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Review

Natural Bioactive Molecules as Neuromedicines for the Treatment/Prevention of Neurodegenerative Diseases

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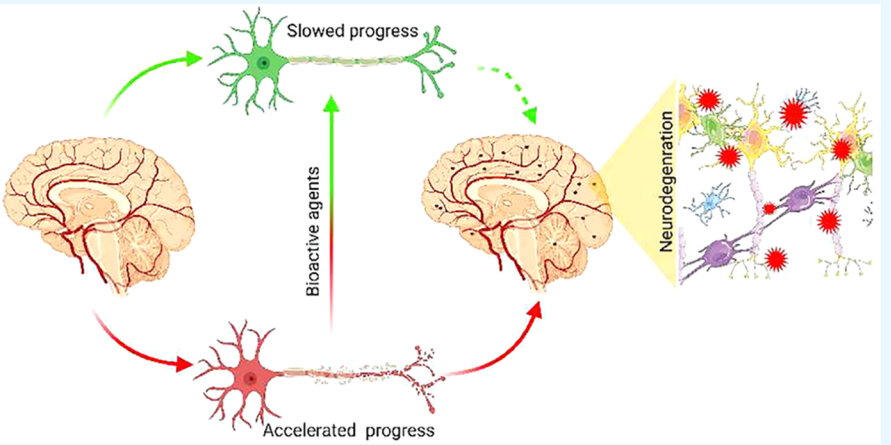

ABSTRACT: The brain is vulnerable to different types of stresses, particularly oxidative stress as a result of oxygen requirements/utilization in the body. Large amounts of unsaturated fatty acids present in the brain increase this vulnerability. Neurodegenerative diseases (NDDs) are brain disorders that are characterized by the gradual loss of specific neurons and are attributed to broad evidence of cell-level oxidative stress. The accurate characterization of neurological disorders relies on several parameters along with genetics and environmental risk factors, making therapies less efficient to fight NDDs. On the way to tackle oxidative damage and discover efficient and safe therapies, bioactives are at the edge of NDD science. Naturally occurring bioactive compounds such as polyphenols, carotenoids, essential fatty acids, phytosterols, essential oils, etc. are particularly of interest owing to their potent antioxidant and anti-inflammatory activities, and they offer lots of brain-health-promoting features. This Review focuses on probing the neuroefficacy and bioefficacy of bioactives and their role in supporting relatively low antioxidative and low regenerative capacities of the brain, neurogenesis, neuroprotection, and ameliorating/treating NDDs.

1. INTRODUCTION

Neurodegenerative diseases such as neuroinflammation, neurodegenerative disorders (NDDs), and brain tumors are an actual problem of modern neurology. The most common NDD is Alzheimer's disease (AD), followed by Parkinson's disease (PD), while others include multiple sclerosis (MS), Huntington's disease (HD), and motor neuron disease (MND). Pathogenesis determines the definition of typical pathological processes, among which great importance is attached to conformational changes in neuronal proteins, excitotoxicity, oxidative stress (OS), and apose. The global prevalence of human brain diseases, and OS, is closely associated with the development of neuroinflammation and NDDs, in part due to the very high oxygen demand of the brain, which is about 20% of total intake (Figure 1).

The OS is a condition in which there is an imbalance between free radicals and radical scavengers with an increase in free radicals, which in turn leads to neuronal damage by affecting neurons.[2] The reactive oxygen species (ROS) further lead to damage to various macromolecules such as nucleic acids, lipids, or proteins. The brain's high demand for oxygen results in a high density of ROS and thus a strong impact of radicals.[3] Oxysterols also play a role in the development of

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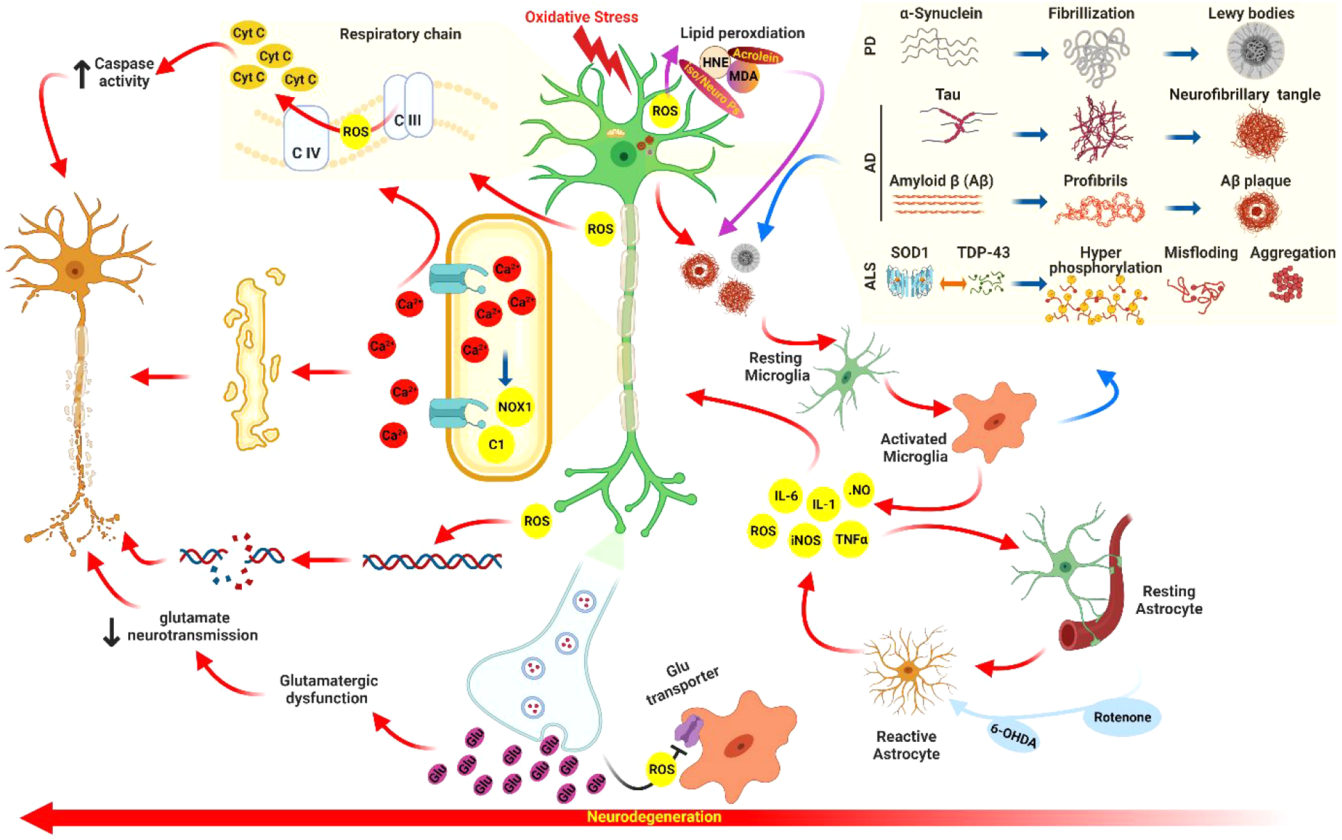

Figure 1. Oxidative stress-induced neurodegeneration. The oxidative stress state can induce neurodegeneration and neuroinflammation. In an OS state, levels of ROS/RNS are increased, which can lead the activation of signaling pathways responsible for major glial inflammatory actions. The glial cells (astrocytes and microglia) secrete proinflammatory agents (TNF-α, tumor necrosis factor alpha; iNOS, inducible nitric oxide synthase; NOX, NADPH oxidase; COX-2, cyclooxigenase-2; RNS, reactive nitrogen species; IL, interleukin; ROS, reactive oxygen species) which leads to neurodegeneration, resulting in neuron injury and death. Myelin is damaged by the increased ROS leading to an increase in Ca^{2+} influx, which further contributes to the rise in NOX1 and Calpain1 (C1), causing OS damage and myelin degradation. Glutamate (Glu) is normally cleared by the glial cell transporters and returns to neurons via repackaging into synaptic vesicles. An inadequate clearance of Glu could lead to excessive entry of Ca^{2+} into the presynaptic neuron, which can cause excitotoxicity that is as a result of damaged synaptic mitochondria, and consequently resulting in ROS formation, altered synaptic transmission, and neuron dysfunction. Moreover, OS leads to lipid peroxidation through an attack of ROS and triggering a chain process, whereby products such as 4-hydroxy-2-nonenal, malondialdehyde, acrolein, isoprostanes, or neuroprostanes (iso/Neuro Ps) are formed, which, in turn, changes protein functions causing neuron dysfunctions.

