute morbidity conditions is relatively lower among those residing in urban areas, belonging to households of high SLI, and having higher mass media exposure. In opposition to this pattern, the corresponding percentage is higher among those having some debt and afflicted with adverse personal habits, whereas a similar did not vary across their living arrangements. The majority of these findings agree with those observed in studies carried out in different settings of the world and India.

An analysis of chronic morbidity conditions and their associated factors suggests that 83 percent of the elderly widows are suffering from chronic morbidities, of which the following ones are stated as major ones: poor vision/cataract (36%), arthritis (31.5%), blood pressure (30%), and diabetes (29%). In addition, elderly widows suffering from multiple morbidities appeared high (27%, 17%, and 13%, respectively, two, three, and four chronic morbidity conditions). On average, the sample of elderly widows is suffering from 2.08 ± 1.22 chronic morbidities. *Multiple linear regression analysis results* highlighted that the likelihood of elderly widows suffering from chronic morbidities is noted as increasing with an increase in their years of schooling (educational status), monthly family income, and caste hierarchy (social strata). Similarly, those conditions are high among those suffering from one or more physical disabilities, dwelling in urban areas, and to some extent living alone. The cross-tabular analysis also found that the mean no. of chronic morbidities from which the elderly widows are suffering is high among the age group of 66–75 years, those dwelling in households of high SLI, those having higher exposure to mass media, and also those having some savings; the comparable mean is lower among economically (partially/fully) dependent. Similar findings were seen in several studies conducted in different settings of the world and India.

These findings indicate that the elderly suffering from acute morbidities has to be provided with curative services at their doorsteps by mobile clinics to the selected

areas at least weekly once from the nearby hospitals/clinics and NGOs to cure their ailments at the earliest. Likewise, geriatric wards have to be established in the government hospitals/PHCs, so that those suffering from chronic morbidities and physical disabilities (especially those living alone) could benefit from utilizing the healthcare services free of cost.

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Chapter 16
Energy Restriction on Cellular and Molecular Mechanisms in Aging

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Abstract Energy restriction (ER) or calorie restriction (CR) refers to adequate intake of essential nutrients while being accompanied by energy restriction. Aging is known to be a risk factor for neurodegeneration, vascular disease and heart failure, and increased general inflammation that leads to type 2 diabetes by aging mechanisms. Energy restriction has been proven to prevent age-related chronic diseases, cancers, and increase average and maximum lifespan, and protect against neurodegenerative diseases, diabetes, hypertension, and vascular disease.

The effects of CR on lifespan may be caused by various mechanisms, including changes and enhancements in metabolism energy, oxidative stress, insulin sensitivity, and structural changes in the sympathetic and neuroendocrine systems.CR with mechanisms such as apoptosis reduces damage to stem cells and protects them, maintains balance and tissue size and homeostasis, and prevents the occurrence of diseases related to aging.

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Energy restriction is beneficial to promote mitochondrial turnover by increasing the biogenesis of new mitochondria and the destruction of damaged mitochondria that generate superoxide radicals. Mitochondrial biogenesis reduces the production of ROS (reactive oxygen species), and in addition to preventing the loss of mitochondrial function in muscles, protecting fat tissue and affecting the energy metabolism of lipids on carbohydrates, glucose production, and glycolysis.

We also elucidated the characteristics of the senescence-associated secretory phenotype (SASP) by which senescent cells provoke self-immune antagonism. The SASP response expresses instructions at the transcriptional level. Post-translational modifications activate a number of SASP genes, especially interleukins.

Agingomics studies RNAs groups together that affect transcription and transcription can classify aging. Age-related gene expression is used to classify aging biomarkers.

Cellular fitness evolves as a final result of entropy through chromosome organization, transcriptional regulation, and nuclear export/import in the nucleus to protein translation, autophagy recycling of organelles, cytoskeleton suspension, and subsequently extracellular matrix suspension and extracellular signaling.

In addition, we mentioned the studies on the antioxidant and anti-aging properties of some plants, which were confirmed by Professor Marotta and his colleagues, and the effect of functional foods by Professor Barbagallo et al and the Mediterranean diet in the use of foods with oily polyphenols, as well as ketone therapy, by some other scientists and we described their effect on the cell with the molecular mechanisms of pathways such as NADH and P450 cytochrome enzymes.

Keywords ER (energy restriction) · CR (calorie restriction) · Ageing · Oxidative stress · SASP (senescence-associated secretory phenotype) · Agingomics · Functional foods · P450 cytochrome

16.1 Energy Restriction: Definition and Characteristics

ER, or energy restriction, also known as caloric restriction, is the only nutritional intervention that maintains adequate intakes of essential nutrients, while restricting energy intake by up to 50% (severe ER). The effectiveness of ER has been proven in yeast, worms, fish, rats, mice, and humans without chronic disease to prevent chronic age-associated diseases/disorders and to increase their median and maximal lifespan. CR's effects on lifespan may be mediated by a variety of mechanisms, including changes in energy metabolism, oxidative damage, insulin sensitivity, and structural alterations in the sympathetic and neuroendocrine systems. DNA, lipids, and proteins are all damaged by reactive oxygen species (ROS) produced in mitochondria, which accelerates biological aging. Research has also centered on CR's ability to protect against age-related changes in endocrine and physiological factors/genes, including leptin concentrations, plasma insulin levels, DHEAS levels, and thyroid hormone levels. To decrease the risk of such diet-related diseases, food and

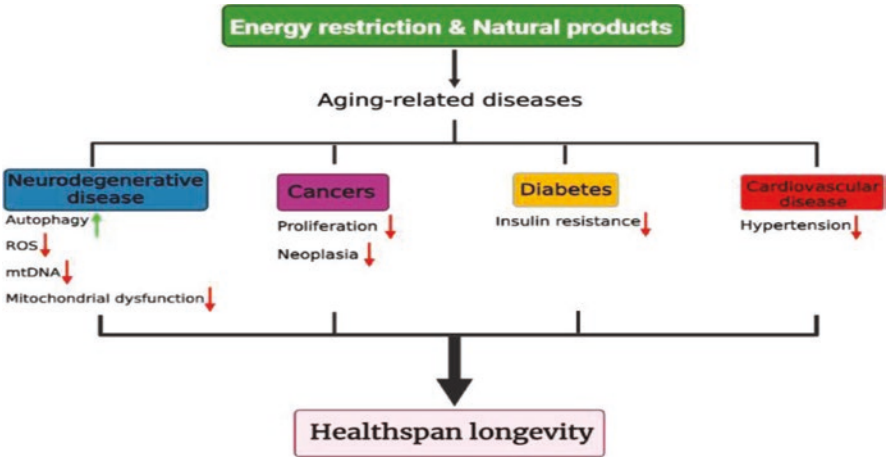

Fig. 16.1 The role of energy restriction and natural products in aging-related diseases such as neurodegenerative disease, cancers, diabetes, and cardiovascular disease, which lead to healthspan longevity. Energy restriction condition or natural product usage,improve aging-related diseases via modulation of several hyper/hypo-activated factors/pathways

health agencies like the USDA (United States Department of Health and Human Services and United States Department of Agriculture) recommend eating foods high in vitamins and minerals, but low in energy density (up to moderate) (Kunduraci and Ozbek 2020; Cantero et al. 2017; Nikolai et al. 2015; Mitchell et al. 2015; Most et al. 2017; Kord et al. 2021; Stern et al. 2016; Mattson et al. 2017; Redman et al. 2018; Pearl 1928; Hambly and Speakman 2005; De Cabo and Mattson 2019; Heilbronn et al. 2006; Organization WH, Canada PHAO, Canada CPHAO 2005; Flanagan et al. 2020; Willcox et al. 2006) (Fig. 16.1).

16.1.1 Energy Restriction (ER) and Cancer and Diseases

Caloric restriction (CR) is recognized as the best organic process intervention for extending life and delaying age-related diseases, as well as cancer interference and chronic diseases (Omodei and Fontana 2011). Different sorts of energy restriction, like periodic fast, intermittent fast, or fasting-mimicking diets, with or while not total caloric intake reduction, mimic the chronic CR effects and supply a spread of health advantages, as well as anticancer properties (Castejón et al. 2020). Additional studies in animal models have found that CR exerts a task in suppressing spontaneous neoplasias and/or tumorigenesis in p53-deficient mice; chemically induced breast cancer, cancer of the liver, bladder cancer, prostate cancer, ovarian cancer, and pancreatic cancer; or cancers caused by radiation (Gross and Dreyfuss 1990; Dunn et al. 1997; Fu et al. 2020; Cohen 2018; Hursting et al. 1994; Chen et al. 2012; Lanza-Jacoby et al. 2013; Bonorden et al. 2009).

It has been advised that ER and CR shield nonhuman and human primates against numerous chronic diseases together with neurodegenerative diseases (Xie et al. 2020), diabetes, abdominal avoirdupois, high blood pressure, and vessel diseases (Omodei and Fontana 2011). Caloric restriction (CR) is understood to increase lifetime in most organisms, indicating that nutrient and energy restrictive mechanisms impact aging. The best risk factor for neurodegeneration is age; therefore, the antiaging effects of CR may decrease progressive necrobiosis and avert the aggregation of abnormal proteins related to neurodegenerative unwellnesss like Alzheimer's disease (Ntsapi and Loos 2016), Considerably attenuated psychological feature deficits and amyloid pathology in transgenic mouse models of AD (Alzheimer's disease), presumably by targeting γ-secretase-dependent amyloid precursor macromolecule (APP) metabolism. Psychological feature operation and underlying cellular, molecular, and physiological mechanisms are celebrated to decrease age (Bettio et al. 2017; Padgaonkar et al. 2017).

Intermittent energy restriction (IER) is an alternate technique to attain weight loss, which may be used for the management of type 2 diabetes (T2D) (Carter et al. 2016). Energy restriction not solely may be helpful for hindrance of T2D (Barnosky et al. 2014); however it can also be helpful for T2D treatment. The worldwide raise in lifetime can cause a dramatic increase in age-related diseases within the coming back decades. During this context, vessel diseases together with coronary artery disease and heart failure (HF) increase exponentially with age. Moreover, type 2 diabetes mellitus (T2DM) is closely connected to aging and may be a major risk factor for age-associated diseases like coronary artery disease and HF (Beckman et al. 2002). The aging method itself and the way it interacts with diseases are incompletely understood. Aging has been related to a change in metabolic pathways. As an example, insulin resistance and changes in body composition are the most important age-related mechanisms leading to diabetes (Morley 2008). Additionally, aging has been related to general inflammation (Franceschi and Campisi 2014), which may be a cause moreover as a consequence of diabetes.

It is well incontestable that in response to an amount of restricted provision of energy and nutrients (energy restriction), an adaptational decrease in whole-body energy expenditure happens, and this can be part owing to a rise in metabolic potency (Ramsey et al. 2000). This adaptation permits the organism to spare energy and slows the speed of depletion of fat stores (Barzilai and Gabriely 2001).

16.1.2 Energy Restriction, Reproduction, and Tissues

It has long been proverbial that obesity, particularly central obesity, will adversely have an effect on fertility in each man and woman (Hunter et al. 2021; Bond et al. 2020). Fat aggravates a predisposition to polycystic ovary syndrome (PCOS) that may be a major reason behind ovulatory sterility (Nehir Aytan et al. 2016; Gambineri et al. 2002; Martinez-Bermejo et al. 2007). PCOS is characterized by hyperandrogenism and oligo, additionally to having polycystic ovaries. In men,

overweight or fat decreases the amount and quality of sperm and will increase the chance of dysfunction (Kratzik et al. 2005; Lim et al. 2007). CR has been shown to scale back oxidative stress, improve hormone sensitivity, and alter system responses and central nervous system (CNS) performance in animals. CR has notably profound and complicated actions upon reproductive health. At the theory level, the foremost crucial physiological performance of any organism is its capability to breed. For a roaring species to thrive, the balance between accessible energy (food) and also the energy expenditure needed for reproduction should be tightly coupled. A capability to coordinate energy balance and fecundity involves advanced interactions of hormones from each of the peripheral and also the central nervous system and primarily centers upon anterior pituitary as the master endocrine (Martin et al. 2008).

Food energy is often held on as fat or glycogen which might then be mobilized for procreative functions like time of life maturation and fertility itself. The foremost basic style of reduced energy intake in laboratory experiments is glucose deprivation, as this is often the prime supply of energy for many mammals. It's been incontestible in animal models (mostly rodents, sheep, or primates) that fast or glucose deprivation affects procreative performance by suppressing pulsatile LH release from the pituitary gonadotropes. The glucose energy deficit is so apace detected and is maybe sent to the hypothalamus where GnRH secretion is noncontinuous to attenuate the pulsatile LH release and to ultimately conserve energy in times of low glucose convenience (Martin et al. 2008).

16.1.3 Energy Restriction and Stem Cells

Importantly, the homeostasis of physique tissues in adults depends on the renovation of stem cells. These cells are self-renewing and regenerative and can also differentiate. Also, these cells are of two types: (1) dormant/quiescent stem cells that do not enter the cell cycle until arrival of a powerful stimuli and (2) active stem/progenitor cells that often enter the cell cycle to take care of tissue homeostasis. It's essential to apprehend that as soon as these cells lose their potency, it's an important and essential spark for the onset of aging-related illnesses (Hoggatt and Scadden 2012; Li and Xie 2005; Cheung and Rando 2013). By decreasing damage to stem cells and keeping them, CR will keep tissue equilibrium and prevent the event of growing older-related ailments (Maharajan et al. 2020).

16.1.4 Energy Restriction and Programmed Cell Death

Apoptosis is a necessary element of the cellular regulation of tissue size regulation and homeostasis (Thompson et al. 2004). The incidence of a neoplasm represents a failure of tissue size regulation. ER inhibits mammary carcinogenesis and ends up

in a marked reduction in neoplasm size, effects probably to be explained by ER-mediated induction of programmed cell death (Thompson et al. 2004). Additionally, the role of ER in kidney protection has additionally been elucidated. In diagnosing studies, adjusting total energy intake or consumption of specific nutrients has prophylactic or therapeutic effects on aging-related disease and acute and chronic renal injury. ER will increase Sirt1 expression within the kidneys of aged rats, inhibits renal tubular epithelial cell programmed cell death, and reduces cisplatin-induced AKI (Ning et al. 2013). In animals, ER will scale back the extent of inflammatory cytokines and mitigate inflammation. The NF-κB transcription and pro-inflammatory protein levels increase with age (Csiszar et al. 2014).

16.1.5 Obesity, Energy Restriction, and Aging

Obese people have shown hyperbolic susceptibleness to infections, bacteremia, and poor wound healing after surgery (Lamas et al. 2004). Fat disorders cause changes in fat distribution and performance, with vital effects on cytokines, chemokines, endocrine expression, and therefore the composition of immune cell populations present in adipose tissue (Weber et al. 1986). Obesity has additionally been related to a poor protein response to hepatitis B plasma immunizing agent (Weber et al. 1986) and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) mRNA vaccine (Watanabe et al. 2022). Despite these clear connections, the molecular mechanisms concerned within the altered immunologic response in obesity square measure poorly illustrious. In fact, it's been urged that obesity may be associate in inflammatory condition within which totally different interleukins are also concerned (Das 2001).

It has been shown that energy restriction is often helpful to revive an antecedently impaired immune performance in diet-induced overweight rats. During this context, energy restriction junction rectified to higher CD4+ lymphocyte set, inflated splenocyte proliferation upon stimulation with phytohemagglutinin (PHA) and concanavalin A (Con A), and increased natural killer (NK) cell cytotoxic activity (Csiszar et al. 2014).

16.2 The Effect of Energy Restriction on Metabolism and Its Relationship with Aging

By altering the body's metabolism, ER reduces the risk of age-related diseases associated with reduced body weight (Patterson and Sears 2017). A major source of energy for many tissues, especially the brain when energy is restricted, is ketone bodies, which are produced when fasting plasma glucose, insulin, glycogen stores, and fatty acid mobilization are reduced in initially overweight as well as normal-weight subjects (Nikolai et al. 2015; Lezcano et al. 2014; Gabel et al. 2018).

ADP-ribosyl cyclase (CD38), poly(adenosine diphosphate [ADP]–ribose) polymerase 1 (PARP1), and poly(adenosine diphosphate [ADP]–ribose) polymerase 1

(PdiP2) are a few of the many proteins and molecules affected by ketones but also regulate health and aging (Veech et al. 2017; Ye et al. 2017; Imai and Guarente 2016). The ER induces gluconeogenesis from lipids and amino acids in order to compensate for reduced glucose intake. Under ER, glycolysis is reduced, as shown in rats. As a result of improved glucoregulation, advanced glycation endproducts (AGEs) are produced in various tissues and bind to their receptors (receptors for AGE, RAGEs), thereby causing renal, vascular, or neurological changes associated with aging (Gabel et al. 2018; Imai and Guarente 2016). A limiting energy supply, however, can be interpreted as a mild stressor that activates a stress response in an organism, thereby improving stress resistance. It is consistent with this hypothesis that heat shock proteins and antioxidant enzymes are enhanced under ER (Yu and Chung 2001; Ristow and Zarse 2010).

It is important to know that mitochondria, the cellular energy supplier's source of ROS, are extremely sensitive to oxidative damage. As mitochondria age, leaking electrons and molecular oxygen create superoxide radicals, decreasing mitochondrial ATP efficiency and forming superoxide radicals during oxidation steps of the electron chain. Thus, it seems useful to promote mitochondrial turnover by enhancing biogenesis of new mitochondria and degradation of old and damaged ones (Murphy 2009; Cadenas and Davies 2000; Chocron et al. 2019).

