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Insights into the Promising Prospect of Medicinal Plants for the Therapeutic Approaches of Alzheimer's Disease

Sheikh Shohag[1], Shomaya Akhter[1], Al Amin[2], Mirza Jaman[2], Eftakharul Haque[3], Md. Mehedi Hasan[2], Mohammad Aslam[2], Dr. Mohammad Nazir Hossain[1*]

[1]Department of Genetic Engineering and Marine Biotechnology, Faculty of Earth and Ocean Science, Bangladesh Maritime University, Mirpur 12, Dhaka 1216, Bangladesh

[2]Department of Biochemistry and Molecular Biology, Faculty of Life Science, Gopalganj Science and Technology University, Gopalganj-8100, Bangladesh

[3]Department of Biochemistry and Molecular Biology, Faculty of Agriculture, Bangladesh Agricultural University, Mymensingh-2202, Bangladesh

Abstract: Dementia and cognitive decline are associated with Alzheimer's disease (AD), a chronic, progressive neurological disorder that mostly affects the elderly. AD is caused by extracellular Amyloid-beta 42 plaques, intracellular hyperphosphorylated Tau tangles, mitochondrial dysfunction, and genetic anomalies. The brain's cells die from faulty signal transduction caused by amyloid and tau tangles. This creates cognitive, behavioral, and mental issues. Shrinking central nervous system direct treatment exists for AD. Researchers have been screening a library of micro-inhibitor compounds or bioactive components to prevent or delay AD. The development of natural products has grown more essential due to their medicinal effects, safety profile, and bioavailability. Diverse animal model systems are being employed to examine a wide range of natural chemicals as therapeutic targets for AD and to determine if they can reverse AD. The study focuses on several pathways, including excessive tau protein digestion, β-amyloid, inflammatory reaction, and cholinergic and free radical damage, to develop effective therapies that can slow or stop AD progression. Because of its neuroprotective, anti-inflammatory, antioxidant, anti-amyloidogenic, anti-cholinesterase, and easy availability, diverse natural products (NPs) played an essential part in clinical studies to minimize AD symptoms and progression. In this study, medicinal plant-derived bioactive chemicals with different properties are thought to promote cognitive function and prevent AD. Therefore, this review focused on potential medicinal plant-based treatment techniques to stop or reduce AD pathogenesis and guide future research.

Keywords: Neurodegenerative Disease; Alzheimer's disease; Pathogenic Mechanisms; Natural Products; Bioactive Compounds.

Review Paper

***Corresponding Author:**
Dr. Mohammad Nazir Hossain
Department of Genetic Engineering and Marine Biotechnology, Faculty of Earth and Ocean Science, Bangladesh Maritime University, Mirpur 12, Dhaka 1216, Bangladesh

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1. INTRODUCTION

AD, first identified in 1906 by Dr. Alois Alzheimer [1], is among the most common neurodegenerative illnesses, affecting 6 million Americans and 50 million globally [2].AD is a prevalent neurodegenerative illness that is linked to a high incidence of dementia (60–80%). Changes in the Central Nervous System (CNS) that have serious both psychological and physiological ramifications characterize degenerative disorders of the central nervous system. Epithelial senile plaques, also known as amyloid plaques, and intraneuronal neurofibrillary tangles (NFT) are two features of AD that can be seen under a microscope. Typical tau protein deposition and hyperphosphorylation cause NFTs to form, whereas systemic A-peptide accumulation in the brain causes mature lesions to form [3]. AD is a neurological illness that affects memory, cognition, and everyday functioning, requiring full-time care. The disease is the fastest in individuals over 65, although it can afflict younger people [4]. The most important risk factor for AD is age. This disease affects around 3% of adults aged 65 to 74, 17% of those aged 75 to 84, and 32% of people aged 85 and up [5,6]. With the aging population growing, it is predicted that by 2050, one new AD case will be diagnosed every 33 seconds, bringing the entire number of cases to 16 million in the United States alone [2]. AD is the most common cause of dementia in older people

and the sixth leading cause of mortality in the United States. It may be ranked third in important causes of death for older people, behind heart disease and cancer [7].

Over the past three decades, a considerable sum of money has been invested in the investigation and creation of AD treatments. There are currently no medications for the illness that have been approved by the Food and Drug Administration (FDA). So yet, the FDA has only authorized clinical drugs to treat AD [8]. Tacrine, donepezil, rivastigmine, and galantamine are only a few of the acetylcholinesterase inhibitors [8] that have been identified. Although the curative potential of the medications had been shown, it was impossible to ignore their unpleasant side effects, which included nausea, vomiting, diarrhea, insomnia, and slowing heart rate. Another drug that works by inhibiting the glutamate neurotransmitter in the brain is called memantine. Although it is unlikely that these treatments will be able to completely restore memory loss in AD patients, they may be able to reduce the rate of the condition. As a result, AD is a very difficult disorder that cannot be effectively treated by focusing only on one therapy goal.[9].

Although the particular genetic origin of AD in most individuals is unclear, the disease's characteristics include aberrant deposition of amorphous-amyloid peptide (Aβ) and buildup of neurofibrillary tangles (NFTs) of oxidized tau protein in synaptic cytoplasm, leading to degeneration and cell death [10].

Neurogenesis, deficiency or inadequate synthesis of neurotransmitters, oxidative stress, calcium stability failure, and abnormal signal transduction are related to neurodegenerative alterations [11]. In turn, brain neuronal and synapses are damaged, impairing learning and other mental functions. Except for metformin, which prevents N-methyl-D-aspartate (NMDA) receptors on the brain's surface from sensory overload, all Alzheimer's medications increase the brain's levels of neurotransmitters to potentially ameliorate deficits. The effectiveness of these medications varies a lot from person to person and is only temporary. Other techniques have been tried, such as targeting Aβ plaques [12] and tau NFTs aggregations, lowering oxidative stress [13] and neuroinflammation [14], and so on, with several new therapeutic candidates undergoing laboratory & clinical experiments [15].

Diverse bioactive compounds with novel therapeutic features are abundant in plants, animals, microbes, and the aquatic environment [16]. In hopes of generating more efficient Alzheimer's treatments, natural products, and their ingredients have been studied extensively [17]. In reality, galantamine, a cholinesterase inhibitor, is a natural chemical [18], while rivastigmine is a semi-synthetic accumulation of physostigmine, a natural product [1]. Because they contain numerous simultaneous target techniques, combinations or extracts of natural products may have benefits over specific natural compounds, which might be a unique therapeutic method for AD provided its extensive pathophysiology [19]. Herbs or herbal preparations combined with another natural origin may help Alzheimer's patients' cognition[17,20]. As a result, numerous natural sources and their extracts are widely used in animal models and individuals with Alzheimer's disease [6,9,21].

This is because combinations or extraction of natural goods include organic bioactive compounds that may be used as a therapeutic approach to treat or prevent AD [22]. Additionally, numerous extracts and plant products are frequently employed in clinical trials and animal models of AD [23–25].

This review emphasises the therapeutic capacity of plant-based natural products that may have neuroprotective effects for the prevention and treatment of AD through a variety of mechanisms, according to the previous discussion, and due to the broad range of preventive and therapeutic options available for natural products of naturally derived.

Until February 2021, a systematic literature search was undertaken using Scopus, ScienceDirect, PubMed, and Google Scholar. as online databases, with key phrases including neuroprotective natural compounds and Alzheimer's disease. We concentrated on natural product extracts and mixes among all the publications that met our requirements.

2. Causes of Alzheimer’s Disease

Alzheimer's disease is hypothesized to occur when excessive concentrations of amyloid-beta (Aβ) form up in the brain as amyloid plaques, tau proteins [26], or neurofibrillary tangles, impairing synaptic activity and connection and resulting in significant cognitive function reduction **(Figure 1)** [27]. Since their various peptides (Aβ-40, Aβ-42) aggregate as a result of certain mutations or situations that favor intra- or extracellular growth, amyloid beta plaque is produced. They are the root causes of various illnesses, both neurological and systemic, and are structurally rich in intermolecular β-sheets [28]. However the fundamental pathogenesis of AD clinical features (Aβ, NFTs, and synaptic loss) remains uncertain [29]. Various hypothesis was postulated as causes of AD, but two are essential, Cholinergic dysfunction is a trigger for some, whereas amyloid alterations are for others. The key initiating factor is protein synthesis and processing [30,31]. There is yet no recognized pathogenesis of AD [32].

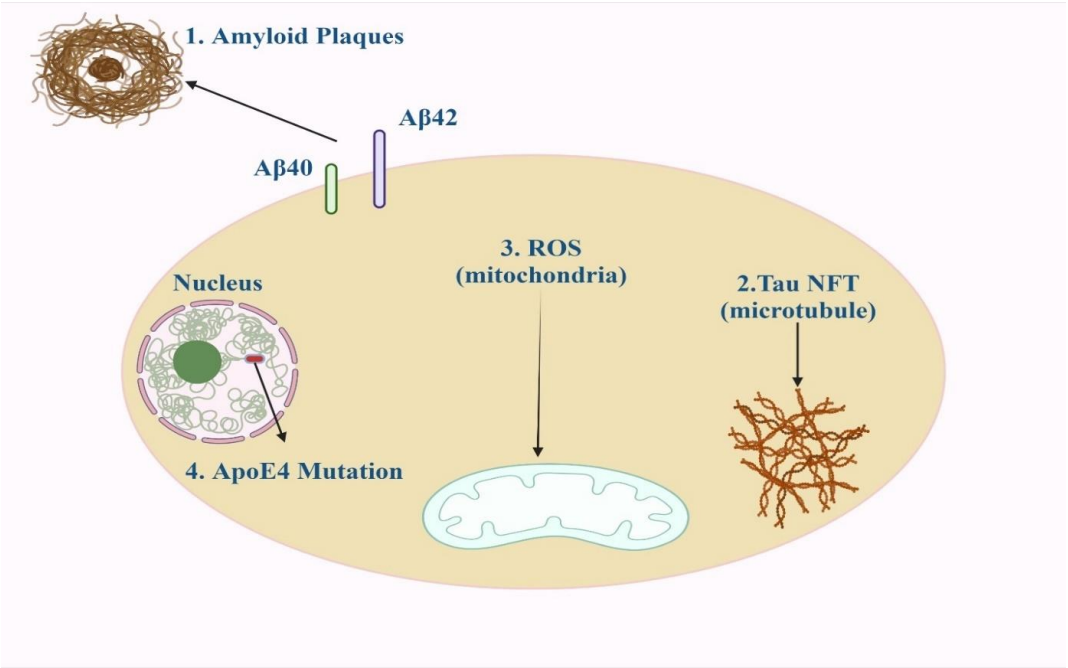

Figure 1: A cartoon depicting the causes of Alzheimer's disease. Alzheimer's disease, a neurodegenerative condition, can be caused by: (i) Extra-cellular accumulation of amyloid-beta 42 (Aβ42) plaques; (ii) intracellular production of hyper-phosphorylated Tau NFT (iii) mitochondrial reactive oxygen species (ROS) formation; (iv) genetic basis of apolipoprotein E (ApoE4)

