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Neuroprotective Effects of Phytochemicals in Brain Ageing

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Dedicated to our beloved mother the late Mrs. Bela Rani Pathak.

Preface

This book, ***Neuroprotective Effects of Phytochemicals in Brain Ageing*****,** deals with the mechanism of brain ageing and the prospective therapeutic approaches rendered by phytochemicals for the treatment.

The effects of ageing on the brain and cognition are widespread and have multiple aetiologies. This book will discuss how natural compounds can modulate brain ageing and repair function of degenerated neurons. This book will also address some recent crucial topics on cognitive impairment, hormetic phytochemicals in brain ageing, and molecular mechanisms of action of phytochemicals to delay neurological disorders and brain ageing.

As we age, our bodies undergo natural changes, and the brain is no exception. It is particularly vulnerable to the impact of senescence, making it even more crucial to explore the connections between ageing and neurological health. Through advanced neuroimaging techniques, scientists have discovered brain age as a biomarker that can predict our chronological age. This discrepancy between predicted and actual age, termed brain ageing, provides valuable insights into age-related brain alterations.

This book explores the details of brain ageing and its potential links to neurodegenerative diseases. This book will explore the effects of ageing on the DNA methylation process and the aggregation of specific proteins like phosphorylated tau, α-synuclein, and Aβ. Yet, it will also uncover the gaps in our knowledge, as we still seek to understand whether these age-related changes lead to cognitive impairment.

Currently, treatments for neurodegenerative diseases are limited, often providing only temporary relief with unwanted side effects. This brings us to an exciting area of exploration—the potential role of dietary interventions and nutraceuticals in mitigating neurological impairment. Phytochemicals hold promise as supportive therapeutic agents. This book will examine the neuroprotective properties of various phytochemicals and their potential to counteract brain ageing.

We genuinely hope that basic scientists, nutritionists, and doctoral students, working on any neurological disorders, or related research, or research linked to alternative medicine for neurological disorders will find this book to be useful.

We sincerely thank Springer Nature for their help in publishing this book.

Chennai, Tamil Nadu, India Surajit Pathak
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About the Editors

Surajit Pathak, Ph.D is currently working as a Professor at Chettinad Academy of Research and Education, Kelambakkam, Chennai, since 2015. He worked as a Principal Research Scientist in Linkoping University, Linkoping, Sweden (2022 June–Dec 2022). He has received his Ph.D. degree from India in 2007 and completed his Post-Doctoral training (2007–2015) at the University of Alabama, USA, University of Padova, Italy, and University of Linkoping, Sweden.

His current research focuses on the role of intracellular and extracellular microRNAs for the early detection of colorectal cancer. He has published more than **125 research and review articles** in peer-reviewed international journals of repute with 3238 citations and 32 h-index. He received various research grants from the national and international funding agencies. He has active research collaboration with top research laboratories in Sweden, Italy, Norway, Turkey, Mexico, and India.

He is the editorial board member of various renowned international high-impact journals. Prof. Pathak has edited several books for **Springer Nature:** ***Cancer Stem Cells: New Horizons in Cancer Therapies*****; MRW book** ***Handbook of Animal Models and its Uses in Cancer Research*****; and** ***Evidence-Based Functional Foods for Prevention of Age-related Diseases***. He is a member of various professional research bodies of India, including **Indian Association of Cancer Research, Indian Science Congress.**

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She has published over **120 research and review articles** in peer-reviewed international and national journals with a citation index of **2403, an i10-index of 56, and an h-index of 25**. She serves as an editorial board member and reviewer of international and national journals. She serves as the editor of books published by Springer, namely ***Cancer Stem Cells: New Horizons in Cancer Therapies*; *Handbook of Animal Models and its Uses in Cancer Research*; and *Evidence-Based Functional Foods for Prevention of Age-related Diseases*.** She is a lifetime member of Indian Association of Cancer Research.

Phytochemicals as Protective Agents for Brain Aging

1

Mohamed Y. Zaky, Hadeer M. Morsy, and Osama M. Ahmed

Abstract

Aging is the major danger agent for many age-related disorders, including neurological diseases. Knowing the biological mechanisms of aging is critical to achieve brain health. In this regard, brain aging is characterized by neurophysiological functions gradually decline, impaired adaptive neuroplasticity, dysregulation of neuronal calcium homeostasis, neuroinflammation, and oxidatively modified molecules and organelles. Several molecular and cellular indicators of brain aging include mitochondrial dysfunction, accumulation of oxidatively damaged molecules, impaired lysosome and proteasome function, dysregulation of neuronal calcium homeostasis, inflammation, and impaired neurogenesis. Thus, therapeutic approaches target the beneficial effects of phytochemicals on aging-associated impairment of brain function. In cellular models of neurological diseases, phytochemicals, or food's second metabolites, preserve neuronal cells against cell death, and the neuroprotective effect is attributed to antioxidant, antiinflammatory, and antiaging properties. Phytochemicals activate the neuronal antioxidant defense and survival. Mechanisms associated with neuroprotective effects of phytochemicals on the brain such as cellular defense against oxidative stress (the Nrf2-ARE antioxidant system), cell survival system (the TrkB signaling pathway), and crosstalk between TrkB signaling pathway and Nrf2-ARE antioxidant system were outlined. The recent evidence in this chapter describes the hallmarks of brain aging which affect impairment in brain function, acknowledgment of antiaging,

Mohamed Y. Zaky and Hadeer M. Morsy contributed equally with all other contributors.