In this line, PPARγ coactivator 1α (PGC1α) is thought to be the key modulator of mitochondrial biogenesis and function via affecting on nuclear respiratory factors 1 and 2, estrogen-related receptors, and mitochondrial transcription factor A (Ye et al. 2017; Dominy and Puigserver 2013).

A state of energy restriction results in declining ATP ranges and an extent in AMP/ATP ratios, which activate the nutrient sensor AMPK. As such, improved stages of phosphorylated AMPK (p-AMPK) indicate inadequate energy supply. SIRT1, PGC1, and some forkhead box O (FOXO) produces in mitochondrial biogenesis and stress protection mechanisms are activated via AMPK phosphorylation. A deacetylation response initiated by using SIRT1 could lead to mitochondrial biogenesis while lowering ROS production. In addition to preventing mitochondrial characteristic loss in muscles, protecting adipose tissue from distributional and practical changes, and affecting energy metabolism, lipids are favored over carbohydrates (Dominy and Puigserver 2013; Hardie 2007; Pimentel et al. 2013; Cantó et al. 2010; Golbidi et al. 2017). In mice, SIRT1-mediated activation of PGC1α had a high-quality effect on glucose production, glucose mobilization, and glycolysis by means of affecting hypoxia-inducible factor1α (HIF-1α) (Houtkooper et al. 2012).

In a study, Marotta et al. indicated that concomitant treatment of human amnion-derived epithelial cell line (FL cells) with *Rhodiola rosea*, an herb which has been used in traditional medicine for several years, and LF, a class of lipoproteins, derived from the fish *Trachurus* sp. (LF-T) increased expression of antiaging genes such as SIRT1, KLOTHO, SERPINA 6, MMP 9, and MMP 2 (Mantello et al. 2017; Marotta et al. 2021). AMPK activation also phosphorylates and inactivates acetyl-CoA carboxylase (ACC). ACC inactivation is accompanied by the suppression of fatty acid synthase and blocking lipogenesis. Recent results also have shown that long-term ER stimulate browning of white adipose tissue (WAT) (Omar et al. 2012). Stimulation of "browning" in WAT by dietary means can influence body weight and the potential

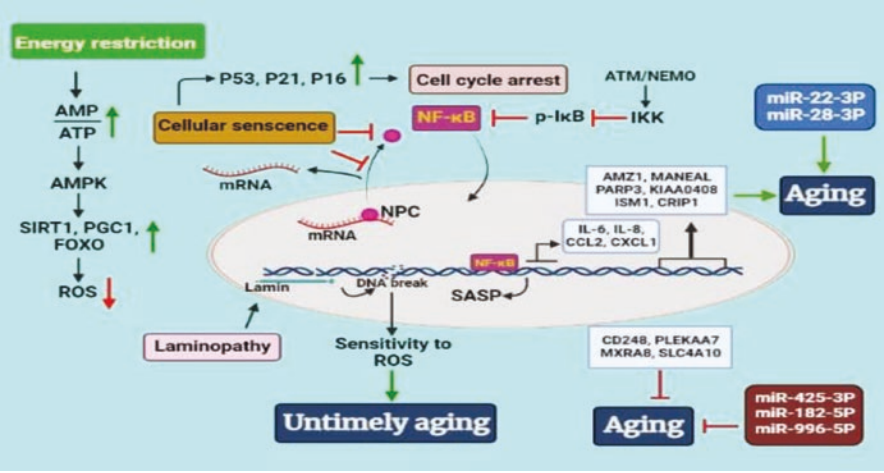

Fig. 16.2 Cellular and molecular mechanisms of aging and energy restriction

success anti-obesity therapies during reduction of cholesterol, LDL, and triglyceride (TAG). In this regard, different food constituents and intermediary metabolites such as lactate, β-hydroxybutyrate, and L-arginine can induce browning of WAT (Houtkooper et al. 2012). In this line, Marotta and colleagues have several successful studies on antioxidant and antiaging properties of a specific fermented papaya preparation (ORI lab, Gifu, Japan) which proved at electron spin resonance to yield remarkably robust properties as compared to other generic fermented papaya extracts and beyond the expected effects of vitamins (A and C) and amino acids (arginine among all) (Marotta et al. 2020; Marotta et al. 2017; Barbagallo et al. 2015) (Fig. 16.2).

Moreover, cytochrome P450 enzymes especially catalyze mixed-function oxidation reactions during interacting with flavoenzymes or iron-sulfur proteins to get hold of electrons from NAD(P)H. So, cytochrome P450 (P450) enzymes have been suggested to be a source of ROS. In a finding by means of Barbagallo et al., it was once shown that functional foods, such as fermented papaya ORI, are antioxidants and have an effect on cells via the NADH and P450 pathways (Barbagallo et al. 2012; Barbagallo et al. 2015).

16.2.1 Association of Energy Restriction with Endocrine Glands, Growth Hormone, Insulin-Like Hormone, and Diabetes

The levels of adiponectin and insulin sensitivity rise upon energy restriction, whereas fasting plasma glucose and insulin are reduced. Therefore, ER is related with a lowered hazard of getting age-related diseases such as T2DM. As insulin secretion decreases, plasma glucocorticoids concentrations commonly rise (Imai

and Guarente 2016; Fontana et al. 2010; Pires et al. 2014). Several species of animals show off lower ranges of anabolic hormones such as leptin, insulin, testosterone, estradiol, and follicle-stimulating hormone upon ER, which is predicted thinking about the reduced increase rates and the slow maturation process. In contrast, plasma concentrations of the catabolic adiponectin and of the steroid hormone-binding protein tend to be improved that is inversely related to body weight, adiposity, and insulin resistance. It is hypothesized that the propensity of adiponectin to shift metabolism from glucose burning to fats burning reduces oxidative stress and promotes toughness (Imai and Guarente 2016; Redman and Ravussin 2009; Cangemi et al. 2010).

On the other hand, human subjects undergoing ER regimens report reduced availability of gonadal steroids like testosterone and estradiol due to higher levels of steroid hormone-binding proteins (Gagnon et al. 2018).

When fed ER, triiodothyronine (T3) declined consistently in rodents, primates, and humans, similar to leptin, insulin, and testosterone. Since T3 and body temperature are positively correlated, the reduced T3 levels of ER-fed subjects seem to fit well with the reduced body temperatures of these subjects (Imai and Guarente 2016; Silva et al. 2021; Tonelu et al. 2021).

A deficit of thyroid-stimulating hormone causes hypothyroidism in dwarf mice, resulting in decreased T3. The mice had increased lifespans due to reduced metabolic rates and reduced reactive oxygen species (ROS) generation. As mitochondrial heat is utilized more efficiently due to increased signaling by mitochondrial uncoupling proteins (UCPs), ROS production and damage to mitochondria could potentially be reduced. Insulin-like growth factor 1 (IGF-1) signaling pathway is also negatively affected under ER which is accompanied by lowered growth hormone (GH) concentrations since GH promotes IGF expression (Yang et al. 2018; Brown-Borg 1996). ER-induced reduction in plasma levels of free IGF-1 is related to proapoptotic and antiproliferative effects and, consequently, survival in long-lived humans. IGF-1 signaling also activates mammalian target of rapamycin (mTOR) that influences cell growth, including proliferation, transcription, and protein synthesis, as well as cell survival (Brown-Borg 1996; Chesnokova et al. 2019; Johnson 2018).

SIRT1 activation also upregulates pancreatic insulin secretion, leading to an increase in hepatic insulin sensitivity. A decrease in the ratio of NAD+/NADH under ER decreases the inhibitory effect of SIRT1 on UCP-2, increasing ATP production and insulin release (Lee et al. 2021; Ghiasi et al. 2019). As well, SIRT1 is capable of activating the transcription factors NeuroD and MafA, which contribute to the secretion of insulin from the Ins2 gene (Nishimura et al. 2022; Avilkina et al. 2022). SIRT1 also repress lipid synthesis and promote lipolysis through downregulation of SREBP-1, SREBP-2, and PPARγ genes during ER (Kyun 2021; Sun et al. 2021). Putative ER mimetics (ERM) are natural/synthetic substances that mimic potential antiaging effects of ER. Metformin (activator of MAPK signaling), rapamycin (inhibitor of mTOR), resveratrol (inhibitor of SIRT1, mainly found in the lingonberry, skin of red grapes, red wine, and roots of the medical plant Japanese knotweed), flavonoids such as quercetin, kaempferol and hesperetin found widely

in flowers and fruits as inhibitors of mTOR and HIF-1α or other undesirable signaling pathways) and spermidine (rich in soya and other beans, green tea, and mushrooms and diets traditionally consumed in Asian and Mediterranean regions) with anti-inflammatory properties, antioxidant functions, enhancement of mitochondrial metabolic function and respiration, as well as improved proteostasis and chaperone activity (Zalpoor et al. 2022; Ashrafizadeh et al. 2020; Choi et al. 2020; Kawamura et al. 2021; Madeo et al. 2018).

16.2.2 The Effect of Energy Restriction on the Nervous System and Its Relationship with Aging

One of the predominant purposes of growing older is postulated to be the contemporary accumulation of cell damage, what has been recently termed as "garbaging," owed to surpassed manufacturing of reactive oxygen species (ROS) from mitochondria (Wang et al. 2019). Brain tissue is in particular sensitive to oxidative stress, the make higher of free oxygen species is associated with neurodegenerative illnesses with the reduction of antioxidant activity and the cut range of the effectivity of restore mechanisms (Barbagallo et al. 2015).

As a cease result of mitochondrial dysfunction, energy is depleted, disrupting neuronal processes, and main to neurodegenerative illnesses such as Alzheimer's, Parkinson's, Huntington's, and so on (Cagin and Enriquez 2015; Casajus Pelegay et al. 2019). According to current research, CR advantages the intelligence via a range of neuroprotective mechanisms, such as antioxidant effects, the formation of ketone bodies, anti-inflammatory effects, and expanded C activities through the expression of neurodevelopmental factors, such as brain-derived neurotrophic element (BDNF), neurotrophin-3 (NT-3), glial cell line-derived neurotrophic element (GDNF), and SIRTs and mTOR (Rubovitch et al. 2019; Mladenovic Djordjevic et al. 2021). Calcium buffering is one of the necessary mechanisms through which CR has the functionality to extensively have an impact on mitochondrial function. Under CR conditions, this may want to suggest that SIRT3-mediated deacetylation and inhibition of cyclophilin D promote mitochondrial permeability transition inhibition by using an exceptional pathway. By doing so, larger calcium is retained in mitochondria or buffered better, and cellular loss of life can be prevented due to overwhelmed buffers (Amigo et al. 2017). In addition to affecting the amplification and enhancement of the brain, sirtuins have an effect on the destiny of the neurotransmitters in neurons thru axon elongation, neurite outgrowth, and branching (Rubovitch et al. 2019; Ran et al. 2015). SIRTs, specifically SIRT1, regulate the ubiquitin-proteasome pathway (UPP). Synaptic protein turnover, plasticity, and long-term reminiscence formation are all due to the UPP, as properly as the ordinary movement of neuronal synapses (Abdullah et al. 2020; Thibaudeau and Smith 2019).

As a target of SIRT1, PGC-1α regulates the enzyme BACE1, involved in Aβ that its generation/expression has been diminished in Alzheimer's patients. Interestingly, it has been said that the downregulation of PGC-1α can be accountable for blunted antioxidant responses (Casajus Pelegay et al. 2019; Vasconcelos et al. 2019).

As a member of Mediterranean diets, there is developing evidence that polyphenols from olive oil (especially hydroxytyrosol) and additionally fisetin, curcumin, sulforaphane, quercetin, and oleuropein induce the expression of SIRT1 (Mladenovic Djordjevic et al. 2021; Bianchi et al. 2021; Vasconcelos et al. 2019). Moreover, research indicates that sulforaphane impairs mitochondrial membrane potential, and quercetin has been shown to stimulate mitochondrial biogenesis and upregulates mitochondrial bioenergetics (Zalpoor et al. 2022; Selvaraji et al. 2019).

Menopausal women may additionally trip improved oxidative stress and reduced antioxidant endeavor along with diminished neurosteroids, which is a chance factor for Alzheimer's. A pilot study used to be investigated the function of an actual Japanese purposeful food (FPP-ORI, Osato Research Institute, Gifu, Japan) on redox and mitochondrial efficiency in postmenopausal female (Marotta et al. 2020).

On the different hand, produced ketone bodies (KB) mediated via ER have been had exceptional tiers of success to forestall neuronal damage, motor changes, and cognitive decline through a number of neuroprotective mechanisms including metabolic, anti-inflammatory, and antioxidant (Camberos-Luna and Massieu 2020; Jensen et al. 2020). As an end result of increased oxidation of NADH and mitochondrial respiration, KB decreased glutamate excitability in remoted cortical neurons (Camberos-Luna and Massieu 2020; Marosi et al. 2016).

An excitotoxic response occurs when glutamate receptors, particularly NMDA receptors, are prolonged activated and intracellular Ca2 levels are increased, leading to mitochondrial dysfunction and ROS production (Bano and Ankarcrona 2018). Ketone therapy is therefore cautioned for the cure of AD, HD, PD, MS, malignant glioma, migraine headache, and motor neuron disease (Ran et al. 2015; Fitzgerald et al. 2018). A lack of oxygen and glucose additionally leads to an extent in the charge of oxygen consumption and ATP synthesis in cultured neurons receiving BHB. By activating the PGC1a-SIRT3-UCP2 pathway, ketone derivatives inhibit oxidative stress and increase TCA intermediates and promote mitochondrial biogenesis (Camberos-Luna and Massieu 2020; Hasan-Olive et al. 2019). Study findings propose that EGCG and coconut oil can enhance ketone bodies in the blood, thereby reducing cardiac risks in human beings with multiple sclerosis (MS) (Benlloch et al. 2020).

16.3 Cellular Senescence, Energy Restriction, and Aging

Aging of the body's cells is precipitated by using various factors in the body, and in addition, the incidence of these elements is most per chance the spark for the structure of this development. Under the have an impact on of therapy, the use of oncogenes in proliferation, senescent cells acquire many characteristics. The cell cycle of these cells is stopped through the stimulating aspects that appear, and it seems that they be in no way successful in reentering the cell cycle. Also, these cells secrete elements that stimulate the immune system, which in some instances is an attribute of the senescence-associated secretory phenotype (SASP). In addition to the preferences mentioned, these cells have their nonpublic appearance, qualities, and

epigenetic expression. Apparently, these cells provoke the immune system's opposition to itself. For example, we have a tendency to agree that these cells have SASP properties. SASP can also additionally act as a neurostimulator at the site of secretion of inflammatory cytokines and chemokines such as IL-6, IL-8, CCL2, and CXCL1 in senescent cells, stimulating immune cells to senescent cells away from the surrounding environment (Birch and Gil 2020) (Fig. 16.2).

16.3.1 Cellular Senescence Modulator: Energy Restriction

Caloric restriction (CR) like energy restriction (ER) is a wonderful way to limit age-associated persistent diseases and increase lifespan that is typically involved in reducing caloric intake while with maintaining sufficient diet in people CR can counteract a number of the mechanisms involved in age-associated diseases. Adequate intake of vitamins and minerals it has been demonstrated that by way of interfering with the source of injury, CR is involved in protection toward cell senescence these sources of harm include oxidative stress by using promotion the expression and undertaking of NrF2 that induces a number of anti-oxidative enzymes, information, repairing, and disposing of existing destruction, raises autophagy (downregulation of the IGF1 signaling pathway) (Pimentel et al. 2013).

16.3.2 Cellular Senescence Biomarkers

16.3.2.1 Oxidative Stress

The accumulation of reactive oxygen species (ROS) reasons oxidative stress. ROS is originated from mitochondria or ultraviolet radiation damages. Destruction of lipids, proteins, and nucleic acids, inter alia protein carbonylation, and the production of 8-hydroxy-20-deoxyguanosine (8-OHdG) are the results of ROS activity. In addition, regulation of the mitogen-activated protein kinase (MAPK) and nuclear factor kappa-B (NF-κB) signaling pathway that consequences to the activation of heterodimer activator protein 1 (AP-1) is the end stop end result of excessive ROS accumulation in senescent cells. In the following, AP-1 degrades collagen and elastin in pores and skin tissues through induction of matrix protein metalloenzymes (MMPs) (Abdullah et al. 2020).

16.3.2.2 Tumor Suppressing and Cell Cycle Arrest

Interestingly, senescent cells are terminally increase arrested. So cell cycle regulators such as p16INK4a, p21CIP1, and p53 are desirable choices for figuring out the senescent cells. As simultaneously upregulation of p16INK4a, p21CIP1, and p53 in human skin fibroblasts post-ultraviolet (UV) radiation have been shown. P16INK4a

is a key issue in cell cycle controlling that is upstream of the retinoblastoma tumor suppressor protein. Several preneoplastic lesions which encompass melanocyte-rich benign human nevi are full of p16INK4a-positive cells; this phenomenon resulted from N-RAS mutation or its downstream goal BRAF. Generally, p16INK4a locus is often mutated in a range of cancers, such as pores and skin epithelial tumors (Wang and Dreesen 2018).

