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Review article

Role of natural bioactive compounds in the management of neurodegenerative disorders

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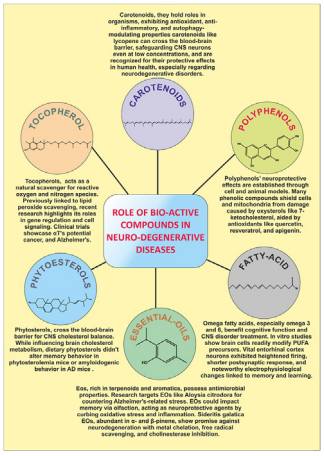
GRAPHICAL ABSTRACT



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ABSTRACT

Lately, substantial exploration and study have focused on natural products, along with their bioactive compounds. Neurodegenerative diseases (NDDs) such as Alzheimer's disease (AD), Huntington's disease (HD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS) involve progressive neural breakdown and cell loss, culminating in neuronal death. The brain is susceptible to various forms of stress, particularly oxidative stress (OS) caused by the body's oxygen requirements and utilization. The vulnerability of the brain is heightened by the significant presence of unsaturated fatty acids. To gain accurate insights into NDD, various factors such as genetics

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and environmental risks must be considered, as they can reduce the effectiveness of therapies for NDDs. Addressing oxidative damage and discovering safe and efficient treatments for NDDs are crucial objectives. In this pursuit, bioactive compounds play a vital role in research. Among these compounds, natural elements such as carotenoids, essential oils, essential fatty acids, polyphenols, and phytosterols are captivating due to their potent antioxidant and anti-inflammatory traits. These qualities hold the potential for enhancing brain health. This review centers on assessing how these bioactive compounds can bolster the brain's limited antioxidant and regenerative abilities, foster neurogenesis, offer neuroprotection, and mitigate NDDs.

1. Introduction

Neurodegeneration refers to the gradual deterioration and loss of both the physical structure and the functional abilities of nerve cells, or neurons, over time. Ultimately resulting in the eventual demise of these cells.[1,2] Various central nervous system (CNS) disorders result in neurodegeneration. The way acute and chronic neurodegenerative conditions manifest clinically is influenced by the specific loss of neuron populations that are interconnected within functional neural networks. The term "NDD" encompasses a broad category of neurological conditions primarily disturbing neurons in the CNS. These conditions are considered by a gradual decline of CNS neurons Certainly, neurodegeneration results in the gradual breakdown of neurons, which in turn causes deficiencies in distinct brain functions like memory, motor skills, and cognitive abilities.[3] Neurodegenerative conditions such as brain tumors, neuroinflammation, and NDDs are major problems in contemporary neurology. The two most common NDDs are PD and AD, respectively. Additional instances of NDD encompass multiple sclerosis (MS), HD, and motor neuron disease (MND).[4] Numerous biological processes, such as aberrant OS, excitotoxicity, protein misfolding and aggregation, neuroinflammation, and apoptosis, have been linked to neurodegeneration.[5–7] Neuronal loss, gliosis, or demyelination may result in cognitive decline, behavioral problems, or motor impairments depending on the site.[8] NDDs have a considerable adverse impact on life quality, as indicated by the high DALYs (disability-adjusted life years) they cause. DALYs are a metric that quantifies the years of healthy life compromised as a result of ailment. Moreover, stroke tops the list of non-traumatic fatalities in developed nations, primarily causing the majority of NDD-related deaths.[9,10] In the present review, the various natural bioactive components therapeutically used for neurodegenerative diseases (NDDs) such as Alzheimer's, Huntington's, Parkinson's, and amyotrophic lateral sclerosis (ALS) have been thoroughly discussed. Recently advancement with respect to the initiations of most NDDs is illustrated by a lot of quotes in PubMed.

2. Elementary mechanisms of neurodegeneration

NDDs entail chronic and progressive CNS abnormalities due to neuron degeneration and eventually result in fatality.[11] Common pathogenic mechanisms fundamental in different NDDs are Abnormal protein dynamics, Oxidative stress (OS) and formation of free radicals, Impaired bioenergetics, mitochondrial dysfunctions, Fragmentation of neuronal Golgi apparatus, dysfunction of neurotrophins (NTFs). These mechanisms are interconnected in complex malicious spheres and finally foremost to cell dysfunction and death.[12] A neurodegenerative condition called Alzheimer's is characterized by the slow, targeted deterioration of brain cells.[13]

2.1. Indications of Alzheimer's disease

A difference between normal brain and AD patients' brains is shown in Fig. 1. Alzheimer's illness is linked to memory loss, cognitive decline, and behavioral changes. The primary neuropathological characteristics of this condition involve the development and gathering of amyloid beta (A) plaques separate from neurons and the buildup of intracellular hyperphosphorylated tau proteins, commonly referred to as neurofibrillary tangles, within the brain.[14]

Alzheimer's is identified by a range of issues related to cognition,

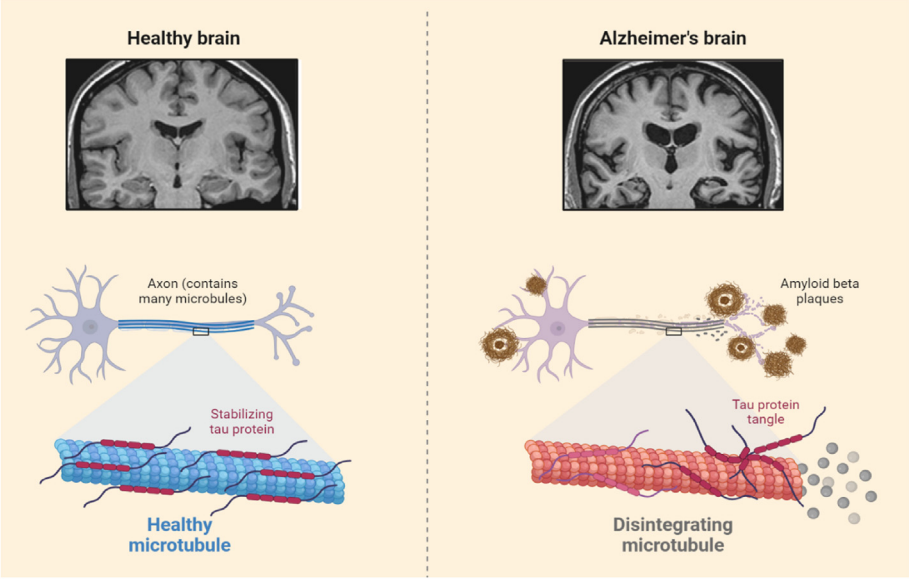


Fig. 1. Difference between normal brain and AD patient's brain.

memory, learning, and synapse function, along with disturbances in behavior. The two primary brain areas responsible for memory regulation are the amygdala and hippocampus.[15] Among the most notable prevalent NDDs associated with the aggregation of tau protein, a category of NDDs that manifest as well as motor and mental abnormalities, is known to be AD. Tauopathies are characterized by abnormal tau protein intracellular aggregation in the brain, which is brought on by hyperphosphorylation and result in oxidative damage, rising intracellular calcium levels, and inflammation. Hyperphosphorylated Tau, which is insoluble can assemble into paired cytotoxic helical structures.[16] According to the amyloid hypothesis, extracellular accumulation of Beta-Amyloids (Aβs), which is likewise considered to be cytotoxic a key AD mediator, is another key feature of AD.[17]