2.1. Cholinergic Hypothesis

The cholinergic hypothesis seems to be a popular theory for explaining how AD develops. According to this theory, a drop in neurotransmitter levels causes AD. Ach is a kind of choline that occurs naturally in the body. There are a lot of medications that are utilized in treatment. The cholinergic theory is used to explain AD [33,34]. Choline acetyltransferase (ChAT), the enzyme liable to acetylcholine generation, was connected to the neocortex and presynaptic cholinergic deficiencies in the 1970s (ACh). Due to ACh's importance in cognition, a cholinergic explanation of AD was proposed. Acetylcholine and acetyl-coenzyme A are converted into ACh in the cytosol of cholinergic neurons. ChAT enzyme and vesicular acetylcholine transporter transfer acetylcholine to synaptic vesicle ACh and play a role in many physiological actions in the brain, including memory, learning, and memory consolidation. Other key functions include concentration, visual receptors, memorization, and others. Alzheimer's involves acetylcholine nerve degradation, affecting brain activity and memory lapses. B-amyloid affects sympathetic nervous system activity and reduces brain receptors, ACh release, and choline absorption. According to studies, cholinergic synaptic atrophy and amyloidosis fibril production are connected to Aβ oligomers and peptides. The opening of calcium channels and the movement of Ca2+ through channels in the presynaptic membrane occur as a result of depolarization of the axonal membrane, which causes the fusion of the brain with the epithelial membrane and the start release of acetylcholine into the synaptic cleft [35]. The receptor goes through a conformational change when two acetylcholine molecules attach to their binding sites, which causes the membrane-spanning sections to shift relative to each other and the channel to open. When activated, the ACh receptor opens to allow passage of tiny cations (Na^+, K^+, and some Ca^{2+}) [36]. Additional factors, such as a decrease in nicotinic acid, play a role in the course of AD. With the deficit in muscarinic (M2) Ach receptors, which are found on presynaptic cholinergic synapses, glutamate, and D-aspartate concentrations in excitatory amino acid (EAA) synaptic transmission. In AD brains, uptake is severely diminished in numerous cortical regions. This is on top of the fact that antagonizes of cholinergic receptors, such as scopolamine, have been discovered to cause amnesia. This is an example of an erect, that can be reversed by employing chemicals that promote the synthesis of acetylcholine [between AChE and ACh] [34,37–39]. As an outcome, the cholinergic hypothesis is dependent on three principles: reduced afferent cholinergic markers in the neocortex, acute atrophy of the nucleus basalis of Meynert (NBM), and the participation of acetylcholine transmitters. Memory declines when antagonists are used instead of agonists, which have the reverse effect **(Figure 2)** [40].

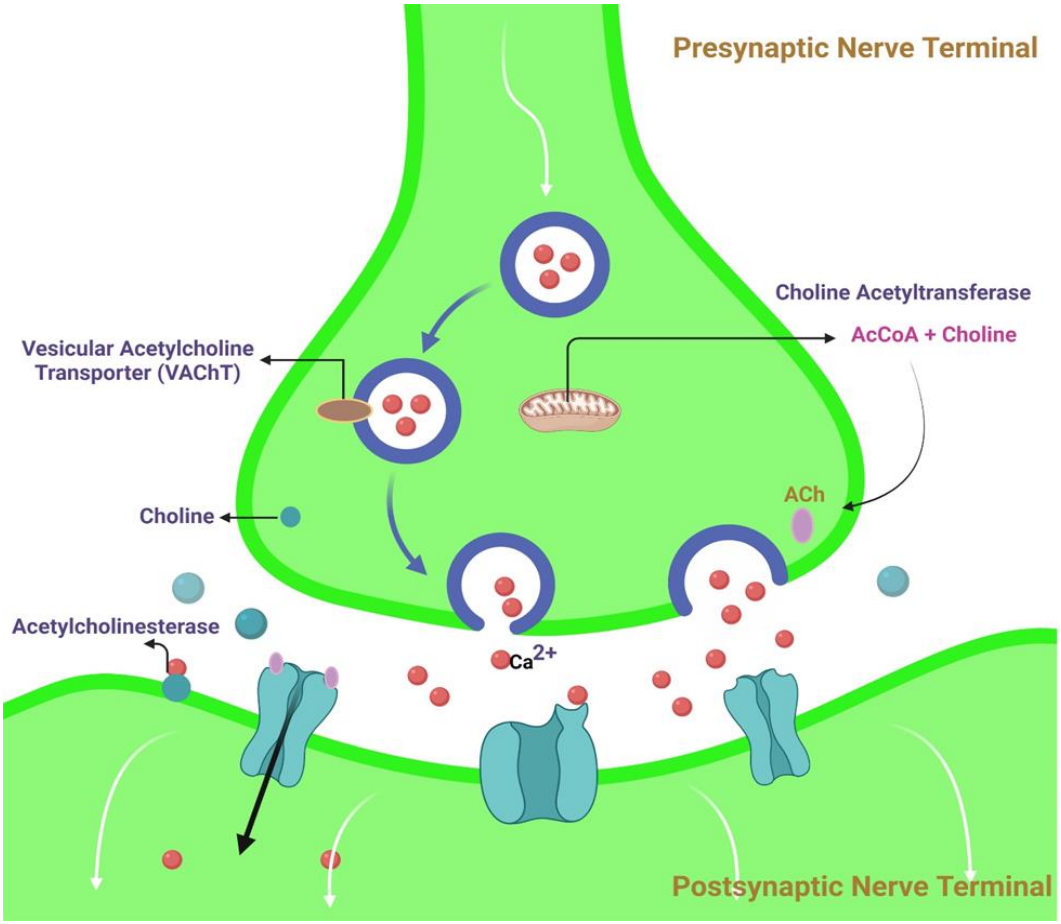

Figure 2: Pathway for acetylcholine production and transfer between nerve terminals in cholinergic hypothesis

2.2. Amyloid Hypothesis

After finding a relationship between abnormal -sheet accumulation in the CNS and dementia, the amyloid hypothesis was generated. When cells age, amyloid plaques (AP) develop in healthy brains. This raises the issue of whether AP accumulation is accountable for AD. In current history, other theories for non-inherited AD (NIAID) have been proposed, although the amyloid hypothesis remains the most commonly accepted pathological factor underpinning genetic disorders. [38,41]. A great deal of research emphasises that oligomers are primarily responsible for AD and neurological dysfunction [42]. In AD, there are lower levels of Aβ 42 in cerebrospinal fluid (CSF) [43]. One of the main factors contributing to AD is amphipathic amyloid- β peptide (Aβ) [44]. AD condition is defined pathologically by amyloid β (Aβ) buildup in the brain. The β 42-residue Aβ42 and the β 40-residue A β40 are the 2 key isoforms of Aβ. Aβ42 and Aβ40 simply vary in just that Aβ42 has two additional residues at the C-terminus. Even though Aβ40 concentration is several times higher than A β42 concentrations, amyloid plaques in AD neurons primarily contain Aβ42 and certain plaques solely consist of Aβ42[45]. The damaging protein Aβ42 is the primary factor in AD progression. It was discovered that a greater amount of A, primarily in the shape of Aβ 42, in the blood of AD patients than in cursor keys. Circulation in the periphery Aβ42 is mostly produced from platelets, and its synthesis is comparable to that of neurons [43]. With the carefully balanced type of Aβ-lipid interactions against the release of Aβ from neuronal membranes being overcompensated by an Aβ-membrane assembly that results in toxic β-structured aggregates in AD, two different biological bases of protein assemblies are engaged in Aβ0 s pathophysiology. Aggregate-free Aβ-40 was present in quick balance as monomers, dimers, trimers, and tetramers. On the contrary, Aβ42 pentamer/hexamer subunits (paranuclei) selectively, which further combined to form embellished infrastructures resembling embryonic protofibrils [46,47]. According to the amyloid hypothesis, age or pathological changes reduce the disruption of Aβ, which is generated from amyloid precursor protein (APP) by –and ɣ -secretase, resulting in the peptides (Aβ 40 and Aβ 42) accumulating effect of Aβ [48]. Enhancing Aβ 42/Aβ 40 causes Aβ amyloid fibril development, neurotoxicity, tau pathology, neural cell death, and neurodegeneration. AD risk factors include APP, Presenilin (PSEN1) variations, and PSEN2 catabolise and anabolise causing a fast buildup of neurodegeneration and Aβ [49,50]

3. To treat Alzheimer's disease with medicinal plants

A wide range of therapeutic options is available in natural medicine for the therapy of AD. Drugs made

from medicinal plants are becoming increasingly popular, both for their scientific value and their potential for commercial success. Drug finding campaigns and advancement methods can benefit from the use of Ayurvedic ingredients and formulations[51], which can provide unique applicable leads for AD and several age-related neurodegenerative illnesses. The Ayurvedic medical system has grown in popularity in recent years because of its emphasis on nutrition and treatment choices. Without a clear understanding of the mechanism of action, early Ayurvedic herbal supplements were developed only based on anecdotal or epidemiological evidence [52,53].

3.1. *Bacopa monnieri*

In India, Ayurveda was refined more than three thousand years ago and is the planet's oldest medicine system. In India, the herb *Bacopa monnieri* is known as Brahmi or Jalanimba. As a memory booster and mood lifter, Brahmi is well-recognized. Brahmi's main ingredient, saponins, is responsible for enhancing the transmission of nerve impulses. Medicinal and functional characteristics have been extensively studied and verified for many years now. Those foods that go above and beyond the scope of typical dietary requirements are referred to as functional ingredients. Unlike other herbs, Brahmi has a distinct herbal flavour and a harsh aftertaste. There is a growing need for food products that are both nutritious and useful as a result of changing lifestyles and a greater awareness of health [54]. Age, AD is a neuron-related disease that progresses at a slow rate over time. Because of the significant rise in its prevalence, more medications have had to be developed. Ayurvedic herbal medicines are increasingly being studied because of their biosafety profile and cognitive benefits [55]. The effects that Brahmi (*Bacopa monnieri*) extracts have on the nervous system have been the subject of a significant amount of research. Several chemicals in Brahmi, including Saponins and related bacosides, are responsible for enhancing nerve impulse transmission [56]. This substance helps to heal injured neurons by increasing the activity of enzymes that help to synthesize new neurons and synapses [54]. For additional protection against the effects of β-amyloid, *B.monnieri* extracts were utilized. It has been suggested that *Bacopa monnieri* extract reduces internal oxidative pressure by decreasing ROS levels in neuronal cells. Polyherbal production comprising *B. monnieri* essence elevated cognitive tasks and lowered inflammation and oxidative stress in people with AD, according to a clinical investigation. To fully analyze *B. monnieri's* possible neuroprotective effects against AD, more research is required [33]. Dendrites, a type of new nerve ending, have been shown to grow in response to the herb *Bacopa monnieri*. Neuronal communication relies on dendrites, which are present at the terminals of the neuron's axons. AD is characterized by a buildup of β-amyloid plaque in the cerebrum. Using mice, Bacopa was found to diminish these plaques by 60 percent. BDNF deficiency has been connected to AD, also bacopa has been shown to raise BDNF levels. Antioxidants in Bacopa help to remove free radicals from the brain's circuits. The brain's cells are damaged by oxidative stress caused by these free radicals.

