Project on

Literature review on

"Multifaceted Role of Phytoconstituents on Alzheimer's Disease: How Far Science Has to be Progressed?"

[In the partial fulfillment of the requirements for the degree of Bachelor of Pharmacy]

Submitted To

The Department of Pharmacy,

Faculty of Allied Health Sciences,
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APPROVAL

This project paper, Literature review on "Multifaceted Role of Phytoconstituents on Alzheimer's Disease: How Far Science Has to be Progressed?" submitted to the Department of Pharmacy, Faculty of Allied Health Sciences, Daffodil International University, has been accepted as satisfactory for the partial fulfillment of the requirements for the degree of Bachelor of Pharmacy and approved as to its style and contents.

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DECLARATION

I hereby declare that this project report, Literature review on "Multifaceted Role of Phytoconstituents on Alzheimer's Disease: How Far Science Has to be Progressed?", is done by me under the supervision of Mr. Pollob Ahmed Shuvo ,Senior Lecturer, Department of Pharmacy, Faculty of Allied Health Sciences, Daffodil International University. I am declaring that this Project is my original work. I also declare that neither this project nor any part thereof has been submitted elsewhere for the award of Bachelor or any degree.

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Jannatul Fardous Khadija

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My Parents,

The persons who always encourage me in every sphere of my life.

Abstract

Amyloid-beta (Aβ), aggregation, neuro-inflammation and several other cellular processes alters these which causes of Alzheimer's disease (AD), a common neurodegenerative brain disease. The most typical kind of dementia, AD, continues to impact a large number of people worldwide. It's unclear what exactly caused the disease. There are currently no cures available that work to slow down or perhaps stop the development of AD. Many natural compounds are extracted from various sources and studied in both preliminary and clinical environments for neuroprotective properties in the prevention and treatment of AD. Moreover, the therapy and prevention of AD have shown promise for natural compounds and their derivatives. Natural bioactive substances actively modulate the pathogenic molecular pathways that lead to the development of AD. The focus of this review is on plant-based natural compounds and their derivatives that have shown neuroprotective properties and may show promise in the treatment and prevention of AD. The literature on using natural items as AD therapy agents is also summarized in this article. Most bioactive compounds for the therapeutics of AD have a number of drawbacks, including rapid metabolism, poor solubility, and impermeable blood–brain barrier, and limited bioavailability. Many methods use for nanotechnology and nano-carriers are possible.

Keywords: Alzheimer’s disease; natural products; amyloid-beta; amyloid precursor protein; neurofibrillary tangles; reactive oxygen species.

Contents

Chapter One
Introduction

1.1 Alzeimer’s Disease

Alzheimer's disease (AD) is a neurological condition that worsens with age and impairs memory and cognitive function [1-3]. Dementia is the sixth greatest cause of death worldwide, accounting for 60–80% of all instances of dementia [4]. Known as a neurodegenerative condition (NDC), Alzheimer's disease (AD) gradually reduces memory, thought, or eventually the capacity to carry out daily tasks, demanding full-time care. Although it can harm younger people as well, the illness is more common in people over the age of 65. One of the most significant risk factors for AD is age. According to study, the age-related Alzheimer's disease of prevalence incidence climbs rapidly, with 3% of individuals in the 65–74 age group, 17% of people in the 75–84 age group, and 32% of people in the 85–plus age group having the disease [5, 6]. Both environmental and genetic factors have an impact on the etiology of AD [7]. In this regard, intracellular neurofibrillary tangles (NFT) and extracellular deposition in amyloid are two significant pathologic markers of AD [8]. Clinical dementia is brought on by amyloid buildup, which also causes cognitive deterioration [9]. Amyloid-beta (Aβ) peptide synthesis and neuronal death are both affected by mutations in the amyloid precursor protein (APP) and presenilin, which are both involved in the development of AD [10,11]. Unexpectedly, Recent studies revealed that neuroinflammation plays a crucial detrimental effect in Alzheimer's [12, 13]. Inflammation and oxidative stress are brought on by the deposition of aggregated Aβ protein in the synapses of Alzheimer's patients (OS). Depletion of cholinergic neurotransmission and excessive glutamatergic neurotransmission are further features of AD [14,15]. The earliest clinical evidence of short-term memory impairment

is typically impairment of immediate memory, although later on, distant memory is also damaged. On the other hand, AD does not affect memory processing [16, 17]. People typically lose their ability to move and speak clearly severe dementia at an advanced stage caused by AD, which causes significant memory loss as well as a diminished sense of time and place. Patients in this circumstance demand additional attention. It is anticipated that therapeutic intervention that can slow the onset or course of AD will significantly lower the number of cases during the next 50 years [18]. The development of drugs for the treatment of AD has successfully and promisingly utilized natural products and their bioactive compounds as possible therapeutic leads [19, 20]. As such, mixtures or extracts of natural goods contain organic biologically active substances that could be used as a treatment strategy for the management or prevention of AD [21–23]. Additionally, several extracts and organic materials are frequently used in human clinical studies and AD animal models [24, 25]. The therapeutic potential of plant-based natural compounds that may have neuro protective characteristics for the control and treatment of AD through a number of mechanisms is highlighted in this review.

1.1.1 Pathology of AD

The pathological signs and symptoms of AD are amyloid plaques and NFTs. In addition, cerebral amyloid angiopathy, neuropil threads, dystrophic neurites, associated astrogliosis, and microglial activation are all observed in AD [28]. These pathologic processes cause synaptic and neuronal loss and neurodegeneration. Another prevalent kind of neurodegenerative dementia in elderly persons is combined pathology, which includes Lewy bodies and vascular disease [29]. In fact, familial AD and Lewy body disease frequently overlap, while the exact mechanism is uncertain [30,31]. Two by-

products of APP metabolism are amyloid plaques, are extracellular clumps predominantly composed of misfolded Aβ proteins with 40 or 42 amino acids (Aβ 40 and Aβ 42). Aβ-42 is more prevalent in plaques than Aβ-40 due to its higher rate of insolubility and fibrillation. Amyloid plaques, in contrast to NFTs, have a negligible effect. As opposed to that, the majority of NFTs are composed of hyperphosphorylated tau paired helical filaments (PHFs). The pathogenesis of NFT is superior linked to the clinical characteristics and AD severity because neuronal and synaptic loss frequently occurs at the same time as tangle growth [32]. Aβ pathology reaches a plateau [33].

1.1.2 Etiology and Pathophysiology of AD

Despite the fact that Aloise Alzheimer, a German physician, first identified AD and the fundamental mechanisms underlying its development since a century ago remain a mystery [34]. Acalculia, apathy, and anomic aphasia are typical signs of AD, as are dementia, memory loss, mobility issues, depression, delusion, impairment in spatial awareness, and hallucinations. Additionally, patients who are towards the end of their lives are unable to talk verbally, have lost their independence, and are unable to perform simple daily duties [35,36]. The cause of this sickness' etiopathogenesis is still not completely known, despite continuous research. However, certain distinctive pathways have been discovered. In this situation, the accumulation of Aβ is a typical sign of AD. Senile plaques APP is created by synthesizing a short peptide called Aβ from naturally occurring APP. Additionally, Aβ controls synaptic plasticity, participates in axonal expansion, and modifies axonal expansion in physiological contexts [36, 37]. Development is frequently accompanied by further pathogenic abnormalities that damage the structure of pyramidal neurons. These mechanisms culminate in the creation

of tau tangles and are brought on by increased protein phosphorylation in tau (**Figure 1**). The physiological stabilization of microtubules and, consequently, the cytoskeleton structure are regulated by tau proteins. In this regard, microtubules serve as cellular proteins and enzyme transporters, ensuring correct neuron activity and synaptic signaling. Tau proteins and tubulins connect to form the delicate structures known as microtubules, which are dependent on these interactions for stability. Tau tangles, which are indicative of AD, are produced more frequently as a result of increased tau phosphorylation, which also causes microtubule disassembly. Similarly, cyclin-dependent kinase 5 has been linked to this process as a result of the elevated Ca2+ ion concentration that is directly brought on by Aβ gathering inside of nerve cells. The cytoskeleton deforms, microtubules depolymerize, intracellular transport is disrupted, etc. as a result, which compromises the neuron's overall function. Tau tangles include toxic aggregates that, when combined, produce neuronal injury, cell death, activation of microglia, and inflammation [38].