Although the precise molecular causes of AD are still unknown, the depletion of acetylcholine, a neurotransmitter has received increased attention, which is important for memory and cognition, as well as any potential implications OS may have on this process.[18] As per accounts, the stress kinase reaction, notably the c-Jun N-terminal kinases (JNK), seems to have a significant role in AD. These pathways may have been activated by Apolipo proteins E (APPs) and Aβs, which have a strong propensity for interacting with Cu and Zn. Under slightly acidic conditions (p^H 6.6), copper ions notably enhance the aggregation of APPs. This mirrors the specific environmental conditions within neutrophils affected by AD. Strong Cu-reducing abilities (generating Cu^+ from Cu^{2+}) are shared by APPs and Aβs, and as a byproduct, hydroxyl radicals (OH•) are produced.[19] The OS in the AD brain can then be increased by OH• and A/APP-associated Cu^+. Membrane lipids' non-saturated carbohydrate side chains are susceptible to oxidation by Aβs (direct induction of OS by A. s.). Furthermore, Aβs may cause a specific environment that is oxidized by subtly inducing a local immunological response.[20]

2.2. Indications of Parkinson's disease

Parkinson's disease ranks as the second most severe NDDs, marked by a distinctive pathological deterioration of dopaminergic neurons dopamine levels in the striatum may decline, which might cause this degeneration, resulting in motor impairments.[21] This is a chronic and advancing NDDs that affects motor function, causing resting tremors, postural instability, bradykinesia, and muscle stiffness.[22] The condition arises due to the gradual decline of dopaminergic nigrostriatal neurons. Symptoms of PD are illustrated in Fig. 2.

2.3. Indications of motor neuron diseases

Motor Neuron disorders encompass conditions such as post-polio syndrome, primary lateral sclerosis, progressive bulbar palsy, spinal muscular atrophy, ALS, and progressive muscular atrophy.[23] A neurodegenerative condition that worsens with time and causes impairments to the brain's motor, mental, and cognitive functions is known as Huntington's disease. Clinically, aberrant movements, psychiatric instability, and cognitive deficiencies are the hallmarks of this disease, which is pathologically defined via heightened dopaminergic activity and decreased basal ganglia gamma-aminobutyric acid (GABA) activity cascading in a normal person and in a diseased person (Fig. 3).

MNDs belong to a category of neurological disorders known as NDDs and are characterized by impaired motor neuron functioning.[24] The most common form of MND is ALS, it affects the spinal cord, cortex, and brainstem and causes selective neuron death. progressive paralysis and Muscle atrophy are the results of neuronal cell death. The name of the illness alludes to the many tissue compartments that are impacted; Amyotrophic means that there is lateral to the spinal cords nerve

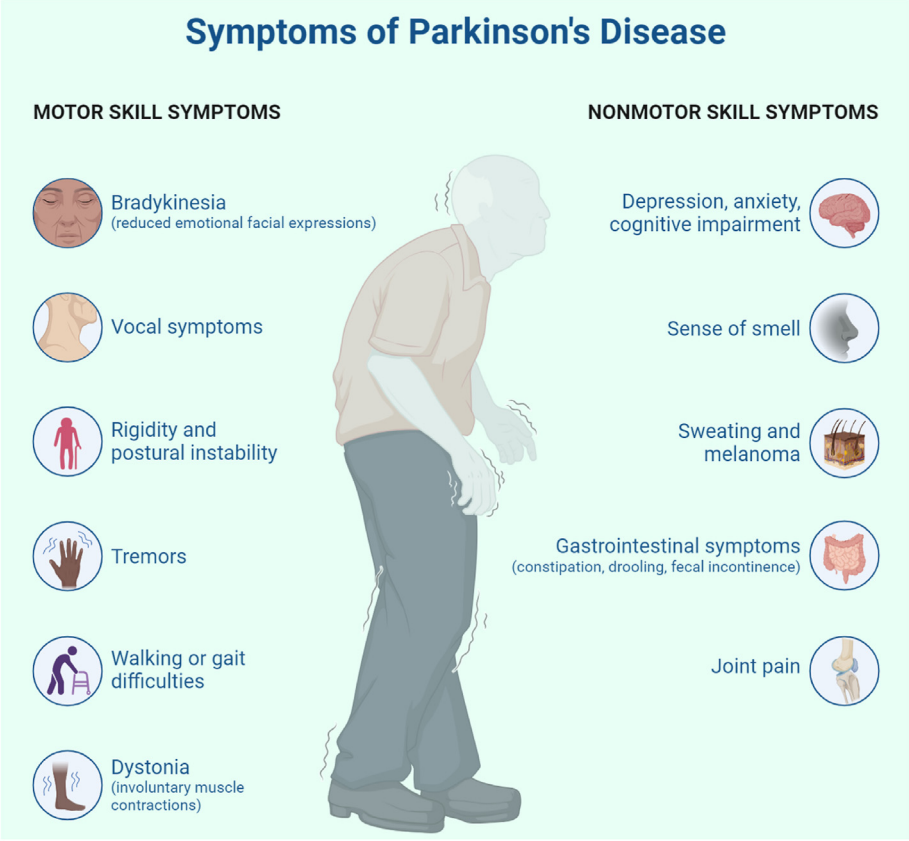


Fig. 2. Symptoms of Parkinson's disease.

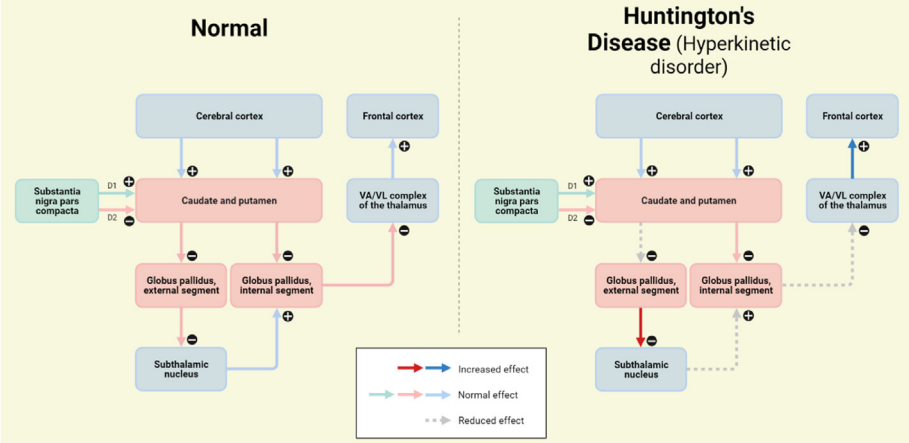


Fig. 3. Cascading in a normal person and in a diseased person.