NDDs, with 24-hydroxycholesterol, 7-ketocholesterol, and 27-hydroxycholesterol, for example, being significant oxysterols in relation to NDDs.[4,5] These result from the oxidation of or radical attack on cholesterol and lead to severe dysfunction of cell organelles, OS, inflammation, and accumulation of amyloid-beta peptides (Aβ).[4,6] Oxysterols thus lead to neuronal damage and have already been identified as an important factor in both AD and PD.[7] In addition, OS leads to lipid peroxidation through an attack of ROS and thus triggers a chain process, whereby products such as 4-hydroxy-2-nonenal (HNE), malondialdehyde (MDA), acrolein, isoprostanes, or neuroprostanes are formed. These in turn influence and change proteins through modifications such as cross-linking as well as DNA resulting in the alteration of the biochemical characteristics.[8] Furthermore, lifestyle as well as diet, gender, various environmental factors, and stress are also critical factors associated with neurodegenerative disorders, some of which may also trigger oxidative stress.[9,10]

A high level of oxidizable polyunsaturated fatty acids (PUFAs) in the brain such as 22:6 and 20:4 fatty acids further attributes to OS vulnerability in the brain. PUFAs are exceedingly prone to lipid peroxidation particularly in the presence of redox-active metals such as Fe and Cu.[11,12] Furthermore, the relatively low level of antioxidant defense systems coupled with low regenerative capacities make the brain more susceptible to OS damage. In addition, the brain's energy metabolism relies exclusively on the complete oxidation of glucose in the mitochondria through the Krebs cycle using the electron transport chain (ETC), which is responsible for generating a large number of ROS during aerobic metabolism. It has been estimated that ~2% of the O_2 consumption during aerobic metabolism results in free radical superoxide anion generation, which could damage the mitochondria if not removed effectively.[13]

There is no effective medical treatment for NDDs, and the current intervention approach for modulating these diseases could only abolish few clinical symptoms. Although advances in chemical drugs in recent years have made some progress, there is a huge level of interest in the search for natural bioactive agents, which have numerous therapeutic features such as anti-inflammatory, antioxidant, and antitumorigenic effects.[14−16] These compounds also have potent health-promoting effects on preventing and or/treating brain disorders though they are facing challenges due to inadequate

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knowledge about their neuroefficacy specifically in the brain. In this Review, the potential roles of bioactive compounds for preventing/treating NDDs will be covered. Each of the reviewed bioactive compounds is of great interest to pave the way for investigations on neurodegeneration pathways and discovering natural therapies for NDDs.

In the following, the effects of bioactive compounds are described and addressed mainly in relation to AD. The focus on the use of dietary bioactive compounds in relation to NDDs is an interesting area of research in the food sector. Such diseases can be positively influenced and regulated via selected foods or their ingredients. This connection is interesting and important not only for pharmacology but also for food science and needs further research and attention as given by this Review. It is worth noting that this Review does not cover chemotherapy for brain diseases, nor does it cover the health-promoting effects of bioactives on cancer or other health disorders, which have been reviewed elsewhere.[17−19]

2. BRIEF OVERVIEW OF BIOACTIVE COMPOUNDS AND THEIR ROLE IN NDDS

2.1. Phenolic Compounds. Polyphenols belong to secondary plant metabolites with structural moieties including one or more aromatic rings that bear hydroxyl (−OH) groups.[20,21] Lots of phenolic substances are characterized either in their molecular form or in specific proportions of divergent herbal extracts. Studying the health-promoting effects of these natural substances is an immense challenge in modern medicinal sciences.[22] The most common phenolic compounds are flavonoids which include several subgroups such as flavones (e.g., luteolin), proanthocyanidins and anthocyanins (e.g., cyanidin and pelargonidin), flavonols (e.g., rutin and quercetin), flavanones (e.g., naringin and hesperetin), isoflavones (e.g., daidzein and genistein), and flavanols (e.g., catechin). Flavonoids are known for their strong antioxidant properties.[12,23] A number of studies have shown that the consumption of polyphenolic compounds reduces the risk for cardiovascular diseases, cancers, and NDDs. Through an antioxidant mechanism, the neuroprotective effects of a polyphenol-rich diet have been shown in various cell/animal model investigations.[24] Several phenolic compounds are shown to have cell-protective activities that protect the cell from oxysterols such as 7-ketocholesterol and avert and mitigate cell damage and mitochondrial dysfunction caused by them.[25] These compounds, such as quercetin, resveratrol, and apigenin, also influence the production of ROS supported by oxysterols and thus counteract oxidative stress.[26]

2.2. Carotenoids. Carotenoids belongs to the pigmented compounds produced by fungi, algae, and plants but not animals.[27] The main carotenoids are α- and β-carotenes, β-cryptoxanthin, lycopene, zeaxanthin, and lutein. They are symmetrical tetraterpenes with a linear hydrocarbon backbone (C40), having important roles in the organisms that produce them. Due to the distinctive structure of carotenoids, they possess biological activities, such as antioxidant, anti-inflammatory, and autophagy-modulatory effects. The protective roles of carotenoids in the human body are well-known and include prevention/treatment of several diseases, such as NDDs. As an example, it is reported that lycopene is able to pass the blood−brain barrier (BBB) and protect neurons in the central nervous system (CNS) at low concentrations.[28]

2.3. Essential Oils. Essential oils (EOs) include some small-molecular-weight terpenoids and aromatic compounds such as thymol, carvacrol, eugenol, cinnamic acid, limonene, and cinnamaldehyde.[29] They are known for their antimicrobial properties,[30] but recent interests include aroma-therapy-based attenuation of neuropathologies such as AD. For example, the potential neuroprotective properties of the EOs derived from of *Aloysia citrodora* against OS and amyloid β-induced neurotoxicity were studied using an *in vitro* neuronal cell line system.[31] Pharmacological studies generally support the traditional applications of aromatherapy; however, more clinical trials are needed to develop a protocol for routine application of EOs in healthcare. The effect of EOs may be related to their action via the olfactory system, which can receive and differentiate various odors, create nerve impulses, and transmit them to the hippocampus via the olfactory bulb. Since the hippocampus is closely linked to memory/learning functions, the EOs may modulate NDDs through the olfactory mechanism. The EOs could also directly act as drugs by modifying the various OS and inflammatory mechanisms associated with NDDs. Studies on *Sideritis galatica* EOs, for example, showed that monoterpene hydrocarbons, especially α- and β-pinene, were the main constituents for metal chelating, free radical scavenging, reducing power, and inhibition of some enzyme activities.[32] In another study on the cholinesterase inhibitory property and anti-inflammatory activity of *Salvia leriifolia Benth* revealed that camphor, camphene, 1,8-cineole, and α-pinene were the main constituents particularly as antioxidant agents. Good levels of cholinesterase inhibitory activities against acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) were also reported.[33] Inhibition of cholinesterase activity to prolong the lifespan of acetylcholine (ACh) neurotransmitters is a valid therapeutic approach to treat/prevent various NDDs including AD.

2.4. Fatty Acids. Fatty acids, specifically the omega series, have been shown to offer lots of benefits on brain function and in ameliorating CNS diseases. The brain ranks second in the lipid content of all organs in the body. The brain lipids (∼35%) belong to long-chain PUFAs, which cannot be produced via *de novo* lipogenesis but can be formed from the omega-6 (ω-6) and omega-3 (ω-3) precursors like α-linolenic acid (ALA) and linoleic acid (LA), respectively.[34] *In vitro* studies suggested that cerebral endothelium cells and astrocytes avidly elongate and desaturate PUFA precursors, although the biosynthesis of PUFAs in the brain occurs at a low level. Thus, the main source of PUFAs originates from the liver biosynthesis pathways. In this regard, 15 week dietary deprivation of ω-3 PUFAs enhances the conversion of ALA to docosahexaenoic acid (DHA, ω-3) in the liver of rats.[35] ALA administration can also increase DHA abundance in the brain homogenates of rats, pigs, and mice. Moreover, high oleic acid and DHA levels were found in mouse brains exposed to diets with monounsaturated fatty acids (MUFAs). Furthermore, brain electrophysiology showed significant changes like a decrement in the postsynaptic response duration, shorter duration of action potentials, and increased firing activity in entorhinal cortex neurons that play critical roles in memory and learning.[36]

PUFAs are generally necessary for normal CNS development activities. In this connection, DHA seems to be engaged in neuropsychiatric disorders like dementia or depression as well as mediating membrane−protein interactions and neurogenesis. It also promotes cell survival through the induction of neuroprotective and antiapoptotic gene expression.[37] PUFA

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deficiency can damage cerebral tasks, disrupt brain development activities, and disturb the cell membrane composition of astrocytes, neurons, oligodendrocytes, synaptosomes, myelin, and mitochondria. Thus, PUFAs and related oxidized metabolites like synaptamides and neuroprotectin D1 (NPD1) are necessary for the physiological activities of the brain.[38] Overall, PUFA supplementation can (i) reverse stress-induced alterations of monoamine levels in the mouse brain,[39] (ii) protect the prefrontal cortex of the rat brain against MK-801-induced neurotoxicity,[40] and (iii) promote mitochondrial biogenesis[41] and regulate gene expressions in the brain related to adenosine triphosphate (ATP) energy metabolism.[42] The cell-damaging effect of 7-ketocholesterol can be counteracted by esterification with fatty acids. Oleic acid thus counteracts, for example, the damaging effect of oxysterol through dysfunction and the production of ROS, thereby protecting the cell.[43] Oleic acid also influences the content of high- and low-density lipoproteins in plasma and can reduce the increase in plasma membrane fluidity.[44]

2.5. Phytosterols. Phytosterols, such as sitosterol, brassicasterol, campesterol, ergosterol, lupeol, and stigmasterol, are the most common forms of plant sterols, which are structurally very similar to cholesterol.[45] Fairly large amounts of circulating phytosterols can irreversibly cross the BBB and accumulate in the brain to maintain the CNS membrane cholesterol homeostasis. Long-term studies have shown that phytosterols can reduce the levels of lipids and cholesterol resulting in prevention of cardiovascular diseases,[46] hypercholesterolemia,[47] and aging.[48] Accumulation of dietary phytosterols in the cerebrum of a phytosterolemia mouse model influenced the cholesterol metabolism in the brain but did not change the memory-related behavior.[49] Additionally, feeding the AD model (APPswe/PS 1dE9) mouse with phytosterols demonstrated altered amyloidogenic activity of the amyloid precursor protein (APP) and decreased generation of Aβ in neurons.[50] Furthermore, feeding C57BL/6NCrl mice with phytosterols has shown effects on the cleavage of APP in lipid rafts through a γ-secretase-mediated pathway, which might be associated with brain functions.[51]

On the other hand, neural stem cells (NSCs) are self-regenerating cells (with limited regenerating capacities) making them potent targets for NDD therapy. Therefore, the promotion of NSC proliferation was investigated using daucosterol (as a phytosterol).[52] The results showed that daucosterol can significantly increase the number of viable cells similar to that of epidermal growth factor (EGF) and basic fibroblast growth factor (bFGF). A set of experiments also showed that insulin-like growth factor I (IGF1) played a key role in gene regulatory activities and promoting NSC proliferation. In addition, increasing the phosphorylation of protein kinase B (AKT) demonstrated that the proliferation-enhancing activity of daucosterol might be associated with the IGF1-AKT pathway.[52] These findings introduced daucosterol as an efficient and inexpensive growth factor alternative that is worth further investigation in the clinical setup of NDDs.