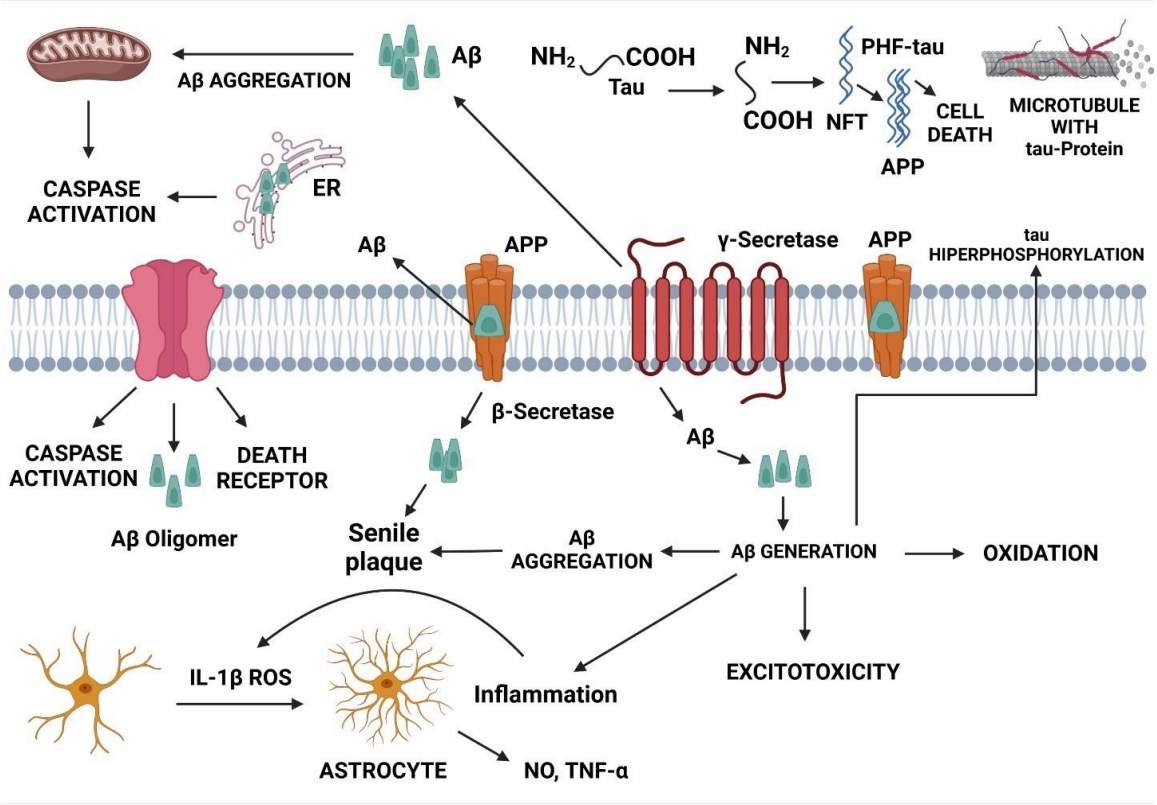


Figure 1. The Alzheimer's disease amyloid cascade. APP indicates amyloid precursor protein, NFT represents for neurofibrillary tangle, and Aβ signifies for amyloid beta. Reactive oxygen species is referred to as ROS; Nitric oxide is referred to as NO, and tumor necrosis factor-alpha is referred to as TNF- α [39].

Although other hypotheses have been proposed to explain the pathophysiology of AD, the precise mechanism is still unclear and complex [40]. Some of the hypotheses that have been put out include the following:

a) Hypothesis of Cholinergic

Cholinergic neurotransmission affects a variety of brain functions, including mental state, brain adaptability, sleep-wake cycle management, cerebral blood flow control, and neuronal function. Studies show that the cholinergic system is also crucial for

cognitive function. As a result, memory loss could be brought on by impairment [41, 42]. During cholinergic neurotransmission, synapses release acetylcholine (ACh). ACh is hydrolyzed by acetylcholinesterase (AChE) and butyrylcholinesterase, which terminates the signal. (BuChE). Several AD patients in this case showed stable or rising BuChE activity.Since it is believed that AChE-induced Aβ aggregation contributes to the onset of AD and the formation of neurotoxic Aβ fibrils, inhibiting AChE and BuChE is a promising strategy for treating AD [43].

b) The Amyloid Hypothesis

Aβ precursor protein (APP) is a type I transmembrane sialoglycoprotein that is encoded by a single gene on chromosome 21's 19 exons. APP comes in three different forms: APP751, APP770, and APP695. The APP regulates synaptic plasticity, neurite outgrowth, or cell adhesion. APP has neurotrophic and neuroprotective effects in its soluble form [44]. APP processing pathways can either be amyloidogenic or nonamyloidogenic. The important event is the α-secretase enzyme cleaving Lys16 of the APP, releasing a C-terminal fragment and an Aβ-soluble peptide. A C-terminal fragment and soluble Aβ peptides are released from the cleavage of APP by β-secretase, p3 is created by splitting the C-terminal region of the protein by **γ**-secretase. Additionally, **γ**-secretase breaks down APP in several places, producing an Aβ monomer with amino acids between 38 and 43. After that, Aβ monomers self-assemble into neurotoxic oligomers, which in turn induce fibrillary aggregates to form, which ultimately result in neuronal dysfunction and dementia [45]. Additionally, the formation of senile plaques, a characteristic of AD, is triggered by aggregated oligomers. The Aβ42 peptide is present at considerably higher levels in Alzheimer's patients than in healthy individuals.

c) Hypothesis of Tau

Tau protein is a phosphoprotein having six isoforms that range in length from 352 to 441 amino acids with 38 phosphorylation sites. In this way, the microtubule connections and/or amino acid composition of domains of Tau are defined. The amino-terminal portion in this instance is known as a "projection domain" because it does not connect to microtubules but instead extends past them. By interacting with tubulin, phosphorylated tau protein contributes to intracellular trafficking and aids in stabilizing axonal microtubule assembly [47]. Microtubules are made unstable by hyperphosphorylated tau, which kills nerve cells. According to research, hyperphosphorylated tau is present in the brains of AD patients at levels that are three to four times higher than those of healthy individuals [48].

d) Neuro-inflammation

By generating pro-inflammatory cytokines including interleukin-1, tumor necrosis factor (TNF-α), and interferon, which have all been found in AD patients and have an impact on the brain, increased numbers of microglia and astrocytes produce chronic neuro-inflammation. This is because Aβ peptide is created when β-secretase cleaves APP,is made more effective by reactive oxygen species (ROS) [47]. As a result, novel chemicals that can be applied to both prevent and treat AD have been created using anti-inflammatory approaches [49].

e) Biometal Dys Homeostasis

Biochemical processes like Stability of protein structure, metabolism, catalytic activity, and transmission of cellular signals all depend on metals like copper, iron, and zinc [50].