pathways a decrease of bulk and atrophy of muscle fibers (where most of the ALS-damaged Neurons are visible), and tissue scarring caused by sclerosis that persists with neuronal degeneration.[25] Elevated oxidative stress, decline in mitochondrial membrane potential, modifications in electron transport, accumulation of misfolded proteins, disrupted balance of calcium ions, excessive neuronal stimulation leading to cell damage, and altered behavior of glial cells. cell activities are pathological markers for ALS.[26]

For the treatment of NDD, natural compounds have drawn interest as potential neuroprotective agents.[27] Since herbal treatments are more affordable and culturally suitable, millions of people with age-related neurodegenerative conditions could benefit from utilizing them instead of conventional medication.[28]

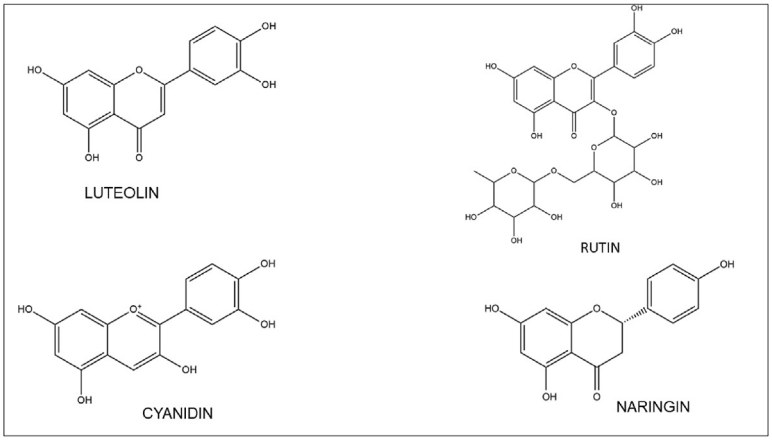
2.4. Indications of Huntington's disease

An autosomal CNS disease called HD is a deadly and progressing NDD. One of the key contributing factors to HD is the HD gene has more polyglutamine repeats than usual. Although the most common symptoms of HD include seizures, uncontrollable movements, emotional disorders, cognitive decline, dystonia, chorea, and intellectual incapacity.[29] The exact cause and advancement of HD remain uncertain, leading to a lack of effective treatments. Aberrations at the cellular level in the development and progression of HD encompass an expanded poly Q protein repeat, along with its interactions with other proteins in the CNS, disrupted mitochondrial dynamics, irregular regulation of transcription, activation of caspases, impaired axonal transportation, and disturbances in calcium balance. Consequently, bioactive substances that have an impact on any of these variables may be helpful in the therapy of HD.[30]

3. Impact of bioactive compounds on pathways of neurodegeneration

3.1. Phenolic and flavonoid compounds

Polyphenols, termed secondary plant metabolites, consist of aromatic rings with hydroxyl (OH) groups as a key structural element.[31] Numerous phenolic substances have been discovered, in either their chemical form or in definite ratios of different botanical extracts. In the field of modern medicine, examining how these natural compounds affect health presents a formidable barrier.[32] Flavonoids, the most common phenolic compounds, consist of subclasses like flavones (e.g. luteolin), Anthocyanins, proanthocyanidins (e.g., cyanidin, pelargonidin), flavonols (e.g. rutin, quercetin), flavanones (e.g., naringin, hesperidin), isoflavones (e.g. daidzein, genistein), and flavonols (e.g., catechin). These compounds are famed for strong antioxidant effects.[33–36] Consuming polyphenolic substances lowers the risk of cardiovascular illnesses, malignancies, and NDDs, according to several studies. Numerous studies with cell and animal models have confirmed the neuroprotective benefits of a diet rich in polyphenols.[37] Numerous phenolic compounds have been shown to possess protective properties on cells, preventing and/or ameliorating damage to cells and mitochondria brought on by oxysterols such as 7-ketocholesterol.[38] Antioxidant substances like quercetin, resveratrol, and apigenin can regulate reactive oxygen species (ROS) formation from oxysterols.[39]



3.1.1. Phenolic and flavonoids compounds in Parkinson's disease

Phenolic amides from *Nicandra physalodes* fruit extract exhibited protection against 1-methyl-4-phenylpyridinium-induced damage in SH-SY5Y cells. This extract contains (7R,8S)-7-(4-hydroxy-3,5-dimethoxyphenyl)-8-hydroxymethyl-V-[N-7(-4-hydroxyphenylethyl] carbamoyl ethenyl-3′-methoxybenzodihydrofuran. Thus, these phenolic amides may be effective medications for treating PD.[40] Dietary phenolic compounds are strong phytocompounds that can be used for a long time to treat PD since they have the potential to resist oxidative stress. The study aimed to explore if natural phenolic compounds quercetin, naringenin, curcumin, and fisetin could serve as neuroprotective agents in the 6-OHDA-induced PD model. Tyrosine hydroxylase (TH)-positive cells can significantly disappear from the SN and the 6-OHDA can lower dopamine levels in the test animal's strata. Rats that were given curcumin or naringenin under these circumstances had exceptional safeguarding against the number of cells expressing TH in the substantia nigra and the level of dopamine present in the striatum. Naringenin and curcumin's capacity to penetrate the BBB and provide neuroprotection may be related to both of their high antioxidant capacities.[41]

3.1.2. Phenolic and flavonoids compounds in motor neuron disease

Plant phenolic extracts are thought to be effective treatments/preventatives for ALS. In a transgenic mouse model of ALS, it was suggested that *Ginkgo biloba* extract might exhibit neuroprotective properties in specific sexes. The extract can be taken orally to greatly minimize motor functioning defects and increase survival. In this ALS mouse model, Additionally, it can significantly reduce the degeneration of motor neurons located in the front portion of the spinal cord. As a result, ALS patients may benefit from the use of *Gingko biloba* extract as a potential therapeutic. In another study, it was discovered that giving transgenic mice a phenolic extract from ginseng root in their water had positive effects. In an ALS mouse model with altered genes, researchers discovered that ginseng had similar positive benefits in reducing motor deficits and lengthening survival time. In experimental animals that have been treated, antioxidant effects, increased nerve growth factor activity, and changed NO levels are potential mechanisms of action.[42,43] As an active ingredient, genistein primarily manifests its effects via blocking various tyrosine kinase activities blockage of the hexose transporter GLUT1, peroxisome proliferator-activated receptors, and activation of Nrf2, topoisomerase, DNA methyl transferase, and cytosine methylation, are just a few of the additional molecular pathways that it may impact.[44] It has been demonstrated that Resveratrol possesses a range of pharmacological and physiological impacts, including anti-aging, antioxidant, anti-AD, and neuroprotective ones, according to pharmacokinetic investigations on the substance. It can also be taken orally.[45] Resveratrol was observed to mitigate the ALS severity by hindering irregularities in the p53 acetylation pathway within the ALS mouse model carrying the G93A-SOD1 mutation. This finding corresponds to the increased survival observed in the G93A-SOD1 transgenic mouse model. This effect was attained by enhancing Hsp70 and Hsp25 expression and activating SIRT1 to deacetylate Heat Shock Factor protein.[46]