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antioxidant, and antiinflammatory effects of phytochemicals against oxidative stress and emphasizes their importance as a protective agent for brain aging and neurodegenerative disease resistance.

Keywords

Brain aging · Phytochemicals · Trkb signaling pathway · Nrf2-ARE antioxidant system

1.1 Introduction

Brain aging is the main risk factor for neurodegenerative diseases, which is defined by continuous declines in memory and cognition. Senescent cells proliferate with age and contribute to brain dysfunction (Rossiello et al. 2022). It is characterized by a progressive deterioration of physiological processes of neurons, diminished neuroplasticity adaptation, uncontrolled calcium homeostasis of neurons, inflammation of neurons, and modified oxidatively molecules and organelles. Lots of methods contribute to brain aging, including oxidative stress (OS) elevation, inflammation, and disruptions in energy utilization, which contribute to neurodegenerative disorders (Zia et al. 2021).

Moreover, the impacts of aging on the brain and cognition are prevalent and have a variety of reasons. Aging influences molecules, cells, vasculature, gross morphology, and cognitive ability. Our brains shrink as a result of age, especially in the frontal cortex. The threat of stroke and ischemia raises as the blood vessels shrink leading to hypertension, and the white matter begins to develop lesions. Impairment of memory occurs due to age, and stimulation of the brain for memory exercises becomes more bilateral. This could be an effort for restitution and acquirement of new networks, or it might be due to specific areas that are not any more readily accessible. Brain aging is affected by neurotransmitters, genetics, experience, and hormones (Peters 2006).

Several of neuron's functions such as chemical, biological, and physical are changed as we age, which causes memory failure, alterations in behavior, dementia, cognitive function loss, and immune system dysfunction. Furthermore, aging is a major danger agent for prevalent neurodegenerative diseases and disorders (NDDs) (Zia et al. 2021).

Rather than just high brain aging, rates of neuron loss have also been attributed to modest modifications in the neural function and structure in specific neural circuits. Neuronal degeneration in the aging brain is compensated by increasing dendritic arbors and synaptic connections. In the case of neurodegenerative disorders associated with age, the brain loses dendritic arbors and synaptic contacts. As a result, it is unable to adjust for neuronal loss (Samarghandian et al. 2019; Huffman 2012). There is no efficient treatment for aging-related neurological disorders.

Nutritional interventions may be regarded as a viable strategy among therapeutic interventions aimed at preventing or delaying the normal and pathological aging processes (Bastianetto and Quirion 2002).

Due to the brain being the greatest complicated body organ, not every medication is approved for the therapy of age-related neurodegenerative diseases and disorders (NDDs). The present treatments are inefficient in treating NDDs with multifunctional pathogenic disorders, including aging (Vijayakumar et al. 2016). In recent years, there has been a rise in scientific study on medicinal plants, and their active ingredients may aid in the discovery of new multifunctional therapeutic agents. In the previous 30 years, the Drug Administration (FDA) and US Food has approved numerous plant-based natural and synthetic neuroprotective medicines (Ramalingam et al. 2018).

Recent research strongly suggests that phytochemicals may have significant protective, immunomodulatory, antioxidant, and/or antiinflammatory effects in the background of brain aging (Corbi et al. 2016; Forni et al. 2019). Phytochemicals are plant nonnutrient active components present in almost all plants. They are linked to a lower chance of chronic and age-related deteriorating diseases (Qaragholi et al. 2022). They have protected neuronal cells from apoptosis in neurodegenerative disease, have neuroprotective activity, and inhibit mitochondrial membrane permeabilization (Wu et al. 2017).

Moreover, the target of this chapter is to acknowledge brain aging's cellular and molecular markers and imply the mechanisms of phytochemicals in protecting brain cells from aging.

1.2 Cellular and Molecular Hallmarks of Brain Aging

Brain aging is marked by a complex interplay of cellular and molecular changes. These include DNA damage and mutations, shortened telomeres (protective caps on chromosomes), alterations in gene expression, disrupted protein balance, mitochondrial decline, the rise of senescent cells, changes in nutrient sensing, and impaired communication between cells. These interconnected hallmarks contribute to the decline in brain function and increased vulnerability to neurodegenerative diseases that often accompany the aging process (Machiela and Southwell 2020).

1.2.1 Mitochondrial Dysfunction

Mitochondria are the "energy powerhouse of the cell" due to cell's allowance to generate ATP production more than that of oxidative phosphorylation alone. They are also essential to our survival because they offer cellular function by supporting biochemical energy (Loh and Reiter 2022). Mitochondria are required for energy production, calcium homeostasis maintenance, and the regulation of different intracellular signaling pathways (Li et al. 2023). Mitochondria can expand, merge with others, and split. Moreover, lysosomes can clear the impairment of mitochondria

(Mattson and Arumugam 2018). Furthermore, it has been noticed that mitochondria play a nonenergetic function in aging, death, and metabolic process regulation (He et al. 2020). Several technological methods had previously been utilized to establish the effect of aging on mitochondria in brain cells (Grimm and Eckert 2017). The majority of mitochondrial genes are transferred to nuclear DNA (nDNA). Mitochondrial DNA (mtDNA) encodes for 13 protein subunits involved in oxidative phosphorylation. The other 76 subunits have been encoded by cytosolic nDNA that is then transported to the mitochondria, where both genomes interact functionally (Lu et al. 2023). Nuclear and mitochondrial DNA functional communication is required for mitochondrial activity and health. The absence of such an association leads to mitochondrial dysfunction and a decrease in ATP synthesis (Zia et al. 2021). Comparisons between mitochondrial structures extracted from animal brain tissue reveal a variety of age changes, including expansion of mitochondria, enhanced oxidative damage, impaired electron transport chain (ETC) function, elevation of depolarized membranes of mitochondria, Ca^{2+} handling impairment, and a lower threshold for triggering mitochondrial membrane permeability transition pores formation (Mattson and Arumugam 2018). The decline in the mitochondrial performance linked to brain aging requires a drop in cellular NAD^+ levels and the NAD: NADH ratio, which is expected to impair the activities of NAD^+-dependent enzymes important for the function and viability of neurons, as protein deacetylases of the sirtuin family (Braidy et al. 2014; Fang et al. 2017). Because of the brain's susceptibility to mitochondrial dysfunction, aging caused a significant drop in mitochondrial performance (Yankner et al. 2008) (Fig. 1.1).