The Fenton process, which is predominantly driven by redox-active Fe2+ and Cu2+, is capable of producing more DNA, proteins, and lipids. Therefore, dysregulation of biometals in neurodegenerative diseases like AD causes oxidative stress, that's why metal chelators are used may be able to prevent AD development [51, 52].

f) Oxidative Stress (OS)

ROS including the superoxide anion radical, peroxide, hydrogen peroxide, and the hydroxyl radical are produced by oxygen consumption and biological signaling. In typical circumstances, the intrinsic antioxidant system controls the balance of ROS [53]. However, in pathological conditions, there is a disparity between ROS formation and clearance, resulting in elevated ROS levels [54]. Brain OS may be a precursor of AD and may influence the course of the disease, according to research [55, 56]. Because the brain uses the most energy, consumes the most oxygen compared to other organs, and engages in mitochondrial respiration, it is more likely to be exposed to ROS. On the other hand, Aβ formation and deposition in AD are influenced by lipid peroxidation and protein oxidation [57, 58].

g) Insulin-degrading Enzyme

Type 2 diabetes and insulin resistance in the brain are connected to AD. Studies link tau hyperphosphorylation and Aβ deposition to the enzyme that breaks down insulin (IDE). Insulin and Aβ see IDE as a competitive substrate that contributes to the pathogenesis of AD. Additionally, IDE is connected to the clearance of Aβ in the brain. Consequently, AD can be treated using IDE activators [59].

h) Homocysteine

Homocysteine (HCy), a nonproteinogenic homolog of cysteine, is produced after methionine is demethylated. Inducing glutamate excitotoxicity, which results in neurotoxicity and ultimately leads to neuronal death, is what happens when HCy attaches to glutamate NMDA receptors. High levels of HCy are associated with oxidative injury, apoptosis, Aβ aggregation, and tau protein hyperphosphorylation [60, 61].

i) Phosphodiesterase

The enzymes known as phosphodiesterase (PDEs) are responsible for converting cyclic guanosine monophosphate (cGMP) and cyclic adenosine monophosphate (cAMP). Moreover, they participate in the regulation of intracellular signaling cascades and synaptic plasticity. Particularly PDE4, PDE7, and PDE8 expression changes have been connected to AD [62].

Chapter Two
Purpose of The Study

2.1 Purpose of the study

- The goal of this study is to know-
    - What is Alzeimer’s Disease (AD) and its pathogenesis.
    - How natural products could play a vital role for the control and treatment of Alzeimer’s disease.
    - To know the ability of preventing Alzeimer’s disease.
    - Relationship of natural products with endoplasmic reticulum stress against oxidation and neuroinflammation.
    - Natural product’s nanotechnology might be the potential alternatives for the management of Alzeimer’s disease.
    - To know about Alzeimer's disease is caused by a complex array of hereditary and epigenetic variables.

Chapter Three
Methodology

3.1 Methodology

After doing a literature search, we were able to find current, pertinent references in a variety of databases, including Elsevier, PubMed, Scopus, Science Direct, and Web of Science. In our search, the terms "medical plant," "neuroprotection," "Alzheimer's disease," "antioxidant," and "inflammation" were used. Selected and reviewed were study summaries, reviews, and until January 2023, original English-language research papers published. Additionally, we looked over the citations therein and added them where needed. An algorithm was employed in accordance with Page et al.'s guidelines [26, 27] to incorporate all of the selections and processes necessary to choose the pertinent data for the study, as shown in the flow chart in Figure 1. We looked at 390 references in total, and we used 254 of them for our review.

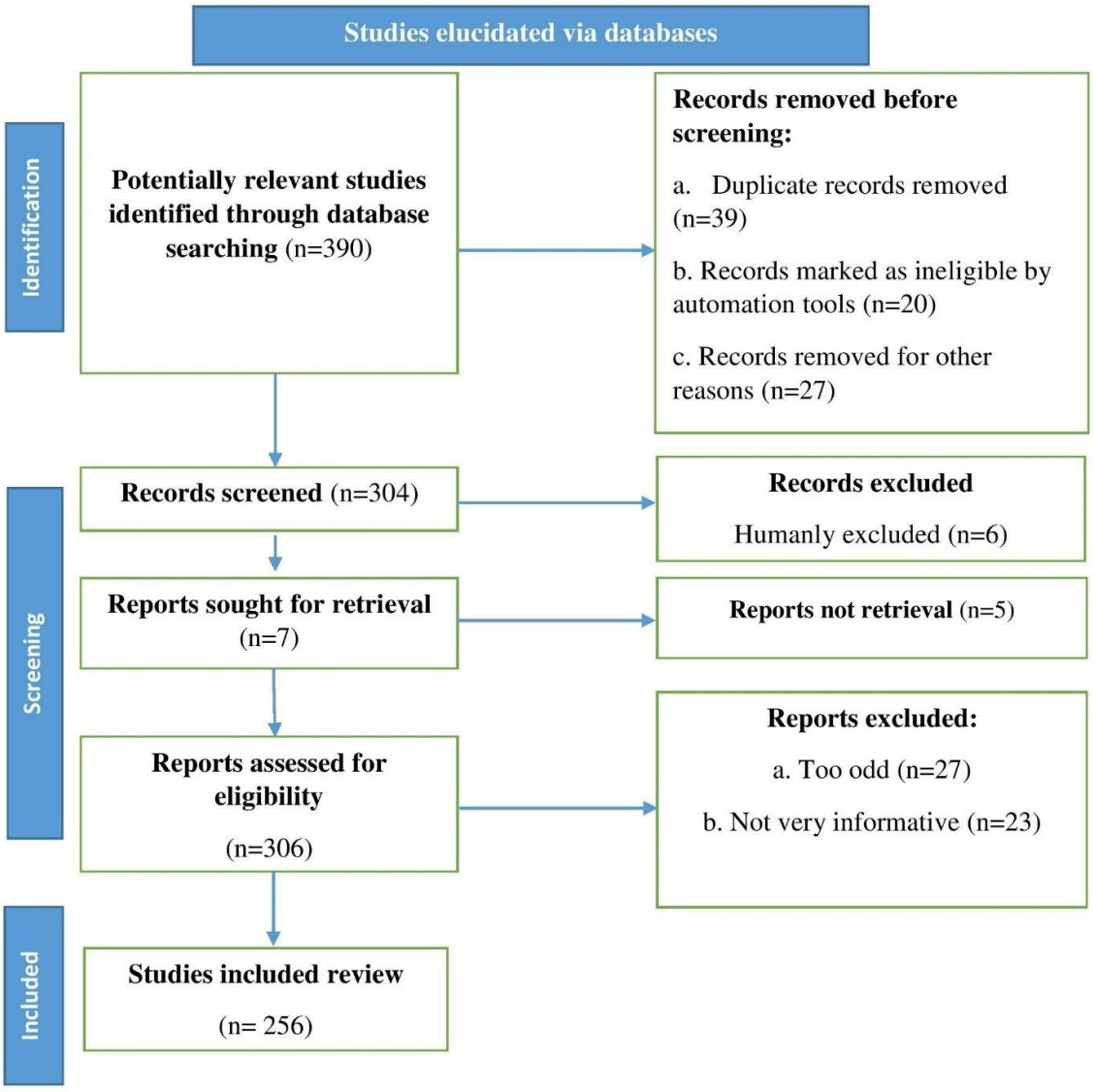


Figure 2: A flow chart illustrating the steps involved in choosing published data to be included in the current study; n = number of literature reports.