3.1.3. Phenolic and flavonoid compounds in Alzheimer's disease

A study examined the potential connection between Enzymes linked to AD (AChE and BChE) and those associated with type II diabetes (α-amylase and α-glucosidase). The deterrent characteristics of a *Sesamia cretica* extract, a plant species, on these enzymes, were investigated *in-vitro*. The extract displayed potent activity against the primary enzymes associated with AD and type II diabetes.[47] The *S. cretica* extract contained twelve phenolic compounds, which comprised kaempferol, hesperidin, chlorogenic acid, benzoic acid, and apigenin. These substances displayed metal ion chelating and radical scavenging abilities. One more similar study concentrated on the phenolic chemicals caffeic acid, chlorogenic acid, gallic acid, rutin, kaempferol, and quercetin that were present in *Senecio biafrae* leaf extract. This extract also exhibited inhibition of key enzymes linked to AD and type II diabetes.[48]

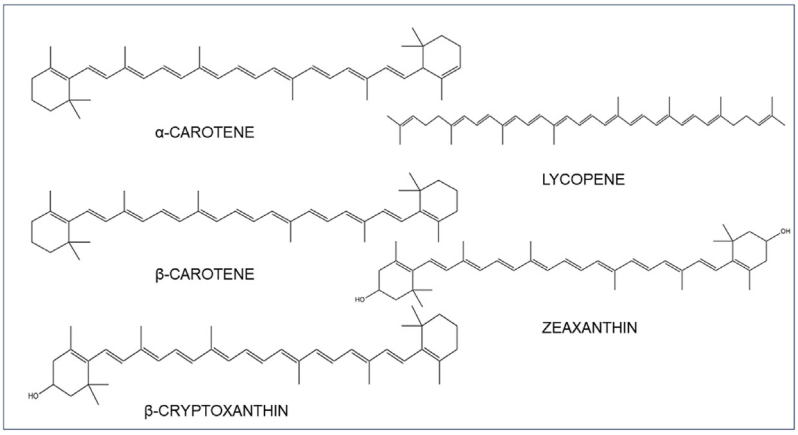
The anti-enzymatic properties of a phenolic extract obtained from *Adiantum capillus-veneris* L. were investigated. The extract contains compounds such as epicatechin, syringic acid, benzoic acid, and catechin.[49] The study reported that the extract exhibited tyrosinase-inhibiting effects, AChE, α-amylase, and α-glucosidase enzymes. However, the impact on BChE was not specifically mentioned in the research. Another study explored. The study examined the impact of a cork oak (*Quercus suber*) extract on the activity of cholinesterase, focusing on the notable effects it had on both AChE (Acetylcholinesterase) and BChE (Butyrylcholinesterase). The findings underscored noteworthy alterations in the activity levels of both enzymes upon exposure to the extract. The results imply that phenolic extracts might hold beneficial compounds capable of relieving symptoms linked to diabetes, AD, and other NDDs.[50] Additionally, an analysis of *Ganoderma applanatum* extracts revealed that the enzymes tyrosinase, cholinesterase, glucosidase, and amylase were all inhibited. These findings suggest the promise of Ganoderma species for creating innovative drug formulations.[51]

Taking 100 or 200mg/kg/day of maple syrup extract (MSX) orally for 30 days can reduce the production of various inflammatory proteins, according to investigations on the anti-inflammation properties of this phenolic-enriched extract fit for human consumption in a mouse model of AD that has been genetically modified (3xTg-AD). These encompass TMEM173, a stimulator of interferon genes, along with SOCS6, the protein associated with AD risk known as TREM2 (triggering receptor expressed on myeloid cells-2), and additional entities such as suppressor of cytokine signaling.[52]

Dietary polyphenols are actively transformed into phenolic acids by the gut bacteria. Scope Studies have revealed that grape seed polyphenolic extract (GSPE) can facilitate this process. leading to significant therapeutic and preventive effects against age-related NDD such as AD. Studies on the metabolism of the microbiota in rats treated with GSPE revealed that these 3-hydroxybenzoic acid and 3-(3-hydroxyphenyl) propionic acid are two phenolic acids significantly increased in the brain accumulations in the rats, preventing the development of neurotoxic Aβ bulk. The study results encourage further preclinical and clinical investigations into the role of gut microbiota in preventing the progression of AD and other NDD.[53] Several perhydro-phenanthrenes (DFs) with phenolic hydroxyl groups that were fused with dihydrofuran demonstrated promising anti-AD effects by having strong dendritic and axonal regeneration capabilities.[54] In the realm of AD's research, curcumin, the major antioxidant derived from turmeric, has undergone pioneering preclinical studies, which involved innovative approaches such as amyloid infusion and experimentation on transgenic animal models. These groundbreaking investigations aim to shed new light on the potential therapeutic effects of curcumin against AD. These studies revealed a favorable safety profile and broad anti-AD effects.[55]

3.2. Carotenoids

In contrast to animals, fungi, algae, and plants are the only organisms that synthesize the colored chemicals known as carotenoids.[56] The primary carotenoids consist of β-carotene, α-carotene, β-cryptoxanthin, lycopene, lutein, and zeaxanthin. They have a linear hydrocarbon backbone (C40) and are symmetrical tetraterpenes. Integral to their host organisms, carotenoids possess distinct structures granting diverse biological traits including actions like antioxidants, anti-inflammatory effects, and modulation of autophagy. These compounds are widely recognized for their protecting roles in the human body, particularly in the diagnosis, treatment, and prevention of illnesses such as NDDs. Research suggests that lycopene can protect neurons within the CNS by easily passing through the blood–brain barrier (BBB), even at low concentrations.[57,58]



3.2.1. Carotenoids in Parkinson's disease

An exploration of the neuroprotective benefits offered by lycopene against PD caused by MPTP in a mouse model demonstrated that lycopene can safeguard against the decrease in striatal dopamine and its derivatives caused by MPTP, and this protection varies depending on the dosage. Lycopene can lessen the motor impairments and OS that MPTP-induced PD animals develop. Additionally, Lycopene has the potential to cure PD because it can reverse OS, physiological abnormalities, apoptosis, and impairments in neurochemical activity in the animal model of the disease.[59] Lycopene's potent capacity to prevent brain neurobehavioral problems and OS in rats with PD brought on by rotenone is demonstrated by its capacity to do so. The study demonstrated that rotenone elevated the levels of MDA (An indicator of oxidative imbalance) by 75% in the striatum. However, when rotenone-treated rats with PD were given lycopene., it effectively reduced MDA levels by 24%. Additionally, rats given rotenone showed a 42% decrease in GSH levels. Rats given rotenone had their SOD activity reduced by 69%, whilst those given lycopene had their activity rise by 12%. Additionally, rotenone-treated rats showed motor and cognitive impairments that were improved by lycopene treatment. Supplementing with lycopene also prevented the mitochondrial release of Cyt C.[60]

3.2.2. Carotenoids in Alzheimer's disease

High blood stratums of zeaxanthin, (+) lycopene, and lutein at baseline stood linked to lower chances of AD mortality, according to research on the effects of carotenoids in the AD patient's serum. Raising serum levels of lycopene, zeaxanthin, and lutein gradually decreased the mortality risk. However, there was no evidence linking other serum carotenoids, such as (−) carotenes and cryptoxanthin, to AD mortality.[61]