1.2.2 Accumulation of Oxidatively Damaged Molecules

All of the primary characteristics of aging are linked to changes in genetic material and its primary metabolic products, proteins, DNA damage accumulation caused by endogenous risks like an error of DNA replication and reactive oxygen species (ROS) generation, both of which elevate with age and help to the resurgence of age-related disorders (Manni et al. 2023). For the following reasons, the brain is especially susceptible to oxidative stress. The brain, which accounts for about 2% of total body mass, expends 20% of total oxygen usage. Furthermore, it contains polyunsaturated fatty acids that are easily peroxidizable. Furthermore, the brain lacks antioxidant defenses (Lau et al. 2005).

Furthermore, an unbalanced oxidative response causes an increase in ROS production and/or decrease in antioxidant defenses, malfunctioning neuron accumulation, proteins that have aggregated, and mitochondria during aging. The most common ROS in neurons is superoxide anion radicals ($^{-}O_2$), and by different oxidases, hydrogen peroxide process produces hydroxyl radicals that react with Fe^{2+} or Cu^{+} and nitric oxide (NO) produced as a result of increased intracellular Ca^{2+} levels (Mattson and Arumugam 2018). Subcellular structures and membranes can be destroyed as a result of neuronal degradation. Indeed, besides too many intrinsic elements malfunctioning, different key groups of large molecules are

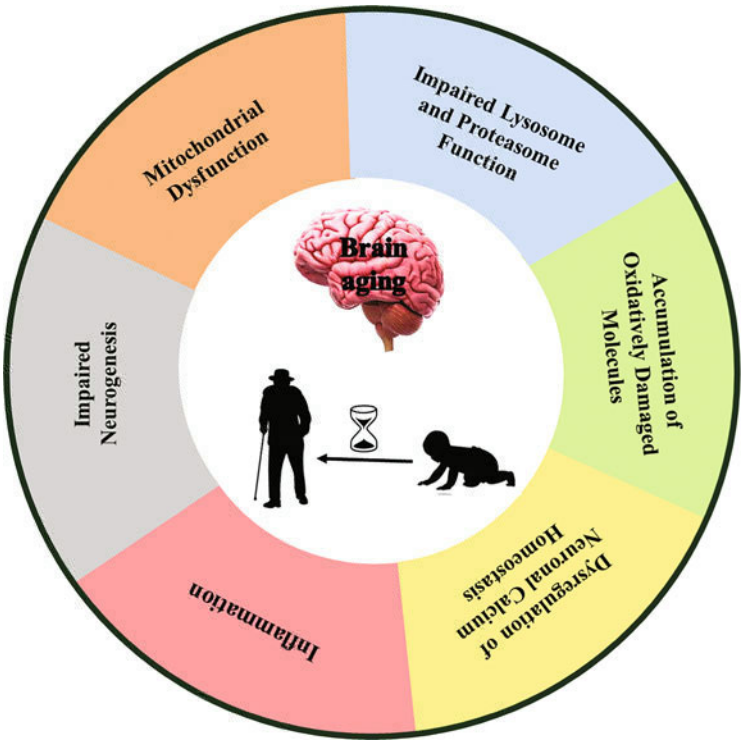

Fig. 1.1 Cellular and molecular hallmarks of brain aging (Mattson and Arumugam 2018)

especially vulnerable to the negative implications of oxidative reaction during brain aging. A number of investigations have found that active oxidative damage to nucleic acids adds to the genesis, occurrence, and progression of NDDs (Davinelli et al. 2016). Furthermore, several groups of neurons, like cerebellar granule cells, retinal ganglion, amacrine, and horizontal cells, showed age-related accumulation of oxidative DNA damage, such as the presence of the modified base 8-hydroxydeoxyguanosine (8-OHdG) (Klein and Ackerman 2003). There is proof that lowered antioxidant defenses, and a reduced capacity to eliminate oxidatively damaged molecules is enough to speed up aging. Ubiquitination frequently targets oxidatively changed proteins for proteasomal degradation, whereas autophagy targets oxidatively damaged membranes and mitochondria to lysosomes. Excessive oxidative stress, on the other hand, can hinder the operation of proteasomes and lysosomes (Mattson and Arumugam 2018).