3.2. *Centella asiatica*

Since prehistoric times, *Centella asiatica* has been employed as a medicinal plant. In South East Asia and India, this herbal treatment has been used for millennia to treat a variety of ailments. As a result, the plant is still utilized in traditional medicine as an effective treatment. When it comes to traditional and modern medicine, *Centella asiatica* falls somewhere in the middle [33]. Cognitive and memory functions are said to be improved [57]. Deterioration of memory and learning skills are two of the trademarks of neurological disease, as are indeed neurofibrillary tangles (NFTs), amyloid (Aβ) plaque buildup, and synaptic dysfunction in the brain. It has been found that d galactose-induced aging in animals is characterized by pathological alterations that closely mimic those seen in clinically diagnosed Alzheimer's patients. Chronic administration of the neurotoxic aluminium (Al) to rats results in oxidative damage, cholinergic dysfunction, and cognitive impairment, all of which have been related to the etiology of AD [57]. Co-stimulated by the herb's other active chemicals, which work in concert with Aβ to produce an enhanced impact. Refreshing *C. asiatica* extract from the leaf greatly enhances neuronal dendritic arborization in the hippocampus, as demonstrated by Rao et al. Because of its reputation as a nerve tonic, *C. asiatica* may offer therapeutic benefits for the nervous system in general [58]. In vitro studies have demonstrated that these substances can reduce H2 O2 caused destructive consequences on cells, reduce free radical levels, and block beta amyloid cell damage. In the brains of AD-model mice, *C. asiatica* echoes lowered beta-amyloid malignancy and the oxidative stress response. *C. asiatica* ethanol extracts have been shown to defend the neurons against A β 1-40- provoked neurotoxicity. Catalase, glutathione peroxidase, glutathione reductase, glutathione, and glutathione disulphide levels, as well as ROS production, can be reduced by *C. asiatica. C. asiatica* would play a significant function in the prevention and treatment of AD [33].

3.3. *Convolvulus pluricaulis*

One of nature's greatest gifts to mankind, the twining perennial herb *Convolvulus pluricaulis* is revered. In Ayurveda (an ancient Indian medical system), it is referred to as a Rasayana [59], a stimulant and memory booster for the brain. The plant resembles a morning glory, with blue blooms arranged in a pattern similar to that of the morning glory. In India, the state of Bihar is the most likely place to find it [60]. All of the plant's parts are medicinally valuable and have a positive impact on health. It's regarded as the only herb capable of enhancing all parts of brain power, such as memory, learning, and recall [61], for its ability to protect neurons

in both *in vitro* and *in vivo* settings. In male Wistar rats, it exhibits the protective effects of aluminum on neurotoxicity caused by aluminum plus scopolamine. neuroprotective effects of *C. pluricaulis* methanolic extract on human IMR32 neuroblastoma cell line's exposure to hydrogen peroxide under oxidative stress. The literature on *C. pluricaulis'* antioxidant status, macromolecule damage prevention, and neuroprotective efficacy is sparse, and there is no evidence of oxidative stress-mediated apoptosis [62]. *C. pluricaulis* has been shown to have antioxidant properties, protect macromolecules from damage, and have neuroprotective action when exposed to H2O2-induced neuronal cell injury. By using Gas chromatography–mass spectrometry (GC-MS) and Fourier-transform infrared spectroscopy (FTIR), we also studied *C. pluricaulis's* chemical composition and functional groups [63]. Stress hormones, adrenaline, and cortisol levels may be regulated by *C. pluricaulis*, resulting in a handy impact on the nervous system.*C. pluricaulis* cures several disorders in conventional healers of the nervous system, such as mental fatigue, distress, and panic, also sleeplessness. Extraction of ethanol of *C. pluricaulis* with its water and ethyl acetate ingredients was spotted to considerably improve rats' ability to learn and remember. It was also found that the dosing by the mouth of *C. pluricaulis* reduced the toxic effects of scopolamine levels by lowering the dose mRNA and protein levels of tau and APP. Sadly, there is no clinical evidence to support the use of *C. pluricaulis* in the good treatment of AD [64].

3.4. *Zingiber officinalis.*

The Zingiberaceae family includes ginger. Up to 24 genera and about 300 species are included in this family. Zingiber is a genus with roughly 20 species. The roots of the ginger plant, whether tuberous or rhizomatous, are perennial. All over India, Bangladesh, Taiwan, Jamaica, and Nigeria, the plant is grown. Warm climates are the ideal growing conditions for this perennial [65]. Ginger is widely used in cooking, as a condiment, and as a medicinal herb throughout the world. As a digestive aid, anti-nausea, and anti-bleeding treatment for rheumatism and baldness, ginger has been utilized in the Chinese medicine cabinet for at least 2500 years. TCM uses ginger as a spicy, dry, and warming yang herb to treat diseases brought on by cold, damp weather. Ayurveda, India's traditional medicine, uses ginger extensively to prevent blood clots (heart disease), lower cholesterol, and combat arthritis. Ginger soup is given to new moms in Malaysia and Indonesia for 30 days following delivery as a way to keep them warm while also allowing them to sweat off any impurities. An aphrodisiac in Arabian medicine is ginger. The belief among certain Africans is that eating ginger daily will keep mosquitoes away [66]. As an extract or as a component of ginger tea, *Z. officinalis* is frequently utilized in dietary supplements. Officinaleis has been identified as a source of key chemicals, including gingerols, shagoloids, Bisabolene and zingiberene, as well as monoterpenes. *Z. officinaleis* has been reported to suppress AChE activity in vitro. ACh levels in synapses are raised, cholinergic pathways are activated, and cognitive abilities in Alzheimer's patients are improved when the AChE enzyme is inhibited. As an added benefit, *Z. officinaleis* has been shown to prevent lipid peroxidation, which is a hazard factor for AD. Rats fed *Z. officinaleis* extract had lower levels of lipid peroxidation, according to an in vivo test. By reducing the Over-activation of NMDA receptors and preventing the production of free radicals, *Z. officinaleis* extract may explain the mechanism of action [33,67]. The "cholinergic theory," which contends that an acetylcholine deficiency is crucial in the development of AD symptoms, has been inspired by the selective deficiency of Ach in AD.

Because of this, enhancing the brain's cholinergic function is a primary method of treating AD. Tacrine, donepezil, rivastigmine, and galantamine are all examples of acetylcholinesterase inhibitors. Other hypotheses contend that AD is primarily caused by inflammation [67].

3.5. *Allium sativum*

Allium sativum of fibrillar Aβ protein. Clinically, preventing or dissolving fibrillar Aβ has a significant impact. The anti-amyloidogenic activities of garlic extract were studied in vitro in this study [68]. The lily family includes *Allium sativum L*. and *Allium ursinum L*., both of which have yet to be determined as to how their botanical names came to be. More than 400 species of Allium may be found in this genus. Garlic and wild garlic are the most significant Allium species, followed by A. PO drum (leek), *A. schoenoprasum* (chives), and *A. ascalonicum* (scallion).

In addition to the pharaohs, it was employed by pyramid builders. Other Greek thinkers, including Aristotle, Hippocrates, and Aristophanes, advocated the medicinal properties of garlic. Naturalist Pliny the Elder and Dioscorides, the Roman army's senior physician, prescribed garlic for a variety of ailments [67]. The blood-brain Barriers (BBBs) and those that do, may further aggravate AD pathogenesis by attracting macrophages and microglia. Natural medicines that lower fat lack of causing any Effects on the body would be even more crucial in clinical practice. Cholesterol levels are reduced by members of the Allium genus. *Allium sativum* (garlic) has the best cholesterol-lowering potential of any plant in the Allium genus. For thousands of years, Ayurvedic medicine has used garlic to treat arthritis and heart disease, and since then, researchers have studied the herb extensively. Garlic, a naturally occurring HMGCoA-Reductase inhibitor, lowers cholesterol without causing any adverse effects on the user. Aside from one study showing that aged garlic can improve learning deficits in SAM mice, there is little or no evidence to support the utilization of *Allium sativum* as a treatment for neurological disease-related pathology

or cognitive deficiencies, despite its long history of hypocholesterolemic benefits [69]. A genetically engineered mouse design of AD that human amyloid precursor protein is overproduced 695 carrying the Double mutation (K670N/M670L) in Sweden was used in this study to test the Viability of ingesting garlic on the reduction of amyloid strain because high cholesterol levels have been associated to the advancement of AD (Tg2576) [67]. AD patients have plaques in their central nervous system that are mostly made of amyloid.

4. Pathogenic Effects and Mechanisms of Bioactive Compound Against AD

The natural products may target proteins or signalling pathway members affected by the disease. In the past, medication was derived from natural components. Several bioactive dyes are being studied in animal model systems to determine if they can treat AD or other neurodegenerative diseases. Most are in clinical studies with encouraging outcomes. As a result, Diverse natural products (NPs) can reduce indications and ameliorate the progression of numerous diseases, including AD, drawing the research community and the pharmaceuticals sector. NPs such as flavonoids, tannins, lignans, gingerols, anthocyanins, triterpenes, lunatic, sterols, and alkaloids have anti-inflammatory, antioxidant, anti-amyloidogenic, and anti-cholinesterase effects [70,71].

4.1. Flavonoids

Flavonoids are a huge nutritional family with about 5000 members. These are phytonutrients found in practically all photosynthetic organisms and, therefore, in plant-based foods. This chemical category is notable for its antioxidant and anti-inflammatory health benefits. Recent research suggests flavonoids can reverse age-related decreases in cognitive ability in dementia and Alzheimer's. This may be due to flavonoids' capacity to counteract common aspects of AD and other neurodegenerative disorders, such as oxidative stress, and/or to their impact on specific molecular mechanisms at the base of these illnesses' pathogenesis [71,72]. Chemical makeup depends on the structural class, hydrogenation intensity, alterations or conjugations, and polymerization degree [73]. They may be categorized into a few fundamental structures, and their enormous variety can be attributed to hydroxylation patterns, methylation, and glycosylation of the hydroxyl groups. Flavones, dihydroflavonols, flavan-3-ols, flavones, anthocyanidins, isoflavones, neoflavones, and chalcones are principal, but not unique [74]. Flavonoids were thought to stimulate cognitive functioning, learning, and memory through their antioxidant properties. Growing data reveals that natural chemicals interact with memory-related molecular and cellular central nervous system components [75]. Flavonoids can promote neurogenesis, stimulate neuronal regeneration, boost neuronal activity, and prevent neuronal malfunction [76–78]. Several Flavonoids and their metabolites interact with cortical signalling pathways to affect neurological functions [79]. The protein tyrosine kinase receptor B (TrkB), nicotinic cholinergic, ɣ -opioid, type A gamma-aminobutyric acid, adenosine, testosterone, and estrogen receptors are biosynthetic pathway sites in brains [80]. Flavonoids modify these molecular mechanisms, reducing oxidative stress, mitochondrial dysfunction, insulin resistance, and memory damage [81–83]. The flavonoids play a role in autophagy that removes damaged cells to rebuild healthier ones. Autophagy regulates Aβ production and clearance [84]. Anti-AD medications target brain Aβ clearance to minimize synaptic defect and neuronal death [85–87]. AD neurodegenerative effects include neuroinflammation, endogenous antioxidant reduction, glutamatergic excitotoxicity, and neurotoxicity. Flavonoids alleviate neuronal damage and slow AD by regulating kinase-signalling cascades, such as PI3K/Akt, PKC, and MAPK (Figure 5 and Table 1) [88–90]. Metabolic processes produce free radicals. Free radicals disrupt normal physiological processes, including antioxidant activity, protein breakdown, DNA fragmentation, and chemokine dysregulation. Free radicals cause neuroinflammatory damage that leads to AD. Oxidative stress biomarkers indicate AD progression [91–94]. Ach is a neurotransmitter that signals between synapses.AChE and butyrylcholinesterase breakdown ACh. Cholinesterase inhibitors are the greatest way to boost ACh levels at synaptic connections in AD brains, where ACh levels are low. Flavonoids have been studied as AChE and BChE inhibitors [37,95,96].

