Phytochemicals in Alzheimer's Prevention: Causes and Potentials

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Abstract: Alzheimer's disease is a prevalent neurodegenerative disorder around the world, characterized by amyloid-beta (Aβ) aggregation and tau hyperphosphorylation, affecting more than 55 million of people worldwide. The pathogenesis of Alzheimer's disease is a complex issue, influenced by aging, air pollution, toxic metals, chronic diseases, and diet. While current treatments provide limited symptomatic relief, phytochemicals, including flavonoids, polyphenolic compounds, alkaloids, terpenes, and polysaccharides, particularly traditional Chinese herbs, have demonstrated their unique potential in AD prevention and therapy. These plant-based substances show potentials in mitigating oxidative stress, reducing neuroinflammation, and enhancing mitochondrial function. This review offers a detailed analysis of typical medicinal plants, especially rose flavonoids, and provides a comprehensive view of both the role of plant-based bioactive substances as a promising alternative in AD prevention and current challenges, like bioavailability and brain penetration. Despite these obstacles, innovative solutions are being explored to improve their therapeutic efficacy.

1 INTRODUCTION

Alzheimer's disease (AD) is the most common form of dementia, characterized by cognitive deficits, behavioral abnormalities, and impaired social functioning, posing a significant public health concern due to its high mortality rate worldwide (Knopman et al. 2021). As a progressive disorder, the progression of AD can be divided into several stages: the preclinical stage, which lasts several years or more, during which patients exhibit only mild symptoms without functional impairment in daily life or clinical signs; the early stage, marked by the onset of more obvious symptoms, including memory loss, reduced concentration, mood changes, and difficulty distinguishing time and place; the moderate stage, characterized by increased memory loss and difficulties with reading, writing, and speaking; and the severe stage, where symptoms may lead to the patient's death (Wang et al. 2020). At present, AD affects more than 55 million patients globally, a number that likely underestimates the true prevalence due to limitations in medical testing in some regions. Moreover, the number is predicted to double every five years, reaching 115 million by 2050 (Jia et al. 2020). In China, approximately 9.83 million people aged 60 and above are suffering from AD, according to a national cross-sectional study in 2020 (Kumar et al. 2020). China has ranked at the top of the incidence rate of AD around the world since 2024, with up to 17 million AD patients. Amyloid-β (Aβ) plaque deposition and hyperphosphorylated Tau protein are the most prominent pathogenic features of AD. Additionally, studies have demonstrated other consequences of AD, including oxidative stress, neuroinflammation, programmed cell death, and metabolic imbalance, all of which contribute to the progression of the disease (Wang et al. 2020). Currently, there are two main hypotheses related to the pathogenesis of AD: the cholinergic hypothesis, linking cognitive decline to a reduction in acetylcholine (ACh) and the amyloid hypothesis, proposing that the accumulation of Aβ peptides leads to neurotoxicity, tau pathology, and neuronal death. While Aβ deposition occurs with normal aging, in AD, genetic mutations accelerate its buildup, particularly in inherited forms of the disease, making Aβ accumulation a central factor in AD progression (Scheltens et al. 2021, Hou et al. 2019).

Currently, existing drugs and treatments for Alzheimer's disease (AD) can only partially alleviate symptoms and do not provide a complete cure. Thus, further investigation into strategies for