2.6. Tocopherols. Tocopherols belongs to a group of eight molecules, each containing a chromanol ring with an aliphatic side chain.[53] They have four isoforms (α, β, γ, and δ) based on the position of methyl group substitutions on the chromanol ring. They have three chiral centers, in which the α-isoform (α-tocopherol, αT) is the most commonly found tocopherol. Although the other isoforms are absorbable by the human intestine, α-TTP (αT transfer protein) cannot recognize them.[54] The αT acts as an important naturally occurring scavenger for reactive oxygen species and reactive nitrogen species (RNS).[55,56] It was thought that αT only acts as a lipid peroxyl radical scavenger, specifically oxidized low-density lipoproteins (LDL), which is the main oxidant mediator for atherosclerosis development. In recent investigations, other important functions of αT have been discovered including gene regulatory and cell signaling properties. Clinical/preclinical trial tests have also shown promising efficacy of αT in the prevention/treatment of cancer, heart disease, and AD.

At the cellular level, Aβ can render oxidative damage to lipids and proteins, stimulate NOS activity, promulgate ROS formation, and oxidize glutamine synthetase (main enzyme in the excitatory neurotransmission pathway). Since ROS generated by oxidized proteins cause neuronal cell death, αT has therapeutic potential for AD. In several oxidant-induced animal studies, the application of αT succinate reduced the levels of brain-damaging ROS.[57] Another clinical investigation showed that supplementing with αT can delay/prevent the appearance of AD symptoms in elderly people with mild cognitive impairments.[58] The cognitive benefits of αT can also be explained by genetic factors such as APOE ε4, which is the most common gene associated with AD predisposition. APOE-associated VLDL particles are most abundant in brain tissue, which is consistent with mounting evidence that AD pathology is associated with cholesterol metabolism.[59,60] This evidence indicates a preventive/therapeutic role for αT in AD, due to its antioxidant and non-antioxidant functions in regulating gene expressions, which may also affect cell signaling pathways. In addition, the cell-damaging effects of oxysterol 25-hydroxycholesterol could be inhibited by α-tocopherol in further studies. Various tocopherols such as α-tocopherol thus have antioxidant effects by acting as radical scavengers.[61]

3. EFFECT OF BIOACTIVE COMPOUNDS ON NEURODEGENERATION PATHWAYS/SYMPTOMS

In the following subsections, first, each of the NDDs will be introduced briefly, and then, different bioactive compounds applied to their treatment will be discussed along with the obtained results.

3.1. Alzheimer's Disease. AD is the most common NDD characterized by a cascade of disorders in memory, progressive learning, cognition, synaptic dysfunction, and behavioral impairments. The amygdala and hippocampus are the most important areas in the brain that are involved in memory regulation.[62] AD is also known for being one of the most common tauopathies, which are a diverse group of NDDs that present as motor and cognitive impairments. Tauopathies are associated with an abnormal intracellular aggregation of tau protein (due to hyperphosphorylation) in the brain resulting in inflammation, oxidative damage, and an increment in intracellular calcium levels. Insoluble hyperphosphorylated Tau can form paired cytotoxic helical aggregates.[63] Based on the amyloid hypothesis, extracellular aggregation of Aβs is another main characteristics of AD, which is also cytotoxic and is reported to be an important AD mediator.

Although the exact biochemical mechanisms of AD remain unknown, more emphasis has been given to the loss of the neurotransmitter acetylcholine, which is critical to memory and cognition, and the possible effects of OS in this process.[22] Excitotoxicity/OS-induced degenerative signaling pathways such as activation of stress kinases (i.e., c-Jun N-terminal

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kinases, JNK) are reported to play major roles in AD. Activation of these pathways could be related to Aβs, which have a high affinity for binding to both Zn and Cu, and APPs. At mild acidic conditions (pH = 6.6), Cu ions induce remarkable Aβ aggregation reflecting the microenvironmental conditions in AD neurophils. Both APPs and Aβs have strong Cu-reducing activities (producing Cu^{+} from Cu^{2+}), which produce hydroxyl radicals (OH•) as a side product. Then, Aβ/APP-associated Cu^{+} along with the OH• can increase OS in the AD brain. Nonsaturated carbohydrate side chains of membrane lipids can be oxidized by Aβs (direct induction of OS by Aβs). Additionally, Aβs may generate an oxidized microenvironment through the indirect induction of a local immune response.[22]

3.1.1. Phenolic Compounds and AD. The concept of enzymatic links might occur between enzymes associated with AD (AChE, IC_{50} = 347.22 μg/mL; and BChE, IC_{50} = 378.79 μg/mL) with enzymes associated with type II diabetes mellitus (α-amylase with IC_{50} = 126.90 μg/mL and α-glucosidase with IC_{50} = 139.66 μg/mL); briefly, IC_{50} is the half maximal inhibitory concentration of the target compound. A study on the inhibitory effects of *Sesamia cretica* extract on the key enzymes associated with AD (AChE and BChE) and type II diabetes mellitus (glucosidase and amylase) showed strong activity *in vitro*. Moreover, 12 phenolic compounds including chlorogenic acid, hesperidin, kaempferol, apigenin, and benzoic acid in *S. cretica* extract were identified as the active principles for the radical scavenging and metal ion chelating activity.[64] In another similar study, the leaf extract of *Senecio biafrae*, containing phenolic compounds like rutin, chlorogenic acid, gallic acid, quercetin, caffeic acid, and kaempferol, showed inhibitory effects on main enzymes related to type II diabetes mellitus and AD.[65]

Enzymatic inhibitory activities of phenolic extract of *Adiantum capillus-veneris L.* (contains benzoic acid, epicatechin, syringic acid, and catechin) were reported against tyrosinase, AChE, α-glucosidase, and α-amylase except for BChE.[66] In another investigation, the most significant effects of cork oak (*Quercus suber*) extract on cholinesterase activity were reported against AChE and BChE. These findings suggest that the phenolic extracts contain useful compounds for potentially alleviating AD symptoms and other NDDs as well as diabetes.[67] Another investigation on extracts from *Ganoderma applanatum* showed enzymatic inhibitory effects against α-amylase, tyrosinase, cholinesterase, and α-glucosidase. These results suggest that the *Ganoderma* species might have the potential for designing new drug formulations.[68]

Neuroinflammation inhibitory studies of maple syrup extract (MSX) as a food-grade phenolic-enriched extract in a transgenic mouse model (3xTg-AD) of AD showed that a 30 day oral administration of MSX (100 and 200 mg/kg/day) can decrease some inflammatory protein expressions. These include the AD risk-associated protein SOCS6 (suppressor of cytokine signaling-6), TREM2 (triggering receptor expressed on myeloid cells-2), and stimulator of interferon genes TMEM173.[69] The polyphenolic extract of Scope Grape seed (GSPE) also showed potent therapeutic/preventative effects on age-related NDDs like AD through the intestinal microbiota, which is known to actively produce phenolic acids from dietary polyphenols. Microbiota metabolism studies showed that treating rats with GSPE considerably increased the brain accumulations of the two phenolic acids [3-(3-hydroxyphenyl) propionic acid and 3-hydroxybenzoic acid] interfering with the accumulation of neurotoxic Aβ aggregates. Outcomes of this study support future preclinical/clinical studies investigating the potent contributions of the intestinal microbiota in protecting against the onset and or/progression of AD as well as other NDDs.[70] Several dihydrofuran-fused perhydrophenanthrenes (DFs) possessing a phenolic hydroxyl group showed promising anti-AD activities by exhibiting potent dendritic and axonal regeneration activities.[71] Preclinical studies on amyloid infusion and transgenic animal models of AD, assessing the phenolic compound curcumin (main antioxidant in turmeric) to target multiple AD pathogenic cascades, showed a good safety profile and general anti-AD benefits.[72]