RBCs are seen in AD patients that are too oxidized and have large quantities of peroxidized phospholipids (PLOOH). Carotenoids might help AD patients via controlling their RBC viability in this aspect. Studies on humans besides in vivo/in vitro animals have shown that carotenoids effectively block RBCP-LOOH accumulation mechanisms. It was demonstrated that RBC carotenoids, specifically lutein, were much lesser in AD patients than in controls, demonstrating an opposite correlation between the levels of PLOOH and RBC lutein. These results suggest that PLOOH buildup inhibition of RBC in AD patients may be influenced by RBC lutein. The risk of AD may be lowered by the accumulation of specific bio-actives in the brain. According to scientific research. In this instance, a research investigation into the influence of additional carotenoids, xanthophyll on the disease development of AD patients found that the illness also slowed down while improving eyesight, memory, and mood.[62] Studies on the enhancement of cognition using the albino mouse model of research on memory decline induced by streptozotocin also indicated that carotene at a dosage of 2.05mg/kg suppressed AChE activity and lowered A aggregates while attenuating the negative effects of biochemical and behavioral deficits. The In-silico investigations further confirmed β-carotene's ability to bind to AChE.[63] Lycopene, another prominent carotenoid, has drawn great interest due to its neuroprotective, antioxidant, and anticancer functions. More research is required to fully understand its systems of action in NDDs. Lycopene may take part in the early stages of AD, and the choroid plexus can modify neuroinflammatory responses by altering cognitive skills. In an experiment using rats, the introduction of lycopene led to considerable memory gains and learning abilities compared to a group of rats that did not receive lycopene. TNF-α, IL-1β, and IL-6β concentrations notably rose in the bloodstream, particularly in the choroid plexus. Additionally, Aβ1−42 administration increased NF–B p65 mRNA and protein expression, along with Toll-like receptor 4 (TLR4) upregulation. This upregulation indicates the activation of an inflammatory response. However, the administration of lycopene through the rat's stomach results in a considerable drop in inflammatory cytokine levels.[64]

$A\beta_{1\text{-}42}$-persuaded elevation of lycopene and TLR4, NF–B p65 mRNA can additionally restrain protein expressions within the choroid plexus. These results provide further proof that lycopene significantly improves cognitive impairments and reduces inflammatory damage by inhibiting cytokine production and the expression of TLR4 and NF–B p. To learn more about the part of lycopene in AD's development, Scientists have examined its concentrations in the plasma of individuals with AD. The results suggest that lycopene holds the capability to significantly delay paralysis in Caenorhabditis elegans (GMC101 strain) transgenic for A1-42. In SH-SY5Y cells overexpressing the Swedish mutant variant of human APPsw, lycopene effectively reduces Aβ42 secretion. Moreover, lycopene exhibits inhibitory effects on APP production in these cells, providing protection against oxidative stress-induced damage caused by Cu/H2O2. These encouraging outcomes propose that increasing lycopene levels within neurons could be a potentially effective strategy to postpone the initiation or advancement of Alzheimer's disease.[65]

Additionally, lycopene (A potent candidate for treating AD) corrects $A_{1\text{-}42}$-persuaded knowledge and spatial memory debits in a dose-dependent method, (ii) lessens the mitochondrial dysfunction brought on by $A_{1\text{-}42}$; (iii) lowers the activity of the pro-inflammatory cytokines TGF-, IL-1, TNF-, NF–B, and caspase-3 in the rat brain in rats treated with A1-42, (iv) increases memory retaining, (v) lessens oxidative damage to mitochondria, (vi) decreases neuroinflammation and increases levels of neurotrophic factor originating from the brain (BDNF), and (vii) regulates amyloidogenesis.[66]

3.2.3. Carotenoids in Huntington's disease

The potential neuroprotective benefits of the well-known antioxidant lutein on OS and 3-NP-induced dysfunctions were investigated. The effects of oral lutein supplementation in the rat brain, which were further supported by histological analyses, included significant increases in the

mitochondrial complex enzymes' activity, changes in neurobehavioral patterns, weight loss, and a decrease in OS. This study showed that lutein has the potential to be a powerful HD management tool. Giving rats either substance alone can greatly enhance sorrow and anxiety in addition to locomotor count and body weight, according to a different study on the synergistic effects of pairing therapies with quercetin and lycopene HD induced with 3-NP.[67]

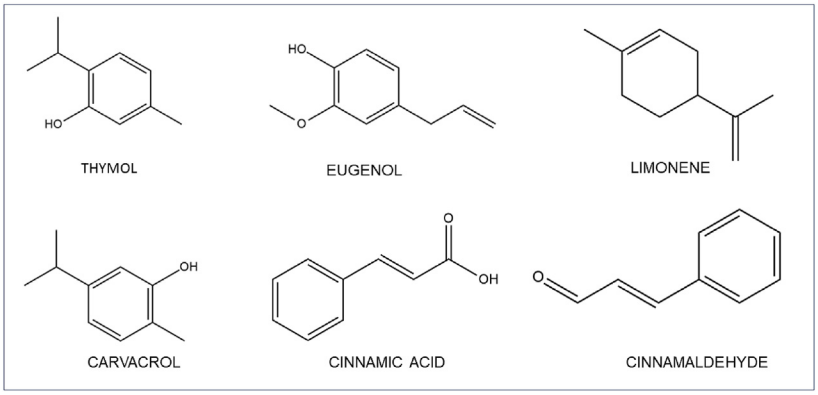
3.3. Essential oils (EOs)

EOs contain certain tiny-molecule aromatic compounds and terpenoids, including cinnamic acid, limonene, cinnamaldehyde, thymol, carvacrol, and eugenol which have antimicrobial properties.[68] But recent research is looking at how neuropathologies like AD can be treated with aromatherapy. To explore the potential neuroprotective benefits of Aloysia citrodora-derived EOs against OS and amyloid-induced neurotoxicity, scientists utilized an in vitro neuronal cell line setup.[69] It gives the close connection between the hippocampus and memory/learning processes, it is possible that EOs can influence NDDs by affecting the olfactory system. Additionally, EOs might directly function as therapies by altering various OS and inflammatory mechanisms related to NDDs. Research conducted on *Sideritis galatica* EOs, for instance, demonstrated that the primary components responsible for activities such as metal chelation, scavenging of free radicals, enhancing reducing power, and inhibiting certain enzyme functions were monoterpene hydrocarbons, particularly pinene.[70]

attenuated $A_{1\text{-}42}$ effect on oxidant-antioxidant balance and AChE activity in the rat hippocampus. These positive outcomes suggest that *Pinus halepensis* EOs possess neuroprotective and nootropic properties, making them a potential therapeutic option to alleviate A-induced neuronal dysfunctions.[73,74]