Chapter Four
Literature Review

4.1 Natural Products

Researchers found that some dietary elements reduced the prevalence of AD, which led them to look into the function of plant bioactive compounds [63]. "Secondary metabolites" of plants are considered to be naturally occurring bioactive compounds. In this regard, a variety of compounds isolated from numerous plant components, such as seeds, rhizomes, leaves, and roots, have been shown to restrict the growth of diverse organisms of detrimental plaque and to improve cholinergic signaling [64, 65] **(Figure 3).**

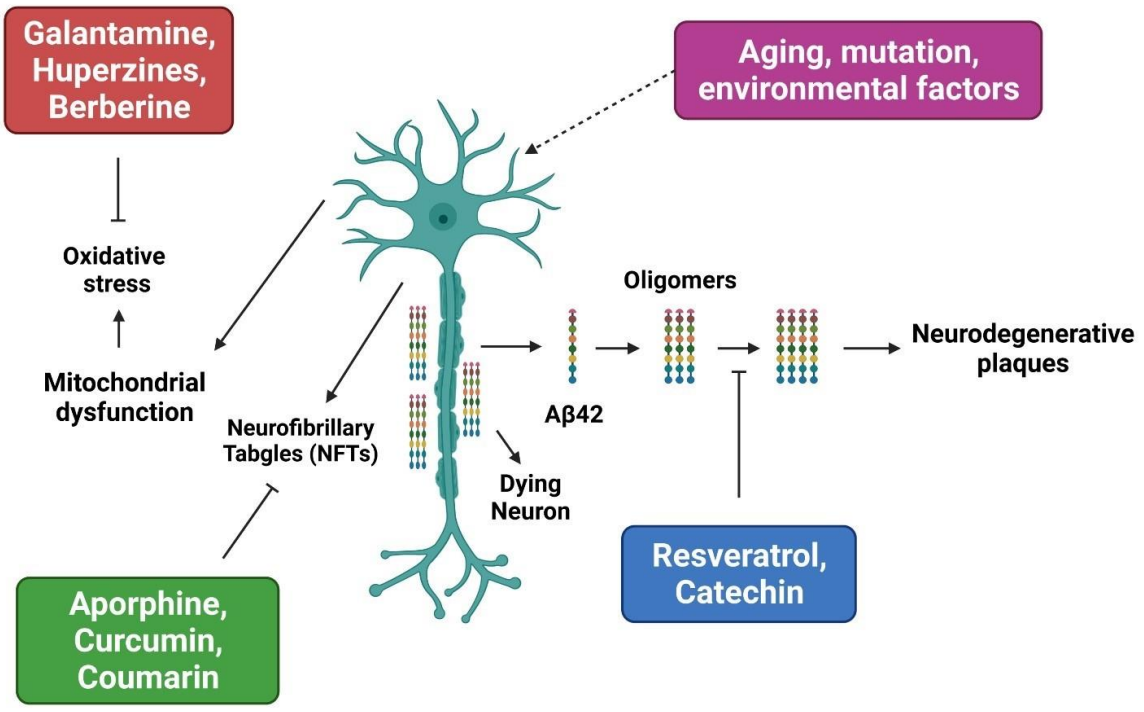


Figure 3: Shows an illustration of how natural products prevent Alzheimer's disease.

Foods high in antioxidants reduce brain oxidative stress. Since of this, scientists are interested in using plant-derived chemicals to create molecules that can treat a variety of diseases since they have a wide range of pharmacological effects [66, 67]. The results demonstrated that for the treatment of AD, a number of naturally occurring bioactive compounds are helpful. Here are some specifics regarding these chemicals**(Figure 4).**

4.1.1 Alkaloids

A class of widely spread nitrogenous compounds known as alkaloids in known groups of flowering plants. While some species only produce a few alkaloids, others, such those in the Ranunculaceae, Solanaceae, Papaveraceae, and Amaryllidaceae families, have many alkaloids [64, 68]. Alkaloids are also produced by fungus like ergot and rodents like the new world beaver, and amphibians like the poison dart frog.

a) Galantamine

Amaryllidaceae species such as Galanthus caucasicus, Galanthus sworonowii, and Leucojum aestivum all generate the isoquinoline alkaloid galantamine in their blooms and bulbs [69]. Nicotinic acetylcholine receptors (nAChRs) are modulated allosterically by galantamine [70, 71].Aβ cell-based assay was used to assess the neuroprotective activity of a few drugs. Furthermore, at subnanomolar concentrations, three of the produced compounds had excellent neuroprotective effects, reducing NMDA-induced neurotoxicity [72]. Then again, rhAChE was docked with a brand-new hybrid dual-site binding compound made of galantamine and indole. Three of the synthesized compounds showed AChE inhibitory action, with IC50 values of 0.011 M, 0.012 M, and 0.015 M [73].

b)Huperzines

Two lycopodium alkaloids, huperzine A and b, are identified from the Chinese medicinal plant huperiza serrata (club moss), which treats illnesses like swell, confusion, schizophrenia, fever, and strain. Huperzine A specifically, effectively, and irreversibly inhibits AChE and BuChE with IC50 values of 0.82 and 74.43 nM, respectively [74, 75]. Similarly, huperzine B has an IC50 of 14.3 M and is a reversible AChE inhibitor [76-78]. Novel huperzine A and imine compounds that have an extra, minutely substituted aromatic ring function as hAChE inhibitors at nanomolar concentrations [79-80].

c)Berberine

A benzylisoquinoline alkaloid known as berberine was discovered in Berberis species and Phellodendron amurense rhizomes, stems, roots, and bark. It demonstrates strong anti-bacterial, anti-cancer, anti-inflammatory, cardioprotective, and neuroprotective properties [82–84]. Additionally, berberine blocks both BuChE and AChE, while AChE is more specifically blocked. Therefore, by enhancing cholinergic activation, berberine reduces cognitive impairment in AD [85, 86]. Additionally, novel triazole and berberine dual-site binding compounds were docked with Torpedo californica acetylcholinesterase (TcAChE) [87]. By substituting a sulfur atom for an oxygen or NH group in the berberine derivatives, the antioxidant capabilities of the resulting berberine-thiophenyl hybrids were increased. Additionally, these hybrids demonstrated antioxidant properties and inhibited Aβ aggregation [88].

d) Aporphine

The opiate alkaloids, which are identified from Menispermum dauricum, belong to the isoquinoline class of alkaloids and have a tetrahydroisoquinoline substructure [89, 90]. Oxoisoaporphine and oxoaporphine, two opioid alkaloids, can prevent telomerase, cholinesterase, and Aβ aggregation in addition to having antioxidant properties [89, 91]. The effectiveness of synthetic oxoaporphine derivatives is reduced by two to three times as AChE inhibitors than their oxoisoaporphine equivalents in this regard. According to studies on molecular modeling ,the oxoisoaporphine alkaloid's water solubility and selectivity for AChE were greatly increased by using amines or ammonium groups as spacers [89]. A brand-new collection of oxoisoaporphine-tacrine hybrids were joined by an amino alkyl tether. These new substances displayed anti-aggregating properties; at ten M concentrations (35.5-85.8%) [91]. Eight nuciferine derivatives were additionally produced by the methods of dealkylation and ring aromatization. Products containing 1,2-dihydroxyaporphine and dehydronuciferine were found to include AChE inhibitors with IC50 values of 28 and 25 g/mL [92].