3.1.2. Carotenoids and AD. An investigation into the effects of serum levels of carotenoids in AD patients showed that high serum levels of lutein + zeaxanthin and lycopene at baseline were related to the lower risks of AD mortality. The mortality risk decrease was progressively pronounced by raising the serum levels of lutein + zeaxanthin and lycopene. In contrast, no data was associated with AD mortality for other serum carotenoids, including α/β-carotenes and β-cryptoxanthin (Min and Min 2014). AD patients have red blood cells (RBCs) suffering from being in an excessively oxidized state and high levels of peroxidized phospholipids (PLOOH). In this regard, carotenoids may benefit AD patients by regulating their RBC viability. Human and *in vivo*/*vitro* studies have confirmed that carotenoids can efficiently prevent RBC−PLOOH accumulation pathways. It was shown that the concentrations of RBC carotenoids, specifically lutein, were remarkably lower than in control people, illustrating an inverse relationship between RBC lutein and PLOOH concentrations in AD patients. These findings indicate that RBC lutein can contribute to PLOOH accumulation suppression of RBC in AD patients.[73] Scientific evidence suggests that accumulations of specific bioactives in the brain may decrease the risks for AD. In this case, a study on the impact of supplemental xanthophyll carotenoids on disease progression in AD patients showed a reduced progression of AD with improvements in sight, memory, and mood.[74] Cognitive enhancement studies using the streptozotocin-induced memory impairment albino mouse model also showed that β-carotene (2.05 mg/kg) attenuated the destructive effects of biochemical and behavioral impairments, while exhibiting AChE inhibitory activity and reduction of Aβ aggregates. The *in silico* studies further verified the capability of β-carotene for binding to the AChE.[75]

Lycopene, another important member of the carotenoid family, has attracted significant interest due to its antioxidant, anticancer, and neuroprotective roles. However, its mechanisms of action in NDDs need more investigations. The choroid plexus can modulate cognitive functions via changing the neuroinflammatory responses, in which lycopene can be involved in the early stages of AD. In a rat-based study, lycopene caused significant improvements in functional deficits of memory and learning in comparison to the control group (without lycopene). At the choroid plexus, the serum levels of TNF-α, IL-1β, and IL-6β were considerably increased, and the expressions of Toll-like receptor 4 (TLR4), NF-κB p65 mRNA, and protein were upregulated, indicating an inflammatory response was initiated following administration of $Aβ_{1-42}$. Inflammatory cytokines were considerably decreased after intragastric administration of lycopene.

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Lycopene can also reverse the Aβ_{1-42}-induced upregulation of NF-κB p65 mRNA, TLR4, and protein expressions at the choroid plexus. These findings demonstrate new evidence for the significant effects of lycopene on improving the cognitive deficits and attenuation of inflammatory injuries by blocking the activation of TLR4 and NF-κB p65 expressions and cytokine production.[76] The lycopene level in the plasma of AD patients has been studied to determine the role of lycopene in the AD pathogenesis. The results showed that lycopene can considerably delay paralysis in the Aβ_{1-42}-transgenic *Caenorhabditis elegans* (GMC101, strain). Lycopene can also decrease Aβ_{1-42} secretion in human dopaminergic neuroblastoma cells (SH-SY5Y) overexpressing the Swedish mutant form of human APPsw. Furthermore, lycopene can downregulate the APP expression in APPsw cells and protect them from Cu/H_2O_2-induced OS damage. These findings indicate that an elevated lycopene level in neurons can be a new approach for attenuating the onset/development of AD.[77]

Furthermore, lycopene (as a potent candidate for AD treatment) (i) remediates Aβ_{1-42}-induced spatial memory and learning deficits in a dose-dependent manner, (ii) reduces Aβ_{1-42}-induced mitochondrial dysfunction, (iii) decreases proinflammatory cytokines TGF-β, IL-1β, TNF-α, NF-κB, and caspase-3 activity in the rat brain, (iv) improves memory retention, (v) attenuates mitochondrial-oxidative damage, (vi) reduces neuroinflammation and restores the brain-derived neurotrophic factor (BDNF) level in Aβ_{1-42} treated rats, and (vii) modulates amyloidogenesis.[78,79] The effects of lycopene on reducing Aβ-induced cellular damage in a dose-dependent manner can be explained by its action on the multiple pathways of the mitochondria-associated pathogenesis. These include amelioration of the altered mitochondrial morphologies, opening of the mitochondrial permeability transition pore (mPTP), cytochrome C (Cyt C) release, depolarized mitochondria membrane potential (MMP), caspase-3 activation, imbalance in Bax/Bcl-2 ratio, and mitochondrial DNA damage. In SH-SY5Y cells, pretreatment with lycopene (0.2 or 0.5 μM for 1 h) inhibited the Aβ_{1-42}-stimulated cellular apoptosis through decreasing ROS production, mitochondrial dysfunction, and the expression of Nucling (a proapoptotic factor recruiting apoptosome complexes).[80] An investigation in tau transgenic mice expressing the P301 L mutation showed that lycopene treatment (5 mg/kg for 8 weeks) reversed the decrease in glutathione peroxidase (GSH-Px) and increased malondialdehyde levels in the serum.[81] Regulation of neuroinflammation and OS by lycopene may be related to effects of lycopene on production of proinflammatory cytokine and OS-triggered Nucling expression in SH-SY5Y cells, which are both mediated by NF-κB.[82,83]

3.1.3. Essential Oils and AD. Aromatherapy using EOs could serve as a potent natural therapy for AD dementia. Studies on *Pinus halepensis* EOs in a rat model of acute Aβ_{1-42} toxicity showed that the EOs reversed the Aβ_{1-42}-induced decrease of the spontaneous alternation and the Aβ_{1-42}-induced increment of the working and reference memory errors. The Aβ_{1-42}-induced modification of the oxidant-antioxidant balance and AChE action in the hippocampus of the rat has also been ameliorated by the EOs. These findings suggested that *Pinus halepensis* EOs have nootropic and neuroprotective activities and can be considered as a therapeutic tool for attenuating Aβ-induced neuronal dysfunctions.[84] A study on EOs from *Rosmarinus officinalis* using the AD dementia model in mice showed that the EOs significantly improved the rate of spontaneous alternation behavior. Additionally, the main components of the inhaled EOs were 1,8-cineole and 1,8-pinene, which may be responsible for improving cognitive functions. Investigating the detailed mechanisms of action is needed for clinical trials of EOs.[85]

The EOs extracted from *Mentha spicata* have sesquiterpene and monoterpene hydrocarbons along with carvone, which exhibit strong inhibitory effects on the key enzymes linked to AD, supporting the utilization of these EOs as a traditional medicine for the management of AD.[86] The effects of inhalation of EOs from *Tetraclinis articulata* were studied on the brain OS and memory in the Aβ_{1-42}-induced AD amyloidosis model. The EOs (containing monoterpene hydrocarbons as the main components) showed an activity profile similar to EOs from *Mentha spicata*. This study suggested that EOs could target dementia through antioxidant mechanisms and modulating cholinergic activity in the rat hippocampus.[87] The EOs extracted from the aerial parts of *Salvia miltiorrhiza* were also studied in an AD mouse model. The oral administration of EOs (containing germacrene D caryop, terpenoids, β-caryophyllene, dihydro-neoprene 6,10,14-trimethyl-2-pentadecanone, and hyllene as the main components) prohibited the cognitive impairments and decreased MDA content and AChE activity.[88]

This suggests that the EOs can improve AD-like symptoms in mice and may be developed as a new drug formulation for AD. In another study, the effects of EOs derived from rose were studied in a *C. elegans* AD model. The results showed that the EOs significantly suppressed the Aβ deposits and decreased the Aβ oligomers to relieve the toxicity caused by overexpression of Aβ. Additionally, the EOs markedly activated the gst-4 gene expression, which further supported the involvement of the SKN-1 signaling pathway in the therapeutic impacts of EOs on the AD *C. elegans* model. These findings illustrated direct evidence for treating AD by EOs on an organism level and a relative scientific foundation for reshaping these EOs as medicine in the future.[89]

Various EOs of *Salvia urmiensis Bunge* have been investigated for their inhibitory activity against enzymes involved in neurodegeneration (AChE and BChE) and diabetes mellitus (amylase and glucosidase). The EOs (containing methyl hexadecanoate, ethyl linoleate, methyl linoleate, and 6,10,14-trimethyl-2-pentadecanone as the main components) exhibited moderate AChE and moderate to high antidiabetic activities.[90] In another study, a scopolamine-induced rat model of AD was used to demonstrate the antidepressant, anxiolytic, and antioxidant properties of EOs derived from *Ferulago angulata*. Moreover, *in silico* studies suggested that the inhalation of these EOs ameliorates scopolamine-induced anxiety and depression by attenuating the OS in the rat amygdala. The EOs derived from *Polygonum hydropiper* showed dose-dependent AChE inhibitory and antioxidant activities. The EOs from the leaves of *P. hydropiper* may be subjected to further *in vitro/vivo* anti-AD studies. The EOs from *Lavandula luisieri* were shown to inhibit the β-site amyloid precursor protein cleaving enzyme1 (BACE1). The inhibitory activity of the EOs was attributed to the main component, monoterpenic ketone (2,3,4,4-tetramethyl-5-methylene-cyclopent-2-enone). Taken together, these results showed that these EOs and relevant components inhibited BACE1 activity, both in cellular and enzymatic levels, indicating their ability to be considered for further research in AD therapy.[91] The effects of EOs extracted from *Zataria multiflora Boiss* (ZM) were investigated in a rat