In a study using mice with an AD dementia model, *Rosmarinus officinalis* EOs greatly increased the frequency of impulsive behavior changes. Additionally, 1,8-cineole and 1,8-pinene, which were the primary ingredients of the inhaled EOs, may be credited for enhancing cognitive processes. Clinical trials of EOs require a thorough investigation into the specific mechanisms of action.[75]

Sesquiterpene and monoterpene hydrocarbons present in the essential oils of *Mentha spicata*, along with carvone, contribute to the potential of these essential oils in traditional medicine for addressing AD. This is due to their potent inhibitory effects on crucial enzymes associated with AD.[76] The impact of inhaling essential oils derived from *Tetraclinis articulata* was studied on brain OS and memory in a model of AD induced by Aβ42 amyloidosis. The EOs, which primarily consisted of monoterpene hydrocarbons, displayed an activity profile resembling that of EOs from *Mentha spicata*. According to this study, EOs may be able to combat dementia by enhancing antioxidant defenses and controlling the rat hippocampal cholinergic system.[77] The essential oils obtained from the above-ground components of *Salvia miltiorrhiza* were also investigated in a mouse model of AD. Oral administration of EOs, which primarily contained, terpenoids, dihydro-neoprene 6,10, 14-trimethyl-2-pentadecanone β-caryophyllene and hyllene, prevented



3.3.1. Essential oils in Parkinson's disease

The essential oils (EOs) derived from *Eplin giella fruticose* (EPL), a Liliaceae family plant that is both aromatic and therapeutic, have been scientifically demonstrated to possess anti-inflammatory properties and antioxidants. In an instance, Cyclodextrins were employed in studies to enhance the pharmacological characteristics of EPL the interaction between EPL and cyclodextrin (EPL-CD) was examined in a PD mouse model behavioral assessment, lipid peroxidation quantification tests, and Immunohistochemistry revealed that EPL-CD can improve memory deficiencies, delay the development of catalepsy, reduce the occurrence of dopaminergic striatal, SN pars compacta depletion and avoid oral dyskinesia. The findings indicate that EPL exhibits strong neuroprotective effects in an evolving animal model of PD[71,72]

3.3.2. Essential oils in Alzheimer's disease

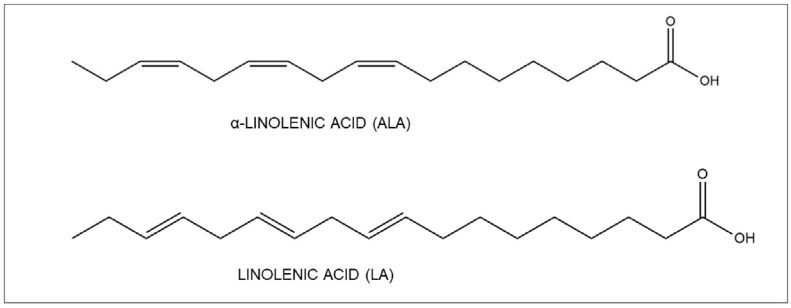
A promising and natural approach to treating AD dementia could involve aromatherapy using EOs. Studies conducted on the EOs derived from in a rat model of acute A1-42 poisoning, *Pinus halepensis* have shown important advantages. The EOs were found to reverse the $A_{1\text{-}42}$-induced decline in spontaneous alternation and reduce the $A_{1\text{-}42}$-induced issues with working and reference memory. Moreover, the essential oils cognitive deficits and reduced AChE activity and MDA content.[78]

According to this, EOs may be advanced as a potential therapeutic preparation for AD, and they can treat symptoms similar to AD in mice. Another study used a C. elegans AD model to examine the effects of EOs produced from roses. The findings demonstrated that the EOs knowingly reduced Aβ oligomers and repressed the A deposits in order to reduce the toxicity brought on by Aβ overexpression. Furthermore, the essential oils significantly increased the expression of the gst-4 gene by a considerable degree. This reaffirms the role of the SKN-1 signaling pathway in the therapeutic mechanism of essential oils for AD in the C. elegans model. These results provided concrete proof that EOs can effectively treat AD at the organismal level It offered a basic scientific foundation for potential future medicinal uses of these Eos.[79]

Salvia ursina the inhibitory properties of Bunge's EOs on the neurodegenerative (AChE and BChE) and diabetes-related enzymes have been investigated (amylase and glucosidase). The primary components of the EOs were methyl hexadecanoate, 6,10,14-trimethyl-2-pentadecanone, methyl linoleate, and ethyl linoleate. The EOs showed reasonable AChE and reasonable to strong anti-diabetic activity.[80]

3.4. Fatty acids

Particularly the (ω) series of fatty acids have been confirmed to have useful properties on cognitive performance and the treatment of CNS disorders. The second-highest level of lipids in the body is found in the brain. Approximately 35% of the lipids found in the brain consist of long-chain polyunsaturated fatty acids (PUFAs). These PUFAs are not synthesized via de novo lipogenesis. Instead, they arise from omega-6 (ω-6) and omega-3 (ω-3) precursors: α-linolenic acid (ALA) for omega-3 and linoleic acid (LA) for omega-6 fatty acids.[81] Although only a small amount of PUFAs were biosynthesized in the brain, in vitro studies revealed that cerebral endothelial cells and astrocytes eagerly lengthen and desaturate PUFA precursors. Therefore, the liver's biosynthesis pathways serve as the primary source of PUFAs. In this context, ALA to docosahexaenoic acid (DHA, 3) conversion in rat's liver is enhanced by a 15-week dietary shortage of 3 PUFAs.[82] Additionally, entorhinal cortex neurons which are crucial for memory and learning showed greater firing activity and a decrease in the duration of the postsynaptic response, as well as shorter action potential durations and other notable changes in brain electrophysiology.[83]



3.4.1. Fatty acids in in Parkinson's disease

Omega-3 PUFAs may be therapeutically beneficial in treating a number of CNS diseases, including PD, according to research from preclinical, clinical and epidemiological studies. PUFAs, such as omega-3 PUFAs, are widely accessible and can be quickly introduced into clinical trial phases to assess their neuroprotective effects.[84] SN compact dopaminergic neurons are protected from PD by ω −3 PUFAs, which also reduce immunological inflammation and enhance limb movement coordination, suggesting possible therapeutic use in the treatment of PD oil can lessen the effects of neuronal terminals in the striatum and 6-OHDA-induced loss of SNpc neurons.[85] The safeguarding impact was associated with a decrease in the response of astrocytes and microglia, as well as the iNOS-immunoreactive cell density. These results suggested that fish oil supplementation's anti-inflammatory and antioxidant properties are strongly related to decreases in dopaminergic damage brought on by 6-OHDA.[86]