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the prevention and treatment of AD is necessary. As an innovative and potentially effective alternative approach, phytochemicals have gained increasing attention. Phytochemicals, natural compounds found in plants, offer a variety of health benefits. These compounds, including polyphenols, flavonoids, vitamins, and organosulfur compounds, demonstrate antioxidant, anti-inflammatory, and neuroprotective properties. By modulating key biological mechanisms, phytochemicals can help mitigate the pathological processes of AD. In recent years, a growing number of studies have focused on using active ingredients from phytochemicals to treat AD, highlighting the potential efficacy of medicinal plants in reducing AD risk. In addition, medicinal plants have been used for Alzheimer's disease prevention in many countries, including China, India, and Japan. In China, they make up over 40% of the pharmaceutical market (Abate et al. 2017). The promising potential of phytochemicals in managing AD progression has attracted global interest in plant-derived solutions for neurodegenerative diseases. This paper extends an in-depth study on the inhibitory effects of rose flavonoids on Alzheimer's disease, further exploring the role of phytochemicals in AD prevention. The research investigates the impact of plant-based compounds, specifically rose flavonoids, on neurodegenerative diseases. By creating an in vitro AD model with neuronal cells and microglia, sequencing cell samples, and supplementing the model with rose flavonoids, the study evaluates changes in gene expression, protein levels, and signaling pathways. These findings suggest a promising approach for delaying AD progression and highlight the potential of phytochemicals in AD management. The purpose of this review is to provide a concise overview of the pathogenesis of AD, and risk factors, emphasizing how phytochemicals can be utilized in AD prevention. Additionally, it analyzes the current status of phytochemical-based treatments for AD in different regions.

2 THE PATHOGENESIS OF ALZHEIMER'S DISEASE

Alzheimer's disease (AD) is a progressive neurodegenerative disorder driven by Aβ aggregation, tau hyperphosphorylation, metal-dependent toxicity, and oxidative stress.

2.1 Aβ Aggregation

One of the hallmark features of Alzheimer's disease is the accumulation of Aβ aggregates, specifically the buildup of neuritic plaques (Abate et al. 2017). These deposits disrupt synaptic function and induce oxidative stress and inflammation. Aβ peptides are generated when amyloid precursor protein (APP) is cleaved. As these peptides aggregate, they form toxic oligomers that interfere with neuronal communication (Huat et al. 2019). This accumulation, particularly in the hippocampus and cortex, accelerates neurodegeneration and promotes the formation of tau tangles. As Aβ levels rise, it triggers cellular dysfunction, oxidative stress, and inflammation in the brain, all of which disrupt normal neural activity and contribute to the progression of dementia.

2.2 Hyperphosphorylation

In Alzheimer's disease, tau hyperphosphorylation occurs due to an imbalance between kinase and phosphatase activities. Aβ aggregates can accelerate the activity of multiple kinases, such as GSK-3β and MAPKs, and stimulate caspase-3 and calpain-1. These enzymes produce small fragments that lead to neuronal death and neurite degeneration. Tau protein contributes to memory loss by damaging microtubules and disrupting cellular functions. The process of tau hyperphosphorylation transforms the protein from a monomer to an oligomer, which is considered the most toxic form. This form induces cellular impairment and results in the formation of neurofibrillary tangles (NFTs), which are toxic aggregates. Consequently, neurotransmitters and neuronal signals are inhibited by the presence of NFTs (Kabir 2019).

2.3 Metal-Dependent Toxicity

Several studies have shown that metal ions are related to the progression of Alzheimer's disease by accelerating the accumulation of amyloid and tau proteins. The increased levels of metals, including copper, zinc, iron, and aluminum, in the brains of AD patients, caused by impaired metal homeostasis, have a strong affinity for tau protein and Aβ peptides, increasing toxicity. The formation of Aβ-copper complexes in the brain contributes to oxidative stress, leading to the production of reactive oxygen species (ROS) and significant neuronal damage. This oxidative stress is associated with disturbances in

metal ion homeostasis and is commonly observed in Alzheimer's disease. It contributes to harmful processes such as tau hyperphosphorylation, Aβ deposition, cross-linking of nerve fibers, and nerve cell damage, all of which are linked to the progression of AD (Breijyeh & Karaman 2020).

2.4 Oxidative Stress and Mitochondrial Dysfunction

Oxidative stress (OS) and mitochondrial dysfunction are key indicators of Alzheimer's disease. Elevated levels of reactive oxygen species (ROS) and reactive nitrogen species (RNS) induce lipid peroxidation, protein degradation, and DNA damage in neurons, exacerbating cellular injury. ROS, such as hydrogen peroxide and hydroxyl radicals, can lead to brain abnormalities and impair mitochondrial function, contributing to the progression of aging and AD. Moreover, neurons are particularly vulnerable to oxidative stress because of high polyunsaturated fatty acid content and low antioxidant levels (Lee et al. 2018). With advancing age, oxidative damage disrupts synaptic function and neuronal communication, which is associated with the development of AD. ROS can also compromise the blood-brain barrier (BBB), increasing its permeability and allowing harmful substances to enter the brain.