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Table 1. Summary of the Cytoprotective Molecules That Have a Positive Effect on AD

molecule class	molecules	selected effects	refs
phenolic compounds	chlorogenic acid, hesperidin, kaempferol, apigenin, and benzoic acid	radical scavenging and metal ion chelating activity	64
	rutin, chlorogenic acid, gallic acid, quercetin, caffeic acid, and kaempferol	inhibitory effects	65
	benzoic acid, epicatechin, syringic acid, and catechin	enzymatic inhibitory activities	66
	curcumin	antioxidants	72
	phenolic amides	protective activity	101
	curcumin and naringenin	antioxidant activities	102
	L-DOPA	antioxidant activities	103
	EGCG	neuroprotective effects	104
	resveratrol	antioxidant activity and neuroprotective effects	105
carotenoids	RBC lutein	contributed to PLOOH accumulation suppression of RBC	73
	xanthophyll	reduced progression of AD with improvements in sight, memory, and mood	74
	β-carotene	inhibitory activity and reduction of Aβ aggregates	75
	lycopene	broad-spectrum action and generally antioxidant, anticancer, and neuroprotective roles affecting, among others, $A\beta_{1-42}$	80
		neuroprotective effects	106
		restoration of the number of movements and body weight and relief from depression and anxiety	107
	lutein	neuroprotective and antioxidant activities	73
essential oils	essential oils	nootropic and neuroprotective activities and inhibitory activity	84, 91
		antioxidant and anti-inflammatory activities and neuroprotective activity	108
fatty acids	ω-3 and ω-6 PUFAs	essential for brain functions	93
	ω-3 PUFAs	neuroprotective effects	109
	long-chain FAs conjugated with carnitine	improvements in locomotor functions	110
	essential FAs	increasing survival rates and decreasing neurologic deficits	111
phytosterol	β-sitosterol and lupeol	inhibitory effects	97
tocopherol	α-T and vitamin E	neuroprotective effects	100

model of AD. The results showed (i) increments in traveled distance, heading angle, and escape latency and (ii) decrements in target quadrant entries in Aβ-induced groups. These findings suggest that ZM may be a potent source of natural therapeutic agents for AD therapy.[92]

3.1.4. Fatty Acids and AD. Fatty acids (FAs), especially the ω-3 and ω-6 series, are essential for brain functions and participate in vision, nervous system, intelligence development, and the metabolism of neurotransmitters. In view of the known neuroprotective effects of ω-3 FAs, their *in vitro* effects on rat brain microvascular endothelial cells were investigated. The results showed that ROS, amount of apoptotic cells, and lipid peroxidation were decreased in RBMVECs when incubated with ω-3 FAs, while superoxide dismutase (SOD), Gpx, and catalase were increased. Also, it was revealed that ω-3 FAs may exhibit a potent therapeutic effect against AD.[93] The consequences of ω-3 FA deficiency during brain development and AD-like pathology were investigated using wild-type female mice. The results indicated that dietary ω-3 FA deficiency during brain development can induce long-term changes in the synaptic marker expression and long-term reductions in the rate of arachidonic acid (AA) degradation in the mouse brain, which are not entirely alleviated by ω-3-enriched diet after weaning. The elimination of differences between transgenic and wild-type mice by an ω-3-deficient diet suggests that mechanisms regulating PSD-95 expression and the oxidative degradation of AA are related and that the timing of dietary ω-3 intake during development may influence AD-related pathological changes later in life.[94]

Another study showed that endogenous ω-3 PUFAs improved learning and the memory ability of AD mice, possibly due to a decrease in the formation of Aβ plaques and neurotrophic factors (NTFs) which can cause injuries on hippocampal neurons. Moreover, endogenous ω-3 were shown to protect the cerebral vasculature of AD mice, thus increasing the metabolism of the brain. Besides, endogenous ω-3 FAs were seen to extend the overall survival of tau AD models, indicating that ω-3 FAs can delay the onset of AD caused by tau protein dysfunction and alleviate the associated symptoms along with significantly prolonging survival *in vivo*.[95] It was determined that the deuterated PUFA (D-PUFA) diet can decrease the concentration of Aβ proteins and oxidation products of both DHA and AA in the brain tissue.[96]

3.1.5. Phytosterols and AD. Considerable *in vitro/in vivo* inhibitory effects of β-sitosterol (obtained from *Polygonum hydropiper*) on cholinesterase activity showed an IC_{50} of 50 and 55 mg/mL against BChE and AChE, respectively, whereas the activities of BChE and AChE were remarkably low in the hippocampus homogenates and frontal cortex of transgenic animals. Molecular docking (*in silico*) studies also showed that β-sitosterol binds to the target enzyme, and the free radical level in the brain tissues was remarkably reduced in the presence of β-sitosterol. Additionally, transgenic animals treated with β-sitosterol exhibited a gradual improvement in spontaneous alternation behavior, working memory, and motor coordination, suggesting that β-sitosterol is a potent bioactive compound for attenuating memory deficits in AD.[97] Additional evidence showed that the −OH group of lupeol, a phytosterol from *Pueraria lobate*, can form two hydrogen bonds with the SER35 and catalytic aspartic residues of BACE1. These findings predict that the inhibitory activities of this phytosterol depend on the presence of the OH group, suggesting that molecular pathways of lupane triterpenoids are through

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BACE1 inhibition, which can be a potent preventive/therapeutic bioactive mitigating AD.[97]

3.1.6. Tocopherols and AD. It has been shown that α-T is able to decrease the Aβ-induced cytotoxicity in SH-S5Y5 cells. Additionally, a transcriptomic analysis reported that treatment with α-T can upregulate the genes contributed in the nonamyloidogenic processing of APP, while downregulating the amyloidogenic pathway. Furthermore, α-T can modulate the expressions of genes contributing in the cell cycle and autophagy that are identified to be altered in AD. Additionally, treating with α-T can also decrease OS, restore nuclear factor erythroid-derived 2-like 2 (Nrf2), and reduce inducible NOS levels.[98] In another investigation, α-T and etodolac were tested individually and in combination for targeting OS and neuroinflammation using transgenic 5XFAD mice. The combinational therapy remarkably improved the functions of the BBB, induced synaptic marker expression, reduced total Aβ, promoted APP processing toward nonamyloidogenic and neuroprotective pathways, and remarkably reduced OS and neuroinflammation both *in vitro* and *in vivo*.[99]

It has been reported that α-TQ can inhibit the cytotoxicity and aggregation of Aβ and decrease ROS production and inflammatory cytokines *in vitro*. Oral administration of α-TQ can ameliorate memory impairment in mouse models of AD, reduce OS and Aβ oligomer levels in the brains of mice, prohibit the production of inducible inflammatory mediators [interleukin(IL)-6 and IL-1β] and NOS, and inhibit the activation of microglia by prohibiting the NF-κB signaling pathway.[70] High intake of vitamin E (tocopherols) from food, but not from supplements (α-T), is negatively associated with AD. It was shown that higher intakes of α-T and vitamin E were inversely associated with a decreased level of AD incidence, indicating the neuroprotective effects of vitamin E on AD.[100] The cytoprotective molecules that have a positive effect on AD are summarized in Table 1.

3.2. Parkinson's Disease. PD is the second most devastating NDD with a specific pathological change in degeneration of dopaminergic neurons, which can cause reduction of dopamines in the striatum as well as motor disabilities.[1] PD presents with abnormalities in muscle rigidity and motor control exhibiting dopaminergic neurons in substantia nigra (SN) atrophy. Pathologically, PD is characterized by increments in OS/damage, death of dopaminergic neurons, and mitochondrial dysfunctions, which are typically caused by the aggregation of α-synuclein in Lewy bodies; they are mainly abnormal intracellular aggregates of α-synuclein protein inside nerve cells.[112] However, DNA mutations in the Parkinson protein 1 and 2 (PARK1 and PARK2), an encoding gene for α-synuclein, as well as other genes, such as phosphatase and tensin homologue (PTEN)-induced putative kinase 1 (PINK1), and polymerase gamma (POLG), can cause PD in atypical cases.[112] The aggregation of α-synuclein can occur due to PARK1 point mutations. α-Synuclein is normally found in glial and neuronal cells with a linear soluble form interacting directly with the inner mitochondrial membrane and inhibits mitochondrial complex I activity in the SN. Hence, α-synuclein might act as a major factor in mitochondrial dysfunction and generating ROS in PD.