4.1.2 Flavonoids and Other Polyphenols

Polyphenols called flavonoids are present in fruits and vegetables. These are prevalent in the plant families [48, 66].Due to their polyphenolic makeup, flavonoids have neuroprotective properties. In polyphenols, the number and placement of hydroxyl groups affect how well they can scavenge free radicals. A new line of flavonoid derivatives was created because of their antioxidant properties [67, 68]. Flavonoids are divided into different subgroups depending on the position of the B ring, level of unsaturation, and degree of oxidation of the C ring. In the following subgroups: flavones, flavonols, flavanones, flavan-3-ol or flavanols or catechins, the B ring is connected to position 2 of

the C ring; the only difference is in the structural characteristics of the C ring [93]. Additionally, flavonoids, a class of phytochemicals with a variety of therapeutic properties, are also commonly used. A vital part of reducing neuroinflammation in AD is played by flavonoids because of their primary repressive activities against pro-inflammatory transcription factors [94].

Additionally, these chemicals stimulate the transcription of antioxidant and anti-inflammatory factors. In preclinical AD models, Despite the fact that parent flavonoids often have low average bioavailability, flavonoids have the potential to be a natural remedy. The blood-brain barrier (BBB) is also crossed by flavonoids due of their extreme polarization [12].

a) Flavones

Many medicinal plants' flowers, leaves, and fruits contain flavones, which have a number of health advantages. Advanced glycation products (AGEs) are inhibited by flavones and their derivatives, which also have bioactive properties like antioxidant, anti-inflammatory, and neuroprotective effects. These substances may also offer promise as AD preventative and therapeutic agents [94-102].

b) Isoflavones

Isoflavonoids can be obtained from microorganisms as well as leguminous plants like soybeans.They serve as the starting point for the production of phytoalexin during interactions between plants and microbes. AChE and MAO-B are inhibited by these substances [103].

c)Flavanones

The flavanones subclass of flavonoids, which includes hesperetin, is a significant one. Flavanones are found in high concentrations in citrus fruits like oranges, grapefruit, tangerines, lemons, and limes . In this regard, citrus fruits have the ability to scavenge free radicals, reduce inflammation, and lower blood lipid levels. Flavanones are now being used more frequently to create multi-target-directed ligands (MTDL) as a result [99-102].

d) Neoflavonoids

Neoflavonoids are organic substances that are part of the polyphenolic compound family. In this context, the neoflavonoid coumarin, which is found in numerous plants, has a number of therapeutic uses. According to molecular modeling studies [99,100], it interacts with the peripheral anionic site (PAS) of AChE and works as a potent inhibitor of AChE, preventing Aβ aggregation. Both scaffolds were joined with a piperazine-based alkyl spacer to provide a derivative, a novel tacrine-coumarin hybrid. Due to its amide linkage, the derivative exhibited substantial inhibitory action against EeAChE (0.092 M) and moderate activity against EqBuChE (0.234 M), in addition to having anti aggregation properties [103-108]. In coumarin-based MTDL derivatives, the 6- and 7-positions of coumarin are linked to alkyl spacers of varying lengths with a terminal diethyl amino group, inhibiting human AChE at nanomolar concentrations. These substances also show remarkable inhibition of Aβ 42 ,they are potential disease modifiers because of their self-aggregation (approximately 60%), which has a neuroprotective impact [109].

4.1.3 Curcumin

A natural substance called curcumin has been used for centuries to treat a number of illnesses [110]. Due to its anti-inflammatory and antioxidant qualities, curcumin works well as a neuroprotective medication. The 40–42 amino acid long Aβ peptide is produced by the endoproteolytic degradation of APP. According to study, when combined with curcumin, Aβ reduces oxidative stress, inflammation, and cognitive impairments in rats treated with Aβ [111, 112]. In vitro and in vivo tests have proven that curcumin has the ability to stop Aβ aggregation and fibril formation. Along these lines, variables that contribute to the formation of amyloid plaques include metal chelation, low cholesterol, lipid peroxidation, accelerated transcription, and decreased A-secretase enzyme production [113, 114]. Curcumin inhibits the formation of heat shock proteins (HSP), the other pathway for suppressing protein aggregation. In this way, HSP function as molecular chaperons to stop protein aggregation. In experimental settings both in vivo and in vitro, curcumin increased HSP synthesis. Additionally, it prevented the development of dangerous amyloid aggregates and cytokines that promote inflammation in the brain [113,115].

On the other hand, a major factor in AD is the accumulation of the tau protein within neurons. The β-sheet in tau protein, which is blocked by drugs like curcumin, causes aggregate formation. Curcumin is a pleiotropic and inexpensive therapy for neuronal dysfunction due to its various systemic effects[3].

4.1.4 Terpenes

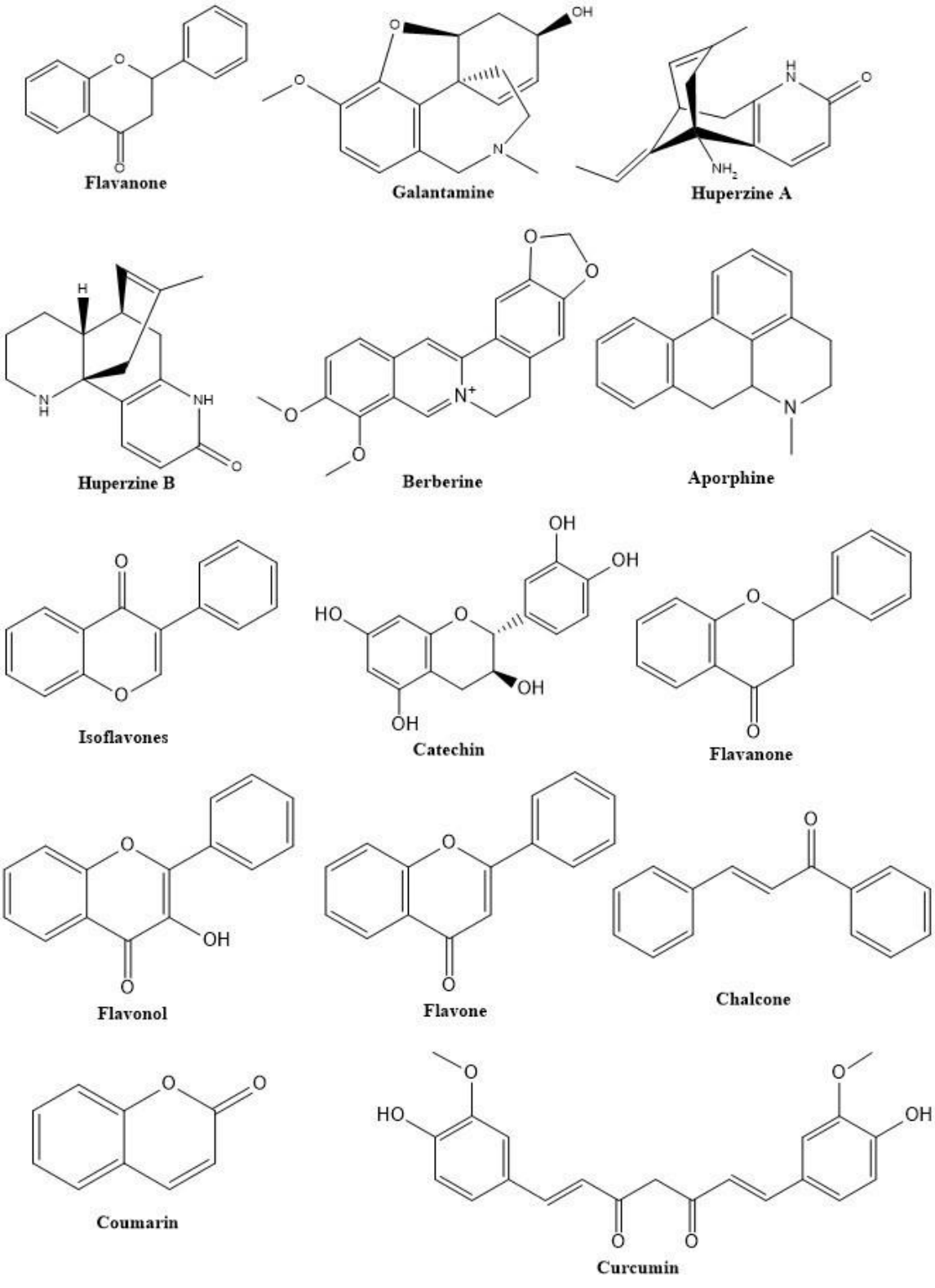
Terpenoids are a collection of chemicals chemically recognized as 2-methyl-1 or 3-butadiene [110,116,12]. However, clinical studies on AD are required to confirm the neuroprotective effects of sesquiterpene lactone. Similar to this, multidrug-resistant malaria was the first condition for which artemisinin,a sesquiterpene lactone isolated from the plant Artemisia annua of the Asteraceae family, was used as a remedy. This chemical and several of its synthetic equivalents have recently been found to have promising neuroprotective effects in AD due to their anti-inflammatory properties [117,118]. Rosmarinus officinalis contains the naturally occurring diterpenes carnosic acid and carnosol, both of which have significant neuroprotective action [119].