4.2. Tannins

Tannins are polyphenol molecules that have health benefits. They're found mainly in fruits and vegetables and are consumed every day, however, rates vary by region. In India, 1.5–2.5 g/day of tannins are consumed, and 1 g/day in the US. Their chemistry depends on their source and molar mass. Their distribution and composition vary in leaves, roots, seeds, and fruits. Tannins are white or light-yellow amorphous powders with astringent taste and odor. Tannins' anti-oxidative potential has drawn the attention of scientists. It reduces oxidative damage, a hallmark of practically every disease [97,98]. Tannins are biologically powerful molecules that regulate human health [99]. Their many therapeutic functions can help treat many ailments. Properties include anti-inflammatory, anti-oxidative, anti-convulsant, and anticancer [100–102].In a streptozotocin (STZ)-induced sporadic Alzheimer model, tannin treatment can prevent memory and cognition deterioration by reducing oxidative stress and acetylcholinesterase activity and boosting Na+, K+-ATPase activation [103]. Tannins have been shown to facilitate the non-amyloidogenic degradation of APP by reducing the production of the BACE1 protein and specifically lowering the function of the BACE1 enzyme [104]. The amyloidogenic C99 fragment, sAPP-, and A polypeptide levels are decreased as a result of this action [105]. Additionally, tannins prevent tau from aggregating by complexation in the R3 peptide's

hydrophobic cavity, which correlates to the third repetition unit of tau's axon region [106]. Tannins have also been noted to have anti-neuroinflammatory actions on BV2 brain cells generated by lipopolysaccharide (LPS). The mechanism might be connected to a decrease in the production of ROS and an inhibition of the stimulation of the NF-kB cascade [107]

(Figure 5 and Table 1). They are active in the pathogenesis of NDDs, especially AD and MS [108]. Natural products are a useful source of tannins with biological sensitivity and various molecular properties, making them suited for accentuating many signaling pathways in AD and other clinical diseases [109,110]. The next sections address tannins' protective function in AD and. Figure 3 shows tannins' health-promoting effects **(Figure 3).**

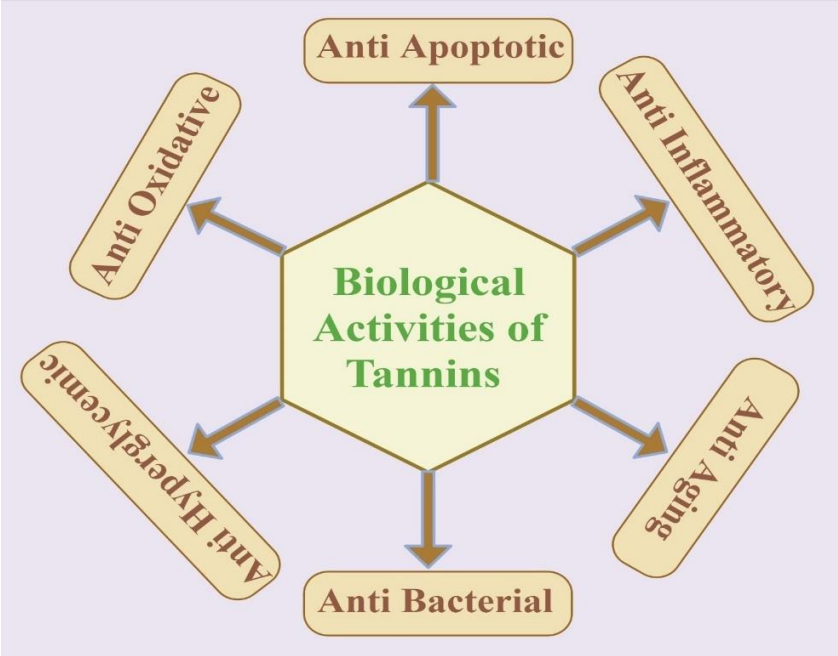

Figure 3: Representation of the Bioactivity of tannins

4.3. Lignans

Polyphenolic lignans are plentiful in flaxseeds, rye, whole wheat, vegetables, and fruits. Vegetable protein lignans secoisolariciresinol diglucoside (SDG) and pinoresinol diglucoside are metabolized by Ruminococcus species to create (+)-dihydroxyenterodiol and (+)-enterolactone [111]. This intestinal microbiome species deglycosylated and de-methylates plant-dependent lignans to create lignans with a wide biological response to anti-cancer Enterolactone. Enterolactone suppresses prostate cancer cell proliferation via a caspase-dependent mechanism in vitro and in vivo. Enterolactone and secoisolariciresinol block carbonic anhydrase, acetylcholinesterase, and butyrylcholinesterase providing neuroprotection [112,113].The beta-secretase 1 and the MAPK biochemical mechanisms were inhibited by the lignans extracts, which had a preventive role towards amyloid-beta1-42 (Aβ1-42)-induced memory impairments and neurodegenerative in mice and primary animal neural cells [114,115]. Additionally, it improved the level of malondialdehyde (MDA) in the mouse brain hippocampus, and cerebellum as well as the functions of all antioxidants. Moreover, the lignans showed therapeutic potential against D-galactose-induced dementia, significantly inhibited the decline in membrane potential, and regulated Bcl-2 expression in Aβ1-42-induced primary mouse neural cells [116,117] **(Figure 5 and Table 1).** At AD, acetylcholine rates in neural synapses are low, causing cognitive impairment. Through acetylcholinesterase inhibition, these lignans give neuroprotection and prevent memory loss in AD patients, suggesting an alternative therapy option to donepezil, galantamine, and rivastigmine [118,119]. Those drugs simply provide symptomatic relief, but lignans may slow AD's progression. Dietary polyphenolic substances influence the gut bacteria and the gut-brain axis and can be utilized to treat AD and other cognitive illnesses. The gut bacterial metabolite enterolactone, generated by intestinal bacterial digestion of the lignan 7-hydroxymatairesinol (a component of Picea abies), attenuates striatal dopaminergic terminal atrophy in AD. HMR, SDG, and enterolactone may be neuroprotective in AD via structural changes [120–122].

4.4. Lunasin

In 1987, Japan, isolated lunatic from soybean (Glycine max) seed while searching for protease inhibitors. Wheat, barley, rye, amaranth, and triticale also contain it. Lunasin, a fermentative protein, should be consumed optimally. Lunasin is anti-inflammatory and anti-cancer. Lunasin is the 2S albumin subunit.

Methionine-rich protein, signal peptide, linker peptide, and Lunasin are encoded by the GM2S-1 gene. It contains 43 amino acid residues, 5.5 kDa, and eight negatively charged aspartate residue sequences. Lunasin contains four motifs: N-terminal, predicted helical, RGD, and poly-D tai. Lunasin inhibits cytokines like TNF- and IL-6, according to animal research. Suppress nitric oxide output. Lunasin might be a potential treatment for inflammatory diseases. Dysregulation of the JNK signal transduction pathway is the innovative neuroprotective mechanism in AD used by the soy protein Lunasin. Aβ42-mediated dementia is significantly rescued when the soy protein Lunasin is misexpressed alongside human Aβ42 in the growing Drosophila eye [123]. By inhibiting the Jun-N terminal kinase (JNK) signal transduction pathway, lunasin restores the Aβ-42-induced decreased eye morphology **(Figure 5 and Table 1)** [70].

Genetic modification flies expressing high amounts of human Aβ42 were utilized to explore the effects of Lunasin on retinal neurons in Drosophila. Fly retinal neurons expressing Aβ42 had hazy eyes and necrotic patches, indicating neurodegenerative [70,124,125]. This work reveals misexpression of extracts in growing Drosophila retinal neurons may repair Aβ42-mediated neuropathy. AD's neuroinflammation is caused by ROS (Figure 4). Lunasin is a possible AD treatment target, and investigations on mammalian models will assist determine its medicinal qualities in mammals **(Figure 4)** [123,126–128].

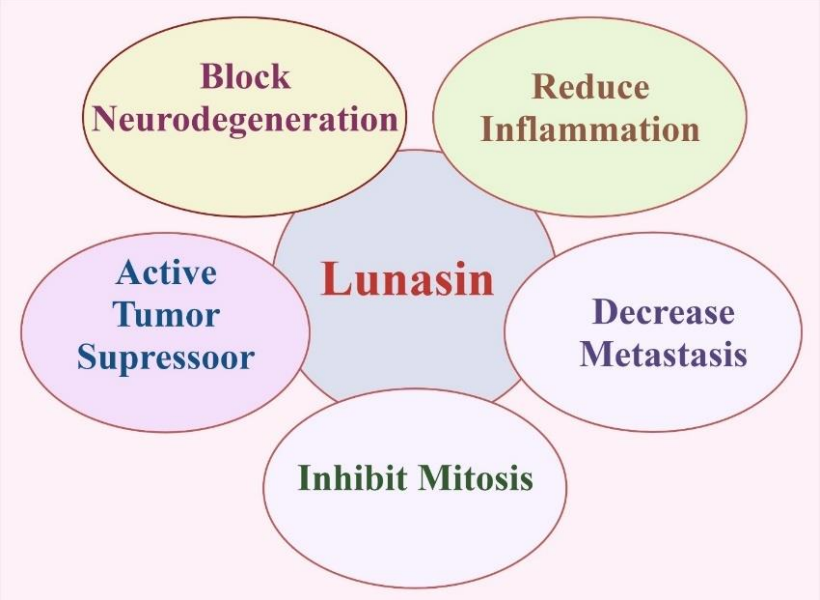

Figure 4: Diagram of Lunasin function. Lunasin activates tumor suppressors, inhibits mitosis, and reduces metastasis, according to reports. Reduces inflammation. Recent investigations show it prevents neurotoxicity from amyloid-beta 42 plaques

4.5. Anthocyanins

Anthocyanins (ANTs) are natural pigments with medicinal effects. The average advanced daily consumption of these substances is 180 mgd1.ANTs are powerful antioxidants that may control the formation of free radicals of Alzheimer's-causing Aβ-amyloids in the brain (AD) [129]. An emphasis has been made on indigenous polyphenolic ANT substances. Numerous berries are abundant in powerful antioxidant phenolic compound ANTs, which may provide prevention from AD via several mechanisms [130]. Red raspberries and green tea, for instance, contain ANTs that are helpful in preventing AD [131]. In a different investigation, bilberry-fed transgenic AD mice had a significantly lower level of solvent Aβ 40 and Aβ42 contrasted to transgenic AD mice administered blackcurrant. Blackcurrant and bilberry extract decreased APP levels in the cerebrum of AD mice models, however neither the transcription nor phosphorylation of tau protein changed [132,133]. Apoptosis, respiratory malfunction, and Abeta neurotoxicity caused by OS are all things that ANTs can prevent by crossing the blood-brain barrier. By controlling Bax, Cyto-C, caspase-9, tau proteins, and BACE-1 in the mitochondrial apoptotic mechanism, ANTs may be able to suppress AD **(Figure 5 and Table 1)** [134,135].