16.3.2.3 The SASP Regulatory Signaling Pathways

Importantly, the SASP response is related to guidelines at the transcriptional level. Convergence of SASP regulators to the transcription elements CCAAT/B enhancer-binding protein β (C/EBP-β) and nuclear aspect kappa-B (NF-κB) co-induces the rules of SASP factors in a broad range of contexts of aging. The stable DNA damage response (DDR) signal at as soon as prompts the SASP program; on the other hand this activation is no longer at once associated with p53, p21, and p16. Interestingly, NF-κB activation relies upon on ATM kinase, which interacts with and phosphorylates the regulatory NF-κB indispensable modulator (NEMO) in the nucleus. Then, the nuclear export of the ATM/NEMO difficult to the cytoplasm and the activation of α and β IκB kinase (IKK) proteins through NEMO are among the posttranslational changes that phosphorylate IκB inhibitory proteins. Finally, the IκB protein launched from the elaborate is degraded with the aid of the proteasome. This degradation reasons NF-κB to translocate to the nucleus and transactivates a number of SASP genes. Notably, interleukin-1α (IL-1α) acts intracellularly or as a cell membrane-bound protein. In the early stage of senescence, this cytokine enhancement initiates a feedforward loop that leads to amplification of C/EBPβ, NF-κB activity, and SASP signaling. Interestingly, upregulation of IL-6 and IL-8 through means of IL-1α and IL-1 receptor engages a positive remarks loop resulting from amplification of C/EBPβ activation (Roger et al. 2021). Energy restriction increases the AMP/ATP ratio activating nutrient sensors such as phosphorylated AMPK (p-AMPK). Elevated p-AMPK ratio causes activation of the nutrient sensor AMPK and its downstream factors such as SIRT1, PGC1, and FOXO leading to a reduction of ROS level to improve inadequate energy supply. Cellular senescence leads to cell cycle arrest via elevation of p53, p16, and p21 which is in favor of aging. The wrong formation of lamins in the nuclear envelope, which structurally modifies nuclear genes, reasons laminopathy and lamin injury will make greater sensitivity to reactive oxygen species, ensuing in oxidative damage and untimely aging

16.4 Aging Genomics and Energy Restriction

Caloric restriction (CR) is one of the novel hypotheses of organismal lifespan and posits that getting older is the ordinary end result of entropy on the cells, tissues, and organs of the animal. We now have proof that growing old is as a substitute at least in partly genetically regulated. Cellular fitness is managed at a range difficulty in the

cell and starts off evolved in the nucleus through chromosome structure/organization, transcriptional regulation, and nuclear export/import, ranging outward to protein translation and great control, autophagy recycling of organelles, suspension of cytoskeletal structure, and subsequently suspension of the extracellular matrix and extracellular signaling (Xiang and Guoqing 2011).

16.4.1 Multi-omics for the Discovery of Aging Biomarkers

Age correlation analyses consist of huge quantities of data acquired from specific omics analyses, such as genomics (epigenomics), transcriptomics, proteomics, metabolomics, and microbiomics (DiLoreto and Murphy 2015).

16.4.2 Aging Epigenomics

Epigenetics is regarded for about alteration in the natural phenotype in avoidance of alternate alteration in the inherent genotype; these transformations are generally produced with the aid of way of the environment. The DNA methylation pattern is the most studied epigenetic feature. The epigenetic getting older clock is in fact an advocated predictor of age-related diseases. Most research on DNA methylation sample analyzed peripheral blood samples and examined that the over- and under-methylation of CpG sites are associated with mortality. The total of 353 CpG sites can be used to estimate physiological aging. On the top notch hand, the immune system station can be characterized through 73 CpG sites, and 10 CpG sites can be used as predictors of most cancers and cardiovascular ailment mortality. DNA methylation GrimAge has been correlated with ailments and can predict mortality. The warning signs and symptoms of epigenetic getting older are in addition related to neurodegenerative diseases. For example, Parkinson's disease (PD) is associated with the first acceleration of epigenetic growing older clock. Higher epigenetic age corresponds with a massive hazard for most cancers and age-related cartilage degenerative diseases. The epigenetic getting older clock will be increase with BMIs in weight troubles and metabolic syndrome, indicating the relationship between the epigenetic clock and style of living, additionally (DiLoreto and Murphy 2015).

16.4.3 Aging Gene Expression

In addition, overexpression of the O3 (FOXO3) gene in organisms has been linked to long lifespan. Polymorphism in the FOXO3 gene is associated with longevity in humans. In addition, the apolipoprotein E (APOE) gene encodes an LDL

cholesterol transporter that helps manipulate LDL cholesterol and lipid metabolism and cell repair. Furthermore, knocking out the tumor suppressor gene p53 in aged mice promotes organ atrophy, osteoporosis, and an anti-stress response (DiLoreto and Murphy 2015).

16.4.4 Telomere-Based Biomarkers

Telomeres are protective nuclear protein caps at the tails of eukaryotic chromosomes that are composed of TTAGGG repeats. They have smart amplify manage factors. Telomere measurement is a general marker of aging, and telomerase is the fundamental telomere-modulating enzyme. Cell division is accompanied through skill of telomere shortening and the use of controllable factors that can cause chromosomal instability with growing (DiLoreto and Murphy 2015). Motile cultures of mammalian cells enter senescence after 40–60 divisions, which is referred to as Hayflick senescence or replication (Xiang and Guoqing 2011). Research in a large populace (n = 105,539) tested that women have longer telomeres than men and that there are sex-related editions in growing older that may also prefer to be due to hormonal differences, such as estrogen degrees and X chromosome characteristics. Age-related decline in immunosurveillance and accelerated contamination with telomere shortening and telomerase decline are related with long-term incidence of many diseases that have been described (DiLoreto and Murphy 2015).

16.4.5 Transcriptional Regulation

Transcriptional regulation is key in coordinating the activation of many genes to expand lifespan. Regulation with the IIS pathway in *C. elegans* consists of chiefly the PQM-1 and DAF-16/FOXO transcription factors, which localize to the nucleus in a requited restrained method and promote both growth/development and stress response/longevity, respectively; their requited limited nuclear localization breaks down with age. The downstream dreams of these pathways consist of genes in manipulation of cell health. The heat shock factor HSF-1 is responsible for control of cytoskeletal probity and heat stress resistance, all of which promote to its effect on *C. elegans* longevity. The Nrf/SKN-1 transcription factor makes longevity, as well as regulation of extracellular collagen matrices (Xiang and Guoqing 2011).

Another ordinary example of agingomics is transcriptomics, which studies mRNA groups together, including lncRNAome, circRNAome, and exosomal RNAome. To emerge the total transcriptome also remains a challenge. Focus on research may affect transcriptomics and assist doctors in selecting suitable biomarkers from various RNA types. The characteristics of six gene expression factors of cell senescence have been identified by Frenk and Houseley. As a control of lipid

homeostasis, phospholipid transport, and macrophage activity, ABCG1 makes the pathway of endothelial cholesterol efflux and protects blood vessels from chronic inflammation. Such alleles usually dictate the human lifespan. A study of the human whole-blood transcriptome including 1016 people aged 70–80 years showed that BIRC2 is an apoptosis regulator of inflammation, cell proliferation, and mitotic kinase signal transduction and was the most downregulated in old age. In another study analyzing whole-blood samples, aging was positively correlated with the expression of 11 genes, namely, AMZ1, MANEAL, PARP3, KIAA0408, ISM1, CRIP1, NEFL, PHLDA3, DDB2, CHN1, and CAPN2, in the event that it was negatively correlated with that of 4 genes, namely, MXRA8, SLC4A10, CD248, and PLEKHA7, thereby demonstrating that transcriptomics can classify the aging. The expression of age-related genes can be used to classify aging biomarkers (DiLoreto and Murphy 2015).

16.4.6 miRNAs-, lncRNAs-, and circRNAs-Based Biomarkers

miRNAs are 21–25 nucleotides, and it performs a function in the vital regulation processes of living organisms. To identify transcriptome-specific biomarkers, the relationship between microRNA expression profiles and chronological age is analyzed. For example, the expressions of miR-22-3p and miR-28-3p are positively associated with age and miR-425-3p, miR-182-5p, and miR-99b-5p are negatively related. miRNA is related to many illnesses, such as cancer, cardiovascular diseases, hypertension, weight problems, and diabetes. Studies on monocytes and the serum of lifespan and aged people have decided age-related miRNAs. In sarcopenia, biomarkers such as miR-181a, miR-434-3p, miR-431, miR-29, and miR-126 are involved in IGF-1, senescence, and apoptosis signaling in cells. miR-19a-3p is determined as a biomarker for ischemic stroke and the gene pathways focused by using miRNAs associated with the production of inflammation, coagulation, and platelet activation. Regarding the relationship between stroke and age and that the aged human beings have a greater hazard of stroke, the identification of miRNAs can be used for greater age-related illnesses to in a while find out biomarkers for ailment therapy and prevention. For example, human hearing loss is related to the expression of miR-34a and miR-21 and may additionally be the important biological markers of inflammation.

miR455-3p has been endorsed as a possibility peripheral biomarker for Alzheimer's disease. lncRNAs have ≥200 nucleotides size that are other type of noncoding RNA and effect as signals and guides during transcription and gene expression on special levels, which includes recombination, transcription regulation, and posttranscriptional modification, as a result affecting the lifespan and aging. The downregulation of lncRNA leads to reduced cell growth and senescence.

Telomere-lncRNA can control cell telomerase function in old age. Age-related lncRNA expression illnesses can reason neurogenesis and synaptic ductility which strengthen neuropathy by means of protein integration and neurodegeneration meg3 to be related to growing older cardiovascular ailments.

circRNAs are RNA transcripts produced by using the reverse splicing of protein-coding exons. These transcripts may additionally serve as really helpful biomarkers that are produced in the brain at aging period. circRNAs can be detected in the blood, serum, and saliva, and they are larger crucial biomarkers of aging.

It has been reported in a latest research, in multiple machine atrophy (MSA) patients, circRNAs are upregulated (Xiang and Guoqing 2011).

Recent research have proven that natural material such as resveratrol is a herbal phytoalexin existing in countless plants, such as grapes, berries, plums, and peanuts. Genistein is an isoflavone naturally located in several plants. The epigallocatechin-3-gallate is the main polyphenol determined in green tea. The indole-3-carbinol (I3C) is a natural glucosinolate located in the *Brassica* plants such as cabbage, broccoli, cauliflower, kale, radish, turnip, and Brussels sprouts, and ellagitannin, a polyphenolic compound extracted from Balanophora japonica, exerts their antiproliferative and/or proapoptotic effects on the rules of one or greater miRNAs; each miRNA is successful of regulating the expression of many genes, permitting them to simultaneously alter more than one cellular signaling pathway and with the mechanisms such as cell proliferation, invasion, migration, angiogenesis, and inflammation, and induces stop cell cycle and apoptosis and additionally has outcomes on number of cancers (Shen et al. 2013).

16.4.7 Nuclear Trafficking and Organization

The eukaryotic nuclear pore complicated (NPC) is one of the most necessary molecular devices of the cell, which performs an important function in the transfer of messages and proteins into and out of the nucleus and is accountable for many manipulate features and imperative functions associated with cell health, inclusive of tumor suppression. mRNA is transported to the cytoplasm by using the NPC, and nuclear trafficking reduced with senescence can cause hyporesponsiveness to cellular stresses. Wrong formation of lamins in the nuclear envelope, which structurally modify nuclear genes, reasons laminopathy, such as illnesses related to untimely aging. For example, patients with Hutchinson-Gilford progeria show symptoms of premature growing older when they are very young. The instability of cell genes due to laminopathies affects DNA to detrimental elements and will expand the incidence of breaks, translocations, and aneuploidies. Correct control of nuclear lamins is quintessential to keep tissues healthful in adults, and lamin injury will make greater sensitivity to reactive oxygen species, ensuing in oxidative injury (Xiang and Guoqing 2011).

16.4.8 Protein Translation

Protein translation is a critical control mechanism in longevity regulation; down-regulation of translation upon reduced nutrient availability extends lifespan in many organisms, including worms and flies, via TOR signaling in dietary restriction (DR) regimes and IIS/FOXO signaling. Loss of the *C. elegans* eukaryotic initiation factor 4F (eIF-4F)/ife-2 extends lifespan, as does loss of ribosomal protein S6 kinase (S6K)/rsks-1. Loss of TOR signaling, eIF-4E/ife-2, or S6K/rsks-1 also increases heat stress resistance (Xiang and Guoqing 2011).

16.4.9 Autophagy

Organelle or protein digestion and rebuilding (homeostasis) and also proteome modulation (proteostasis) are carried out with the aid of autophagy.

Autophagy is required for senescence paradigms in many species, consisting of DR and IIS mutants, and inhibition of autophagy all at once induces signs and symptoms of senescence. Dependence on autophagy for sturdiness suggests that autophagic clearing of destroyed proteins, protein aggregates, organelles, lipids, and one-of-a-kind cargoes is required to put together new elements for a strong cell. Autophagy performs a worrying attribute in neurodegenerative health problem as right in Parkinson ailments brains, autophagy is downregulated and CMA deregulated then as soon as more autophagy is upregulated in the brains of sufferers with Alzheimer's and ALS regulatory variations exhibit off up at exclusive steps in the autophagy pathway suggesting a frustrating attribute of autophagy in maintaining fitness (Xiang and Guoqing 2011).

There are signs and symptoms that autophagic common performance is dysfunctional in age-related ailments. Autophagy declines with getting old. Triggering NLRP3 activation and improving the irritation strategy diminished NLRP3 activation and extended autophagy can lengthen the lifespan.

In this understanding, the extraordinarily ideal attribute of autophagic uptake in the clearance of dysfunctional mitochondria reduced oxidative stress and impaired NLRP3 activation is vital to conserving cell homeostasis. Developing observations indicate that some components containing natural compounds such as resveratrol, catechins, EGCG, propolis extracts, creosol, and luteoloside are labeled as antiaging molecules. There is advice that dietary consumption of these compounds can in addition promote fitness and lengthen the lifespan with the ordinary overall performance of a couple of mechanisms which consists of the limit of oxidative stress, induction of autophagy, and suppression of NLRP3 activation. This can lead to a greater health and longer lifespan (Phuah and Nagoor 2014). Energy restriction (ER) is one of the new longevity hypotheses, which posits that aging is the normal

end result of entropy. Management of cellular fitness through chromosome structure/organization, transcriptional regulation, and nuclear export/import to protein translation and great control, autophagy recycling of organelles, suspension of cytoskeletal structure, and subsequently suspension of the extracellular matrix and extracellular signaling is included. Aging biomarkers age correlation analyses include data obtained from omics analyses, such as genomics (epigenomics), transcriptomics, proteomics, metabolomics, and microbiomics. DNA methylation pattern is the most important epigenetic characteristic studied. The epigenetic aging clock is actually a predictor of age-related diseases. CpG sites are associated with mortality and it predicts cancers and cardiovascular diseases and is associated with neurological diseases such as Parkinson. Overexpression of the senescence gene O3 (FOXO3) is associated with long life span in organisms. The Apolipoprotein E (APOE) gene contributes to lipid metabolism and cell repair by encoding the LDL cholesterol transporter. Knockdown of the tumor suppressor gene p53 in aged mice causes limb atrophy, osteoporosis and anti-stress response. Telomere measurement is a general indicator of aging. Heat shock factor HSF-1 is responsible for cytoskeleton control, resistance to heat stress, which affects life span. The transcription factor Nrf/SKN-1 causes longevity and also regulates extra cellular collagen matrices. Another example of agingomics is transcriptomics, which studies groups of mRNA together. ABCG1 as a control of lipid homeostasis, phospholipid transport and macrophage activity, it creates an endothelial cholesterol efflux pathway and protects blood vessels against chronic inflammation. Aging is positively associated with the expression of 11 genes namely AMZ1, MANEAL, PARP3, KIAA0408, ISM1, CRIP1, NEFL, PHLDA3, DDB2, CHN1 and CAPN2. The expression of miR-22-3p and miR-28-3p is positively correlated with age and diseases. Induction of autophagy and suppression of NLRP3 activation induces signs and symptoms of aging and neurodegenerative diseases.

Table 16.1 Important molecular biomarkers in agingomics and ER

Aging epigenomics	Aging gene expression	Telomere-based biomarkers	Transcriptional regulation	miRNAs-, lncRNAs-, and circRNAs-based biomarkers	Nuclear trafficking and organization	Protein translation	Autophagy
DNA methylation of CpG sites	FOXO3 gene Apolipoprotein E, gene p53	TTAGGG repeats	PQM-1 and DAF-16/FOXO, HSF-1, Nrf/SKN-1, lncRNAome, circRNAome, exosomal RNAome, ABCG1, BIRC2 AMZ1, MANEAL, PARP3, KIAA0408, ISM1, CRIP1, NEFL, PHLDA3, DDB2, CHN1, and CAPN2	miR-22-3p, miR-28-3p, miR-181a, miR-434-3p, miR-431, miR-29, and miR-126. miR-19a-3p. miR-34a and miR-21, miR455-3p. lncRNAs. Telomere-lncRNA. circRNAs	The eukaryotic nuclear pore complicated (NPC), lamins	eIF-4F/ife-2, loss of ribosomal protein S6 kinase (S6K)/ rsks-1. Loss of TOR signaling	Autophagy and suppression of NLRP3 activation

16.5 Conclusion

Nutritional intervention with maintenance of adequate intakes of essential nutrients is the main role of ER. This causes longevity mediated by a variety of mechanisms, such as changes in energy metabolism, oxidative damage, insulin sensitivity, and structural alterations in the sympathetic and neuroendocrine systems. There is accruing evidence that some diet regimens or natural products are associated with increased lifespan in human and mice, via different pathways involved in regulation of crucial hormones/factors related in normal cell function. Energy restriction (ER) has been demonstrated as one of the most effective nutritional interventions for extending lifespan and delaying age-related diseases, including cancer prevention and chronic diseases such as neurodegenerative diseases, diabetes, and cardiovascular disease. In addition, ER and using a variety of natural products have shown neuroprotection through modulation of mitochondrial biogenesis, increasing autophagy and reducing oxidative stress. ER also exhibits beneficial effects on stem cell maintenance, which improves tissue regeneration, self-renewal, and differentiation.