Ginkgo biloba extracts were used in clinical research, and the results were inconsistent. According to the findings of a randomized controlled study (RCT), they improved cognitive function [12,120,121].

4.1.5 Resveratrol

Resveratrol, an essential non-flavonoid, is found in red wine, almonds, and grapes[122]. Numerous pharmacological properties of resveratrol include antioxidant, anti-inflammatory, anti-carcinogenic, and anti-mutagenic properties [123]. In vitro and in vivo models of AD also showed neuroprotective effects. In addition to its anti-inflammatory and antioxidant effects, research indicates that resveratrol promotes the division of nonamyloidogenic APP and aids in the removal of neurotoxic Aβ peptides, both of which are essential for avoiding and slowing the progression of AD pathology [124,125]. Resveratrol also inhibits the production of ROS, boosts the levels of GSH and intracellular Ca21 in neurons, and modifies the actions of nitric oxide and calcium-dependent AMP-activated protein kinase (cAMP), which are second messengers.

Additionally, it also suppresses AChE activity in vitro cells and binds to Aβ plaques, eliminating the Aβ peptide [127].



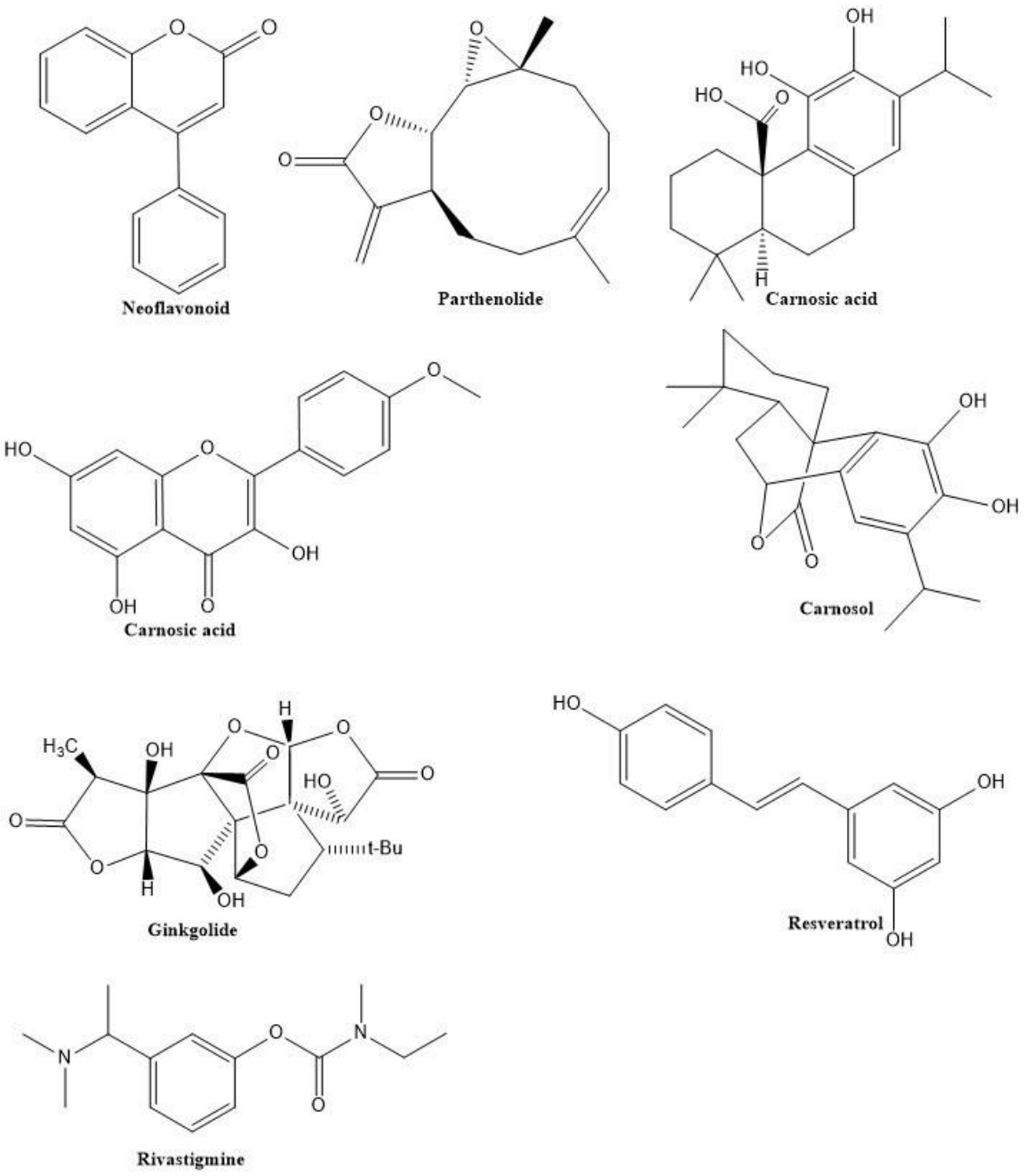


Figure 4. Several chemical substances that can prevent Alzheimer's disease.

4.2 Natural AD Neuroprotective Mechanisms

4.2.1 Natural Products Antioxidative Neuroprotective Activity in AD

The highly reactive molecules reactive nitrogen species (RNS) and reactive oxygen species (ROS) comprise both radical and nonradical oxidants [128-132]. OS affects the brain more than other parts of the body due to the brain's reduced capacity for cellular renewal and higher metabolic activity [133-134]. As a result, OS is widely recognized as a key element in the slow destruction of neuronal structure and one of the primary causes of NDDs, including AD, is a decrease in neuronal activity [129]. According to published research, OS plays a significant part in the progression of AD, and antioxidants serve to counteract OS's negative effects [135]. The most well-known natural antioxidants include carotenoids, flavonoids, and the vitamins A, C, and E. They all work to protect an organism from damage brought on by ROS.