Table 1: Natural products and their bioactive compounds with neuroprotective activities in treating Alzheimer's Disease

SI No	Natural products/chemical compounds	Model	Mechanism of Action	References
01	Flavonoids	ICV STZ-induced dementia model of rats/3xTg-AD mice	Decrease CNS Aβ levels and reverses tau hyper-phosphorylation via downregulating GSK-3 in the hippocampus and cortex. Reduces the β - amyloid process boosts mitochondrial function and prevents apoptosis.	[136,137]
02	Tanins	Ethanol tolerance in rats	Increase neuroplasticity and Ach transcriptional regulation, Demonstrate anti-ChE activity, Lower oxidative stress, Excitotoxic, Aβ formation, and depositing	[138,139]
03	Lignan	Amyloid-β-induced neurodegeneration in animals	Enterolactone reduces prostate cancer cell growth in vitro and in vivo, acetylcholinesterase inhibition, Cognitive function	[140]
04	Lunasin	Drosophila melanogaster	reduce Jun-N terminal kinase (JNK) activation loop, Neuroprotective and cognitive function.	[123]
05	Anthocyanins	ALS mouse model with hSOD1G93A mutation	(hSOD1)G93A rat illness onset reduced, lifespan increased, restored hamstrings neural connections	[141]
06	Alkaloids	APPswe/PS1dE9 Alzheimer's mice	Decreases Aβ plaque accumulation, Increases mitochondrial activity, Inhibits acetylcholinesterase function	[142]
07	Sterols	APP23 transgenic animals	anti-inflammatory promise, induced oxidative neurodegeneration	[143]
08	Quercetin	Rats	Anti-free radicals, NFB inhibitor	[144]
09	Epigallocatechin-3-gallate	Mice	EGCG reduces oxidative stress and neurorescues rats from MPTP-induced impairments	[145]
10	Resveratrol	AbetaPP/PS-1 transgenic mouse/ Cultured hippocampal neurons Zebrafish	Decrease A plaque accumulation and stimulates the brain and cortex astrocytes, Preventing inactivating production of nitric oxide, and pro-inflammatory molecules.	[146,147]
11	Berberine	TgCRND8 mouse	Reducing amyloid plaques and AD pathogenesis	[148]
12	Huperzine A	In vivo	Reduces brain amyloid	[142]
13	Luteolin	AD flies	Lowers oxidative stress, AChE activity, Aβ42 peptide deposition, ROS-inhibition	[149]
14	Rosmarinic acid	Mice model	TNF- inhibits ROS production, NF- κ B activation, and apoptosis, Alzheimer's prevention	[150]
15	Curcumin	APP/PS1 transgenic mice	Removing beta amyloid improves symptoms.	[151]
16	Galantamine	Masculine C57BL/6Hsd APPswe/PS1d E9 mice	Lowers cholinergic effects. Reduces oxidative stress	[152]
17	Rifampicin	APPOSK (Aβ oligomer), Tg2576 (AD), and tau609 (tauopathy) mice	decreases Aβ clustering and tau hyperphosphorylation.	[153]
18	Cinnamaldehyde	Non-transgenic AD rats	Improvements in insulin signaling and ameliorating cognitive dysfunction. Increases p-GSK3β and inhibits AChE activity	[154]

SI No	Natural products/chemical compounds	Model	Mechanism of Action	References
19	Betaine	Caenorhabditis elegans AD model	Decrease homocysteine levels and Aβ toxicity	[155]
20	Apigenin	APP/PS1 double transgenic AD mouse	Improvement in memory and learning and reducing the fibrillar amyloid accumulation	[156]
21	Phenol	apps/Tg 2576 mice	Reduce chronic oxidative stress. Improvement in memory and anxiety-related behavioral disorders	[157]
22	Epicatechin	PC12 cells treated with A β 25–35	Reduces A β -induced neurotoxicity	[158]
23	Boswellic acids	Rotenone-induced rats	Increased motor functions, Increased striatal dopamine level	[159]

4.6. Alkaloids

This work reveals misexpression of Extracts in growing Drosophila retinal neurons may repair A β42-mediated neuropathy. Several alkaloids extracted from natural resources, such as physostigmine, block acetyl- and butyrylcholinesterase (BChE). Synthetic alkaloids from the steroidal/triterpenoid, quinolizidine, isoquinoline, and indole families are important anti-enzymatic sources [160,161]. Alkaloids are the most highly promising AD treatments owing to their sophisticated nitrogen-containing structures [162]. Polarized nitrogen interacts with one of AChE's binding sites to enable inhibition by non-alkaloid chemicals, particularly terpenes, xanthones, and coumarins [163–165]. AChE inhibitors have been studied as therapeutic options for AD after it was observed that physostigmine (eserine), an alkaloid acquired from the cereals of *Physostigma venenosum Balf*. (Fabaceae), conventionally used as a ceremonial poison in Africa, could restore the disturbance of cognition generated by scopolamine in animal studies.A powerful selective negative feedback loop of AChE is huperzine A. With an IC50 of 0.1 M, which is about 1000 times stronger than its inhibition of BChE, it inhibits AChE . Both in vitro and in vivo, it guards against the damaging effects of Aβ on mitochondrial functioning. Through the release and signaling of nerve growth factor, huperzine A also has neuroprotective benefits. By functioning as an NMDAR antagonist, it lessens glutamate neurotoxicity. By controlling the expression of pro-apoptotic genes and proteins and upregulating the expression of anti-apoptotic genes and proteins, huperzine can also prevent neuronal cell death in AD.Huperzine-A is a strong, transient, specific AChE antagonist with oral bioavailability and a lengthy half-life [166] **(Table 1)**. Various alkaloids that inhibit cholinesterase have been mentioned in different families, including isoquinoline-type alkaloids from Amaryllidaceae (especially *Narcissus sp, Galanthus sp, Hyppeastrum sp*) and Papaveraceae, steroidal alkaloids from Buxaceae (*genera Buxus* and *Sarcococca*), quinolizidine-type alkaloids from Lycopodiaceae (*genera Huperzia*) [167–171]. Due to their anticholinesterase action, structural variety, and physicochemical qualities, alkaloids are potential AD therapy candidates [161].

4.7. Marine Sterols

Marine species offer many useful bioactive molecules, and anti-medicines Alzheimer's obtained from marine biodiversity is a viable method for treating AD pathogenesis. Marine sterols have been studied for their anti-cancer, anti-obesity, anti-diabetes, anti-aging, and anti-characteristics. Alzheimer's Marine sterols engage with proteins and enzymes tumor suppressor, antioxidant defense, immunological response, and cholesterol regulation [172]. About 70% of the Planet's surface is seas, and marine species provide natural chemicals. Recent findings have focused on marine natural compounds for treating AD [173,174]. Ocean sterols, a type of sterol chemicals, are physically and physiologically equivalent to cholesterol and are essential to human health and nourishment [175]. Ocean sterols, particularly fucosterol and saringasterol, target oxidative stress, inflammation, cholinergic deficiency, amyloidogenesis, cholesterol regulatory route, and cerebral surviving signaling systems. Endogenous antioxidants include catalase (CAT), glutathione peroxidase (GPx), glutathione peroxidase (SOD) and non-enzymatic antioxidants like glutathione and ascorbate help cells fight oxidative stress. Natural substances' adaptogenic potential may boost the antioxidative defense system [176]. Naturally occurring substances may affect signal transduction pathways, including Nrf2/heme oxygenase-1 (HO-1), to boost IDS [177]. Ocean sterols' preventive actions versus oxidative damage imply their efficiency against induced oxidative neurological diseases, including AD. Marine bioactive antioxidants, particularly phytosterols, reduce inflammation AD indicators can be helpful in administration [178,179]. Marine sterols have anti-inflammatory promise. Fucosterol therapy of LPS- or A-stimulated oligodendrocytes reduced IL-1, IL-6, TNF-, NO, and PGE2. Fucosterol suppressed COX-2, iNOS, and NF-B activation in LPS-stimulated RAW 264.7 macrophages. Fucosterol suppresses LPS-mediated inflammation by activating alveolar macrophages. Anti-inflammatory sea sterols may prevent AD inflammatory diseases **(Table 1)** [180,181]. AD pathogenesis causes cholinergic deficiency. Ace inhibitors reduce cholinergic neurotransmission and ameliorate AD. Marine sterols have now been known to decrease cholinesterase.

Fucosterol inhibited AChE and BChE dose-dependently. Fucosterol inhibits AChE non-competitively, according to dynamics and physical studies **(Figure 5)** [181,182].

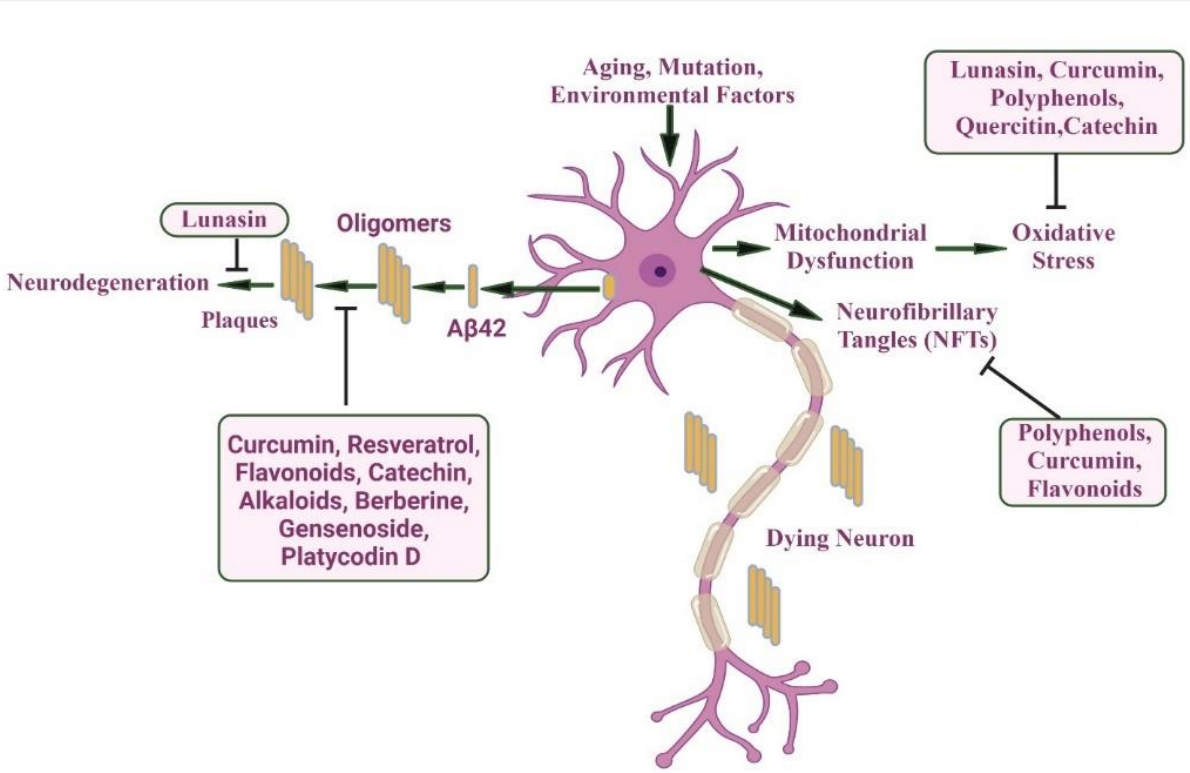

Figure 5: Schematic illustrating how natural products stop Alzheimer's

Natural products can prevent neurodegeneration by eliminating oxidative stress, prohibiting the formation of neurofibrillary tangles (NFTs), or amyloid-beta 42 (Aβ42) plaque derivative and thereby block Aβ42 mediated neurodegeneration.