1.2.3 Impaired Lysosome and Proteasome Function

Removing damaged cellular components to maintain protein homeostasis is essential for cell survival. The ubiquitin-proteasome pathway and lysosomal pathway are the two main systems that accomplish this by targeting and removing damaged cell proteins. The ubiquitin-proteasome pathway targets and selectively degrades short-lived and misfolded soluble proteins that are specifically marked for elimination by ubiquitin. The lysosomal system can eliminate proteins with long half-lives, insoluble proteins, or whole organelles by cellular autophagy (Bustamante et al. 2018). With aging, the ability of neurons to maintain protein homeostasis declines. Compared with young neurons, aged neurons demonstrate greater intracellular accumulation of undegraded proteins and greater amounts of proteins that have undergone polyubiquitination, a sign of proteasome dysfunction (Graham and Liu 2017). In autophagy, a membranous phagophore holds the cargo and combing it with a lysosome and allows its contents to be released into the acidic lysosomal lumen where hydrolases degrade the phagophore's contents. Ubiquitination directs proteasomal breakdown of protein, a mechanism which consists of three enzymes (E1, E2, and E3) with the E3 being a ligase that shifts the ubiquitin to a lysine residue of the target protein. Multiple ubiquitins are subsequently linked together to produce the detected ubiquitin chain by the unfolded 19S regulatory subunit of the proteasome, which then is degraded when it goes through the barrel of the 20S subunit (Mattson and Arumugam 2018). Proteasome activity was measured in numerous brain regions of aging rats and found to be significantly lower in some areas unlike others, implying that neuronal populations are vulnerable to malfunction of proteasome differently during aging (Keller et al. 2000).

1.2.4 Dysregulation of Neuronal Calcium Homeostasis

Evaluations of proteasome action in aged rats' brain areas demonstrated notable reductions in a number of regions, but not others, implying that neuronal populations are vulnerable to malfunction of proteasome differently during the age (Burgoyne et al. 2019). The stimulating neurotransmitter glutamate induces Na^+-fluxing AMPA receptors on the postsynaptic dendrite upon discharge from presynaptic axon terminals, leading to membrane depolarization and Ca^{2+} influx via the NMDA glutamate receptor channel and voltage-dependent Ca^{2+} channels (Mattson and Arumugam 2018). This triggers a transient elevation in cytoplasmic Ca^{2+} concentration as K^+ channels and Na^+ "pumps" are caused to maintain membrane potential, and Ca^{2+} is eliminated via Ca^{2+} ATPases located in the plasma membrane and endoplasmic reticulum membrane. Cytosolic kinases and phosphatases are elevated due to temporary Ca^{2+} release, which can affect the phosphorylation of dendritic proteins involved in glutamate receptor trafficking to and from the membrane, cytoskeletal reorganization, and local protein synthesis (Mattson and Arumugam 2018). Dysregulated calcium flux may be a potential parallel between ionizing radiation exposure and brain aging, as ionizing radiation can alter calcium flux in

both target and bystander cells (Lyng et al. 2006; Shao et al. 2006). Furthermore, proteins related to calcium transport and signaling were upregulated after exposure to low doses of ^{56}Fe irradiation (Britten et al. 2017).

1.2.5 Inflammation

In human brains, aging is linked with abnormal inflammatory responses. Proinflammatory cytokines, in particular, increase with age, while antiinflammatory molecules decrease (Corbi et al. 2016). Inflammation is closely related to increased ROS production. Neurodegenerative diseases have also been linked to oxidative stress-mediated inflammation. Neuroinflammation is linked to increased signal transmission, which results in the release of genes like inducible nitric oxide synthase (iNOS), interleukin-1 (IL-1), tumor necrosis factor-α (TNF-α), and nuclear factor kappa B (NF-κB). Inflammation has been shown to activate neural-protecting microglial cells, causing them to generate high levels of ROS and cytokines (Lau et al. 2005). Oxidative stress caused by inflammatory pathways enhancement, which results in mitochondrial damage and dysfunction, looks to be playing a crucial function in neuronal degeneration and in the development of NDDs (Godos 2022). In addition, when neurons are damaged due to aging or degeneration of neurons, the release of neurotransmitters, ATP, cytokines, and ion changes triggers microglia. Neuroinflammatory activation of microglia has been linked to neuronal loss, reduced behavioral function of neurons, and cognition malfunction. Inflammation of neurons creates complex interactions with oxidizing agents through redox sensors that have been detected in receptors, transcription factors, and enzymes. These variables influence neuronal connectivity and function, culminating in neurodegenerative changes. Furthermore, following being activated, microglial cells generate a form of NOS that can be stimulated and produce large amounts of NO, which promotes oxidative neuronal damage (Zia et al. 2021). Furthermore, the neuropathological changes caused by oxidative stress and a pro-inflammatory state involve the accumulation of insoluble materials like amyloid-β (Aβ) plaques and neurofibrillary tangles (NFTs), which are the primary causes of cell apoptosis and dementia (Davinelli et al. 2016).

In various human and mouse tissues, the NF-κB transactivation pattern found to be most strongly associated with aging (Adler et al. 2007). Furthermore, the most popular antiinflammatory factors that improve lifespan are AMP-activated protein kinase (AMPK) and silent information regulator 1 (SIRT1) (Salminen et al. 2012). It was revealed that several signatures of aging are most notably involving an activation of inflammation/immune response genes (de Magalhães et al. 2009).