3.2.1. Phenolic Compounds and PD. Phenolic amides {*cis*-*N*-phydroxycinnamoyl-7′-methoxyethyltyramine and (7*R*,8*S*)-7-(4-hydroxy-3,5-dimethoxyphenyl)-8-hydroxy methyl-V-[*N*-7″-4″-hydrxyphenyflethyl]carbamoyl etheny1−3′-methoxybenzodihydrofuran} of the fruits extract of *Nicandra physalodes* revealed protective roles on 1-methyl-4-phenylpyridiniumion-induced damage in SH-SY5Y cells. These phenolic amides may thus be promising drugs for the treatment of PD.[101] Diet-derived phenolic compounds have the ability to combat OS and hence can be considered as potent phytocompounds for long-term use in PD. In this case, a study was conducted to investigate if natural phenolic compounds like curcumin, fisetin, naringenin, and quercetin can act as neuroprotective agents in the 6-hydroxydopamine hydrochloride (6-OHDA)-induced model of PD. The 6-OHDA can produce a significant loss of tyrosine hydroxylase (TH)-positive cells in the SN and decrease dopamine content in the striata of test animals. Under this condition, rats pretreated with naringenin or curcumin revealed remarkable protection against the number of TH-positive cells in the SN and dopamine levels in the striata. The neuroprotective ability of naringenin and curcumin may be associated with their high antioxidant activities as well as their ability to cross the BBB to reach the brain.[102]

Levo-dihydroxy phenylalanine (L-DOPA), the dopamine precursor, is rich in fava bean sprouts, which may be used in the management of PD. It was shown that microwave treatment of fava bean sprouts can remarkably stimulate the Parkinson's relevant L-DOPA content and also display an antioxidant effect due to the phenolic constituents (Randhir and Shetty 2004). In PD animal models, the toxicity of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) is mediated by OS via nitric oxide (NO). Inhibition of NO synthase (NOS) in the brain can induce neuroprotection in MPTP-induced PD. Green tea contains high levels of epigallocatechin gallate (EGCG), in which green tea and oral administration of EGCG or green tea containing high levels of EGCG could attenuate the MPTP-induced PD pathology in mice by inhibiting NOS expression and preventing the loss of TH+ cells in the SN. Both EGCG and green tea could decrease the expressions of neuronal NOS (nNOS) in the SN, suggesting the neuropreventive roles of tea and EGCG.[113]

3.2.2. Carotenoids and PD. An investigation on serum levels of antioxidant vitamins (α- and γ-T, retinol, α/β-carotenes, lycopene, lutein, zeaxanthin, and 13-cryptoxanthin) and their associated roles in PD pathogenesis and progression was conducted in patients with idiopathic PD and compared with healthy controls. In comparison to PD controls, patients had lower levels of lycopene and α/β-carotenes. The levels of α/β-carotene and lycopene were remarkably reduced in advanced PD patients and negatively correlated with Hoehn and Yahr stage and the PD rating scale (UPDRS). Thus, serum levels of these carotenoids (lycopene, carotenoids, and α/β-carotene) were less in PD patients and inversely correlated with clinical variables of the disease progression. These findings suggest that a decrease in serum levels of lycopene and α/β-carotene may be related to PD progression and pathogenesis.[83] The neuroprotective effects of lycopene on the MPTP animal model of PD were also reported via decreased level of OS by the lycopene intervention on dopamine level. Additionally, lycopene can upregulate the protein expression of cyto-2 and Bcl-2 and downregulate the Bax and caspase 3, 8, and 9 expressions, exerting a neuroprotective effect on PD in mice. Thus, lycopene treatment attenuates the PD-induced neurodegeneration via reducing apoptosis, OS, and physical anomalies.[106]

Another investigation on the neuroprotective effect of lycopene against the MPTP-induced mouse model of PD showed that lycopene can dose-dependently protect MPTP-

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induced depletion of striatal dopamine and its metabolites. Lycopene also can attenuate the MPTP-induced motor abnormalities and OS in PD mice. Lycopene can reverse apoptosis, deficits in neurochemical activities, OS, and physiological abnormalities in the mouse model of PD, suggesting its promise for treating PD.[114] The potent neuroprotective activity of lycopene on neurobehavioral abnormalities and OS in rotenone-induced PD rats showed that rotenone can increase the levels of MDA by 75% in the striatum, while administrating lycopene in rotenone-treated PD rats can decrease the MDA levels by 24%. Additionally, a 42% reduction in levels of GSH was seen in rotenone-treated rats. The inhibition of SOD activity was 69% in rotenone-treated rats, while, the activity increased by 12% in the lycopene-supplemented group. This was complemented by motor and cognitive deficits in rotenone-treated rats that were reversed with lycopene treatment. Lycopene supplementation also prohibited Cyt C release from mitochondria.[115] In another investigation, administrating lycopene-enriched tomato powder showed a decrease in MPTP-induced dopamine in PD mice, while administrating a tomato diet suppressed 6-OHDA-induced dopamine in rats.[116] Further studies on the prophylactic and/or therapeutic effects of lycopene-enriched substances in PD patients are thus well warranted.

3.2.3. Essential Oils and PD. The EOs of *Eplingiella fruticosa* (EPL), a medicinal and aromatic plant belonging to the *Lamiaceae* family, have shown to have antioxidant and anti-inflammatory activities. In this case, an investigation was carried out using cyclodextrins for enhancing the pharmacological profile of EPL. The complexation between EPL and β-cyclodextrin (EPL-β CD) was evaluated in a mouse model of PD. Immunohistochemistry, lipid peroxidation quantifying tests, and behavioral evaluations showed that EPL-β CD can decrease the levels of membrane lipid peroxides in the striatum, delay the catalepsy onset, reduce the frequency of oral dyskinesia, restore memory deficits, and protect against dopaminergic depletion in the striatum and SN pars compacta. The results suggest that EPL has a potent neuroprotective activity in a progressive animal model of PD. Additionally, EPL-β CD improved these protective effects, suggesting its promise as a therapeutic agent for ameliorating the symptoms of PD.[108]

3.2.4. Fatty Acids and PD. Preclinical, clinical, and epidemiological evidence suggests that ω-3 PUFAs might have therapeutic potential for treating several CNS disorders such as PD. PUFAs including ω-3 are readily available and can be easily transferred to the clinical trial stages to evaluate their neuroprotective effects.[109] It was shown that the number of calcium-binding protein (CB) and TH-positive neurons in the SN of ω-3 PUFA-treated PD mice was remarkably higher than that in Madopar-treated mice. Decreased levels of NO, TNF-α, and IFN-γ were seen in the ω-3 PUFA group, when compared with mice in the Madopar group, but higher behavioral scores were obtained in ω-3 PUFA-treated mice relative to Madopar-treated mice ($p < 0.05$). Thus, ω-3 PUFAs protect SN compact dopaminergic neurons against PD, alleviate immune inflammation, and improve the coordination of limb movement indicating potential therapeutic application in the management of PD.[117]

In another study, ω-3 PUFAs showed various benefits on NDDs. In this case, the potent therapeutic effects of DHAH, DHA, and a hydroxylated derivative of DHA in a PD model showed their benefits on behaviors of animals in the studied model, which was further confirmed by TH immunostaining. Moreover, the ω-3 PUFA administration showed a decrease in the microgliosis and astrogliosis, in both the SN and striatum, with a greater decrement in Iba-1(+) and GEAP(+) cells for the group treated with DHAH. Also, this DHAH group especially revealed promising antioxidant activities suggesting their benefits treating PD through mechanisms including neuroinflammation, the dopaminergic system, and OS.[118] Fish oil can mitigate the 6-OHDA-induced loss of nerve terminals and SNpc neurons in the striatum. The protective effect was attributed to a reduction in the iNOS-immunoreactive cell density, and astrocyte and microglia reactivity. These findings suggested that the anti-inflammatory and antioxidant features of fish oil supplementation are closely associated with reductions in dopaminergic injuries caused by the 6-OHDA.[119] The cytoprotective molecules with a positive effect on PD are summarized in Table 1.

3.3. Motor Neuron Diseases (MNDs). MNDs belong to a group of NDDs with motor neuron dysfunctions. Amyotrophic lateral sclerosis (ALS) is the most prevalent MND, having selective neuron death in the brainstem, cortex, and spinal cord. Neuronal cell death causes muscle atrophy and progressive paralysis. The disease name refers to the different affected tissue partitions, in which *amyotrophic* reflects muscle fiber atrophy and muscle mass loss, *lateral* reflects the nerve tracks running down the spinal cord (where most of the injured neurons by ALS can be seen), and *sclerosis* reflects the tissue scarring remaining with degeneration in neurons. Epidemiological studies categorize ALS into two forms of familial (around 5−10%) and sporadic (around 90−95%). ALS is pathologically specified by increments in OS, mitochondrial membrane potential loss, alterations in electron transport, protein aggregations, changed Ca^{2+} homeostasis, excitotoxicity, and divergent functions of glial cells.[120]

3.3.1. Phenolic Compounds and MND. Phenolic extracts of plants are regarded as potent sources for treating/preventing ALS. In this regard, the extract of *Ginkgo biloba* was reported to possess a gender-specific neuroprotective effect on a transgenic ALS mouse model. Oral administration of the extract can remarkably mitigate the motor functioning abnormalities and raise the survival time. It can also remarkably decrease the loss of spinal-cord anterior motor neurons in this ALS mouse model. Therefore, the extract of *Gingko biloba* may be used as potential therapy in ALS patients. In another study, the phenolic extract from *Ginseng* root was shown to have beneficial roles on transgenic mice when administered via drinking water. It was observed that *Ginseng* exhibited similar beneficial effects on alleviating motor impairments as well as enhancing survival time in a transgenic mouse model of ALS.[121] The possible mechanism of action in treated experimental animals includes antioxidant effects, increment in nerve growth factor action, and an altered NO level.[121]

Genistein, as an active component, can show its effects mainly by inhibiting different tyrosine kinase activities.[122] However, it can affect other molecular pathways including activation of Nrf2 and peroxisome proliferator-activated receptors, inhibiting hexose transporter GLUT1, topoisomerase, cytosine methylation, and DNA methyl transferase.[123] It was reported that administration of 16 mg/kg genistein (at least twice) is able to suspend the familial ALS onset and decrease the rate of mortality in an ALS mouse model, suggesting that genistein has non/estrogenic neuroprotective roles in familial ALS. EGCG, a highly potent bioactive agent in