5. Neurological effects of some Natural Products for Potential Treatment of Alzheimer's disease (AD)

5.1. Honey

Honey is a sweet, viscous biological food product made by honeybees (*Apis mellifera*; Family: Apidae) from the nectar of flowering plants [183]. In addition, honey is a great source of polyphenols, which are substances that have a positive effect on the body's physiology. It contains around 80% carbohydrates (40% fructose, 35 % glucose, and 5% sucrose) and 20% water, and natural honey has more than 200 different substances including protein (amino acids and enzymes), minerals, vitamins (vitamin B6, riboflavin, niacin, and thiamine), phenolic compounds (flavonoids and phenolic acids), and volatile substance [184,185]. It must be extensively used as a dietary supplement and in herbal medicine causes, it has containing antioxidants such as polyphenols and flavonoids. In addition, honey is used not only as a nutritional product but also in the treatment of Neurological disorders namely AD, Parkinson's disease (PD), Huntington's disease(HD), multiple sclerosis (MS), stroke and so on [186].The ingredients of honey are including antioxidant, anticancer, anti-inflammatory, Anti-metastatic, Antidiabetic, antimicrobial, and antiproliferative effects [187]. Honey may help prevent and cure a wide range of diseases including diabetes mellitus, cancer, asthma, and even cardiovascular, neurological, and gastrointestinal conditions, according to numerous pieces of evidence [188]. The dysfunction or death of brain cells causes AD. This is caused by an increase in oxidative stress due to a depletion of anti-oxidants, neuro-inflammation, prions, protein, and mitochondrial dysfunction, glutamatergic excitotoxicity, and genetic changes [189].

5.2. Propolis

Propolis also called "bee glue" is another product made by bees. It is a mixture of resinous, gummy, and balsamic substances that bees get from the buds of some of these trees, such as poplars, palms, pines, and conifers [190,191]. In propolis, researchers have found over 300 different components, including phenolics and aromatic acids as well as essential oils, waxes, and amino acids [191]. Neurological problems such as cerebral ischemia, neuroinflammation, shock and memory loss, and other mental illnesses like anxiety and depression, are treated with propolis [187,192].

5.3. *Withania somnifera*

Withania somnifera (WS), also known as ashwagandha, Indian ginseng, and winter cherry, is an important medicinal plant that has been an essential therapeutic herb in Ayurvedic and traditional medicine over the last 3,000 years [193]. It is a perennial herb covered with hairs and belongs to family Solanaceae [194]. It possesses a wide variety of pharmacological effects, including anti-inflammatory, antitumor, anticarcinogenic, anxiety, neurodegenerative, antibacterial, hypolipidemic, and CVS-associated activities, as well as many other pharmacological qualities[195]. In an animal model of neurological disease, *Withania somnifera* root extract improved mice behaviour reduced oxidative stress and mitochondrial dysfunction, reduced glutathione (GSH) level, lipid peroxidation, enhancing human immediate and general memory [196–198].

5.4. Ginseng

Ginseng is an Araliaceae perennial plant. It has been used as a medicinal plant for thousands of years in East Asian countries, such as Japan, China, and Korea [199]. It has also been formed as the treatment of neurological diseases like AD, PD, HD, traumatic brain injury, and so on. In addition to having great therapeutic effects against various conditions, such as immune regulation, antitumor, antifatigue, antiaging, antioxidation, depression, diabetes, inflammation, dyspepsia, nervous system diseases, and another aspect [200–203]. Although each ginsenoside has a unique chemical composition, they are all acquainted with the four-ring hydrophobic structure [204]. Rb2, Rb1, Re, Rg1, and Rc are the primary ginsenosides found in fresh ginseng, accounting for 70–80 percent of the total ginsenosides [205]. Rg1 is a type of monomer found in ginseng .Recent pharmacological investigations have demonstrated that Rg1 can act on the nervous system treatment [206].

5.5. *Uncaria rhynchophylla*

Uncaria rhynchophylla, which belongs to the family Rubiaceae, is a medicinal herb used in traditional Chinese medicine [207]. In Asia, Africa, and South America, it has been included in traditional medicine. In traditional Chinese medicine, *U. rhynchophylla* is mostly used to treat diseases of the heart and central nervous system, like neurodegenerative diseases, lightheadedness, dizziness, seizures, numbness, and high blood pressure [208–210]. The alkaloids are the active components that can be detected in the extract of the *Uncaria rhynchophylla* plant [211]. Not only alkaloids but also rhynchophylline, isorhynchophylline, corynoxeine, isocorynoxeine, and hirsutine are found in *Uncaria rhynchophylla*. *Uncaria rhynchophylla* extract reduced lipid peroxidation in a rat model of kainic acid-induced excitotoxicity **(Table 2)** [212,213].

Table 2: List of some medicinal plants and their extract that have shown neuroprotective activity

SI No	Plant Name	plant parts used	Extract	Method/Models	Neuroprotective activity	Ref
1	*Allium Sativum*	Fruits	Ethanol	Y-maze, Passive avoidance test	Both LDH leakage and ROS levels were suppressed	[214]
2	*Abrus precatorius*	Leaves	Methanol	Elevated plus maze, Active avoidance paradigm	Catalase and superoxide dismutase enzyme activity was elevated by PCA	[215]
3	*Bacopa monnieri*	Aerial parts	Ethanol	Morris water maze	By increasing the cell survival (Akt) pathway, BM extract conserved cellular redox equilibrium and mitochondrial activity	[216]
4	*Centella asiatica*	Leaves	Ethanol	Invitro models (inhibition of AchE or BchE activity)	ROS generation, GSH reduction, caspase3 activation, and Bcl-2 down-regulation were inhibited by PCA	[217]
5	*Convolvulus Pluricaulis*	Whole plant	Chloroform	Invitro models(inhibition of AchE or BchE activity)	Inhibited IkappaB-alpha degradation and NF-kappaB activation in BV-2 cells in a dosdependentnt manner.	[218]
6	*Curcuma longa*	Rhizome	Aqueous	Morris water maze, Step-through passive avoidance test	Antioxidant, anti-inflammatory, and anti-apoptotic activities	[219]

SI No	Plant Name	plant parts used	Extract	Method/Models	Neuroprotective activity	Ref
7	*Enhydra fluctuations*	Stems and Leaves	Chloroform	Invitro models(inhibition of AchE or BchE activity	AP lowered ROS generation, prevented the enhanced rate of apoptosis, and decrease the Bax/Bc12 ratio	[220]
8	*Ferula asafoetida*	Gum	Aqueous	Elevated plus maze, Two compartments passive avoidance test	SAC increased CuZn-superoxide dismutase action as well as decreased the generation of superoxide radicals.	[221]
9	*Ginseng*	Root	Ethanol	Elevated plus maze, Hebb William maze	Ginsenosides decreased the Bax/Bcl-2 ratio and inhibited the formation of ROS	[222]
10	*Glycyrrhiza glabra*	Root	Aqueous	Elevated plus maze, Hebb-William maze, Morris Water maze	Through the p38 MAPK/Nrf2 pathway, glycyrrhizin increased the production of heme oxygenase-1(HO-1) in neuron cells	[223]
11	*Huperiza serrata*	Whole plant	Ethanol	Y-maze, Passive avoidance test	Huperzine A (HupA), reduced the elevation of ROS levels, and decrease the Bax/Bcl-2 ratio and PARP proteolysis.	[224,225]
12	*Morus alba*	root bark, leaves, branches, and fruits	Methanol	Invitro models(inhibition of AchE or BchE activity	Decreasing ROS and enhancing cellular anti-oxidative capability (SOD) and GR).	[226]
13	*Marine macroalgae*	Whole plant	Ethanol	Hebb William maze, Passive avoidance test	Increasing expression of PGC-1 alpha and anti-apoptosis.	[227]
14	*Nigella sativa*	Seeds	Methanol	Morris water maze	Thymoquinone (TM) controlled the redox balance by inducing Thioredoxin-1 and inhibited apoptosis signaling.	[228]
15	*Ocimum sanctum*	Leaves	Ethanol	Open field test, Elevated plus maze, Porsolt's swim Test	Tyrosine hydroxylase expression has been restored.	[229]
16	*Apium graveolens Linn*	Leaves	Ethanol	Y-maze, Passive avoidance test	NBP decreased mitochondrial permeability while increasing cellular GSH concentration.	[230]
17	*Uncaria rhynchophylla*	Leaves and fruits	Ethanol	Two compartments passive avoidance test	Rhynchophylline increased DA levels and expression of the growth of factors	[231]
18	*Valeriana wallichii*	Rhizome	Ethanol	Elevated plus maze	Blocking the active caspase-3 fragment (17kDa) and proteolytic poly (ADP-ribose) polymerase (PARP	[232]
19	*Chrysanthemum indicum Linn (CI)*	Leaves	Methanol	Elevated plus maze, Hebb William maze	The CI extract suppressed ROS generation, decreased the Bax/Bcl-2 ratio, and	[233]

SI No	Plant Name	plant parts used	Extract	Method/Models	Neuroprotective activity	Ref
					repressed prostaglandin E-2 synthesis and cyclooxygenase type-2 expression(cox-2).	
20	*Cruciferous vegetables*	Leaves	Dimethyl sulfoxide	Morris water maze	It raised the levels of depleted GSH and induced mRNA synthesis of the gamma-glutamylcysteine ligase catalytic subunits (GCLC), nGR, and NQO1.	[234]
21	*Valeriana jatamansi*	Leaves	Methanol	Elevated plus maze, Hebb William maze	The mechanism of their neuroprotective action is still to be investigated.	[235]
22	*Selaginella lepidophylla*	Root	Water	Elevated plus maze	Induced reduction of TH and DAT in the SN	[236]
23	*Turbinaria decurrens*	Rhizome	Water	Y-maze,	Turbinaria decurrens raised the number of TH proteins and DA in striatal neurons.	[237]
24	*Withania somnifera*	Root	Ethanol	Y-maze, Morris water maze	Induced autophagosomes and increased the expression of LC3-II.	[238]

6. Medicinal plant ingredients for AD

AD is a slowly progressing neurological disease. 60–70 percent of dementia cases can be attributed to it. Most people first notice that they have trouble recalling recent events. Disorientation, mood changes, lack of motivation, and self-neglect can all be signs of the condition as it progresses. Behavioral disorders are also possible. The more ill a person becomes, the more he or she tends to isolate himself or herself from friends and society. As biological processes decline, they eventually lead to a person's death. This disease has a median overall survival time of three to nine years, although individual cases can proceed at different rates. This disease is crucial for patients so medical ingredient is super prominent for alleviating AD. Many disorders, including AD, would be helped via using natural products. There are other natural chemical structures, Flavonoids, polyphenolic compounds, sterols, triterpenoids, and naturally occurring substances are painkillers and anti-inflammatory chemicals,anti-amyloidogenic, and anticholinesterase properties [33]. About 75% to 81% of people all over the world rely on herbal medicine for basic body care, primarily in the poorer nations, due to cultural tolerance, being more suited for the human body, and less adverse effects. But in recent years, their use in the developed world has increased significantly. According to preliminary clinical data, several herbal medications can enhance cognitive duty in mild to intense AD patients. The therapeutic benefits of these herbs are not confined to the suppression of cholinesterase inhibitors, beside include the modulation of Aβ processing, defense against apoptosis and anxiety from combustion, and anti-inflammatory properties [64]. About 3.5 percent of the population in the United States aged 65 to 74 is believed to be at least in the early stages of AD. Nearly three-quarters of patients with end-stage renal disease are 85 years old or older. AD is more common in women than in men. Neuropathologically, amyloid (Aβ) deposition is a key feature of AD and a possible source of neuronal damage. Medicines for AD are currently absent a "magic bullet" that can stop, slow, or even reverse the illness's progression. These can be split into three categories based on whether they prevent the disease from forming or slow its advancement after it has. New research suggests new approaches to treating AD. Neurotransmitter system disruption appears to be the most practical option at the present [64].