1.2.6 Impaired Neurogenesis

Aging is associated with impaired neurogenesis, specifically decreased self-renewal, proliferation, and capacity for regenerating neurons to integrate into the central

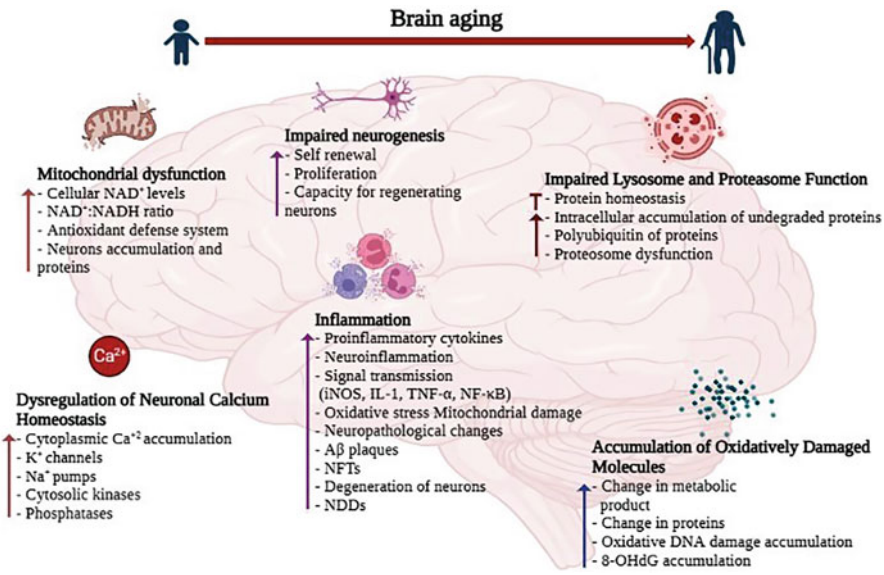

Fig. 1.2 Cellular and molecular hallmarks of brain aging (Mattson and Arumugam 2018)

nervous system network (Cavallucci et al. 2016). In age-related neurodegenerative diseases, individuals have markedly lower numbers of new neurons compared with age-matched healthy controls (Moreno-Jiménez et al. 2019). Evidence suggests that radiation-induced cognition malfunction causes changes in blood vessels of the brain and glial cell groups. In general, brain radiation injury causes a long-term change in the brain's environment, with inflammation playing a critical part (Pazzaglia et al. 2020). Many other aging characteristics may add to neurogenesis impairment throughout aging. Diminishing of mitochondrial oxidative metabolism and genetic compromise of mitochondrial electron transport chain (ETC) function as a result of aging neural progenitor cells. Furthermore, age-related neurogenesis decreases may be exacerbated by oxidative stress, poor DNA repair, and inflammation (Mattson and Arumugam 2018) (Fig. 1.2).

1.3 Phytochemicals

Phytochemicals are a potent class of compounds that are secondary metabolites of plants and include a wide variety of chemical entities (Tousson and El-Gharbawy 2023). Phytochemicals enhance health by way of their numerous antioxidant, antimicrobial, anticarcinogenic, antiinflammatory, neuroprotective, and antiaging properties (Okoro et al. 2021). Several lines of bioactive phytochemicals have been established as antioxidants in in vivo and in vitro studies by eliminating free radicals and ROS, modulating cell aging, besides, neurons preserving from cell

apoptosis. However, neuroprotection is now thought to be dependent not only on antioxidant mechanism, but also on the ion and Ca^{2+} chelation, anti-inflammation, modulation of signaling in cells, and the stimulation of pro-survival antiapoptotic Bcl-2 proteins and neurotrophic compounds (Wu et al. 2017). As a result, phytochemicals function as moderate stressors, triggering stress-protective genes that are expressed adaptively in neural cells and enhancing opposition to brain aging processes (Davinelli et al. 2016).

Phytochemicals represent a major light for the creation of novel drug classes for treating aging-associated conditions. These compounds may trigger aging-related pathways such as autophagy and DNA repair, as well as combat aging-related systemic inflammation as well as oxidative stress (Vaiserman et al. 2021). Similarly, numerous pharmacological studies have proven the benefits and improvements in the therapy of phytochemicals in dementia cure, depression, and NDDs, which offer nutrients to normal cells combat agents of disease, and boost immunity (Balakrishnan et al. 2021).

Several studies have also found that some phytochemicals' antioxidant activity can trigger nuclear factor E2-related factor 2 (Nrf2)/antioxidant response element (ARE) signaling pathways. Furthermore, phytochemicals activate the phosphatidylinositol 3-kinase/protein kinase B (PI3K/Akt) and extracellular signal-regulated kinase (ERK) pathways which inhibit NF-κB pathways (Mandel and Youdim 2004; Firuzi et al. 2015). Phytochemicals have also been shown to decrease mitochondrial dysfunction and prevent the formation of inflammatory responses and α-synuclein accumulation-induced oxidative stress (Balakrishnan et al. 2021).

1.3.1 Activating of Neuronal Antioxidant Defense by Phytochemicals

Various plants with biologically active compounds are said to have ROS neutralization and boost the antioxidant system (Hannan et al. 2020). Neuroprotective effects of phytochemicals are associated with reduced levels of oxidative stress due to possessing antioxidant properties (Mattson and Cheng 2006).

Furthermore, phytochemicals may enhance the survival of cell pathways by stimulating many growth signaling pathways, as well as nontoxic aggregate formation and proteolytic system activation to alleviate A-induced neuronal mitochondrial dysfunction. Furthermore, phytochemicals stimulate α-secretase or suppress β-secretase activity, besides, hindering fibril and toxic oligomer production (Rahman et al. 2020). Furthermore, phytochemicals have been proven to safeguard neurons from oxidative stress by triggering TrkB signaling pathways and the Nrf2-ARE system, which are considered therapeutic targets for NDD treatments (Hannan et al. 2020). This chapter examines the research on the phytochemicals that have neuroprotective properties that can activate these neural defense systems.