Senescent cells have special characteristics and the most important is SASP, by which they recruit immune cells by releasing inflammatory cytokines and chemokines. On the other hand, CR as a calorie reduction method can prevent many mechanisms that induce cellular senescence. Cellular senescence has many characteristics. For example, increased oxidative stress in senescent cells destroys proteins, lipids, and nucleic acid. Another characteristic of cellular senescence is cell cycle arrest, which is the result of increasing factors such as p53, p16, etc. We said that SASP is one of the most obvious features of cellular senescence. This phenomenon in the cell is driven by NF-κB, whose stability is dependent on ATM kinase.

Regarding the genomics of aging and its relationship with energy restriction, we stated that entropy changes in cells cause changes in lifespan. Cell health is managed by regulating transcription and maintaining chromosomal structure, messenger RNAs, protein translation, and autophagy.

The environment causes epigenetic changes and the phenotype of organisms. The epigenetic aging clock is related to age-related diseases such as osteoporosis, Alzheimer's, Parkinson's, cardiovascular diseases, and cancers. These changes are caused by DNA methylation and mutations in genes, such as o3, APOE, and p53. Obesity and body mass and metabolic diseases that are related to lifestyle are related to epigenetic changes.

Regarding the role of telomeres in relation to aging, it was said that cell division causes telomere shortening and shortening lifespan and the occurrence of aging and age-related diseases.

Transcription of many genes by mRNAs plays a role in cell health, material and signal transmission, macrophage activity, and apoptosis. We mentioned plant and natural substances that have antiaging and proapoptotic compounds such as phenols and participate in the regulation of cell cycle activities and aging signaling and age-related diseases through the expression of genes with the help of miRNAs.

Autophagy causes the digestion of harmful cell organelles and proteins, which decreases during aging, and diseases such as Alzheimer's and Parkinson's are related to the decrease of autophagy; compounds such as resveratrol, catechin, papaya, propolis extract, creosol, and luteoloside have autophagic properties, are proapoptotic, reduce oxidative stress, and play a role in reducing aging and increasing cellular health and related diseases.

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Chapter 17
Age-Related Neurodegenerative Diseases

Aging and Neurodegeneration

Narmadhaa Sivagurunathan and Latchoumycandane Calivarathan

Abstract Aging is one of the major risk factors for several neurodegenerative diseases, the most common being Alzheimer's and Parkinson's diseases. Besides increasing the lifespan, poor lifestyle, exposure to environmental contaminants, and comorbidities directly or indirectly increase the prevalence of neurodegenerative diseases in the elderly population. Even though several factors contribute to neurodegeneration, oxidative stress and neuroinflammation are critical factors that trigger neuronal cell death. Since various nutraceuticals have anti-inflammatory and antioxidative properties, they slow the progression of neurodegeneration and neuroinflammation, thereby preventing neurodegenerative diseases. This chapter discusses various functional foods and their components that help relieve the symptoms or prevent the progression of neurodegeneration in aging and age-related neurodegenerative diseases, including Alzheimer's and Parkinson's. Functional food contains physiologically active components from either plants or animal sources and has essential nutritional functions such as decreasing the risk of many chronic diseases and providing some physiological benefits. Functional foods contain various therapeutic bioactive components such as carotenoids, flavonoids, polyphenols, minerals, and vitamins, which prevent several diseases, including neurodegenerative diseases. The morbidity, mortality, and cognitive impairment caused by neurodegenerative disorders remain the primary health concern for society, and various studies are focused on preventing and suppressing the symptoms of these diseases, such as Alzheimer's disease, Parkinson's disease, and Huntington's disease.

Keywords Alzheimer's disease · Functional foods · Neurodegeneration Nutraceuticals · Parkinson's disease

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Abbreviations

6-OHDA	6-Hydroxydopamine
AChE	Acetylcholinesterase
AD	Alzheimer's disease
ALA	α-Lipoic acid
AMPK	AMP-activated protein kinase
APOE	Apolipoprotein E
APP	Amyloid precursor protein
ATP	Adenosine triphosphate
Aβ	Amyloid-β
BACE1	Beta-secretase 1
BAG2	Bcl-2-associated athanogene 2
BBB	Blood-brain barrier
BChE	Butyrylcholinesterase
BDNF	Brain-derived neurotrophic factor
COX-2	Cyclooxygenase 2
DNA	Deoxyribonucleic acid
EGCG	Epigallocatechin gallate
ER	Endoplasmic reticulum
EVOO	Extra virgin olive oil
GPx	Glutathione peroxidase
GSH	Glutathione
GSK3	Glycogen synthase kinase-3
IL	Interleukins
iNOS	Inducible nitric oxide synthase
LPS	Lipopolysaccharide
MCFA	Medium-chain fatty acid
MCP	Monocyte chemoattractant protein 1
MPP^+	1-Methyl-4-phenylpyridinium
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
NFκB	Nuclear factor-kappa B
NO	Nitric oxide
PARP	Poly(ADP-ribose) polymerase
PD	Parkinson's disease
PI3k	Phosphoinositide 3-kinase
ROS	Reactive oxygen species
SIRT1/2	Sirtuin 1/2
SNpc	Substantia nigra pars compacta
TNF	Tumor necrosis factor

17.1 Introduction

Age-related neurodegenerative diseases are the major problems in the aging population that occur due to the progressive loss of structure and function of neuronal cells during aging. Aging is a crucial factor that increases the risk of pathogenesis and progression of several neurodegenerative diseases. Aging is an irreversible process that alters genomic stability, telomere attrition, epigenetic changes, loss of proteostasis, mitochondrial dysfunction, cellular senescence, deregulated nutrient-sensing stem cell exhaustion, and altered intercellular communication (Hou et al. 2019). Under pathological conditions, several factors contribute to increased neuronal aging at the cellular and molecular levels, including mitochondrial dysfunction, dysregulated metabolism, accumulation of oxidatively damaged biomolecules, compromised DNA repair, aberrant Ca^{2+} homeostasis, activation of inflammasome signaling, and neuroinflammation (Fig. 17.1). Neuroinflammation, a significant contributor to neurodegeneration, occurs due to the activation of inflammasomes that increase the release of proinflammatory cytokines, including pro-IL-18 and pro-ILβ, from the microglial cells (Brahadeeswaran et al. 2022). The formation of abnormal proteins and aggregates are the two most common characteristic features of neurodegenerative diseases that promote cytotoxic processes by enhancing ROS production, excitotoxicity, synaptic dysfunction, ER

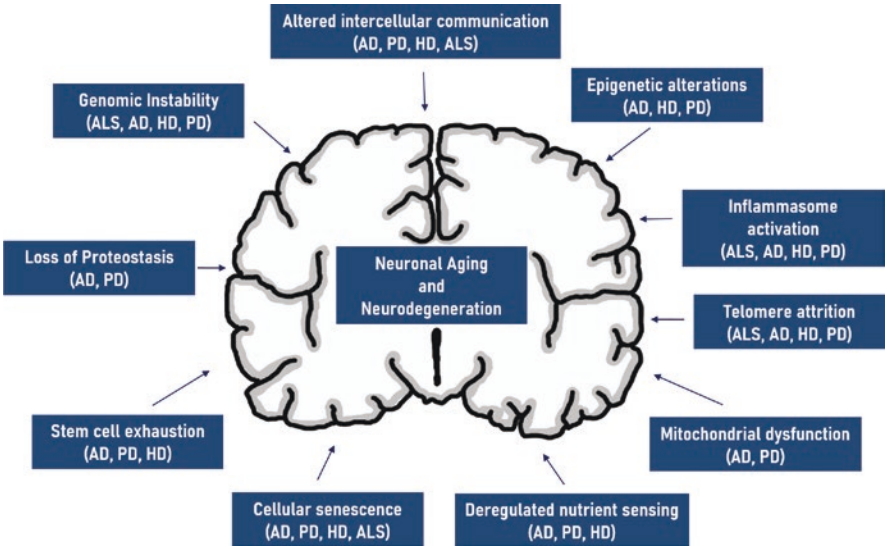

Fig. 17.1 Factors contributing to neuronal aging and neurodegeneration. Genomic instability, loss of proteostasis, stem cell exhaustion, cellular senescence, deregulated nutrient sensing, mitochondrial dysfunction, telomere attrition, activation of inflammasomes, epigenetic alterations, and altered intercellular communication are the major contributing factors for premature neuronal aging and age-related neurodegenerative diseases. AD, PD, HD, and ALS stand for Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis, respectively

stress, DNA damage, mitochondrial dysfunction, and neuroinflammation. Some key proteins commonly involved in the pathogenesis of neurodegenerative disorders include amyloid-β, tau, α-synuclein, and prion protein, and deposition of these proteins alters the physicochemical properties of the central nervous system, which is associated with the development of various age-related neurodegenerative diseases. Although currently, there is no treatment to cure or halt the progression of such diseases, researchers are focused on the neuroprotective and anti-inflammatory activities of natural food products with low toxicity and high efficacy.

17.2 Age-Related Neurodegenerative Diseases

Alzheimer's and Parkinson's are the two most common age-related neurodegenerative diseases affecting thousands of people worldwide. Alzheimer's disease (AD) is caused due to the degeneration of neuronal cells, resulting in a decline in their cognition, whereas the same results in the deterioration of motor activity in PD patients. AD is the most common form of dementia, and the primary characteristic features of AD include the accumulation of intracellular neurofibrillary tangles and extracellular amyloid-β protein, which contributes to the formation of Aβ plaques. Aging, family history, genetic factors, infections, traumatic brain injury, obesity, hypertension, depression, cardiovascular and cerebrovascular disease, APOE e4 allele, smoking, and diabetes are some risk factors for AD (Cummings et al. 2019). The major clinical manifestations of AD include cognitive impairment, dementia, and impairment of comprehension, language, attention, reasoning, judgment, and memory. AD symptoms depend on the stage of disease, such as preclinical/presymptomatic, mild, and dementia stages. In the initial stage, the most common symptom is short-term memory loss, followed by cognitive impairment, language disorders, and problems in visuospatial skills. In the mid-stages of AD, symptoms like social withdrawal, agitation, psychosis, and apathy are also observed. In the later stages, patients exhibit olfactory dysfunction, motor disturbances, sleeping problems, and parkinsonian symptoms (Tang et al. 2019).

The neuropathological changes in AD include the accumulation of amyloid plaques, neurofibrillary tangles, dystrophic neurites, and neuropil threads in the brain. Amyloid plaques are spherical microscopic lesions composed of β-amyloid peptides derived from the amyloid precursor protein (APP). APP is cleaved by α-secretase, β-secretase, and γ-secretase to form β-amyloid 42 peptide, which, when accumulated, forms aggregates and causes neuronal toxicity. Another pathophysiological hallmark of AD is the formation of neurofibrillary tangles from the tau protein. Due to the extracellular aggregation of β-amyloid, tau hyperphosphorylation occurs, followed by tau aggregation within neurons, which further

leads to the formation of twisted helical fragments of neurofibrillary tangles (Vik-Mo et al. 2019). Similarly, neuroinflammation, oxidative stress, loss of cholinergic neurons, and synaptic functions also contribute to the changes in the AD brain (Serrano-Pozo et al. 2011). Currently, the treatment for AD focuses only on controlling the symptoms with cholinesterase inhibitors and N-methyl D-aspartate antagonists.

PD is the second most common neurodegenerative disease, following AD. This progressive neurodegenerative disease affects the dopaminergic neurons in the region of the brain, the substantia nigra pars compacta, and 50–70% of the neurons have already degenerated when clinical symptoms arise. The risk factor for PD includes aging, brain injury, and exposure to toxic chemicals, pesticides, and drugs. The significant PD symptoms are categorized into motor and non-motor, and the motor symptoms include bradykinesia, rigidity, gait disturbances, and postural instability. The non-motor symptoms include behavioral deficits, cognitive changes, and sensory and sleep disturbances, which affect the quality of day-to-day life. The neuropathological changes in PD include the accumulation of abnormal proteins in Lewy bodies, which contributes to the neurodegeneration of specific dopaminergic neurons. Lewy bodies are cytoplasmic inclusions found in the neurons, mainly composed of filamentous α-synuclein and other abnormal proteins such as ubiquitin, parkin, tau, heat shock proteins, cytoskeletal proteins, etc. Factors such as α-synuclein aggregation, mitochondrial dysfunction, neuroinflammation, and abnormal protein homeostasis play a significant role in the onset and progression of the disease (Kouli et al. 2018). Parkinson's disease is currently diagnosed based on clinical features from the patient's history and examination and, over time, depending on how the patient reacts to dopamine-boosting drugs and the emergence of motor fluctuations. PD is currently treated with dopaminergic drugs, stopping the disease's rapid progression by targeting motor symptoms. Levodopa is the most common drug used to treat patients with PD at the initial stage of the disease. Other medications prescribed for PD patients include monoamine oxidase type B inhibitors and antagonists of NMDA receptors (Sveinbjornsdottir 2016). However, no drugs are currently available to prevent the development of neurodegenerative diseases or halt their progression.

17.3 Functional Food and Neurodegeneration

Functional foods include the nutrients from fruits, vegetables, fibers, and probiotics taken along with diets; apart from providing beneficial effects, they also lower the risk of developing diseases. Functional foods provide health benefits by improving antioxidants, anti-inflammatory, and anti-lipidomic activities and have been reported to prevent or improve insulin resistance, diabetes, and cardiovascular and

neurodegenerative diseases. Because of its positive impact on health and preventive effects against the onset of several diseases, functional food is now widely accepted by people for a healthy lifestyle. The loss of neurons in a particular brain area is the primary distinguishing feature of neurodegenerative disorders like Alzheimer's and Parkinson's diseases. Neurodegeneration is also accompanied by chronic neuroinflammation and mitochondrial oxidative stress, which are considered critical pathological features in the progression of the diseases. However, one can induce the other, and both are interlinked to contribute to developing neurodegenerative diseases. Hence, functional food with specific compounds is also proposed to play a significant role in slowing down the rate of neurodegeneration by inhibiting oxidative stress and neuroinflammation. Various functional food compounds with antioxidative and anti-inflammatory properties from various fruits and vegetables have been identified to prevent disease progression (Griffiths et al. 2016).

Along with this functional food, other dietary supplements like vitamins effectively prevent neuronal cell death (Fig. 17.2). Resveratrol, lycopene, carotenoids, curcumin, quercetin, and epigallocatechin-3-gallate are some compounds that can actively reduce neuroinflammation and oxidative stress in the central nervous system (Table 17.1). Hence, consuming functional food as an effective component in the patient's diet will also be beneficial in slowing down the symptoms of diseases (Abuajah et al. 2015). Since functional foods have therapeutic potential, they can be further studied and modified for drug development by improving their bioavailability and efficacy. This review summarizes the role of functional foods in age-related neurodegenerative diseases.