6.1. Quercetin

Flavonoid Quercetin has prominent pharmacological action as well as offers therapeutic properties. It can be found in a wide variety of foods, including fruits and vegetables, but it is most commonly found in the plant kingdom. Quercetin has been shown to protect neurons in vitro. Studies have shown that it both protects synapses from cellular damage and shrinks lipid peroxidation. Furthermore, being an antioxidant, it stops amyloid beta proteins from clumping together into fibrils. preventing organelle lysis and mechanisms in the inflammation response [239]. Scavenging reactive oxygen species (ROS) is a one-way quercetin exerts its potent antioxidant properties. furthermore, it has a variety of useful characteristics, features like being anti-viral, anti-inflammatory, anti-cancer, and anti-amyloidogenic. The compound concentration of 10μM has been displayed to have anti-amyloidogenic properties by reducing the buildup of beta-amyloids. The apoptosis-inducing effects of Aβ- were also reduced by quercetin. Nevertheless, at higher concentrations (40μM), quercetin induces cytotoxicity. Quercetin nano encapsulated in zein nanomaterials drastically enhanced

intellect also remembrance impairments in senescence-accelerated P8 rats, according to a recent study. The decreased GFAP expression in the hippocampal astrocytes may be a factor in the mechanism [33]. These potentially damaging effects can be neutralized by quercetin's presence. If quercetin can be used to counteract cell and molecular signals in the regulation of normal physiological functions, then ROS could be a key factor in AD progression. Data on quercetin's cellular mechanisms, on the other hand, are sparse. The neuroprotective consequences of quercetin are primarily caused by the Possible cytokine up- and down-regulation through Nrf2, Paraoxonase-2, c-Jun N-terminal kinase (JNK), Kinases, Mitogen-activated protein kinase (MAPK) signaling cascades, and PI3K/Akt systems. [68].

6.2. Epigallocatechin-3-gallate

One of the flavonoid-type catechins that can be *Camellia sinensis* is a source of it. It is called epigallocatechin-3-gallate (EGCG). Epigallocatechin-3-gallate possesses powerful action as an anti-oxidant, with numerous research have looked at the impact of epigallocatechin-3-gallate on a variety of cancer and other debilitating diseases cardiovascular and neurological salvo [33]. It's a catechin and a combination of epigallocatechin and gallic acid. Various dietary supplements contain EGCG. Because the compound is a plenty potent polyphenol present whereas in herbal tea, is linked to green tea's cancer-fighting properties [240]. The reduction of neuroinflammatory cytokines generated from astrocytes by EGCG inhibits memory loss and amyloidogenesis, suggesting that EGCG might have been an effective treatment for neuroinflammation-associated AD [241].

As a result, green tea may help lessen the risk of developing the neurological disease by reducing the number of reactive oxygen species (ROS) in our bodies. The anti-inflammatory function of EGCG has also been researched and is deemed a strong anti-inflammatory agent by numerous groups and cell types. There is no evidence that EGCG modulates the cytokine secretion from astrocytes induced by the pathological development of AD [242]. EGCg's multi-target exact mechanism of action and synergistic effect on protein misfolding, oxidative stress, and neuroinflammation make it an ideal treatment for a variety of conditions. EGCG's actions that have anti-apoptotic,anti-amyloidogenic, and anti-inflammatory properties have been identified as contributing to its function in the treatment of neurodegenerative disease (ND). The formation of misfolded protein aggregates in the brain is a common pathogenic feature of many NDs. It appears that targeting protein misfolding may be a potential way to avoid NDs. Protein misfolding and aggregation are two of the primary causes of neurodegeneration, which makes them a viable target for ND prophylaxis.

More and more, protein misfolding and the subsequent self-association into potentially toxic oligomers and amyloid deposits are being recognized as critical etiological factors in various neurodegenerative diseases, such as Alzheimer's and Parkinson's. And the rarer prion diseases that result from it. In the molecular process, in the end, the protein was formed misfolding as well as collection appear to be identical even though each ND is linked to defects in protein folding. These findings suggest that a common treatment for NDs may be achievable based on these findings. The protein misfolding proteins Aβ, tau, α -synuclein (α-syn), transthyretin (TTR), and going on a hunt can all interact along EGCG, according to research [243].

6.3. Resveratrol

As an antioxidant, resveratrol comes from a plant. Red wine, grapes, some berries, and peanuts are among the most nutritious foods available. In 1940, resveratrol was isolated [244]. Scavenging ROS, boosting glutathione levels, and enhancing the body's antioxidants are just a few ways resveratrol works as a powerful antioxidant. Cleavage of APP that is not amyloidogenic and increased the value of amyloid are two additional ways that resveratrol can reduce -amyloid levels. AChE activity in neuronal cells was also decreased by resveratrol (15, 45, and 135 mg/kg). Resveratrol was found to be safe, well-tolerated, and capable of reducing, CSF and serum levels of Aβ40 in a randomized clinical trial AD drug trial utilizing a dual, placebo-controlled design. Resveratrol has been shown to keep the cell from being too phosphorylate to d facilitate, the inactivation of tau protein according to recent research. To make matters worse, researchers found that resveratrol relieved cholinergic channels in a rat model of AD and lowered cell damage, both of which boosted memory function. The activation of SIRT1 by resveratrol has also been shown to influence neuroinflammation and generate adaptive immunity [33]. The three hydroxyl groups in the structure of resveratrol may be responsible for its great effectiveness. As a result, the usage of resveratrol as a dietary supplement is on the rise in the existing economy [245].

In both Vivo and in vitro studies, several flavonoids were revealed to exhibit neuroprotective characteristics. Due to their neuroprotective characteristics, resveratrol and its derivatives have taken precedence over all other polyphenols in this group.

Resveratrol monohydroxylated compound piceatannol, which has an additional hydroxyl group at the 3rd benzene position, is called piceatannol. It has been found to have antidepressant properties against β-amyloid-induced neuronal cell damage via preventing Aβ-driven ROS buildup in neurons. There is evidence that Pterostilbene can improve cognition and cellular oxidative stress, which are hallmarks of AD. Monomers aren't the only ones that have been developed. Scirpus A and the glucose of ε-vinifera, stilbene dimers besides a

portion of glucose and extra hydroxyl group, both showed a strong reduction of the aggregation of fibrils and utilized in this way as effective Prevention of AD with fibril blockers [246].

6.4. Berberine

In traditional Chinese medicine, Plants' roots, rhizomes, and branch barks all contain the yellow plant isoquinoline alkaloid berberine (BBR), which glows yellow when exposed to UV light, including Berberis, *Hydrastis canadensis*, and *Coptidis rhizome*. Some of the bioactivities associated with BBR include anti-inflammatory properties as well as cardiovascular protection as well as anticancer, antimalarial, and antioxidative properties [247]. This plant metabolite, which belongs to the isoquinoline alkaloids, has significant biological and pharmacological effects [248]. In the therapy of neurodegenerative disease, it is utilized Many neurological diseases, including AD, may benefit from its use as a phytoconstituent. Neurofibrillary tangles and extracellular amyloid plaques are reduced. As a result, it can be utilized as a preventative agent for atherosclerosis and AD [249]. Oxidative stress is the primary mechanism by which Berberine is beneficial in the treatment of different neurologic and other inflammatory conditions. Different inflammatory factors are controlled by it, including the up-and down-regulation of GPx and CuZn-superoxide dismutase, the elevation of potential, and inhibition of RhoA/ROCK signaling activation [249]. Statements of neuroprotection or neurotrophic ensure that the cells remain healthy even under disease-specific pathological conditions. This category can include interventions aimed at reducing inflammation or other AD pathobiology-related indicators. The mechanisms of decrease of AD progression are not yet apparent, although the cholesterol-lowering and anti-inflammatory qualities have been demonstrated to be useful in treating AD. The decrease of Aβ by these drugs has been reported earlier. Non-steroidal anti-inflammatory drugs (NSAID) research with randomization and placebo control, on the other hand, has come up empty. There have been mixed results with statins as well. AD patients should not use statins, according to the research on religious orders and cardiovascular health. On the other side, the lower burden of NFT in individuals utilizing statin has been documented. A prospective clinical trial of donepezil with atorvastatin was completed but no significant drug-placebo variation could be demonstrated [249]. Berberine treatment of BV2 microglial cells prevented the -amyloid-induced expressions of IL-6, COX-2, and iNOS from occurring. The PI3K/PKB and MAPK pathways were likewise severely inhibited by Berberine, which lowered the expression of NF-kB. Furthermore, BBR dramatically improved spatial memory deficits in an AD rat model, even though it elevated the production of 2 provocative things markers, inflammatory cytokine-1b (IL-1b) and I NOS. BBR has been found to lower Aβ levels to protect neurons, according to recent research. Extracellular Aβ production is inhibited until a concentration of around 5 mM at which it is 50% inhibited. Considering BBR's impact on manufacturing of the amyloid precursor is neurological toxic, it appears to get the potential to succeed therapy option for AD. NGF-potentiating effect of there was even a BBR (10 mg/ml) observed towards promoting NGF-induced neuronal outgrowth in rat phaeochromocytoma cell culture, absent cytotoxicity (PC12 cells). Inhibition of acetylcholinesterase (AChE) or acetylcholine accumulation was not linked to BBR's NGF potentiating effect [249].

6.5. Huperzine A

Huperzine-A was first derived from the *Huperzia serrata* (Thunb. ex Murray) Trev. herb, a traditional Chinese medicine known as Qiang Ceng Ta., has drawn great because it comes the public's remarkable anticholinesterase Mechanisms detected by Chinese researchers. A range of illnesses was managed using Huperzia and Phlegmariurus species in Chinese medicine, including concussions, pathogens, inflammations, dementia, muscular dystrophy, and pesticide poisoning are all symptoms of organophosphate toxicity. As an anti-disease Alzheimer's pharmaceutical, Hup-A was already introduced in China and its derivative ZT-1 has been explored in both China and Europe [250]. Researchers in China found Huperzine-A, an ingredient isolated from *Huperzia serrata*, a Chinese botanical, as a strong, reversible, and specific inhibitor of the enzyme acetylcholinesterase (AChE) in the 1980s [251].

Huperzine-A, like donepezil, serves as protection from glutamate poisoning. Glutamate-encouraged calcium mobilization and cytotoxicity in rat primary neuron cells were decreased by pretreatment with huperzine- A. N-methyl-D-aspartate (NMDA) receptor antagonism appear to be the mechanism behind this action. Central cholinergic neurons benefit from NGF's ability to support their survival and proliferation. Nerve growth Factor (NGF) expression and secretion were found to be boosted by Huperzine -A. Huperzine-A may increase, Neuronal longevity, and performance is boosted by NGF. which may aid in the recovery of damaged neurons in neurodegenerative illness. This outcome suggests. Oxidative stress in the form of hydrogen peroxide can also be prevented by Huperzine-A. Antioxidants, as evidenced by studies that show a decline in the progression of AD neurodegeneration, may help treat this disease by reducing oxidative stress. Huperzine- A has been shown to reduce oxidative stress markers in the blood, including plasma and erythrocyte lipoperoxides, in a clinical trial in China. Huperzine- A was reported to have a neuroprotective effect in C6 rat glioma cells after oxygen-glucose deprivation caused damage. Huperzine-A prevents the long-term potentiation of rat hippocampus slices from being suppressed by β -amyloid peptides. Huperzine- A restored the cholinergic and monoaminergic dysfunction in rats caused by β -amyloid peptide injection into the

nucleus basalis [252]. Distinctive chemical composition, AChEI activity, recollection properties proved in animal and clinical testing, and low toxicity of Hup-A have all attracted considerable interest from all around the world Hup-A [253]. Amyloid precursor protein processing is regulated by Huperzine-A via the PKC and mitogen-activated protein kinase (MAPK) activation, respectively, according to research.