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green tea, also showed neuroprotective effects in the ALS mouse model. Oral administration of EGCG can significantly delay the ALS onset, increase the number of motor neurons, and increase the survival times. It was shown that EGCG exhibits neuroprotective effects on OS-induced apoptosis by upregulating GSK-3 and PI3K/Akt pathways and down-regulating caspase-3, mitochondrial damage, and PARP.[104]

Pharmacokinetic reports on resveratrol showed that it can be absorbed via oral intake and possesses a variety of pharmacological and biological activities such as antiaging, antioxidant, anti-AD, and neuroprotective activities.[124] The neuroprotective effects of resveratrol were reported on ALS/cerebrospinal fluid-induced neurotoxicity in the cortical motor neurons of the animals' brain. It was reported that resveratrol upregulates the expression of sirtuin 1 (SIRT1) in the cell cultures to improve cell viability, increase ATP levels, and inhibit apoptosis.[125] Another investigation also showed that resveratrol possesses protective roles in an ALS cell model through its antioxidant activity.[105] It was found that resveratrol reduces the severity of ALS by mitigating abnormality in the p53 acetylation pathway in G93A-SOD1 mutant mouse model of ALS, which is consistent with enhanced survivability in the G93A-SOD1 transgenic mouse model of ALS via upregulation of Hsp70 and Hsp25 as well as activated SIRT1 to deacetylate Heat Shock Factor protein 1.[126] These reports on resveratrol and other phenolic compounds suggest their potential application for treating ALS.

3.3.2. Fatty Acids and MND. ALS patients suffer from weight loss, dyslipidemia, and hypermetabolism, in which deficits of cellular energetics can be detected before denervation. Although scientific evidence clearly indicates the profound metabolic alterations in ALS, the mechanisms of such dysregulation and the contribution of metabolism alteration pathways to ALS are poorly understood. In this case, an ALS model (*Drosophila*) based on Tar-DNA binding protein (TDP-43), which is a hallmark of ALS in locomotor dysfunction and reduced lifespan, showed some lipid metabolism-related alterations. These include a significant increment in long-chain FAs conjugated with carnitine, and remarkable decreases in β-hydroxybutyrate (precursor for ketone), acetyl carnitine, and carnitine were reported. Investigations on combined dietary and genetics in *Drosophila* indicated misexpressed carnitine shuttle components in the TDP-43 proteinopathy context. In addition, feeding *Drosophila* with β-hydroxybutyrate or medium-chain FAs showed improvements on locomotor functions. These results highlight the potential contribution of the lipid β-oxidation and carnitine shuttle in MND/ALS suggesting possible therapeutic strategies based on lipid metabolism restoration in motor neurons.[110] The cytoprotective molecules with a positive effect on MND are summarized in Table 1.

3.4. Huntington's Disease. HD, an autosomal disease occurring in the CNS, is a fatal and progressive NDD. An expansion in polyglutamine repeats in the HD gene is a main causative factor for HD. Although symptoms such as dystonia, intellectual impairment, involuntary movements, seizures, cognitive decline, chorea, and emotional disorders are most common, there is no clear mechanism for explaining the onset and progress of HD. Consequently, there is no effective treatment for HD. Cellular level changes in HD pathogenesis and progression include calcium dyshomeostasis, transcriptional dysregulation, caspase activation, defective axonal trafficking, expanded repeat of polyQ protein and its interactions with other proteins in the CNS, and abnormal mitochondrial dynamics. Therefore, bioactive compounds having any effect on each of these parameters could be useful for HD treatment.[127]

3.4.1. Carotenoids and HD. 3-Nitropropionic acid (3-NP) can irreversibly hinder the succinic acid dehydrogenase-induced energy deficits in cells and OS-induced neurotoxicity by inhibiting succinate dehydrogenase (mitochondrial complex enzyme II) irreversibly. Systemic administration of 3-NP can begin neurobehavioral deficits and loss of body weight which can be proved by motor coordination, hind-limb impairment, and memory dysfunction tests. Biochemical analysis shows that administration of 3-NP can significantly increase the nitrite concentration and lipid peroxidation, decrease glutathione and AChE levels, and deplete the activities of catalase in the rat brain.

Lutein, a well-known antioxidant, was explored for its possible neuroprotective effects on OS and 3-NP-induced dysfunctions. Oral administration of lutein showed significant improvements in activities of mitochondrial complex enzymes, neurobehavioral changes, body weight loss, and reduced OS in the rat brain, which were further confirmed by histopathological examinations. This study revealed that lutein can be a potent agent for HD management. Another investigation on synergistic impacts of combinational treatments with lycopene and quercetin on 3-NP-induced HD showed that treating rats with quercetin and lycopene individually can remarkably restore the locomotion count and body weight as well as alleviate depression and anxiety.[128] Another attempt in this regard showed that treatment with lycopene for 2 weeks can reverse 3-NP-induced OS and mitochondrial dysfunctions via mechanisms including (I) a reduction in activity of mitochondrial complexes, (II) a decrease in mitochondrial respiration, (III) an increment in the levels of ROS/NO and peroxidation of mitochondrial lipids, and (IV) a reduction in the activity of SOD and thiol content in brain tissues. These findings strongly suggest lycopene as a potential therapeutic agent for ameliorating HD symptoms.[107]

3.4.2. Fatty Acids and HD. In the Huntingtin gene, Exon 1 mutation causes a stretch in polyQ residues near to the huntingtin protein N-terminal. Aggregation of polyQ residues can be highly toxic to neurons after entering the nucleus. The neurodegeneration inducing action of aggregated polyQ can be described by the binding of this protein to cyclic adenosine monophosphate response element binding protein. In an attempt to find a therapy for HD, it was shown that increasing survival rates and decreasing neurologic deficits can be achieved by supplementing food with essential FAs, implying that PUFAs may benefit HD patients. These findings show the feasibility of PUFAs in inhibiting histone deacetylase, preventing or arresting polyQ aggregation, and/or activating the ubiquitin-proteasome system. The observed encouraging effects of essential FAs on HD may also suggest their potential application for other NDDs.[111] In a relevant study, HD patients were assessed based on the Unified HD Rating Scale (UHDRS) and the Rockland−Simpson Dyskinesia Rating Scale. The results showed that treatment of HD patients with PUFAs can improve the motor scale. In another investigation, R6/1 transgenics and normal mice were randomly given a combination of placebo and essential FAs. The results illustrate that early treatment by essential FAs can protect R6/1 transgenic mice against motor deficits.[129] The cytoprotective

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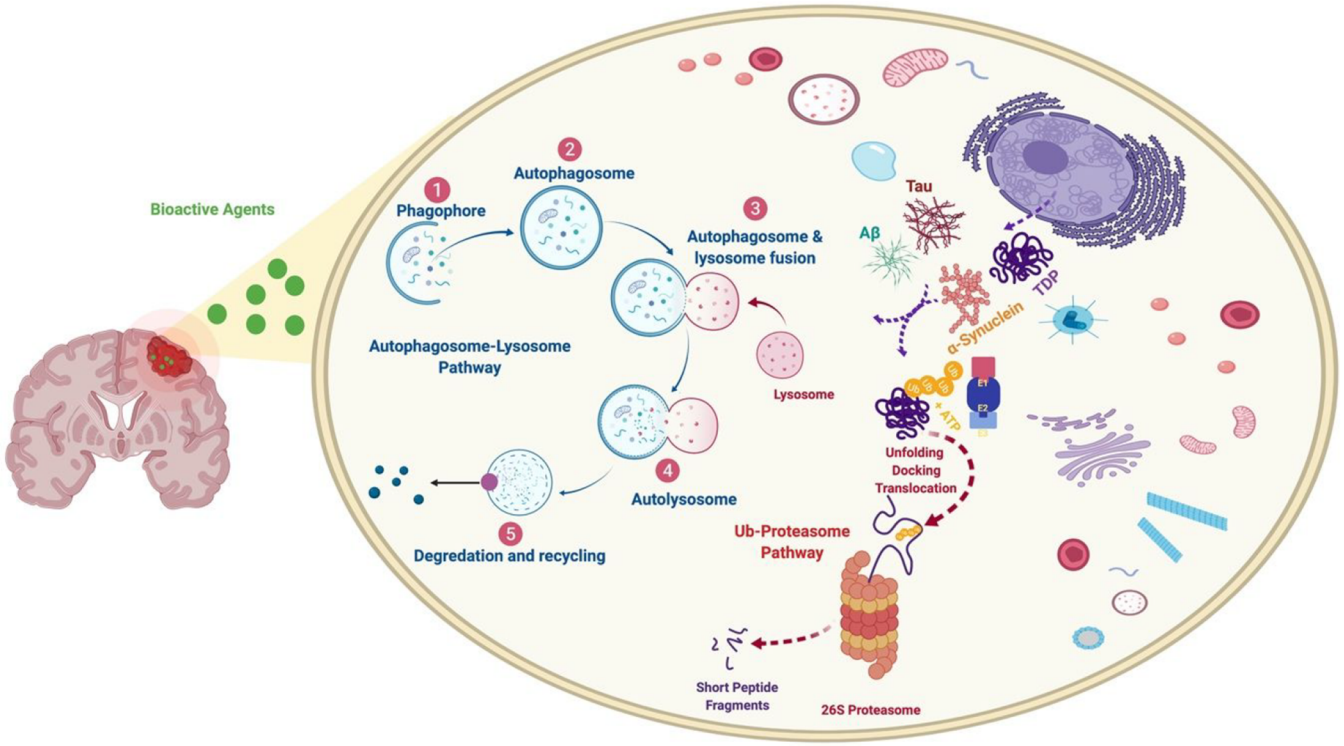

Figure 2. Possible effects of bioactive agents in the clearance of protein aggregates in neurodegenerative disease. Bioactive agents are potent agents to enhance neuroprotection by enhancing protein clearance pathways and clearing aggregated proteins which are one of the main causative factors in neurodegenerative diseases. TAR DNA/RNA binding protein (TDP), tau, and α-synuclein are the main protein aggregations in ALS, Azheimer's, and Parkinson's diseases. The enhancement may occur through two main protein clearance pathways: the ubiquitin−proteasome pathway and autophagy−lysosome pathway.

molecules with a positive effect on HD are summarized in Table 1.