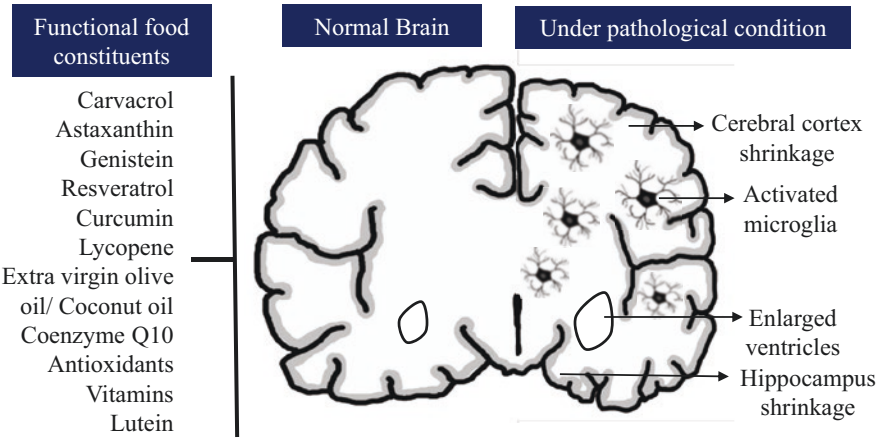

Fig. 17.2 Diagrammatic representations of the brain under normal and pathological conditions. The left half of the brain shows the usual pattern, but the right side shows the brain under pathological conditions. The functional foods' constituents prevent or partially ameliorate pathological shrinkage of the cerebrum and hippocampus, enlarged ventricles, and microglial activation, ultimately preventing age-related neuroinflammation and neurodegeneration

Table 17.1 List of chemical compounds from food sources and their biological functions and possible neuroprotective mechanisms in aging and age-related neurodegenerative diseases

Name of the compound and its biological functions	Mechanism of neuroprotection	References
Genistein *Anti-apoptotic* *Anti-inflammatory* *Antioxidative*	• Blocks the binding of NFκB to the DNA • Inhibits acetylcholinesterase • Reduces H_2O_2 levels • Inhibits cytochrome c release and neuronal cell apoptosis	Shi et al. (2012), Wang et al. (2016)
Resveratrol *Anti-apoptotic* *Anti-inflammatory* *Antioxidative* *Prevents Aβ accumulation*	• Alters the soluble and fibrillar Aβ into nontoxic forms • Inhibits ROS, ILs, NO, MCP-1, TNFα, iNOS, and NFκB and prevents mitochondrial damage • Depletion of glutathione	Ge et al. (2012), Ladiwala et al. (2010), Palle and Neerati (2018)
Curcumin *Anti-apoptotic* *Anti-inflammatory* *Antioxidative*	• Inhibits AChE, BChE, β-secretase, BACE1, and GSK3β • Scavenges free radicals and upregulates antioxidant enzymes • Inhibits apoptosis through the Bcl-2-mitochondria-ROS-iNOS pathway • Prevents tau phosphorylation	Di Martino et al. (2016), Fan et al. (2017)
Carotenoids—astaxanthin *Anti-apoptotic* *Antioxidative*	• Reduces ROS production and promotes the activity of antioxidant enzymes • Prevents apoptosis	Chang et al. (2010)
Carotenoids—lutein *Antioxidative* *Prevents Aβ accumulation*	• Increases the activity of antioxidant enzymes • Destabilizes the Aβ fibrils	Hadad and Levy (2012), Katayama et al. (2011)
Lycopene *Anti-apoptotic* *Anti-inflammatory* *Antioxidative*	• Inhibits cytochrome C release and reduces the level of apoptotic proteins • Inhibits NFκB signaling and decreases the expression of proinflammatory cytokines such as TNFα, IL-1β, and IL-6	Liu et al. (2018), Qu et al. (2016)
Extra virgin olive oil (EVOO) *Antioxidative* *Prevents Aβ accumulation*	• Reduces ROS and inhibits mitochondrial impairment	Gambino et al. (2018), Leri et al. (2019)
Epigallocatechin-3-gallate (EGCG) *Anti-apoptotic* *Prevents Aβ and α-synuclein and accumulation*	• Inhibits tau phosphorylation and neuronal apoptosis • Inhibits the fibril formation of Aβ and α-synuclein proteins	Liu et al. (2014)

(continued)

Table 17.1 (continued)

Name of the compound and its biological functions	Mechanism of neuroprotection	References
Coconut oil *Anti-inflammatory* *Antioxidative* *Prevents Aβ accumulation*	• Inhibits tau phosphorylation • Reduces the BACE 1 expression and expression of genes regulating inflammation and oxidative stress	Bansal et al. (2019), Mirzaei et al. (2018), Nafar et al. (2017)
Ubiquinone/coenzyme Q10 *Anti-inflammatory* *Antioxidative*	• Free radical scavenger • Inhibits release of IL-6, IL-8, and TNFα	Shults (2005)
α-Lipoic acid *Anti-inflammatory* *Antioxidative* *Prevents α-synuclein accumulation*	• Free radical scavenger • Inhibits NFκB • Increases glutathione activity	Jalali-Nadoushan and Roghani (2013), Suzuki et al. (1992)
Carvacrol *Anti-inflammatory* *Antioxidative* *Anti-apoptotic*	• Reduces ROS • Increases the activity of antioxidant enzymes • Prevents neuronal apoptosis	Dati et al. (2017), Hamzehloei et al. (2019)
Quercetin *Anti-inflammatory* *Antioxidative* *Prevents α-synuclein accumulation*	• Free radical scavenger and inhibits NO synthase, xanthine oxidase • Increases the activity of antioxidant enzymes • Inhibits α-synuclein fibrillization	Magalingam et al. (2014, 2016), Zhu et al. (2013)

17.4 Effective Functional Food for Alzheimer's Disease

Several studies have shown that functional food improves the cognitive functions of patients with AD (Atlante et al. 2020). AD is characterized by dysfunctional cholinergic neurons and a lack of acetylcholine, a neurotransmitter, resulting in decreased cognitive ability in the patients (Duan et al. 2021). Genistein is an active natural isoflavone in soybeans that antagonizes Aβ by inhibiting the β-site of the amyloid precursor protein (APP)-cleaving enzyme, BACE1 (Li et al. 2013; Youn et al. 2018). Genistein has an anti-inflammatory effect on the neurons as it blocks the binding of NFκB to the DNA (Jantaratnotai et al. 2013). Genistein protects neuronal cells from DNA damage, apoptosis, endoplasmic reticulum stress, and tau hyperphosphorylation (Park et al. 2010). In the AD rat model, genistein pretreatment reduces tau hyperphosphorylation by regulating calcium/calmodulin-dependent protein kinase IV (Ye et al. 2017). Genistein possesses potent antioxidant properties and alleviates Aβ-induced mitochondrial toxicity by reducing the levels of reactive oxygen species in neurons (Vina et al. 2007).

Resveratrol, a polyphenolic compound, belongs to the class of plant secondary metabolites known as stilbenes. This compound is extracted from medicinal plants and grapevine leaves and is also found in peanuts, pistachios, grapes, and berries

such as blueberries, cranberries, bilberries, lingonberries, partridgeberries, mulberries, strawberries, and their products. Resveratrol inhibits Aβ aggregation by directly binding to the Aβ proteins, specifically in the medial cortex, striatum, and hypothalamus (Ghobeh et al. 2014). Resveratrol binds to fibrillar and monomeric forms of Aβ with varying binding affinity and specificity and alters the soluble fibrillar Aβ into nontoxic compounds. When incubated with Aβ fragments, resveratrol reduces the length and number of the fibrillar Aβ and thus slows down the progression of the disease (Ge et al. 2012; Ladiwala et al. 2010). Resveratrol also ameliorates hippocampal injury, restoring memory, spatial memory, and cognition in rats, suggesting that this polyphenolic compound has the potential to treat neurodegenerative diseases (Moorthi et al. 2015; Sharma et al. 2005). Resveratrol also inhibits molecules that contribute to inflammation, such as ROS, interleukins, nitric oxide (NO), monocyte chemoattractant protein-1 (MCP-1), tumor necrosis factor-α (TNFα), inducible nitric oxide synthase (iNOS), and nuclear factor-κB (NFκB) (Ahmed et al. 2017). Sirtuins (SIRTs) are a group of enzymes that regulate various biological processes, including aging and inflammation. SIRT1 has a neuroprotective function, but in contrast, SIRT2 promotes neurodegeneration in neurons. Oral administration of resveratrol increases the levels of SIRT1 in the neurons and prevents the binding of endogenous SIRT1 inhibitors to the SIRT1, preventing the cells from neurotoxicity (Ahmed et al. 2017; Calliari et al. 2014). Resveratrol also has antioxidative properties, preventing the loss of mitochondrial membrane potential due to ROS. Resveratrol downregulates the proteins that induce oxidative stress, such as glycogen synthase kinase-3β and AMP-activated protein kinase (AMPK) (Kwon et al. 2010). Hence, resveratrol is a potential phytomolecule for treating and managing various neurodegenerative diseases, including AD.

Curcumin, a natural phenolic phytochemical extracted from the plant *Curcuma longa*, has anti-inflammatory and antioxidant properties and ameliorates the pathophysiological changes in patients with AD (Tang and Taghibiglou 2017). Curcumin inhibits AChE, butyrylcholinesterase (BChE), β-secretase, and glycogen synthase kinase-3β (GSK3β), which significantly induce the pathological changes in AD. Curcumin also inhibits Aβ formation and accumulation in the brain, thus reducing the oxidative stress induced by Aβ (Chainoglou and Hadjipavlou-Litina 2020). Aβ formation is prevented by downregulating the BACE1 expression in the AD mice model, alleviating synaptic degradation and improving memory (Zheng et al. 2017). Curcumin also inhibits the BACE1 enzyme in vitro, thus resulting in decreased formation and accumulation of amyloid-β (Di Martino et al. 2016). In AD rat models, curcumin shows a reduced accumulation of Aβ in the hippocampus and improved cognition, spatial learning, and memory (Ge et al. 2012). Curcumin also prevents tau hyperphosphorylation by inhibiting the GSK-3, which regulates the phosphorylation of tau (Samy et al. 2016). In primary cortical neurons, curcumin upregulates BAG2, a molecular chaperone involved in tau clearance through proteasomal degradation (Carrettiero et al. 2009). Oxidative stress plays a significant role in the development and progression of the disease due to increased accumulation of Aβ and tau phosphorylation. Curcumin acts as an antioxidant by scavenging free radicals and upregulating genes encoding antioxidant proteins, including heme

oxygenase-1, catalase, and superoxide dismutase (Gibellini et al. 2015). Curcumin inhibits intrinsic apoptosis by regulating the anti-apoptotic proteins and blocking the cleavage of poly(ADP-ribose) polymerase, activation of caspases, and ROS-mediated DNA damage (Fan et al. 2017).

Carotenoids are secondary metabolites that play an essential role in various biological functions and show therapeutic potential in preventing neurodegenerative diseases. Astaxanthin, a member of this family, reduces ROS production and plays a beneficial role against oxidative stress by promoting the activities of antioxidant enzymes, catalase, and superoxide dismutase (Zhang et al. 2014). Astaxanthin prevents the neuronal cells from the damaging effects of $A\beta_{25\text{-}35}$ by downregulating apoptotic factors and suppressing IL-1β and TNFα (Chang et al. 2010). Lutein, a type of carotenoid, has anti-inflammatory and antioxidant potential, inhibits NFκB activity, reduces the production of proinflammatory molecules, increases the activity of antioxidant enzymes (Hadad and Levy 2012), and destabilizes the Aβ fibrils formed in the AD brain (Katayama et al. 2011). Food sources containing high carotenoids act as a functional food to prevent the development and progression of neurodegenerative diseases. Lycopene is also a carotenoid widely present in tomatoes, watermelons, and papayas, and they have strong antioxidative, anti-inflammatory, and antiproliferative properties. Lycopene improves memory retention, reduces mitochondrial oxidative stress and damage, restores BDNF levels, and reduces neuroinflammation in $A\beta_{1\text{-}42}$-treated rats (Prakash and Kumar 2014). Lycopene improves the mitochondrial complex activities and ameliorates the Aβ-induced opening of mitochondrial pores and release of cytochrome c (Qu et al. 2016). Lycopene also reduces the neuroinflammation induced by Aβ by inhibiting the NFκB signaling and decreasing proinflammatory cytokines, including TNFα, IL-1β, and IL-6, in the hippocampus, cerebral cortex, and choroid plexus in the rat AD model (Liu et al. 2018). Lycopene also reduces LPS-induced neuroinflammation, oxidative stress, Aβ accumulation, and cognitive impairments (Wang et al. 2018), suggesting that lycopene has neuroprotective effects.

Extra virgin olive oil (EVOO) is considered a nutraceutical as they have more than 200 bioactive constituents. EVOO is commonly present in the Mediterranean diet and modulates various physiological processes for beneficial health. Oleuropein, hydroxytyrosol, and oleocanthal are phenolic compounds in EVOO, which have antioxidative properties, reducing ROS and preventing amyloid plaque formation and accumulation (Gambino et al. 2018; Leri et al. 2019; Rigacci 2015). EVOO polyphenols also prevent the cell damage induced by $A\beta_{1\text{-}42}$ by reducing ROS and inhibiting mitochondrial impairment (Leri et al. 2021). Epigallocatechin-3-gallate (EGCG) is a polyphenol mainly found in tea leaves, which has been shown to slow down cell death, reduce the Aβ aggregation, and inhibit tau aggregation in the cellular model of neurodegeneration (Chan et al. 2016; Walker et al. 2015; Wobst et al. 2015). EGCG ameliorates cognitive impairments and suppresses APP and Aβ accumulation, inhibiting neuronal apoptosis in APP/PS1 transgenic mice (Liu et al. 2014). Coconut oil has a high percentage of polyphenols and medium-chain fatty acids (MCFAs) and is involved in Aβ degradation by increasing the secretion of the insulin-degrading enzyme, which is critical in maintaining Aβ homeostasis (Mett

et al. 2021). Para-coumaric acid, ferulic acid, caffeic acid, and catechin are the powerful polyphenols in coconut oil, and a coconut oil-enriched Mediterranean diet improves cognitive functions (De La Rubia Orti et al. 2018, 2017; Hu Yang et al. 2015). Coconut oil provides neuroprotection via antioxidant and anti-inflammatory pathways and reduces the expression of the BACE-1 enzyme in AD rat models. Virgin coconut oil significantly improves memory and learning, normalizes the expression of genes regulating inflammasomes and oxidative stress, and reduces the Aβ accumulation and tau hyperphosphorylation in AD models (Mirzaei et al. 2018).

17.5 Effective Functional Food for Parkinson's Disease

CoQ10 is an electron transport chain component involved in cellular respiration and acts as a free radical scavenger, protecting neuronal cells against toxicants. Patients with PD show low levels of CoQ10 in platelet mitochondria that correlate with reduced activities of complex I and complex II/III in the ETC in the brain and platelets (Shults 2005). CoQ10 attenuates the MPTP-induced loss of striatal dopamine and dopaminergic axons in an animal model of PD (Beal et al. 1998; Shults et al. 1997). Phase II clinical trial shows various dosages of CoQ10 reduce disability in the patients and slow down the progression of symptoms of PD (Shults et al. 2002). CoQ10 supplementation reduces oxidative stress and inflammation by inhibiting NFκB transcription and the release of proinflammatory cytokines, including IL-6, IL-8, and TNFα, by the endothelial cells (Maiuolo et al. 2019). α-Lipoic acid, also known as thioic acid, is synthesized within the human body and is a natural antioxidant, as they act as a free radical scavenger and cofactor of mitochondrial pyruvate dehydrogenase, which prevents the neuronal damage induced by ROS in various neurodegenerative diseases (De Araujo et al. 2011). As an anti-inflammatory molecule, α-lipoic acid inhibits the NFκB transcription factor (Suzuki et al. 1992). α Lipoic acid is also beneficial when administered along with L-DOPA to an in vivo mouse PD model in the early stages, reducing the L-DOPA-induced dyskinesia (Zhang et al. 2018). As an antioxidant, α-lipoic acid reduces malonaldehyde levels, a lipid peroxidation product, and increases glutathione levels (Zhang et al. 2018). ALA pretreatment attenuates rotations on behavioral testing and prevention of loss of SNpc neurons in a 6-OHDA-induced PD mouse model (Jalali-Nadoushan and Roghani 2013). α-Lipoic acid also protects the dopaminergic neurons in the LPS-induced inflammatory PD mouse model by improving motor dysfunctions, reducing α-synuclein accumulation, and activating proinflammatory molecules (Li et al. 2015; Tancheva et al. 2020; Toth et al. 2021). Carvacrol is a phenolic monoterpene compound in the plant *Zataria multiflora Boiss*, which has several biological properties, including antioxidant, anti-inflammatory, antibacterial, antifungal, antinociceptive, anti-apoptosis, and anticancer properties. In hemiparkinsonian rat models, carvacrol improves rotational behavior, reduces memory deficits, and decreases lipid peroxidation levels in the striatum and hippocampus (Dati et al. 2017; Hamzehloei et al. 2019). Carvacrol also exerts neuroprotective effects through an

antioxidative mechanism in both in vitro and in vivo models of PD (Haddadi et al. 2018; Manouchehrabadi et al. 2020).

Curcumin has antioxidant, anti-inflammatory, anti-apoptotic, and neuroprotective properties that protect the dopaminergic neurons in both in vitro and in vivo models of PD. Curcumin also inhibits the formation of fibrils and has fibril-destabilizing properties in vitro *(*Ono and Yamada 2006*)*. Similarly, curcumin prevents the aggregation of α-synuclein complexes and increases their solubility (Pandey et al. 2008). Curcumin has the ability to cross the BBB and alleviate the toxicity induced by α-synuclein in the neuronal cells by reducing ROS and preventing apoptosis (Wang et al. 2010). Curcumin targets BDNF/PI3k/Akt signaling and c-Jun N-terminal kinase pathways to reduce inflammation and oxidative stress in PD models (Jin et al. 2022; Yu et al. 2010). Curcumin also prevents apoptosis through attenuating p53 phosphorylation and reducing the Bax/Bcl-2 ratio in a 6-OHDA-induced model of a human dopaminergic cell line (Jaisin et al. 2011). Curcumin inhibits depletion of GSH, monoamine oxidase B activity, and lipid peroxidation in the striatum and midbrain (Rajeswari and Sabesan 2008), and chronic administration of curcumin prevents degeneration of dopaminergic neurons in the substantia nigra by inducing the γ-glutamyl cysteine ligase activity, increasing GSH levels, and inhibiting protein nitration (Mythri et al. 2011).