Many plant-derived natural antioxidants, including carotenoids and antioxidant vitamins, contain hydroxyl groups on their aromatic rings and share phenolic and polyphenolic substances' chemical structures. As free radicals scavenged and donated hydrogen atoms, these natural compounds showed strong antioxidant activity [136]. These phenolic and polyphenolic compounds also have antioxidative properties as a result of their structural features, particularly the hydroxyl groups [137]. The most prevalent polyphenolic substances are flavonoids, which have a wide range of antioxidant characteristics [138-139].

4.2.2 Neuroprotective and Anti-neuroinflammatory Activity of Natural Products for AD

Although the precise pathophysiological mechanism behind AD is still unknown, a number of theories, Many theories, including those explaining this complex illness in terms of the Aβ, tau, cholinergic, and inflammatory systems, have been put forth [140].In keeping with this, neuroinflammation has been related to Aβ buildup in the brain, a key element in the pathophysiology of AD [141-142].Additionally, the activation of immune cells triggers the release of proinflammatory cytokines such as IFN-γ, IL-1β, and TNF-α [143], which stimulate nearby astrocytes to form Aβ-42 oligomers [141].High levels of these proinflammatory cytokines have been seen in the brains, blood, and cerebrospinal fluid of AD patients [144].In this regard, studies have linked increased cytokine levels in AD at all disease stages to memory impairment [145].

Furthermore, it has a relationship with brain activity, particularly in neurological diseases like AD [146,147]. It has been found in the brains of people with Alzheimer's disease [149] and its activation has been linked to Aβ-initiated neurotoxicity [148]. Natural remedies have fewer side effects than synthetic ones and help prevent AD neurodegeneration. Furthermore, natural substances with anti-inflammatory properties might function as a pharmaceutical intervention to lessen AD symptoms in their early phases [150-151]. As potential therapeutic alternatives for treating AD, natural compounds assessed for their multi-target anti-inflammatory effect [152]. The neuroprotective properties of a few plant-based natural products, extracts, and combinations are listed in **Table 1**.

Table 1: lists some plant-based natural goods, extracts, and mixtures and their level of neuroprotection

Plant	**Extract**	**Neuroprotective Outcomes**	**Study Model**	**Reference**
Panax ginseng	Root extracts	AChE was inhibited, Aβ production and aggregation of Aβ was decreased, and synaptophysin and ChAT activity was restored.	In vitro, in vivo	[153-159]
Ginkgo biloba	Leaf extract	Free radicals were neutralized, mitochondrial dysfunction was avoided, the JNK and	In vivo	[160-162]

		ERK pathways were triggered, and neuronal death was prevented.		
Pistacia vera	Kernel	Improved cisplatin or vincristine-induced cognitive and motor impairments.	In vivo	[163-165]
Spirulina maxima	Ethanol extract	AChE activity was downregulated, hippocampal OS was decreased, and BDNF levels were increased.	In vivo	[166-169]

Juglans regia	Defatted protein	Decreased NF-κB expression, significantly increased antioxidant enzyme levels, decreased AChE and pro-inflammatory cytokine production.	In vivo	[170-174]
Almond (*Prunus dulcis*)	Paste	Improved learning and memory, decreased AChE activity, decreased cholesterol and triglyceride levels, raised brain tryptophan monoamine	In vivo	[175-178]

		levels and serotonergic turnover.		
Hazelnut (*Corylus avellana*)	Kernel	Memory enhancement, worry reduction, and decreased neuroinflammation and apoptosis	In vivo	[175,179, 180]
Vitis vinifera	Juice, polyphenolic extract	Exhibited antioxidant, anti-neuroinflammatory, anti-amnesic, and Aβ aggregation-inhibiting effects.	In vivo	[181-187]

Zingiber officinale	Root extract	Acted as an AChE inhibitor, reduced lipid peroxidation, overstimulated NMDA receptors, and prevented the production of free radicals.	In vivo	[188, 189]
Fuzhisan	Herbal complex	Showed anti-apoptotic and anti-Aβ buildup action, elevated ACh levels, and offered neurotrophic advantages.	In vivo	[190-195]
Phyllanthus acidus	Methanol extract	Elevated brain antioxidant	In vitro	[196-197]

		enzymes enhanced mental performance, and decreased OS.		
Hedera nepalensis	Crude extract	Superoxide dismutase (SOD) and catalase (CAT) levels are elevated, while glutathione (GSH) levels are reduced.	In vivo	[198-200]
Bacopa monnieri	Extract	Enhanced cognitive function, decreased cholinergic degeneration,	In vivo	[212-218]

		and suppressed AChE activity		
Pistacia Atlantica	Ethyl acetate and aqueous extracts	AChE's inhibitory effect.	In vitro	[219-220]
Phyllanthus amarus, Cynodon dactylon	Methanol extract	Elevated amounts of catalase, NADH dehydrogenase, and superoxide dismutase	In vivo	[221-227]
Curcuma longa	Ethanol extract	OS induced by CeCl3 was lessened, antioxidant enzyme activity was enhanced, and AChE	In vitro, in vivo	[110,201-207]

		activity was inhibited.		
Allium sativum	Aged garlic extract	Reduced inflammatory reaction, IL-1 levels, and microglial activation. Reduced psychological stress by controlling the brain's OS response and stress hormones.	In vivo	[208-211]

4.3 Therapeutic Targets for AD

4.3.1 The Related Enzymes of Amyloid-(Aβ)

The proteolytic digestion of APP by β- and γ-secretases results in the formation of amyloid beta peptide (Aβ) [228]. According to published studies, immunization against changing the burden of Aβ plaques, Aβ improves memory impairments in transgenic

animals [229, 230]. These findings show that Aβ in plaques may not be the primary cause of synapse degeneration and that Aβ in other forms of Aβ plays a significant role in neurotoxicity in AD brains [231]. In keeping with this, and in light of the evidence suggesting that Aβ is a major contributor to the etiology of AD, a number of therapeutic studies utilizing passive and active vaccination against Aβ were carried out [232]. However, due to adverse effects like encephalitis and insufficient treatment efficacy, neither technique was successful in clinical trials [233-235]. Presenilin gene mutations are the root cause of AD with early start [236-237]. The therapeutic goal of medications that lessen amyloid plaque, whose accumulation is thought to induce AD, is the activity of γ-secretase.

The primary target for developing an AD therapy is γ-secretase, which is related to notch signaling in the interim. Regarding this, numerous medications are currently being researched as possible treatments that modify A production by γ-secretase without impacting Notch proteolysis and signaling. It is significant to remember that the γ-secretase modulator flurbiprofen was the first drug to go through a clinical trial. However, it was a failure due to a lack of therapeutic success. One of the numerous strong Notch-sparing inhibitors that have recently been discovered and evaluated in various clinical trial phases is GSI-953 from Wyeth [238].

4.3.2 Glycogen Synthase Kinase 3 (GSK3) and Tau Protein

Tau is a developed neuron's main microtubule associated protein (MAP). Tau is deposited in the areas of the sick brain, and this contributes significantly to the pathogenesis of AD and other disorders that are related to it, collectively known as tauopathies [240]. Tau is three to four times more hyperphosphorylated in AD brain than in healthy adult brain.

Pathologic tau in AD is unusually cleaved and hyperphosphorylated [241]. Thus, preventing abnormal tau hyperphosphorylation represents a potential therapeutic target for treating AD and other tauopathies [230]. Recent studies have linked neurodegeneration to early changes in the soluble tau proteins' structures, particularly their phosphorylation [242, 243]. GSK3 is a possible kinase in this situation that regulates tau aggregation by phosphorylating tau protein and regulating tau binding to microtubules, tau breakdown, and tau aggregation [244]. Additionally, research revealed that Aβ increases tau phosphorylation and GSK3 activation in AD [245]. Several GSK3 inhibitors are presently being investigated for their promise as a treatment for AD [246-247].