1.4 Mechanisms Associated with Neuroprotective Effects of Phytochemicals on Brain

1.4.1 Effect of Cellular Defense Against Oxidative Stress: The Nrf2-ARE Antioxidant System

Antioxidant defense mechanisms exist in cells including antioxidant enzymes and other molecules that protect against OS-mediated injury. The main cellular mechanism that controls the mechanism of antioxidant defense is the Keap1-Nrf2 pathway. Nrf2 is a primary redox homeostasis regulator in cells, and its stimulation is controlled in a variety of strategies. Under normal circumstances, Keap1 sequesters Nrf2 in the cytoplasm, where it is polyubiquitinated and triggers a proteasomal breakdown. The Nrf2 Keap1 complex has been disturbed, resulting in Nrf2 release and nuclear translocation (Hannan et al. 2020). When Nrf2 enters the nucleus, it creates heterodimers with small musculoaponeurotic fibrosarcoma (MAF) proteins, and these Nrf2-MAF heterodimers recognize an enhancer sequence known as ARE, which is found in over 250 genes in the regulatory regions (Ma 2013). Stimulation of the Nrf2-ARE pathway via Keap1-Nrf2 impairment generates an increase in the expression of several genes encoding a network of collaborating enzymes that compose an antioxidant defense system. This antioxidant system's functions include redox homeostasis, involving SOD, CAT, sulfaredoxin (Srx), thioredoxin (Trx), and peroxiredoxin (Prdx); GSH synthesis and metabolism, involving Gpx, GR, g-glutamine cysteine ligase (GCL) and synthase (GCS); quinone recycling, involving NAD(P)H quinone oxidoreductase (Nqo1) and iron homeostasis-heme oxygenase 1 (HO-1) (Hannan et al. 2020).

Nrf2 is mainly found in the cytoplasm of the degenerative brain, implying that Nrf2 activity is inadequate to facilitate effective antioxidant reactivity (Ramsey et al. 2007). Proof suggests that knocking out Nrf2 makes neurons more vulnerable to oxidative stress, but Nrf2 elevation reverses the impact (Lee and Johnson 2004). As a result, it is thought that stimulating the antioxidant defense system through the Nrf2 signaling targeting provides a possible treatment for NDDs, brain injury, and brain aging (Hannan et al. 2020).

1.4.2 Cell Survival System: The TrkB Signaling Pathway

Neurotrophin signaling is critical for the survival of neurons and synaptic plasticity, besides memory and learning (Costa et al. 2022). Among the neurotrophins found in the mature central nervous system, brain-derived neurotrophic factor (BDNF) is the most abundant. BDNF binds TrkB and promotes the survival of neurons and plasticity of synapses by activating conventional signaling pathways such as the mitogen-activated protein kinase (MAPK) route, the PI3K/Akt system, and the phospholipase C-γ (PLCγ) pathway (Kowiański et al. 2018). The main TrkB-mediated survival strategy that enhances the survival of neurons while also protecting against death is the PI3K/Akt signaling pathway. Activated Akt

additionally regulates cell viability by balancing proteins that promote and inhibit apoptosis. The MAPK and PLCγ pathways control neuronal growth and survival by expressing numerous genes in a CREB (cAMP response element binding protein)-dependent pathway, which encodes BDNF and other proteins linked with synaptic plasticity (Hannan et al. 2020).

Meis et al. (2018) reported that Fear learning impairments are observed in BDNF heterozygous knockout mice. Also, Jiang et al. (2019) there is a strong link between low BDNF levels and degeneration of neurons in NDDs. These findings indicate that the BDNF/TrkB signaling pathway is critical for survival, plasticity of synapses, and development of neurons. Various natural components have proven to trigger the TrkB signaling pathway and support the longevity of cells, making them potential treatments for NDDs, brain injury, and brain aging (Hannan et al. 2020).

1.4.3 Cross-Talk Between TrkB Signaling Pathway and Nrf2-ARE Antioxidant System

Networks of neurotrophin signaling such as PI3K/Akt, MAPK (Ras/ref./Erk), and PLCg (PKC or CaMK) keep neurons alive and connected. According to the evidence, the TrkB signaling pathway, which is the primary neurotrophin route in neurons that have matured, might function as an elevation of the Nrf2-ARE system. Phosphorylation of Akt, by way of example, facilitates Nrf2 nuclear translocation and triggers the Nrf2-ARE system, which leads to the transcription of many antioxidant enzyme-encoding genes (Qi et al. 2017). The PI3K/Akt pathway controls hemeoxygenase-1 (HO-1) which is important in cellular homeostasis preservation (Pischke et al. 2005). Furthermore, data indicate that the Nrf2-ARE antioxidant system and the TrkB signaling pathway may interact. Another low signaling mechanism of the TrkB pathway, the MAPK (ERK/p38 MAPK) pathway, has been demonstrated to control Nrf2 transcriptional activity (Singh et al. 2010; Tufekci et al. 2011). The TrkB signaling pathway and the Nrf2-ARE antioxidant system are thus complementary, and concurrent stimulation of these pathways demonstrated that conferring neuroprotection toward oxidative stress besides mitigating cognition impairments and memory among individuals suffering from NDDs such as aging or brain injury (Hannan et al. 2020). TrkB is linked with $p75^{NTR}$ signaling dependent on BDNF, which may also stimulate the Nrf2 pathway. TrkB is the main BDNF receptor, with two functional isoforms: TrkB.FL (full-length) and TrkB.T1 (truncated) receptors. TrkB.FL suppresses ceramide production via its tyrosine kinase activity at its low-affinity receptor, $p75^{NTR}$. In contrast, TrkB.T1, which lacks an intracellular tyrosine kinase domain, promotes ceramide synthesis after BDNF activation. The $p75^{NTR}$ signaling pathway has the potential to be a sword with two edges (Ishii and Mann 2018).