Resveratrol is neuroprotective in various in vitro PD models and protects the cells from oxidative stress and apoptosis by regulating the expression of pro- and anti-apoptotic genes (Albani et al. 2009; Bournival et al. 2009; Zhang et al. 2015). Resveratrol also prevents the mitochondrial damage induced by MPP^+ via the Akt/GSK-3β pathway by altering the Bcl-2/Bax ratio and increasing the levels of Bax and caspase-3 and caspase-9 (Zeng et al. 2017). Resveratrol activates PI3K/Akt pathway to ameliorate the neuronal damage induced by neurotoxins and delay PD's progression. Resveratrol also protects rodents from motor impairment and hydroxyl radical overloading through free radical scavenging, increasing dopamine and GPx activities and thereby reducing MPTP effects (Anandhan et al. 2010; Da Rocha et al. 2015). Resveratrol restores the redox balance by suppressing xanthine oxidase activity and activating glutathione peroxidase (Palle and Neerati 2018; Yu et al. 2010). Some studies report the anti-inflammatory activity of resveratrol, which also prevents neurons from cell death. The COX-2 protein and TNFα are significantly reduced in the SNpc of the 6-OHDA-induced PD model, demonstrating that resveratrol reduced neurodegeneration by reducing inflammatory action (Jin et al. 2008). This also significantly reduces the levels of myeloperoxidase enzyme in the glial cells, which oxidizes the NO and inhibits NO-induced inflammation, thereby protecting the dopaminergic neurons from rotenone-induced neuronal injury (Chang et al. 2013). Resveratrol administration and the L-DOPA also reduce the activation of astroglial cells in the nigrostriatal pathway of mice in the MPTP PD model (Liu et al. 2019). Resveratrol and its derivatives are shown to have neuroprotective effects in the PD models and hence could be promising agents for treating PD.

Vitamin E and β-carotene protect the cells from oxidative stress and damage by neutralizing the effects of ROS. Consumption of vegetables and fruits with such vitamins reduces the risk of developing PD in Japan (Miyake et al. 2011).

Advanced-stage PD patients had considerably lower levels of α- and β-carotenes and lycopene than early stage of PD (Kim et al. 2017). In an animal model, lycopene prevents depletion of dopamine and its metabolites in the SNpc by reducing TBARS and other pro-apoptotic proteins such as Bcl-2-associated X proteins (Bax), caspase-3, caspase-8, and caspase-9 and also increasing the levels of GSH (Suganuma et al. 2002). In the PD mouse model, lycopene ameliorates MPTP and 6-OHDA-induced behavioral deficits, oxidative stress, apoptosis, and other physiological abnormalities (Prema et al. 2015). Epigallocatechin-3-gallate is a polyphenolic compound in green tea, which binds to the naturally unfolded polypeptides of α-synuclein and inhibits fibril formation, preventing their conversion to toxic forms for aggregation. EGCG disaggregates the accumulated α-synuclein in the cellular model of PD model (Ge et al. 2012) and alleviates motor impairments, dopaminergic neuronal injury, and α-synuclein aggregation in MPTP-intoxicated parkinsonian monkeys (Chen et al. 2015). Quercetin is a natural bioactive flavonoid studied for its beneficial antioxidative and anti-inflammatory properties attenuating the neuronal damage caused by oxidative stress by scavenging free radicals. Quercetin reduces ROS generation by inhibiting NO synthase and xanthine oxidase (Echeverry et al. 2010; Yu et al. 2010). Isoquercetin attenuates the neuronal damage induced by 6-OHDA in neuronal cells by increasing the activity of antioxidant enzymes, such as superoxide dismutase, catalase, and glutathione peroxidase (GPx) (Magalingam et al. 2014, 2016). Quercetin and other oxidized quercetin species such as chalcanthite, benzofuranone, quercetin quinone, and other derivatives inhibit the α-synuclein fibrillization (Zhu et al. 2013). Quercetin upregulates the activity of mitochondrial complex I in the electron transport chain to prevent neuronal cell death in the rotenone-induced PD model (Islam et al. 2021; Karuppagounder et al. 2013), thereby acting as a potent, natural, antioxidative, and anti-inflammatory compound.

17.6 Conclusion and Future Perspectives

The present review gives a comprehensive insight into the biological activities of the components present in the functional foods, their involvement, and the mechanism of action in preventing the most common age-related neurodegenerative diseases such as Alzheimer's and Parkinson's diseases (Fig. 17.2). The biologically active food exerts therapeutic activity through various mechanisms, including anti-inflammation, antioxidant, antiproliferative, and antimicrobial properties (Table 17.1). Some of these components, such as resveratrol, quercetin, curcumin, and EGCG, play a significant role in managing oxidative stress and neuroinflammation, thereby preventing neurodegeneration. Compounds in functional foods are associated with the low incidence and risk of chronic diseases; hence, these compounds and their mechanism for preventing these diseases and promoting health are discussed in this chapter. Over 8000 such compounds are identified in plants, and more are yet to be discovered and should be focused on for their role in ameliorating

various diseases. Due to growing knowledge of health advantages of functional foods, such as enhancing our well-being and simultaneously reducing the risk of various diseases, there is a rising demand for them. Nutraceutical compounds can also be considered for drug development due to their natural therapeutic potential and require further studies on their source, efficacy, dose, safety, stability, delivery methods, cost, and bioavailability. In addition, given the recent scientific developments in human nutrition and food science, functional foods still need to be investigated from a technological and commercial perspective. New research should focus more on the multidisciplinary view of functional foods and their impact on primary metabolism.

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Chapter 18
Preventive Role of Nutraceutical Agents Against Aging

R. Jayasree, C. Thangam, Langeswaran Kulanthaivel, and Gowtham Kumar Subbaraj

Abstract The biological process of aging is intricate and progressive, and it is influenced by both environmental and hereditary variables. These days, eating a diet that is unbalanced and weak in many vital nutrients is also connected to aging. Nutraceuticals are now valued and regarded as a vital component in enhancing life and supplying antioxidant-containing compounds. Numerous fruits and vegetables include antioxidant molecules that have advantageous qualities that can slow down the aging process. Additionally, these nutraceuticals have a positive effect on the digestive system and do not manifest any undesirable effects. Therefore, the use of nutraceuticals as food supplements holds great promise for slowing down and preventing the aging process. The advantages of nutraceuticals encourage their inclusion in the diet for better health and longevity. The anti-aging effects of plant-based supplements and plant-derived metabolites are systematically summarized.

Keywords Aging · Nutraceuticals · Antioxidants · Free radical scavengers DNA damage

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18.1 Introduction

The biological process of aging impairs cells' and tissues' normal activities, putting the person at risk for illness and mortality. It is the process of developing and aging for the layperson. Aging is influenced by both internal and external influences. The normal biological activities of the cell make up internal variables, whereas external factors include things like smoking, pollution, prolonged sun exposure, hormone imbalances, dietary inadequacies, and exposure to ultraviolet (UV) radiation. By adopting the right preventive steps, such as eating a healthy diet, using skincare products, and taking antioxidant-rich supplements, wrinkle-causing skin aging can be lessened. These steps can be performed to reduce the potentially harmful effects that free radicals may have (Fig. 18.1).

Numerous bioactive substances included in food are crucial for preserving human health. Therefore, humans typically and regularly provide their bodies with nutrients through dietary consumption. Although the hypothesis of aging has not yet been established, it has long been hypothesized that some diets, or specific components in foods, have therapeutic and preventive properties against diseases. Despite the fact that no specific meals or minerals in foods have yet been linked to longevity, it is important to note that some studies have revealed that consuming foods that are relatively high in antioxidants can lower mortality.

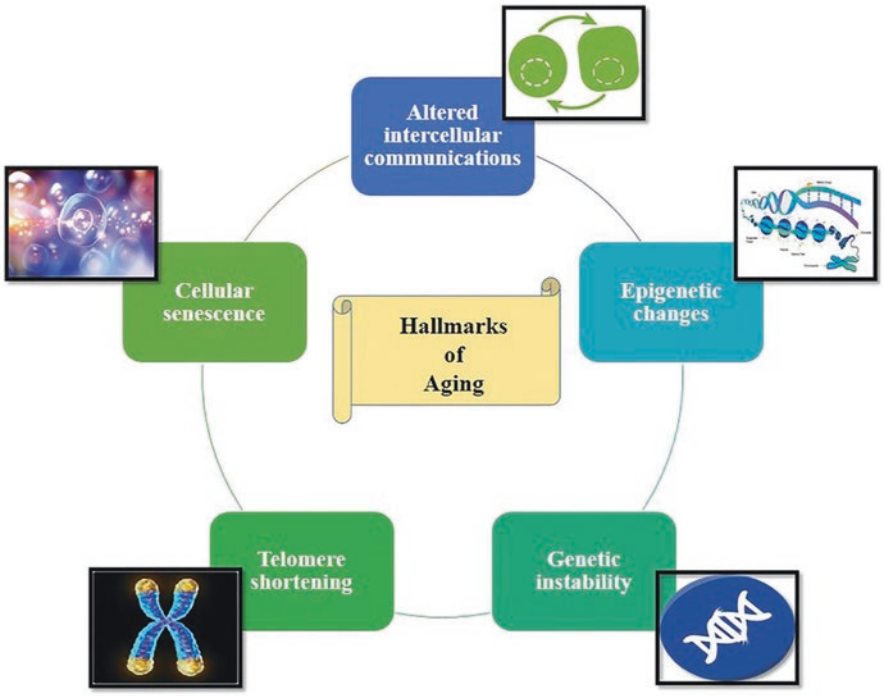

Fig. 18.1 Represents the hallmark of aging

The connection between aging and nutrition has been thoroughly investigated in animals and people as well over the past few decades. With "nutra" standing for food and "ceutical" meaning therapeutic properties, nutraceuticals are nutritious components with medical properties. Nutraceuticals are "food and food products" that have therapeutic properties and offer health advantages, particularly in the prevention and treatment of aging-associated disorders, as per the description of "Foundation for Innovation in Medicine (FIM)" (Derevyanko et al. 2017). These goods, which can be added to the diet as supplements, include functional foods, herbal extracts, and nutritional supplements that have long-term health advantages. Antioxidants may benefit both chronic and age-related illnesses, particularly cancer and neurological diseases, according to researchers. Carotenoids, flavonoids, and vitamins, among other food supplements that have antioxidant capacity, prevent and treat chronic illnesses linked to ROS, leading to healthier and longer lifespans. Food supplements have favorable effects on the immunological and digestive systems as well as antagonistic effects on the body's inflammatory and degenerative processes, thereby enhancing quality of life (Fig. 18.2).

It is widely recognized that plants and their inborn components have antioxidant properties, such as vitamins, carotenoids, and flavonoids, which help in the inhibition and management of chronic illnesses linked to ROS (Kasote et al. 2015). These nutritional supplements have opposing effects on the body's inflammatory and degenerative progressions while exhibiting positive effects on the immunological and digestive systems, thereby enhancing quality of life (Chen et al. 2018).

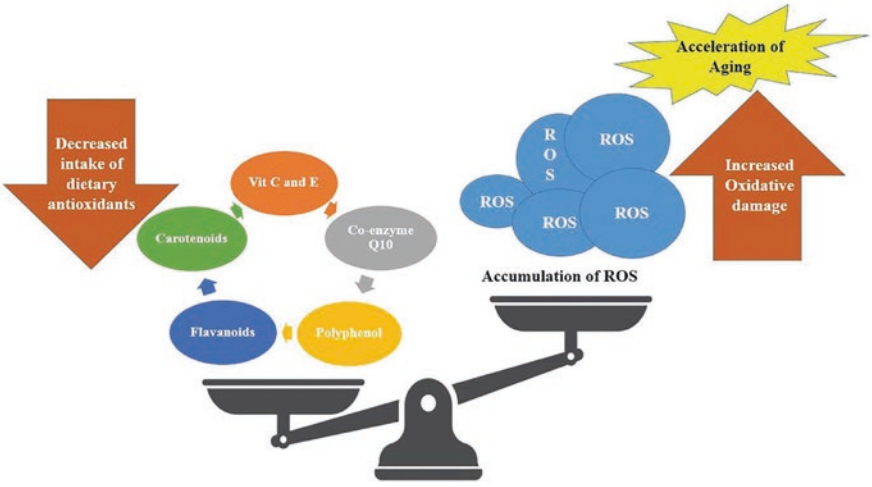

Fig. 18.2 An example of how food antioxidants affect the body's redox balance

18.2 Vegetables and Fruits

The abundance of fruits and vegetables in the Mediterranean diet has also been linked to aging in specific fruits and vegetables. Consuming vegetables and fruits may lower the incidence of heart-related disease (Bazzano et al. 2002). Increased consumption of vegetables and fruits has been linked to a decreased risk of mortality (Leenders et al. 2013). Increased intake of vegetables and fruits was linked to lower mortality among smokers and hypertensive patients (Stefler et al. 2016). Vegetable eating, as noted in this section, appears to be linked to lifespan; nevertheless, consuming simply vegetables might not promote longevity. For example, the mortality rates from all causes for vegetarians and nonvegetarians were nearly equal (Appleby et al. 2016).

18.3 Nuts

Worldwide, people eat nuts, which are prevalent in the Mediterranean intake. Eating nuts altered inflammation, glucose metabolism, and plasma lipids and was associated with a lower risk of dying from heart-associated complications (Imran et al. 2021). Peanuts, almonds, hazelnuts, and walnuts were among the varieties of nuts that were said to significantly lower cancer death rates (Bonaccio et al. 2015). According to a Japanese cohort research, men's all-cause mortality was inversely correlated with total nut intake (chestnuts and peanuts) (Yamakawa et al. 2022). It's interesting to note that the Golestan Cohort Study, which was carried out in Iran, provided evidence that eating nuts—including peanuts, tree nuts, and other types of nuts—reduces mortality without requiring a healthy lifestyle (Eslamparast et al. 2017). Among nuts, walnuts have been the subject of a sizable number of research looking at its connection to longevity. Consuming walnuts may lower mortality, according to several cohort studies (Luo et al. 2014; Guasch-Ferré et al. 2013). On the other hand, irrespective of the type of nut consumed, a cohort research in China found that intake of nuts is dose-dependent and improved long-term survival in breast cancer survivors (Wang et al. 2022). Therefore, additional research and scientific data on the constituents of each variety of nut are necessary to determine the crucial element in the decreased mortality caused by different types of nuts.

18.4 Beverages

The consumption of beverages on a daily basis is thought to affect aging. The drinking of green tea has the prospective to lower the risk of mortality from cardiovascular-associated disease, according to several cohort studies of Japanese people (Abe et al. 2019; Unno and Nakamura 2021). Hao et al. (2016) evaluated the effects of life expectancy and the consumption of minerals in food and drinking water. The intake of Zn, Se, and Cu from water and food was positively connected with

lifespan, but Pb was adversely correlated. There is an opposite relationship between total coffee consumption and the likelihood of dying (Navarro et al. 2018).

18.5 Aging-Accelerating Foods

While eating has been linked to a lengthier life expectation, some have claimed that it may also hasten aging and increase death. Traditional diets, for instance, have been shown to increase mortality under some circumstances. The idea of "ultra-processed food (UPF)" has gained significance as food processing technology has advanced in contemporary culture. It gradually became apparent that consuming UPF would make people more likely to die (Gourd 2018). According to the NOVA classification, UPF is defined as "formulations of ingredients, mostly of exclusive industrial use, typically manufactured by a succession of industrial procedures and processes," and is distinguished from unprocessed and lightly processed foods, processed culinary ingredients, and processed foods (Monteiro et al. 2019). UPF is a term used to describe industrially produced, ready-to-eat foods that include a high concentration of chemicals such as salt, sugar, solidified oil, flavorings, preservatives, and emulsifiers (Monteiro et al. 2018). Eating a diet that is classified as UPF permitting to the NOVA classification is linked to a higher risk of developing cancer (Fiolet et al. 2018). An increase in UPF consumption was linked to a higher risk of total mortality in this adult population (Schnabel et al. 2019). UPFs, particularly ones high in sugar, were associated with an increased risk of death, according to a cohort study of Italians (Bonaccio et al. 2021). Despite being delicious and widely consumed, fried meals have been shown to raise mortality risk conditions such as cardiovascular disease and type 2 diabetes. The consumption of fried foods, especially fried seafood and fried chicken, was connected with risk of death among US women, including from heart-related diseases (Sun et al. 2019). The intake of non-fried and fried potatoes also affects mortality of senior individuals in the USA, and it was found that more than thrice weekly consumption of fried potatoes raised mortality risk (Veronese et al. 2017).

18.6 Individual Food Antioxidants and Aging

It appears practically certain that the composition of the human food has a major impact on aging based on the findings of the numerous investigations that studied the effect of diet on the risk of aging and death reported in the previous chapter. However, it is still unclear which cellular, molecular, and physiological alterations contribute most to aging in different creatures and how they interact (da Costa et al. 2016). It appears challenging to evaluate the impact of "whole foods," which are made up of numerous components, on aging using present scientific methods. There are few theories are there such as (Matsumaru and Motohashi 2021), cross-linking theory (Kim et al. 2011), autoimmune theory (Jalel et al. 2009), and glycation theory (Najjar et al. 2017).