3.4.2. Fatty acids in motor neuron disease

Patients with Amyotrophic Lateral Sclerosis experience hypermetabolism, dyslipidemia, and weight loss, and deficiencies in cellular energetics can be found prior to denervation. Even though there is overwhelming scientific evidence that ALS causes major metabolic changes, it is still unclear how these changes are caused and how these pathways contribute to the disease. In this case, a Drosophila ALS model targeting Tar-DNA binding protein (TDP-43), a hallmark of ALS, revealed lipid metabolism changes along with impaired movement and shortened lifespan. One significant improvement in these is the amount of long-chain fatty acids conjugated to carnitine and notable decreases in acetylcarnitine, -hydroxybutyrate (a ketone precursor), and carnitine. Regarding TDP-43 protein-related issues, research conducted on Drosophila highlighted a connection between genetics and nutrition, revealing altered expression of components related to the carnitine shuttle pathway. Additionally, Drosophila that were fed with medium-chain FAs or hydroxybutyrate displayed improved locomotor abilities. These discoveries underscore the likely engagement of the shuttle of carnitine and oxidation of lipids in diseases like MND/ALS, presenting potential avenues for treatment that focus on restoring motor neuron lipid metabolism.[87]

3.4.3. Fatty acids in Alzheimer's disease

FAs, especially ω-6 and ω-3 series, play a vital role in the nervous system and visual development, neurotransmitter regulation, and intelligence. We assessed the effects of ω-3 fatty acids on rat brain microvascular endothelial cells in vitro, focusing on their recognized neuroprotective traits. The findings demonstrated that when RBMVECs were treated with ROS, ω-3 FAs, Gpx, catalase, and Superoxide dismutase (SOD) were improved, while lipid peroxidation and the proportion of apoptotic cells were reduced. It was likewise discovered that ω-3 FAs might have a strong beneficial impact on AD.[88] Using female wild-type mice, the consequences of a deficiency in ω-3 fatty acids on brain development and the development of pathologies resembling AD were investigated. The results indicated that an insufficient intake of dietary ω-3 fatty acids could lead to enduring alterations in the expression of synaptic markers throughout brain development. Moreover, prolonged reductions in brain Arachidonic Acid deficiency were observed in mice, partially countered by a post-weaning omega-3 fatty acid-rich diet. Notably, a ω-3 deficient diet erased differences between transgenic and wild-type mice, implying a link between PSD-95 expression regulation and AA oxidative degradation. Furthermore, the timing of ω-3 intake during growth might influence the development of AD-associated changes later in life.[89] A different study demonstrated that naturally occurring omega-3 PUFAs enhanced cognitive functions such as learning and memory in mice with AD. This enhancement could be elucidated by a reduction in the creation of A plaques and neurotrophic factors (NTFs), which could potentially inflict damage on hippocampal neurons. Additionally, the cerebral vascular system of AD mice was revealed to be protected by endogenous ω-3, which raised the brain's metabolic rate. Moreover, natural omega-3 FAs were found to increase the survival of tau-associated AD models, suggesting their potential to delay AD onset linked to tau protein dysfunction, ease symptoms, and significantly extend in vivo survival. AD is caused by the dysfunction of tau proteins.[90] It was shown that a diet high in deuterated PUFAs (D-PUFAs) can lower levels of A proteins and oxidized AA and DHA in the brain tissue.[91]

3.4.4. Fatty acids in Huntington's disease

The Exon 1 mutation in the Huntingtin gene lengthens the polyQ residues near the protein's N-terminal, which, upon entering the nucleus, poses risks to neurons due to accumulation. Neurodegeneration from aggregated polyQ involves its interaction with cyclic adenosine monophosphate response element binding protein. Exploring HD treatment, essential FAs added to diets have shown increased survival rates and reduced neurological issues, hinting at PUFA benefits. These findings suggest PUFAs might inhibit histone deacetylase, hinder polyQ aggregation, and/or activate the ubiquitin-proteasome system. These positive effects on HD could extend to treating other NDDs.[92] In a pertinent study, HD patients underwent assessment with the Unified HD Rating Scale (UHDRS) and the Rockland–Simpson Dyskinesia Rating Scale. The outcomes demonstrated that providing PUFAs to HD patients can enhance the motor scale. In a different study, essential FAs and a placebo were administered at random to normal and R6/1 transgenic mice. The findings show that necessary FAs can prevent motor impairments in R6/1 transgenic mice when given early therapy.[93]

3.5. Phytosterols

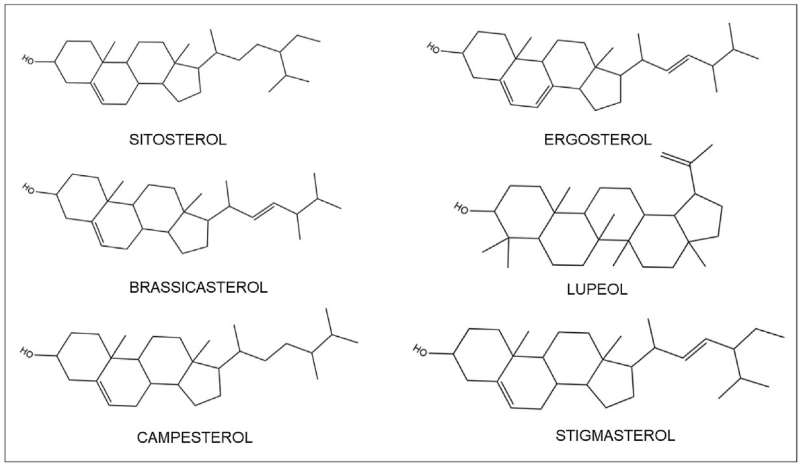
The most common plant sterols, closely resembling cholesterol in structure, are referred to as phytosterols. In this group, campesterol, lupeol, stigmasterol, sitosterol, Brassicasterol, and ergosterol are sterols.[94] In order to maintain a balanced cholesterol level in the CNS membrane, significant amounts of circulating phytosterols can permeate the BBB and assemble in the brain in an irreversible manner. Studies conducted over a long period of time have demonstrated that phytosterols can lower lipid and cholesterol levels, preventing hypercholesterolemia, cardiovascular illnesses, and aging.[95–98] Consumption of dietary phytosterols altered the metabolism of cholesterol in the brain but had no effect on memory-related behavior in a mouse model of phytosterolemia.[99] Moreover, administering phytosterols to mice carrying the model of AD (APPswe/PS 1dE9) resulted in modified amyloidogenic behavior of the amyloid precursor protein (APP) and reduced production of Aβ in neurons.[100] Furthermore, administering phytosterols to C57BL/6NCrl mice has been shown to influence APP breakdown in lipid rafts through a γ-secretase pathway, possibly connected to brain functions.[101]

3.5.1. Phytosterols in Alzheimer's disease

Although β-sitosterol significantly inhibited cholinesterase activity *in-vitro* and *in-vivo*, In the frontal brain and hippocampal homogenates of transgenic rats, the levels of BChE and AChE activities were notably minimal. The IC_{50} values for these enzymes were 50 and 55mg/mL, respectively. Studies using molecular docking software (in silico) demonstrated that when β-sitosterol was present, free radical levels in the brain tissues were found to be much lower because β-sitosterol ties up with the intended enzyme.[102] Furthermore, transgenic animals given β-sitosterol treatment showed a steady development in spontaneous interchange behavior, motor coordination, working memory, indicating that β-sitosterol is an effective bioactive substance for reducing memory deficits in AD. Added data demonstrated that the SER35 and catalytic aspartic residues of BACE1 can create two hydrogen bonds with the –OH group of lupeol, a phytosterol from *Pueraria lobata*. These results imply that this phytosterol's inhibitory properties are dependent on the presence of the –OH group, Additionally, they contend that BACE1 inhibition is the molecular pathway via which Lupane triterpenoid's function, and that this bioactive can be used to prevent or treat AD.[103]