The overproduction of $p75^{NTR}$ leads to excess ceramide accumulation and is referred to as being linked to death (Kropf and Fahnestock 2021). Activity of TrkB.FL receptor tyrosine kinase, on the other hand, restricts sphingomyelinase, securing cells from ceramide toxicity and inhibiting the $p75^{NTR}$-mediated prodeath signaling

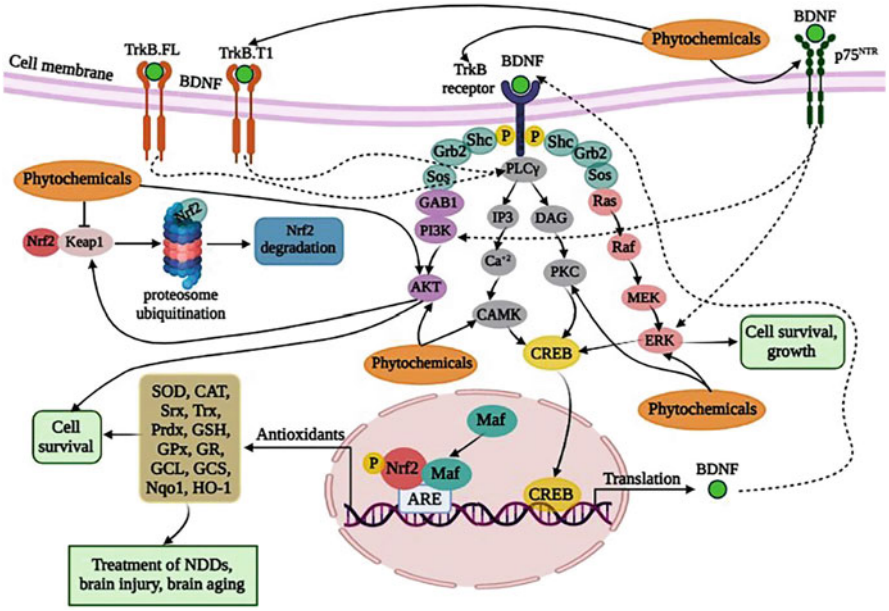

Fig. 1.3 Mechanisms associated with neuroprotective effects of phytochemicals on the brain (Alam et al. 2016; Guerzoni et al. 2017; Hannan et al. 2020)

cascade (Ishii et al. 2018). Besides, the BDNF TrkB.T1-p75^{NTR} signaling affects physiological accumulations of ceramide to stimulate protein kinase CC (PKCC) resulting in stimulation of casein kinase 2 (CK2) and Nrf2; consequently, the antioxidant capacity of cells is regulated (Ishii et al. 2018). TrkB.FL and TrkB.T1 receptors are expressed by neurons, but the receptor ratio amounts vary depending on neuronal activation (Gomes et al. 2012). Excitotoxic stimulation of rat hippocampus neurons in culture associated with TrkB.FL downregulation and TrkB.T1 expression upregulation altered the frequency considerably different between the two receptors (Gomes et al. 2012), which permits BDNF to control Nrf2 stimulation when there is p75^{NTR} (Ishii and Mann 2018). This action shields neurons from oxidative damage during excitotoxic glutamate activation, which is a common event in neural NDDs, injury, and stroke (Ishii and Mann 2018). Furthermore, BDNF-TrkB.T1-p75^{NTR}Nrf2-induced neuroprotection is context-dependent, meaning that it is based on the level of activation (Hannan et al. 2020) (Fig. 1.3).

1.5 Conclusion

Brain aging is the main risk factor for a variety of neurodegenerative diseases. Brain diseases associated with aging have lately emerged as the leading causes of disability and death. It caused brain dysfunctions on the cellular and molecular level like

mitochondrial dysfunction, accumulation of oxidatively damaged molecules, impaired lysosome and proteasome function, dysregulation of neuronal calcium homeostasis, inflammation, and impaired neurogenesis. Moreover, phytochemicals are secondary metabolites of plants and have antiaging, antioxidant, and antiinflammatory properties. In this chapter, we briefed the possible mechanisms of phytochemicals for protecting from aging. In conclusion, phytochemicals are expected to be a promising approach as a protective agent for brain aging. This suggests that while both treatment approaches offer benefits, a combination tailored to the patient's specific needs might be most effective. Further research is needed to explore how factors such as age, severity of the condition, and individual response affect the optimal treatment plan.

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Phytonutraceuticals Modulate Cell Survival Signaling and Regulate Sympathetic Innervation in Aging and Disease

2

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Abstract

As individual's age, they experience an upsurge in cellular oxidative stress levels, autophagy, and chronic inflammation, resulting in several physiological and metabolic changes. Phytochemicals are secondary metabolites produced in plants that boost survival mechanisms and can modulate the psychological parameters of various life forms inhabiting specific environments. Polyphenols, a phytochemical derived from fruits, nuts, and vegetation, possess antioxidant properties that counteract oxidative stress and metabolic dysregulation. Preventing age-related diseases and cognitive deterioration and promoting mental agility, particularly among older people, has become a matter of vital public interest. Aged individuals face an elevated risk of contracting diseases due to a decline in immune functions and defense mechanisms and a chance of an increase in autoimmune diseases. Due to defective T cell receptor signaling, chronic low-grade inflammation attenuates disease progression with advancing age. Abnormal signaling cascades ERK, CREB, PI3K/Akt/GSK-3β, and NF-kB pathways were observed in aging and neurodegeneration. To enhance the immune and metabolic functions and improve cognition levels imposed by old age, one should consider adopting dietary practices that center around consuming fruits, nuts, and vegetables. Combining evidence-based pharmacological therapies with naturally derived compounds may provide a practical approach to slow down age-related pathological progression while minimizing side effects.