4. COMBINATIONAL ROLES OF BIOACTIVES IN NDDS

A combination of bioactive compounds have been reported in the literature to provide synergistic effects for treating/preventing NDDs through different mechanisms such as (i) effects on protein clearance systems of the cells (Figure 2) and (ii) cellular pathways (Figure 3). Studies on vitamin complexes (α-T, ascorbic acid, and β-carotene) showed that the increment in the concentration of vitamin complex reduces the production of ROS along with enhanced reduction capacity in the cells of AD patients. The antioxidant activity of the vitamin complex was effectual in decreasing the OS of AD patients via enhancing antioxidant capacities at the cellular level, lowering production of ROS, and regulating cytokine-induced inflammation.[130] Another investigation on the potential effects of the combination of vitamin A and β/α-carotenes showed that α-carotene serum levels did not change meaningfully between AD control groups and AD patients, while vitamin A and β-carotene levels were remarkably low in the AD patients, suggesting that low levels of β-carotene in the serum of AD patients could be attributed to a dietary deficiency of this provitamin.[131] Other data revealed that ω-3 long-chain PUFAs like EPA and DHA have multidirectional anti-inflammatory activities via generating specialized pro-resolving mediators and anti-inflammatory cytokines or reducing proinflammatory eicosanoids. This study clearly showed the synergistic action for combinational dietary intervention, which can have stronger benefits than individual bioactives. The combination of ω-3 FAs with vitamin D_3, vitamin B complexes, curcumin, and resveratrol was also suggested to be helpful.[132]

5. FUTURE TRENDS

Understanding the molecular mechanisms of action in naturally occurring bioactive compounds and their roles in neuroprotection and OS will accelerate our understanding of the prophylactic effects of medicinal plants, herbal extracts, and nutritional supplements. Bioactive compounds can be involved in signaling pathways in neurons and regulating the expression of genes in the brain. The published data, so far, support the neuroprotective effects of bioactives; however, further investigations are still needed before we introduce them as definite neuromedicines.

6. CONCLUSION

NDDs are complex brain disorders with multiple dysfunctional pathways. Due to the growing population of older people around the world and extension of the lifespan, the number of age-related brain disorders, most commonly dementia, is expected to increase in the near future. Diagnosing cognitive and memory disorders in the preclinical phase provides the opportunity to slow down the progress of NDD onset by taking appropriate actions such as cognitive training, physical activity, and dietary interventions. Since the hypothesis on NDD-causing factors has gained considerable attention, finding dietary interventions seems to be a more practical solution for modulating the inflammation, preventing/delaying the disease onset, and slowing down the disease progression. Dietary interventions in NDDs can modify physiological functions in

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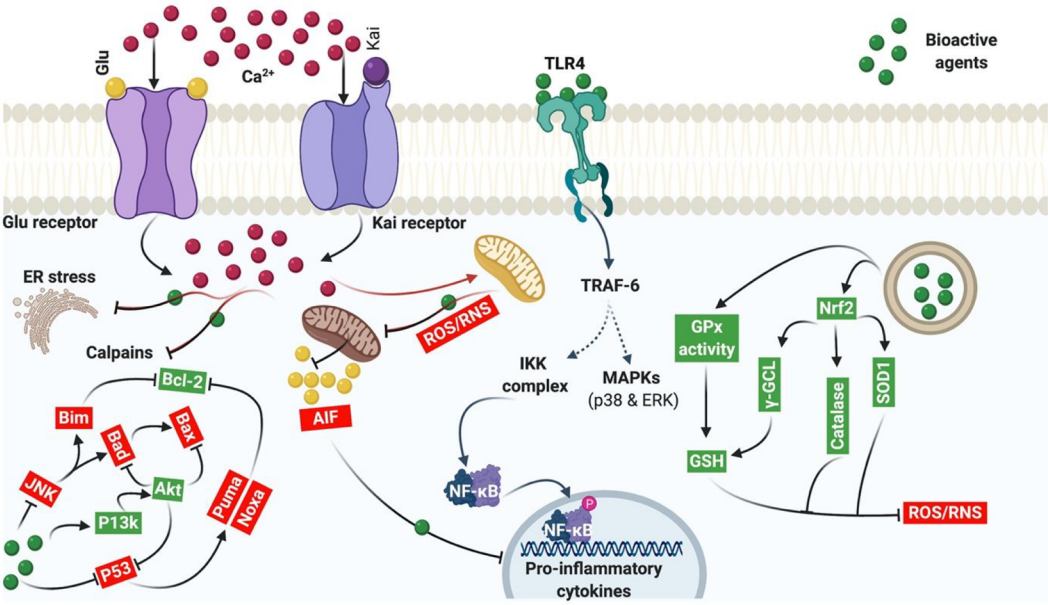

Figure 3. Neuron health-promoting effects of bioactives in neurodegeneration. Bioactives can show their antioxidant roles in neurons by modulating damage caused by ROS and/or RNS using several pathways. These are enhancing glutathione peroxidase (GPx) activity directly, ROS RNS scavenging capacity, activating nuclear factor erythroid 2-related factor 2 (Nrf-2) transcription of antioxidant enzymes, and promoting functionality and health of mitochondria. Genes that can be activated by Nrf2 include gamma-glutamylcysteine ligase (γ-GCL), glutathione (GSH), and Cu,Zn-superoxide dismutase (SOD1) which can then be used in conjunction with GPx and glutathione reductase, detoxifying ROS/RNS to avoid apoptosis. Another neuron health-promoting effect of bioactive compounds is based on calcium homeostasis and excitotoxicity which can be achieved through binding to the excitatory compounds kainite (Kai) or glutamate (Glu). The massive calcium influx caused by their interfering cognate receptors can interfere with the endoplasmic reticulum (ER) protein folding functioning, causing ER stress, activating proapoptotic signaling cascades, depolarizing the mitochondria, and uncoupling the electron transport chain, resulting in mitochondrial dysfunction, OS, permeability transition pore openings (releasing apoptogenic substances into the cytosol), and activating proapoptotic factors (calpains) directly, which can cause neuron death. Bioactive compounds are potent agents protecting neurons from excitotoxicity by avoiding increments of intracellular Ca^{2+} through Glu and Kai signaling pathways. Effects of bioactive compounds on neuroinflammation can be achieved via inflammatory stimuli, such as depositing aggregated proteins, activating toll-like receptor-4 (TLR4), and downstream induction of Akt, extracellular regulating signal kinase 1/2 (ERK1/2), and p38-mitogen-activated protein kinase (p38-MAPK), which subsequently activate nuclear factor-kappa B (NF-κB) in astrocytes and microglia followed by translocation of NF-κB to the nucleus and initiating transcription of proinflammatory genes such as cyclooxygenase-2 (COX-2), NADPH-oxidase-2 (NOX-2), inducible nitric oxide synthase (iNOS), and tumor necrosis factor-α (TNF-α). It is thought that bioactive agents inhibit this pathway through blocking activation of TLR4, Akt, ERK1/2, and p38-MAPK. Effects of bioactive agents on prosurvival/apoptotic signaling pathways can be achieved by modulating some signaling pathways that play roles in neuron death or survival. Bioactive agents can inhibit the c-Jun N-terminal kinase (JNK) and p53 activities, which are responsible for activation of proapoptotic proteins like B-cell lymphoma-2 (Bcl-2), Bad, Puma, Bim, and Noxa. Puma, Bim, and Noxa are identified for inhibiting the prosurvival functionalities of Bcl-2, resulting in activating the Bax (a proapoptotic protein). Then, Bax can form mitochondrial membrane pores, causing the Cyt C release. Cyt C then can interact with caspase-9 and apoptosis protease activating factor-1 (APAF-1) and form the apoptosome complex. Then, apoptosome can cleave procaspase-3 to form active caspase-3, stimulating apoptosis. In addition to inhibiting p53 activity, bioactive agents can also enhance the phosphoinositide-3-kinase (PI3K)/Akt prosurvival signaling pathway activity, which inhibits Bcl-2, Bim, Bad, and Bax activities. This neuron health-promoting activity of bioactive agents can prevent neurons from going to caspase-dependent apoptosis. Moreover, bioactive agents might also prohibit caspase-independent apoptosis via blocking the translocation of apoptosis inducing factor (AIF) from mitochondria to the nucleus.

the brain, thereby promoting or preserving normal functions in both the youth and elderly population.

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Notes

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