4.3.3 Acetylcholine Related Molecules

Additionally, nAChRs in the brain interact with acetylcholine and nicotinic ligands, and nicotinic ligand activation of nAChRs can protect neurons [248-249]. As a result, specific nAChR agonists and acetylcholinesterase (AChE) antagonists that restrict acetylcholine hydrolysis have been found [250]. AChE has emerged as a crucial treatment target for achieving clinical improvement in AD because cholinergic deficiency is a persistent and early consequence of disease development [251]. In this regard, three of the four drugs currently on the market for the therapy of AD are galantamine, rivastigmine, and donepezil. A number of nations have approved the use of galantamine, a compound made from the bulbs of common snowdrops and different Amaryllidaceae, to treat the symptoms of senile dementia linked to AD [252].

Chapter Five

Results & Discussion

5.1 Results & Discussion

The most common NDD is AD, which is a significant social and economic problem for society. AD is having difficulty overcoming barriers to treatment due to a lack of precise diagnostic and therapeutic procedures. The treatment and prevention of AD are discussed here using a number of bioactive compounds and natural preparations. Only a small number of molecules have been recovered from animal or marine sources, while most natural chemicals studied to date have come from plant sources. Given the complexity of AD, these organic compounds were connected to a range of therapeutic approaches. The ability of natural compounds to cross the BBB, however, determines how neuroprotective they are. The challenge of crossing the BBB and drug bioavailability remain major obstacles to the creation of novel therapeutics. Experimental and observational studies both demonstrate that bioactive substances improve cognitive performance in AD patients. The main advantageous impacts of their various mechanisms of action are as follows:

- Decrease in the levels of Aβ and the rate of tau phosphorylation
- Preventing the clustering of Aβ and tau
- Protection from oxidative damage
- Inflammatory-reduction action
- Prevention of neuronal apoptosis and defense of cellular structures

Clinical research should look into substances that have been shown to have neuroprotective qualities in vivo.

Chapter Six

Conclusions

6.1 Prospects for the Future

In conclusion, AD is a dreadful neurological disorder that has plagued people for a long time. No drug or plant extract was able to effectively reverse the symptoms of the disease, while several plants and their extracts have been extensively utilized in animal research and AD patients, there are currently only a few drugs approved for the treatment of AD [253-256]. AD is a complicated disorder with numerous underlying causes. While some symptom alleviation is provided by the existing treatments, neither the morbidity nor mortality of the sickness are affected. They work by blocking NMDA receptors or inhibiting AChE. More thorough research is required to comprehend the traits of NDDs, their historical context, and alleged therapeutic options as a result of these faults.The use of nanotechnology and nanocarrier-based delivery methods for natural products and their individual components may improve and increase the efficacy and effectiveness of therapeutic responses. The bioavailability of natural products and their components can be enhanced by the use of nanoparticles in the delivery mechanism.

6.2 Final thoughts

In managing AD cases, a number of abnormal physiologic aspects should be taken into account due to the diversity and intricacy of the underlying genetic and epigenetic causes of AD. Additionally, more thorough and practical quality control laws to safeguard the security and effectiveness of these neuroprotective drugs. Additionally, the use of novel approaches and strategies to increase CNS direct exposure to these neuroprotective agents, such as the transmission of natural products using

nanotechnology, may be essential in slowing the spread of dementia. This review has demonstrated how AD can be prevented and treated using natural therapies. This is because vital bioactive molecules found in fruits, spices, nuts, and herbs help prevent and treat a range of disorders, including AD, with no discernible side effects.

Chapter Seven
References

7.1 References

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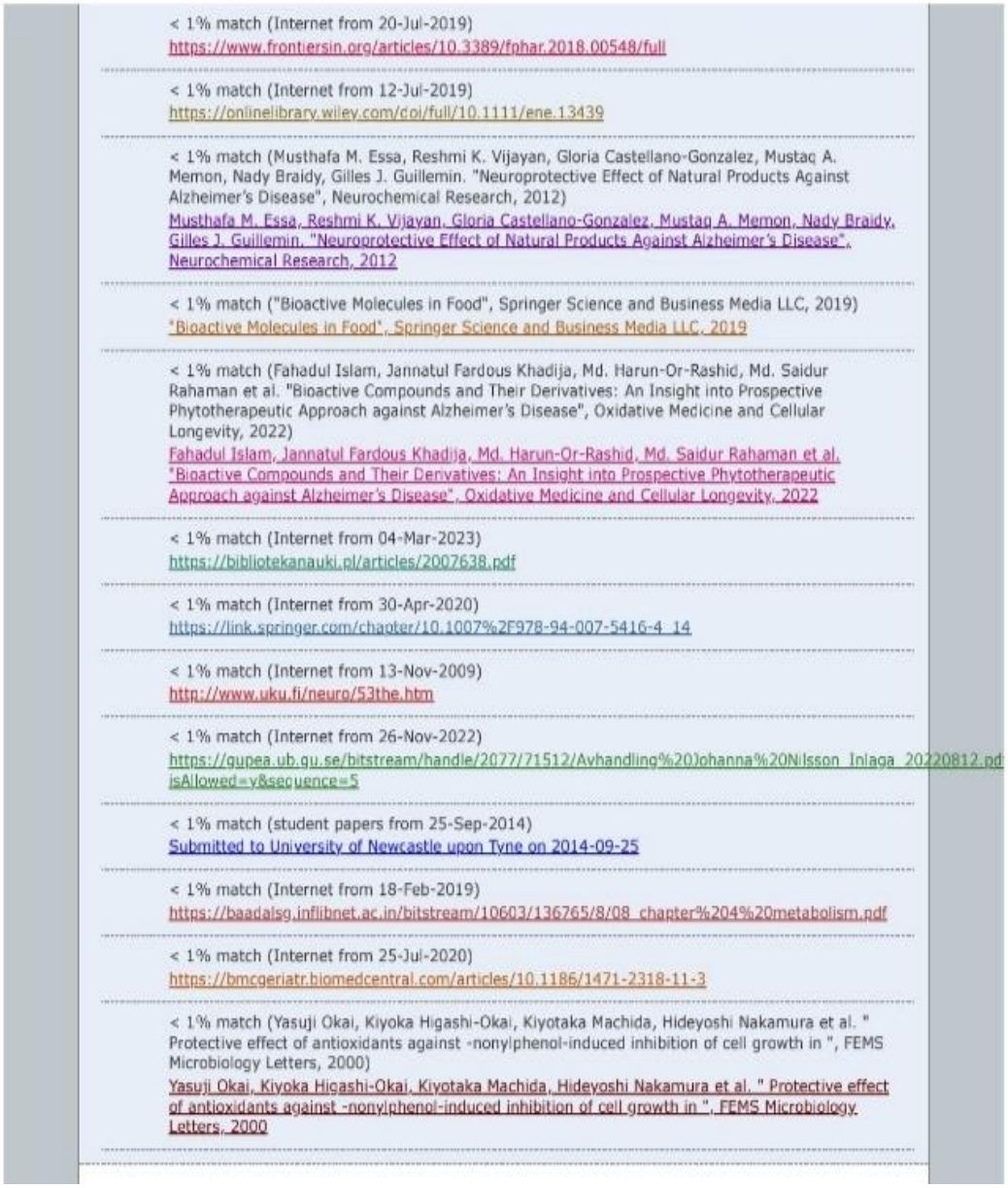
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