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Targeting the sympathetic nervous system's involvement would help minimize age-related immune dysfunction and diseases. Resveratrol, quercetin, epicatechin, and curcumin are plant-derived nutraceutical components with antioxidant activities that can improve cognitive functionality across different age groups and mitigate age-related functional losses of synaptic and neuroplasticity.

Keywords

Aging · Phytochemicals · Resveratrol · Epicatechin · Quercetin · Curcumin

2.1 Introduction

Within stationary autotrophs, each plant genus or species has developed the ability to produce a unique combination of "phytochemicals." These compounds, known as "secondary metabolites," do not contribute to the plant's primary metabolism or provide essential macronutrients. However, their synthesis enhances the plant's capacity to adapt to local challenges by facilitating environmental interactions. The roles of these phytochemicals encompass various aspects such as general protection (e.g., antioxidant, ultraviolet light absorption, and antiproliferative properties), regulation of the plant's interactions with pathogenic and symbiotic microorganisms above and below the ground, defense against neighboring competitor plants, and management of the plant's interactions with more complex organisms (Kennedy 2014a, b; Kennedy and Wightman 2011).

Increasing evidence shows that aging is highly associated with a chronic increase in reactive oxygen species (ROS), a low-grade pro-inflammatory phenotype accumulation, and a reduction in age-related autophagy. This suggests that these factors may play essential roles in promoting aging. Indeed, reducing ROS and low-grade inflammation and promoting autophagy by calorie restriction or other dietary manipulation can extend lifespan in a broad spectrum of model organisms. The class of phytochemicals known as polyphenols mainly consists of phenolic rings. These are plant products found in a variety of fruits and vegetables. These secondary metabolites are a buffer when plants experience environmental or biological stress. These are also recognized to protect certain disorders linked to aging when included in the human diet. The antioxidant qualities of polyphenols are well recognized and protect against oxidative stress (Deepika and Maurya 2022). Several plant foods high in polyphenols, anti-inflammatory dietary patterns, and plant-based dietary patterns like the Mediterranean diet, which contains a range of fruits, vegetables, legumes, nuts, and whole grains, all appear to benefit brain health. These dietary patterns contain bioactive substances such as polyphenols, unsaturated fatty acids, antioxidant vitamins, and other phytochemicals (Rajaram et al. 2019). Aging is associated with weakened immune reactivity increasing vulnerability to infections, neurodegeneration, and cancer. Cognition involves intricate mental processes for information processing and navigation. Human studies utilize tools like the Mini-Mental State Examination (MMSE) to assess various functions, including

orientation, recall, language, praxis, attention, and calculation (Vasantharekha et al. 2017). Elderly individuals commonly experience cognitive decline, highlighting the need to address it in services for older people. Dementia, which affects 37 million individuals in Europe, is expected to increase due to the aging population (Park et al. 2003).

Researchers are investigating the role of the sympathetic nervous system in age-related immune dysfunction and neurodegenerative diseases (Madden et al. 1997). Eating more fruits, nuts, and vegetables improves cognitive function and can delay cognitive decline with age (Miller et al. 2017). Phytochemicals hold potential against oxidative stress-related diseases, especially when combined with drugs like DMARDs. Repurposing existing drugs, including those from traditional medicine, is gaining importance due to socioeconomic factors. The future will see increased interest in phytochemical-based drugs for inflammation and oxidative stress-related diseases (Forni et al. 2019). The roles of phytochemicals such as Resveratrol, Epicatechin, Quercetin, Curcumin, Green tea extract (EGCG), and a few others affecting aging and cognition have been discussed.

2.2 Aging Process

Age-related cognitive decline increases the likelihood of developing dementia and other brain illnesses connected to it. The outcome of cognitive aging and its progression to pathological states are determined by genetic predisposition and environmental exposures (Singh et al. 2021). In the general population, some cognitive abilities degrade with age, along with some forgetfulness, a lower capacity for maintaining attention, and a decreased capacity for problem-solving (Howes et al. 2020). The biological activities of an organism gradually deteriorate as it ages due to a range of morphological and functional changes. For many chronic illnesses, aging is a significant risk factor.

Age-associated cognitive decline and mild cognitive impairment are frequently observed both in men and women of the elderly population. To illustrate the challenges involved in this endeavor, the accumulation of β-amyloid (Aβ) proteins, neurofibrillary tangles (NFT) formation, and deposition of Lewy bodies in the brain have long been regarded as the primary pathological mechanisms in neurodegenerative diseases like Alzheimer's disease (AD), which is the primary contributor to cognitive deterioration in the elderly (Herrup 2015). The information storage process, a fundamental aspect of normal cognition, is not yet comprehensively understood. However, several mechanisms have been implicated, including excitatory and inhibitory neurotransmitters such as acetylcholine, GABA, glycine, and glutamate, the biosynthesis of biogenic amines dopamine, epinephrine, norepinephrine serotonin and cortisol, synaptic structures like dendritic spines, and neurophysiological responses such as short and long-term potentiation (LTP) (Howes et al. 2020). As individuals age, certain cognitive functions may decline, accompanied by varying degrees of forgetfulness and reduced ability to maintain focus and problem-solving skills, commonly observed in the general population. Biomarkers associated with