S. no.	Theory	Description
	Program theory	The program theory has a close relationship with telomeres and telomerase. When DNA's terminal bases are lost during replication, it loses its capacity for replication. Mammals' DNA ends in a TTAGGG repeat structure known as a telomere, which safeguards the genetic material and permits replication. Telomerase increases the length of telomeres. As a result, it is thought that telomere length influences how many cell divisions occur, which affects aging and longevity (Vidaček et al. 2018). Telomeres, however, are shortened with aging and have an impact on the aging process since they partially renew with each replication. More recently, it has been demonstrated that decreased neural development and neurogenesis can be seen in telomerase-deficient mice (Ferrón et al. 2009). According to studies using mice, the restoration of telomere length and function can prevent physical aging and increase animal longevity (Derevyanko et al. 2017; Bernardes de Jesus et al. 2012)
	Error theory	According to the error theory, a buildup of mutant proteins results from random mutation in DNA to RNA process and RNA to protein process, which promote cellular malfunction and aging (Orgel 1963). There hasn't been any concrete proof of the age-dependent failure of translation process documented as of yet (Troen 2003). Additionally, a different investigation utilizing *Escherichia coli* has shown that the introduction of gene mutation enhanced the mutation frequency but did not result in death of bacteria (Edelmann and Gallant 1977). As a result, there have been less recent reports that lend weight to this notion
	Wear-and-tear theory	According to Weismann's wear-and-tear theory, which was put forth in 1882, aging progresses when tissues and cells weaken over time as a result of risk factors (Weismann 1891). However, a number of phenomena ruled out this notion. For instance, hyperactive mice can live more than typical mice (Hanson and Hakimi 2008), but their tissues are worn down faster. Caterpillars can live longer when they are unable to express antioxidant enzymes (Van Raamsdonk and Hekimi 2009). Recent research suggests that the wearing down must be taken into account in terms of natural selection from an evolutionary perspective and cannot simply be explained as a physical inevitability of aging
	Cross-linking theory	According to the cross-linking theory, cross-linking of weakly degradable protein, carbohydrate, and lipid molecules affects the function of the cell and speeds up aging by accumulating molecules with multiple reactive units. The extracellular environment becomes more viscous as a result of decreased solubility, flexibility, and permeability brought on by the cross-linking of molecules like collagen. Aging developments as a result of the minimized nutrients circulation and waste products in the cells (Bjorksten 1971). It is well-known that the Maillard reaction's products, which involve the cross-linking of collagen and glucose, increase with aging in the body (Monnier et al. 2005). Because the body produces free radicals that trigger cross-linking reactions with other molecules including collagen, Bjorksten et al. observed that the free radical theory is also a type of cross-linking hypothesis (Rockstein 2012). Even though this notion has been supported by quantitative and qualitative evidence of cross-linked molecules, it is still unclear if the molecules play a significant role in biological aging

S. no.	Theory	Description
	Autoimmune theory	It has been thought that the autoimmune system is at least loosely related to aging. Innate immunity and acquired immunity are the two main immune systems present in higher vertebrates. In terms of aging, the failure of acquired immunity is very important. Aging is linked to both an increase in self-reactive B cell populations and a loss in B cell generation in the bone marrow. In the USA, one of the primary causes of death for women under the age of 65 is aged adaptive immunity, which when combined with other factors encourages development that leads to the body's own tissues being harmed (Shanley et al. 2009; Gs and Stroehla 2003)
	Glycation theory	Maillard first described the aminocarbonyl reaction (also known as the Maillard reaction) in 1912; this phenomenon is regarded as a component of biological body aging (Tessier 2010). At body temperature, a condensation process between the lysine and glucose residues in proteins produces advanced glycation end products (AGEs). The developed AGEs accumulate in a variety of tissues, including the blood vessel walls, and cause tissue stiffness, which results in vasodilator dysfunction and hypertension, which are thought to be aging-related factors (Simm 2013)
	Oxidative damage theory	Reactive oxygen species (ROS) are created during the metabolic process of aerobic organisms as a result of oxygen consumption for energy metabolism. Harman postulated in 1956 that ROS causes aging by harming cells and tissues (Harman 2002). Antioxidants have frequently been emphasized as chemicals that inhibit ROS formation and help to lengthen (Stadtman 1992; Agarwal and Sohal 1994; Miyazawa 2021), whereas older people have higher amounts of oxidized products, such as DNA, lipids, and proteins, than young aged individuals. In aging people, there is a larger level of ROS in cellular organelles. Additionally, in mammals, there is an opposite correlation between the ROS present in the mitochondria and lifespan, indicating that impairment to the membrane lipids and DNA of the mitochondria may possibly be a significant contributor to aging (Cadenas and Davies 2000). However, ROS also contributes to biological defense against intracellular pathogens in the mammalian immune system (Kulinsky 2007). Therefore, it is well accepted that redox balance disruption causes inflammatory reactions. This is related to the notion of aging as it relates to innate defense, which relates to (Colloca et al. 2020) persistently (Gladyshev and Gladyshev 2016) no interaction with intruders, etc., and (López-Otín et al. 2013) impaired inflammation, which has given rise to the term "inflammaging" (Franceschi et al. 2018). On the basis of the "inflammaging concept," it has recently been demonstrated that prolonged tissue inflammation brought on by ROS significantly affects the immune and nervous systems' regulatory mechanisms, as well as on the aging process (Fülöp et al. 2019; Santoro et al. 2020). Chronic tissue inflammation can also be brought on by suppressing the immune system's control of inflammatory factors

S. no.	Theory	Description
	Other biological aging-related theories	Growing interest among gerontologists has been focused on the concept of "senescent cells," which speed up aging process. Cells that are older and no longer divide are often eliminated from the body by the process called phagocytosis. Despite the fact that cell division has ceased, senescent cells still build up in the tissues. Recent research has demonstrated that the accumulating senescent cells emit inflammatory chemicals that cause excessive inflammation, accelerate the senescence of nearby cells, and cause tissue malfunction (Laberge et al. 2012). Senescent cells cannot all be removed by the body's immune system; hence certain anti-aging strategies have started to evolve that specifically target these cells (Gasek et al. 2021). Further clarification of the physiological phenomenon may be required because the exact information on the connection is still lacking between these senescent cells and aging There is a hypothesis that claims all factors have no effect on how quickly people age, in contrast to the belief that certain factor(s) speed up the process of aging. According to Colchero et al. (2021), there is a significant linear relationship between lifespan equality and life expectancy in a variety of primates, which is mostly related to mortality of the newborn or the improvement of mortality irrespective of age and has no bearing on the aging rate. This finding implies that longevity is solely determined by the biological limit

The "oxidative damage theory," which was discussed in the first half of this review, is the foundation for the majority of these earlier investigations. With a lot of experimentally based data being documented from the past period to the present period, this theory has been one of the most well-liked theories in aging research (Viña et al. 2007). There is mounting substantiation that ROS may function as signaling molecules that ultimately increase lifespan as well as cause oxidative stress (Tapia 2006). These developments gave rise to the theory of "mitohormesis," according to which ROS accelerates aging but, at the right concentrations, can strengthen the body's natural defenses (Miyazawa et al. 2019; Ristow and Schmeisser 2014). Since the formation of ROS during ATP synthesis in the mitochondria is essential for aerobic organisms to obtain energy, the management of redox equilibrium in the body is a crucial factor in aging. Additionally, it is anticipated that each antioxidant found in food will help to control the redox balance. The anti-aging benefits of antioxidants appear to depend on cell signaling pathways associated with this equilibrium, including MAPKs, NF-B, and Nrf2 (Santos et al. 2021; Chen et al. 2022; Tian et al. 2019; Wang et al. 2019, 2020) (Fig. 18.3).

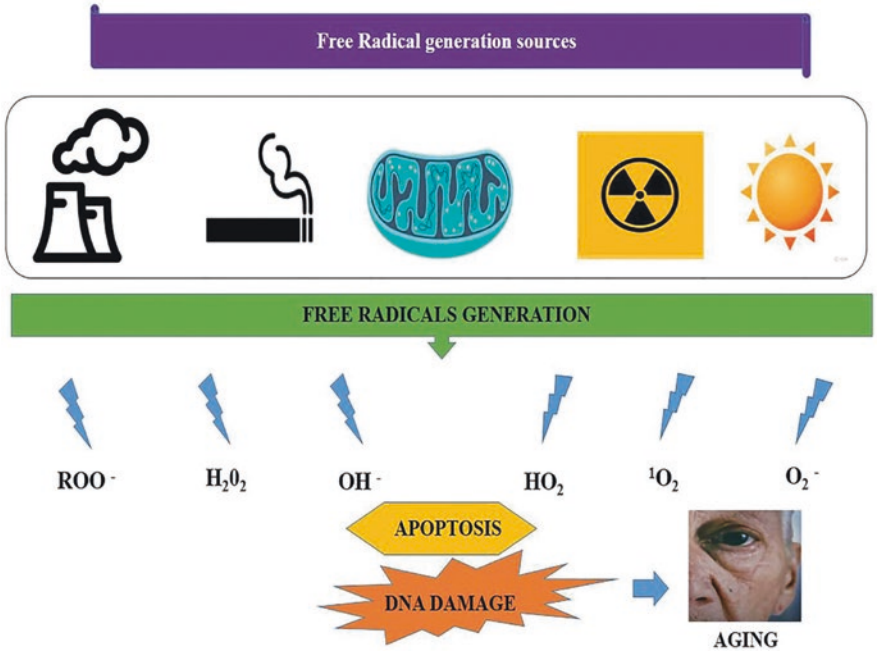

Fig. 18.3 Represents the free radical-mediated DNA damage and aging

18.7 Adaptogens

Adaptogens are herbs and mushrooms that improve your body's capacity to deal with stress, anxiety, exhaustion, and other health-related issues. Adaptogens can be consumed as tinctures, added to food or drinks or both. By controlling both physical and emotional stressors, adaptogens help your body regain a stable balance (Liao et al. 2018). These substances lessen cellular susceptibility to stress and boost the body's ability to protect itself from numerous risks (Bhatia et al. 2011). Additionally, they support and aid in restoring typical physiological activity (Singh et al. 2017).

18.8 *Ginkgo biloba*

Gingko, sometimes referred to as *Ginkgo biloba*, is a functional food that increases the tissues' ability to absorb oxygen (Isah 2015). The glucose levels and blood flow in the brain have been demonstrated to be significantly maintained by ginkgo leaves (Dhanjal et al. 2020). Additionally, it enhances the brain's capacity for thought (Zuo et al. 2017). Some of the flavone glycosides that are produced from the ginkgo leaves extract and are active scavengers of free radicals are lactone derivatives (ginkgolides), catechin, shikimic acid, isorhamnetin, and ascorbic acid (Van Beek 2002). Huang carried out a study to determine how *Gingko biloba* extract affected the functions of the liver in old rats. As a result of the administration of *Gingko biloba* extract, liver metalloproteinase and

malondialdehyde levels were decreased, and SOD activity was increased to reduce oxidative stress (Huang et al. 2005). According to a different study, giving old female rats *Ginkgo biloba* extract improves their cognitive performance (Belviranlı and Okudan 2015). The effectiveness of Gingko biloba extract in the management of Alzheimer's disease was well documented. A thorough analysis has shown that taking *Gingko biloba* extract helps people with moderate dementia operate more cognitively (Liu et al. 2020).

18.9 Ginseng Panax

Ginseng, or *Panax ginseng*, is well-known for its therapeutic properties (Rokot et al. 2016). The roots of this plant are where the bioactive chemical ginsenoside is found (Yu et al. 2019). This bioactive substance modifies immunological function and increases the body's tolerance to stress, tiredness, anxiety, and trauma (Kumar et al. 2012). Additionally, it exhibits stress subsidence qualities and enhances learning and memory (Rokot et al. 2016). According to an investigation, giving juvenile leukemia-affected mice ginseng extended their lives (Wee et al. 2011). By reducing oxidative stress, a different study on *Panax ginseng* found that it can lower lipid peroxidation and boost antioxidant potential (Lee et al. 2017). Additionally, ginseng eating enhances a person's psychomotor ability, according to double-blind clinical research (Caldwell et al. 2018). Additionally, *Panax ginseng* has been linked to the activation of foxo3a gene, known as the longevity gene, and has been claimed to have anti-melanogenic properties (Kim et al. 2017). According to certain research, *Panax ginseng* delays the aging process of the skin. Additionally, a study was carried out to evaluate the effectiveness of ginsenosides and *Panax ginseng* in delaying the aging process of the skin. The findings revealed a substantial decrease in wrinkle creation, and no participant experienced any side effects (Hwang et al. 2015).

18.10 *Glycyrrhiza glabra*

The Fabaceae family includes *Glycyrrhiza glabra*, widely known as licorice (Pastorino et al. 2018). This plant's rhizomes and roots act as a brain tonic that aids in controlling blood sugar levels (Frattaruolo et al. 2019). The key bioactive compound isolated from this antioxidant-rich plant is glycyrrhizin, which improves memory, prevents oxidative damage to the brain, and maintains typical nervous system function (Grodzicki and Dziendzikowska 2020). Licorice, a phenolic molecule found in *Glycyrrhiza glabra*, has antioxidant potential, making it useful in scavenging free radicals and chelating metal ions (Ciganović et al. 2019). According to reports, *G. glabra* improves memory in the scopolamine-induced dementia mouse model (Balmus and Ciobica 2017). Additionally, Dhingra and associates noted memory improvements in mice given *Glycyrrhiza glabra*. Various doses of *Glycyrrhiza glabra* extracts 75, 150, and 300 mg/kg were given orally over the course of 7 days. The outcomes indicated that the mouse model's memory was improved by a dose of 150 mg/kg (Chinkwo 2005).

18.11 *Curcuma longa*

The ginger family member *Curcuma longa* generates the substance known as curcumin (Kocaadam and Şanlier 2017). It is well-known for a variety of biological functions, including its antioxidant, anti-inflammatory, and anticancerous qualities (Wachtel-Galor 2011). Curcumin is a possible therapeutics for many malignancies because of its natural features (Tomeh et al. 2019). Numerous investigations have shown that curcumin can inhibit the activity or expression of tumor necrosis factor (TNF), prostaglandin E2 (PGE2), COX-2, and other pro-inflammatory cytokines (Desai et al. 2018). Curcumin's antioxidant capabilities can help to lower ROS generation, prevent lipid peroxidation, and scavenge free oxygen radicals (Engwa 2018). Oral ingestion of curcumin in mice has been proven to improve cystic fibrosis and stop tumor growth; however, studies in people are still being conducted (Tomeh et al. 2019). According to a study, curcumin activates the phosphatidylinositol 3-kinase/Akt pathway and redox signaling in human fibroblasts to cause a cellular stress response. This demonstrates the potential efficacy of curcumin-triggered cellular antioxidant defenses as an anti-aging therapeutic strategy (Lima et al. 2011).

Additionally, it has been observed to lengthen the lives of mice, nematodes, and fruit flies (Soh et al. 2013; Shen et al. 2006; Lee et al. 2010). Curcumin has even been reported to lessen and control the signs of age-related illnesses like diabetes, cancer, and atherosclerosis (He et al. 2015; Olszanecki et al. 2005). In addition to this, curcumin has been noted to exhibit defense against radiation- and chemotherapy-induced dermatitis in patients with breast cancer (Swamy et al. 2012; Ryan et al. 2013). Due to its ability to postpone cellular senescence, curcumin has been suggested in certain studies to have anti-aging properties (Hamidie et al. 2015). In a trial involving healthy people between the ages of 60 and 85, Cox et al. evaluated the impact of solid lipid curcumin on cognition and mood.

18.12 *Emblica officinalis*

The Phyllanthaceae family includes *Emblica officinalis*, widely known as amla (Yadav et al. 2017). Amla churn is renowned for lowering cholesterol levels and enhancing cognitive capacity (Kapoor et al. 2020). The use of amla as part of a diet is effective in reducing blood and brain cholesterol levels (Wilson et al. 2017). Additionally, it has been touted as an advantageous functional meal for the treatment of Alzheimer's disease (Hasan et al. 2016). In order to assess the skin-lightening capability of a topical formulation containing *E. officinalis* extract, kojic acid, and glycolic acid, Draelos and colleagues undertook a double-blind trial. Because the topical formulation performed 4% stronger than hydroquinone in the study, investigators suggested that it might work as a natural substitute for treating facial dyschromia (Lauer et al. 2013). Free radical buildup in numerous tissues is linked to a variety of stress-induced situations, which accelerate the aging process

(Bhattacharya et al. 2002). Due to their antioxidant activity, tannins derived from *E. officinalis* also have a protective effect in a tardive dyskinesia (Bhattacharya et al. 2000a, b). Additionally, the *E. officinalis* extract has antidepressant characteristics by reducing the activity of GABA and MAO-A in combination with antioxidant activity (Dhingra et al. 2012).

18.13 *Bacopa monnieri*

A perennial herb with purple blooms and tiny oblong leaves is called *Bacopa monnieri*, or brahmi (Singh and Dhawan 1997). This medicinal herb contains highly useful nootropic compounds like bacosides (Jain et al. 2016). The two primary phytochemicals that are primarily derived from this herb are brahmine and herpestine (Tewari et al. 2014). The phytochemicals derived from brahmi help to shield the brain from the effects of ROS while also enhancing learning and cognitive function (Vollala et al. 2010). It is understood that frequent brahmi oil use lowers the risk of a number of illnesses, including amnesia and Alzheimer's disease (Simpson et al. 2015). In a dose-dependent manner, Bhattacharya et al. (2000a, b) discovered that extracts of *Bacopa monnieri* increase antioxidant enzymes activity such as superoxide dismutase (SOD), glutathione peroxidase (GPX), and catalase (CAT). After 14 and 21 days, the results of this investigation in rats' brain regions were examined (Bhattacharya et al. 2000a, b). Using *Bacopa monnieri* extract and 3-nitropropionic acid (NPA), a fungal toxin that causes neurotoxicity in both animals and humans, Shinomol and associates conducted an in vitro and in vivo investigation. The results revealed that NPA was effective in causing oxidative stress in the mitochondria and dopaminergic (N27) cells of the striatum of rats, whereas *Bacopa monnieri* extract was found to be beneficial in controlling the NPA-induced oxidative damage and lowering the thiol and glutathione (GSH) levels (Shinomol and Bharath 2012). A study was conducted by Kumar and his associates to determine the impact of *Bacopa monnieri* extract on the cognitive abilities of medical professionals. The study's findings revealed a sizable improvement in the pupils' cognitive performance (Kumar et al. 2016).