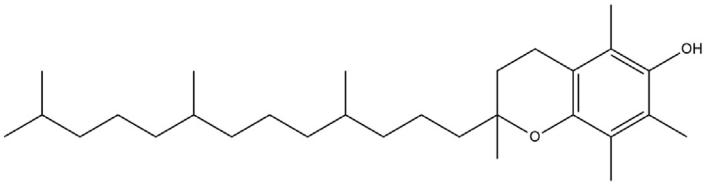
3.6. Tocopherols

Tocopherols are one of a family of eight compounds that each have an attachment of aliphatic side chain to a chromanol ring. The distinction among the tocopherol isoforms (α, β, γ, and δ) arises from methyl group positions on the chromanol ring. These tocopherols possess three chiral centers, with α-tocopherol (αT) being the most common α-isoform. While the human intestine can absorb the other isoforms, α-tocopherol transfer protein (α-TTP) is unable to identify and utilize them.[104] αT plays a significant role as a natural scavenger for reactive oxygen species (ROS) and reactive nitrogen species (RNS). Previously, it was believed that αT primarily functions as a scavenger for lipid peroxyl radicals, particularly oxidized low-density lipoproteins (LDL), which play a critical role in the development of atherosclerosis. Recent studies have unveiled more roles for αT, including gene regulation and cell signaling. Trials show promising results of αT in preventing and treating heart disease, cancer and AD.[105]



3.6.1. Tocopherols in Alzheimer's disease

α-T has shown the ability to reduce Aβ-induced cytotoxicity in SH-



α-TOCOPHEROL

S5Y5 cells. According to a transcriptome investigation, Treatment with α-T (alpha-tocopherol) can lead to the upregulation of genes implicated in APP processing that isn't amyloidogenic (amyloid precursor protein, simultaneously causing a decrease in the amyloidogenic pathway. Additionally, α-T can regulate genes related to the cell cycle and autophagy, both linked to AD. Moreover, treatment with α-T can lower inducible nitric oxide synthase NOS levels, lower OS and the restoration of nuclear factor erythroid-derived 2-like 2 (Nrf2).[106] Another study used transgenic 5XFAD mice to assess the effectiveness of α-T and etodolac in treating OS and neuroinflammation. The combined treatment notably reduced oxidative stress and neuroinflammation, in both *in-vitro* and *in-vivo* settings. It elevated synaptic marker expression, lowered total Aβ levels, shifted APP processing toward non-amyloidogenic pathways and significantly improved BBB function. The combination therapy considerably improved BBB functioning, decreased total A, reduced total A, Shifted APP processing towards nonamyloidogenic and neuroprotective pathways, resulting in a substantial reduction of oxidative stress and neuroinflammation in both laboratory settings and living organisms.[107]

In laboratory experiments, it has been demonstrated that α-TQ has the capacity to diminish the generation of ROS and inflammatory cytokines. Including cytotoxicity and aggregation of Aβ. When α-TQ is administered orally, it has the ability to enhance memory deficits in mice afflicted with AD. Additionally, it effectively reduces OS and levels of Aβ oligomers in the mouse brain. Another advantageous outcome is its capacity to inhibit the synthesis of inflammatory agents, such IL-6, interleukin-1β (IL-1β), and NOS. Moreover, α-TQ inhibits microglia activation by blocking the NF-κB signaling pathway.[108] Consuming a diet rich in vitamin E (tocopherols) from food sources, rather than relying on vitamin E supplements (specifically α-T), is linked to a lesser risk of AD. Research has indicated that an increased consumption of α-T and tocopherol is linked to a decreased occurrence of AD. This suggests that vitamin E holds neuroprotective properties against the disease.[109]

4. Combinational roles of bioactive in NDDS

According to research on vitamin complexes (ascorbic acid, -carotene, and -T), an increase in vitamin complex concentration lowers ROS production while also enhancing the cells' capacity to remove ROS in AD patients. By boosting antioxidant capabilities at the cellular level, reducing ROS formation and controlling cytokine-induced inflammation, the vitamin complex's antioxidant activity effectively reduced OS in AD patients. There were no discernible variations in serum levels of -carotene between AD control groups and AD patients, according to another investigation on the possible benefits of vitamin A and/or carotenes.[110] Despite the fact that retinol and -carotene levels in AD patients were astonishingly low, this shows that a dietary deficiency in this provitamin may be to blame for the low levels of -carotene in AD patients' serum. Another study indicates that ω-3 long-chain PUFAs, such as EPA and DHA, exhibit diverse anti-inflammatory effects by generating specialized pro-resolving mediators, and anti-inflammatory cytokines, or by reducing proinflammatory eicosanoids. This study amply demonstrated the synergistic effects of dietary combinations, which have the potential to be more beneficial than single bioactive. It was also recommended that ω-3 FAs work well when combined with vitamin D3, vitamin B complexes, curcumin, and resveratrol.[111]

5. Conclusion

NDDs, which are intricate brain disorders characterized by various dysfunctional pathways, are anticipated to become more prevalent in the future due to the increasing global population of older individuals and extended lifespans. The most common age-related brain disorder, dementia, is expected to originate as an outcome. By putting suitable measures in place like cognitive training, physical exercise, and nutritional interventions, it is possible to delay the onset of NDDs by identifying memory and cognitive deficiencies during the preclinical phase. Given the significant attention towards factors that contribute to NDDs, investigating dietary therapies seems to be a useful strategy for controlling inflammation, avoiding or postponing the start of the disease, and slowing the progression of the disease. Dietary changes in people with NDDs can affect how the brain works physiologically, increasing or preserving normal functions in younger and older populations. Utilizing natural products and the potent bioactive substances they contain is crucial for the treatment and prevention of various neurodegenerative illnesses without having negative side effects. It is essential to use neuroprotective techniques that incorporate numerous modes of action for the prevention and therapeutic treatment of such disorders since the pathological process of neurodegeneration has a multifaceted nature. Therefore, natural products are chosen because they include bioactive chemicals that have neuroprotective benefits through various modes of action.

Author contribution

Mohd Mursal: Writing – the original draft.

Arun Kumar: Visualization validation and correction of the manuscript.

Syed Misbahul Hasan: Visualization validation and correction of manuscript.

Sahil Hussain: Writing – the original draft.

Kuldeep Singh: Visualization validation and correction of manuscript.

Shom Prakash Kushwaha: Drawing of chemical structure.

Muhammad Arif: Visualization validation and correction of the manuscript.

Rajeev Kumar Singh: Formal analysis, and Data curation.

Deepshikha Singh: Declares that he has no conflict of interest.

Ali Mohammad: He helps in editing, and reviewing of the manuscript.

Syed Kaynat Fatima: She helps in editing, and reviewing of manuscript.

Declaration of competing interest

All authors declares that they have no conflict of interest.

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