Together, these findings indicate that huperzine-A may have favorable disease-modifying activity in AD, in addition to the symptomatic, cognitive-enhancing benefit of cholinesterase inhibition. Apoptosis and oxidative stress caused by beta-amyloid are protected, as is the metabolism of beta-amyloid precursor proteins, which are regulated by these non-cholinergic actions [252].

6.6. Luteolin

As a flavonoid, luteolin occurs naturally across a wide range of plants, including vegetables, herbs, and fruits [254]. Constituent of the amyloid plaques expression with the development of beta-amyloids could be decreased by luteolin. Apoptosis can also be prevented by reducing ROS generation, enhancing the brown natural defense systems, for instance increasing Involving SOD, CAT, and GPx; as well as getting NRF2 into action. Chronic hypoperfusion-induced cognitive dysfunction has been relieved by the ability of Luteolin, mini to mize lipid peroxidation by strengthening the antioxidant enzyme activities a controlling role inflammatory reactions in brain cells of rats. A rat model of AD produced by streptozotocin showed enhanced cognition and memory after treatment with the antioxidant luteolin. Despite these findings, more clinical trials are required to verify that luteolin protects against AD [33]. Luteolin does its job via using many paths Another treatment that has been demonstrated to be neuroprotective for stroke patients in neurorehabilitation is the administration of an ultrafine-ground mixture of luteolin and palmitoylethanolamide (140 mg/day for 60 days). As an added benefit, luteolin can pass the blood-brain barrier. These studies indicate that luteolin may be useful in the treatment of neurodegenerative illnesses, such as AD [255].

Mast cell suppression is one of the luteolin's known actions, and it's thought to be the basis for its ability to prevent the activation of other glial cells. There is evidence that Coronavirus-induced inflammatory response can be prevented by mast cells, It suggests a function against which luteolin acts the neurological diseases covariant with the current coronavirus pandemic of 2019. There are around 10% to 15% that is only found in the brain. Microglial cells are substantially more prevalent in areas of the brain affected by brain cells made up of cells of the immune system, which are affected by AD Aβ plaques than in healthy brains. As an alternative, binding of A to The NOD and the CD36-TLR4-TLR6 sensor combination, LRR and an inflammasome complex including pyrin domain protein-3 (NRLP3) can activate microglial cells. Aβ. Microglial cells release inflammatory cytokines, viz TNF-a, IL-1a, and IL-12 within the response to the stimuli provided by Aβ. In the brain, astrocytes fulfill a variety of activities, including water and ion balance, blood-brain barrier maintenance, and synaptogenesis regulation. They are not specifically immune cells. According to the sort of stimuli that led to their activation, activated astrocytes can have distinct characteristics. A1 phenotype, which is associated with neurodegenerative disorders, can be induced by immune signals, such as TNF α -1, IL- α1, and C1q from microglia cells. In experimental animals, luteolin has been shown to reduce insulin resistance in the brain and hence protect against the onset of Alzheimer's-like illness. BBB-crossing luteolin serves as an inhibitor of A-secretase and β-secretase to reduce the amount of Aβ that accumulates in the brain and becomes neurotoxic [255].

6.7. Rosmarinic Acid

Rosmarinic acid is a caffeic acid ester derived from 3,4-dihydroxy phenyl lactic acid. In species of Boraginaceae and the Lamiaceae family, the Nepetoideae, it is prevalent. Some kinds of fern and hornwort, as well as those from other higher plant families, have been shown to contain it. For example, rosmarinic acid is an antiviral and antibacterial agent as well as an antioxidant. In herbal ingredients, spices, and traditional medicinal, the presence of rosmarinic acid is useful and healthy [256]. It has also been shown that rosmarinic acid can reduce the activity of the nervous system, as well as cognitive recollection and short-term visual recall changes in AD-related brain tissue in the rat mode [33]. PC12 Cells Protected an antidote to the neurotoxic effects of amyloid β-peptides by rosmarinic Acid, an Active Ingredient [257]. Rosmarinic acid has been shown to greatly reduce the effects of amyloid on memory, which may be due to its ability to decrease NF-B and TNF- expressions. It has also been found that rosmarinic acid protects neuronal PC12 cells from β -amyloid-induced cell damage, as well. In addition, it may reduce the protein's hyperphosphorylation. Rosmarinic acid's ability to prevent ROS production and caspase-3 activation may explain why it inhibits apoptosis [33]. Neuritic plaques with amyloid-peptide (A β) cores, tau protein NFTs, and neurotransmitter deficits are all hallmarks of AD. Presenilin mutations have been linked to familial AD, which is amyloid-bearing tissue deposits and knots of neurofibrillary even though amyloid plaques are the key clinical markers of Alzheimer's. Neuronal death and hyperphosphorylation of tau protein are the primary events caused by RA when it is applied to cultured neurons [257]. In vitro animal research has been conducted. indicated the potential of AD medication with RA. sing docking simulations with direct binding investigations, Taguchi *et al.*, studied the structural characteristics of RA that allowed it to directly engage with A β1–42. This study demonstrates the significance of the functional group of catechol on the

side of caffeic acid for binding. On the other hand, favorable chain-length substituents might be used to replace the on the danshensu side, an ester thatch could break down in vivo. As a result, they've discovered two chemicals that are both adequately antioxidant (as measured by DPPH radical scavenging and xanthine oxidase) and prevent Aβ1–42 aggregations **(Figure 6)** [258].

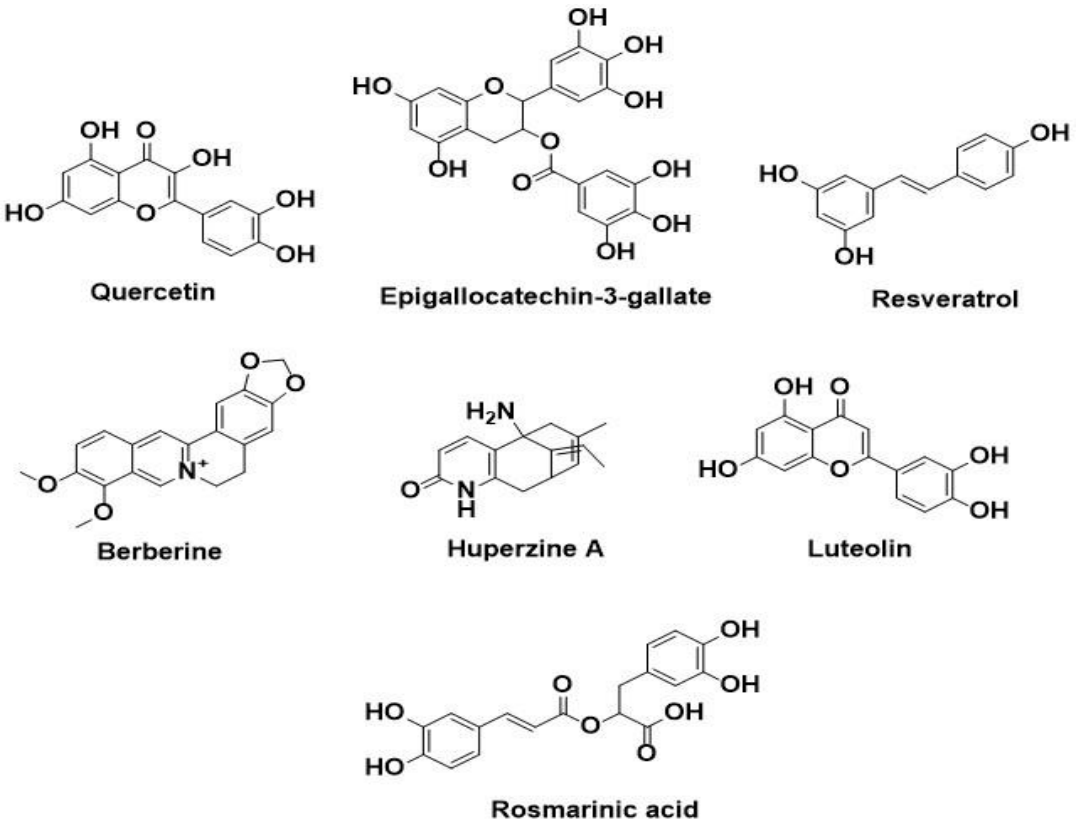

Figure 6: Chemical structure of the compounds containing activity of Alzheimer's disease

7. CONCLUSION AND FUTURE DIRECTION

AD is a progressive neurological illness that currently lacks effective treatment. Currently approved pharmacological treatments are exclusively focused on reducing symptoms and slowing the progression of the disease. Potential therapeutic interventions for AD can be provided by natural bioactive components having pharmacological properties. These organic compounds could lower ROS or stop the development of the harmful Aβ-42 plaque. Alternately, these substances may function after the development of Aβ42 plaques and regulate the altered signaling events brought on by Aβ42 aggregates in AD. Animal model studies clearly show that several of these natural remedies can reduce the risk of developing and try and stop AD (figure 5 and table 1). Targeting numerous disease-causing factors is important for managing or curing AD. Potential treatment targets could be found by performing in vivo trials on animal model systems to understand the disease's molecular process. Numerous animal models are being employed to investigate the molecular basis of these compounds' actions. The natural compounds appear to be intriguing and possible therapeutic targets for neurodegenerative illnesses like AD. Though having the strength of the usage of natural compound liese in their bioavailability. In contrast, it has been observed that changes in lifestyle, altered eating patterns, excessive stress brought on by the workplace, and environmental factors have contributed to the rise in the prevalence of neurodegenerative diseases like AD. Thus, there is a good chance of discovering treatments for AD if one adheres to a strict diet plan and places a focus on natural goods with potential medicinal capabilities. Due to their effectiveness and lack of adverse effects, natural products have recently become highly popular as supplements or alternative medicines. Therefore, additional study is required to discover the natural bioactive compounds of medicinal plants and understand the effects or mechanism that may potentially treat Alzheimer's.

Abbreviations

Alzheimer's disease (AD), natural products (NP), Central Nervous System (CNS), neurofibrillary tangles (NFT), Food and Drug Administration (FDA), N-methyl-D-aspartate (NMDA), Choline acetyltransferase (ChAT), Acetyl choline (Ach), excitatory amino acid (EAA), nucleus basalis of Meynert (NBM), amyloid plaques (AP), non-inherited AD (NIAID), cerebrospinal fluid (CSF), amyloid- β peptide (Aβ), amyloid precursor protein (APP), Gas chromatography–mass spectrometry (GC-MS), Fourier-transform infrared spectroscopy

(FTIR), blood-brain Barriers (BBBs), protein tyrosine kinase receptor B (TrkB), streptozotocin (STZ), lipopolysaccharide (LPS), secoisolariciresinol diglucoside (SDG), malondialdehyde (MDA), Jun-N terminal kinase (JNK), Anthocyanins (ANTs), Parkinson's disease (PD), Huntington's disease(HD), multiple sclerosis (MS), reactive oxygen species (ROS), epigallocatechin-3-gallate (EGCG), berberine (BBR), Non-steroidal anti-inflammatory drugs (NSAID), N-methyl-D-aspartate (NMDA), Nerve growth Factor (NGF), mitogen-activated protein kinase (MAPK), pyrin domain protein-3 (NRLP3).

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