18.14 Polyphenols

Secondary metabolites, particularly polyphenolic chemicals, are prevalent in vegetables, fruits, grains, and drinks and are mostly produced by plants (Fereidon and Ambigaipalan 2015). Due to their natural qualities, such as antioxidant potential and anti-inflammatory and anticarcinogenic effects, polyphenols have drawn the attention in recent days (Quero et al. 2020). Due to these properties, polyphenolic substances can help treat conditions like diabetes, asthma, cardiovascular disorders, microbial infections, and cancer (Pandey 2009). Numerous polyphenolic

substances, including silymarin, proanthocyanins, and resveratrol, have been the subject of studies. Their effectiveness on animal models exposed to oxidative stress, DNA damage, and UV-mediated skin irritation has been examined (Dunaway et al. 2018). Additionally, these polyphenols can effectively protect the skin from UV radiation-related skin issues and help lower the risk of skin cancer when combined with sun protection cosmetics (D'Orazio et al. 2013). Below are several polyphenols that have medicinal qualities.

The skin of grapes and peanuts contains resveratrol (also known as stilbenes), a naturally occurring polyphenolic molecule with possible antioxidant properties (Adhikari et al. 2019). Due to its use as an anti-aging component, it has been a focus of intensive research for the past 20 years (Camins et al. 2009). It also has anti-inflammatory effects, has the ability to scavenge free radicals, and can operate as a chelating agent (De Vries et al. 2018). It is showing prospective in the treatment of a number of illnesses, including cardiovascular and Alzheimer's disease, according to studies (Gomes et al. 2018). Additionally, resveratrol has the potential to be a cancer chemopreventive, according to Bhat and Pezzuto (2002). According to a study done on HaCat cells exposed to sodium nitroprusside, it also has a protective effect (Bastianetto et al. 2010). To evaluate the effectiveness of resveratrol on the proliferation and inhibition of collagen activity, Giardina and associates carried out an in vitro study on skin fibroblast. The outcome revealed a significant suppression of collagenase activity and a dose-related increase in cell proliferation rate (Giardina et al. 2010). Resveratrol is said to have the ability to slow down cellular aging and may represent a breakthrough in geriatric and anti-aging treatment; however there is no evidence to back up this claim in the human population (Demidenko and Blagosklonny 2009; Xia et al. 2008; Giovannelli et al. 2011). The biogenesis receptor gamma coactivator 1-alpha (PGC-1) through activating the peroxisome was controlled by resveratrol (López-Lluch et al. 2008; Lagouge et al. 2006).

Phlorizin is a kind of flavonoid that is only synthesized by a small number of plants (Wang et al. 2018). For more than a century, the pharmaceutical industry has greatly benefited from it and used it as a stage to assess physiological function assessment (Dunaway et al. 2018). The advantages of phlorizin in terms of nutrition have been the subject of numerous investigations. In a latest investigation, the anti-aging benefits of phloretin and phlorizin were investigated on senile osteoporosis mouse models. According to the study, phlorizin assisted in controlling the ratio of osteoprotegerin (OPG), a biochemical marker of osteoporosis, to receptor activator of nuclear factor kappa-B ligand (RANKL), a nuclear factor kappa-B ligand. The quantity of osteoclast cells that express tartrate-resistant acid phosphatase (TRAP) was likewise decreased by phlorizin (Antika et al. 2017). Unripe apples contain significant quantities of phlorizin. Unripe apples containing phlorizin have been shown to be helpful in reducing postprandial hyperglycemia, according to a preliminary study on human volunteers. The study, which involved six healthy participants, found that eating unripe apples decreased postprandial glucose response and raised urine glucose levels statistically significantly (Makarova et al. 2015). In a study by Mela and colleagues reported that, the effects of eight plant extracts and their

combinations apple, mulberry fruit, elderberry, mulberry leaf, turmeric, white bean on postprandial insulin (PPI) and glucose (PPG). According to the study's findings, PPI and PPG response might be decreased by using extracts of apple, mulberry fruit, and mulberry leaf extracts (Mela et al. 2020). Phlorizin may be able to slow down the effects of aging and hence improve quality of life because hyperglycemia has been shown to speed up the aging process (Laiteerapong et al. 2011). Numerous more plant extracts have shown to be rich sources of substances with antioxidant activity (Ayaz et al. 2019). It has been discovered that metabolites such silymarin, genistein, and apigenin have a favorable effect on the signs of skin aging (Isah 2015). The true anti-aging potential of phlorizin has yet to be revealed through clinical or human research.

18.15 Apple

Apple is rich in phytochemicals, particularly polyphenols, which have an important antioxidant potential (Zhang et al. 2015). Apples contain a variety of polyphenolic substances, including rutin, epicatechin, catechin phloretin, chlorogenic acid, and proanthocyanidin B2 (Kschonsek et al. 2018). According to certain studies, eating apples every day can lower your risk of developing hypercholesterolemia and cardiovascular disease (Boyer and Liu 2004). Consuming apples may significantly reduce the risk of developing lung cancer, especially in women, according to research (Vafa et al. 2011). Numerous investigations have proved that apple is efficient in preventing oxidation of low-density lipoprotein (LDL) (Boyer and Liu 2004). In order to determine how apple polyphenols affect the gene expression of the SOD, CAT (catalase), Rpn11, Mth (methuselah), and CcO (cytochrome c oxidase) subunits III and VIb, a study was carried out. The study's findings showed that apple polyphenols gave fruit flies a 10% longer lifespan. Additionally, fruit flies showed downregulation of Mth; overexpression of SOD1, SOD2, and CAT; and no appreciable change in the gene expression of VIb, Rpn11, or CcO subunits (Peng et al. 2011). Furthermore, research on both normally aging mice and animals with genetic flaws demonstrated the neuroprotective potential of concentrated apple juice. However, the anti-aging properties of apples and the processes underlying them are yet unknown (Peng et al. 2014).

18.16 Blueberry Extract

Compared to other fruits and vegetables, blueberries contain a higher concentration of polyphenols (Cory et al. 2018). The reduction of signs of aging has been linked to the strong antioxidant potential of blueberry extracts (Kalt et al. 2020). According to studies, regular eating of blueberries may make senior populations more

susceptible to memory-related problems (Shukitt-Hale et al. 2019). Consuming blueberry extract has been said to delay age-related functional and physiological decline (Joseph et al. 2005). Blueberry extract administration was observed to restore the age-related reduction in the hippocampus heat shock protein (HSP) by Galli et al. (2006). In older rat models, blueberries have also been shown to effectively improve motor and cognitive performance (Goyarzu et al. 2004). To comprehend the underlying mechanism, fruit flies have also been used to study the ability of blueberry extracts to prolong life. The study's findings demonstrated that adding 5 mg/mL of blueberry extract to the meal considerably extended fruit flies' longevity by 10% (Peng et al. 2012).

18.17 Theaflavins and Catechins from Tea

Tea has become the most popular beverage in Asia (Su et al. 2003). Theaflavins and catechins, two of tea's inherently beneficial components, are responsible for these health benefits (Musial et al. 2020). Studies have indicated that drinking green or black tea regularly can prevent DNA molecule oxidation (Yan et al. 2020). Theaflavins and catechins have been shown to extend the average lifespan in other in vivo investigations on *Drosophila* (Li et al. 2007). According to numerous published studies, oral tea polyphenol ingestion and topical green tea application both prevent UV radiation- or chemical-mediated skin carcinogenesis in a variety of animal models (Oyetakin et al. 2012). Theaflavins and catechins from tea are anti-inflammatory and anticarcinogenic (Musial et al. 2020). To determine the impact of tea polyphenol extract on variables related to acute UV harm, Elmets and his team carried out a study. For this, volunteers' skin was initially treated with extract of green tea or its components, and then the treated areas were exposed to two low doses of solar-simulated radiation to cause erythema. The biochemical, clinical, and histologic signs of UV-induced DNA damage were subsequently studied in the skin. The outcomes showed that tea extract had an inhibitory effect on the erythema response brought on by UV irradiation in a concentration-dependent fashion. The results of the histologic analysis also revealed less Langerhans and sunburn cells (Elmets et al. 2001).

Additionally, tea polyphenol extracts also lessened DNA deterioration in the skin. As a result, scientists claimed that tea polyphenol extract might work as a healthy substitute for photoprotection (Elmets et al. 2001). Chiu and colleagues studied the histological and clinical aspects of photoaging to determine the impact of a combination therapy course of topical and oral green tea. In this trial, 40 women with reasonable photoaging were randomly assigned to receive either a placebo or a regimen of 300 mg of tea oral supplements (to be taken twice daily) and 10% green tea cream for 8 weeks. The study's findings did not reveal any appreciable variations in the clinical signs of photoaging between the green tea treatment group and the placebo group. However, the treated participants showed a histologic advancement in the amount of elastic tissue (Chiu et al. 2005).

18.18 Anthocyanins in Black Rice

Black rice is rich in antioxidants, and it has been shown that taking antioxidant supplements helps Alzheimer's patients feel better (Liu et al. 2018). Additionally, it has an anti-inflammatory and anticarcinogenic activity (Shaikh et al. 2014). Peonidin-3-glucoside and cyanidin-3-o glucoside are two anthocyanins that are abundant in it as well (Azevedo et al. 2010). Black rice may be able to increase the lifetime of fruit flies, according to research done by Zuo and colleagues. The impacts on the SOD1, SOD2, CAT, MTH, and Rpn11 gene expressions were assessed for determination. The study's findings showed that fruit flies' lifespans were increased by 14% by consuming 30 mg/dL of black rice anthocyanins. Additionally, Mth's gene expression was downregulated, whereas SOD1, SOD2, CAT, and Rpn11 gene expression was elevated (Zuo et al. 2012). To evaluate the impact of black rice anthocyanins, Huang et al. used a subacute aging mouse model. They discovered that these anthocyanins have anti-aging, anti-fatigue, and anti-hypoxic effects (Huang et al. 2006).

18.19 Carotenoids

Lycopene and -carotene are examples of carotenoids, which are vitamin A derivates with significant antioxidant potential and photoprotective properties (National Research Council 2000). Skin texture can be slightly improved by lycopene and -carotene (St Stahl and Sies 2012). Carotene can be found in a variety of plants, including carrots, mangoes, papaya, and pumpkins (Pritwani and Mathur 2017). Due to its features, including lipid radical scavenging activity, pro-vitamin A activity, and single oxygen-quenching qualities, it has become an important carotenoid (Jaswir et al. 2011). According to studies, -carotene has great photoprotective capabilities and can prevent erythema brought on by UV radiation (Parrado et al. 2018). There have been reports linking low plasma levels of -carotene to cellular aging. The telomerase activity of older persons may be modulated by -carotene, according to a study (Boccardi et al. 2020) that involved 68 elderly participants. The adverse effects of more beta-carotene for smokers, on the other hand, are well-known and can hasten the development of lung cancer. The α-tocopherol, β-carotene cancer prevention study group released a groundbreaking report; according to this study, men who received supplemental β-carotene had an unexpectedly higher occurrence of lung cancer than those who did not (Cockcroft et al. 1994).

Various vegetables and fruits, including carrots, watermelons, papayas, tomatoes, and others, contain lycopene, a red carotene, carotenoid, and phytochemical (Schagen et al. 2012). Although it lacks vitamin A action, it has a great potential for quenching single oxygen (Evans and Johnson 2010). A study further supported the function of lycopene in tissues by preventing oxidative stress. It was shown that more skin lycopene was damaged after exposure to UV light than -carotene (Ascenso

et al. 2016). In addition to having the capacity to drastically lower MMP-1 activity, which is known to destroy collagen, products of lycopene have also been demonstrated to be effective against malignant cells (Przybylska 2020). The major carotenoids present in human blood and tissues, lycopene and carotene, are both known to control skin characteristics (Johnson 2002). Cheng and colleagues found that lycopene promotes the base excision repair pathway in vitro in A549 cells in a publication that was just published. A molecular pathway has been revealed by this study and needs to be further investigated in vivo and using animal models (Cheng et al. 2020).

Ascorbic acid, the name by which vitamin C is frequently referred to, is a highly water-soluble vitamin (Singh et al. 2020). Due to its intense reducing nature, this colorless molecule possesses excellent antioxidant potential (Carr and Melcher 2017). The hydrophilic environment is ideal for the photosensitive ascorbic acid to function (Hemila 2017). Humans cannot produce this crystalline substance; as a result, it must be consumed as part of a normal diet (Souyoul et al. 2018). To prevent the health issues linked to vitamin C deficiency, such as cardiovascular illnesses, scurvy, and others, diets should be supplemented with vitamin C-rich sources, such as grapefruit broccoli, strawberries, green peppers, Brussels sprouts, kiwifruit, and oranges (Brickley et al. 2020). The elevated antioxidant potential and scavenging of free radical capabilities of ascorbic acid aid in preventing free radicals from oxidizing macromolecules (DNA and proteins), cell membranes, and tissues diet (Souyoul et al. 2018).

Vitamin E is a fat-soluble, membrane-bound substance with significant free radical scavenger (Galli et al. 2017). Vegetables, nuts, corn, almonds, soy, peanuts, meat, sunflower oil, safflower oil, and wheat germ oil all contain this nonenzymatic antioxidant (Sivakanesan 2018). Infants may have a variety of health issues, including edema, depigmentation, papular erythema, and dryness if their bodies have vitamin E deficiencies (Leonard et al. 1966). Due to its effectiveness in preventing the peroxidation of lipids and the cross-connection of collagen fibers, vitamin E consumption aids in the prevention of skin aging signs (Schagen et al. 2012). Sunburn and UV-related skin damage can both be treated with vitamin E, according to research (Abid Keen and Hassan 2016).

The two vitamins C and E complement one another. For instance, a chain reaction of lipid peroxidation begins in the membrane rich in polyunsaturated fatty acids when UV-induced molecules oxidize the components of the cell. During this process, the antioxidant d-tocopherol is converted to the tocopheroxyl radical, which then regenerates through ascorbic acid (Fryer 1993; Chan et al. 1991). Tocopherol is abundant in a variety of foods, including corn, seeds, vegetable oils (sunflower oil and safflower oil), and soy (Schagen et al. 2012). Vitamin E from natural sources also protects against lipid peroxidation and collagen cross-linking, two processes linked to skin aging. Additionally, vitamin E administered topically has been shown to lessen photocarcinogenesis, erythema, burnt cells, and persistent UVB-induced skin damage (Makrantonaki and Zouboulis 2008; McVean and Liebler 1999). Depigmentation and dryness in premature newborns are also linked to vitamin E insufficiency, along with a condition of edema with seborrheic alterations (Passi

et al. 1991). After reviewing their work, Ekanayake-Mudiyanselage and Thiele concluded that the quantity of sebaceous glands in the skin affects the level of vitamin E. It has been demonstrated that taking tocopherol orally for 3 weeks significantly raises the levels of vitamin E in sebaceous glands, particularly those on the face (Ekanayake-Mudiyanselage and Thiele 2006). Oral vitamin C and E supplementation has been demonstrated in a comparative study to enhance the photoprotective efficacy in comparison to monotherapies (Eberlein-König and Ring 2005). Another trial involved 33 volunteers who received either a placebo or 100 or 180 mg of vitamin C daily for 4 weeks. According to the study's findings, taking vitamin C orally increased the skin's capacity to scavenge free radicals by 22% for 100 mg and 37% for 180 mg when compared to the baseline (Lauer et al. 2013). It was discovered that vitamin E had negligible impact on the prevention of lung cancer in the study of the alpha-tocopherol and beta-carotene cancer prevention study group (Cockcroft et al. 1994). Several different groups of substances that are well-known to enhance health are included in nutraceuticals, functional foods, and dietary supplements (Shahidi 2012). Due to its ability to reduce the signs of aging skin, functional foods have attracted interest on a global scale (Dhandevi and Jeewon 2015). Notably, fruits are an important source of the active metabolites that are used to reduce the signs of aging skin because they are rich in phenolic compounds, carotenoids, and ascorbic acid and have a strong antioxidant potential (Petruk et al. 2018).

18.20 Conclusion

Dietary supplements are both nutraceuticals and nutrition supplements that are meant to be used orally. Supplement use is advised, but does not guarantee the diagnosis, treatment, mitigation, or prevention of disease. Adopting low-carbohydrate diets or eating a diet high in fruits, vegetables, nuts, grains, fish, and unsaturated fats that are rich in antioxidants, potassium, and omega-3 fatty acids decreased the risk of obesity and cardiovascular disease, protected the brain from aging, decreased the risk of shortening of telomere, and encouraged a healthier lifestyle. The prevalence of cancer, cardiovascular diseases, diabetes, and telomere attrition may be reduced as a result of a low-fat diet that is also high in antioxidants, which also helps to minimize DNA oxidation and oxidative stress. These diets can extend the life and improve one's quality of life.

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