3 FACTORS CONTRIBUTE TO ALZHEIMER'S DISEASE

Alzheimer's disease is influenced by a multitude of risk factors, including age, gender, alcohol consumption, depression, high blood pressure, sleep apnea, diabetes, obesity, smoking, mitochondrial DNA, air pollution, free radicals, exposure to metals, and neuronal damage, among others (Li et al. 2016, Naik 2025). The following paragraphs delve into several of these risk factors.

3.1 Aging

Aging is the primary risk factor for Alzheimer's disease (AD), as many pathological changes in AD resemble those in normal aging. Most AD cases occur after age 60, characterized by brain volume reduction, synapse loss, amyloid-beta (Aβ) deposition, and neurofibrillary tangles (NFTs). Two additional aging processes impact AD: the breakdown of myelin and damage to locus coeruleus (LC) cells. This damage induces microglia to reduce Aβ clearance and transmits noradrenaline through terminal varicosities to the cortex (Nogales 2000). Vascular factors also contribute to Alzheimer's disease, and the blood-brain barrier (BBB) may deteriorate with aging due to cell death in the LC. Furthermore, decreased glucose metabolism, mitochondrial dysfunction, psychological abnormalities, and memory loss all develop during the normal aging process, making it difficult to distinguish early cases of Alzheimer's disease from normal aging (Grudzien et al.2007, Hou et al.2019).

3.2 Environment

Environmental factors, including air pollution, diet, and mineral imbalances, contribute to Alzheimer's disease (AD) by triggering oxidative stress and neuroinflammation.

3.2.1 Air Pollution

Air pollution, which results from the introduction of physical, chemical, or biological contaminants into the atmosphere increases the risk of asthma, cardiovascular disease, and Alzheimer's disease. In the United States, pollutants such as ozone, carbon monoxide, nitrogen oxides, particulate matter, sulfate, and lead are known to pose significant health risks. Prolonged exposure to high levels of air pollution not only affects the frontal brain region but also damages the mucosal lining of the olfactory tract and bulb. In individuals exposed to air pollutants, a correlation exists between chronic oxidative stress, neuroinflammation, and neurotoxicity. This link is characterized by increased levels of phosphorylated tau and amyloid-beta (Aβ) plaques in the cortex of the frontal lobe (Nogales 2000).

3.2.2 Diet

The role of diet in Alzheimer's disease (AD) has recently attracted significant attention. While a high intake of saturated fats and excess calories is associated with an increased risk of AD, some research suggests that certain dietary components—such as antioxidants, vitamins, polyphenols, and fish—may help reduce this risk. Food processing can lead to the breakdown of heat-sensitive micronutrients, significant water loss, and the formation of harmful compounds (AGEs). Aging-related enzymes are hazardous as they disrupt the structure and function of cell receptors and amino

acids, hence intensifying oxidative damage and neuroinflammation. Elevated blood levels of AGEs have been linked to cognitive decline and the development of Alzheimer's disease (Abate et al. 2017). Dietary deficiencies are also a significant factor in Alzheimer's disease. Insufficient levels of folic acid, vitamin B12, and vitamin D—which functions as an antioxidant—can contribute to cognitive impairment and dementia. Additionally, individuals with Alzheimer's disease often experience difficulties with swallowing and nutrient absorption, which can further worsen their nutritional status.

3.2.3 Metals

Metals can be classified as bio-metals (e.g., zinc, copper, iron) essential for biological functions, or hazardous metals (e.g., mercury, lead) harmful to health. Aluminum exposure deserves special attention. This metal, widely used in food packaging, cosmetics, and medical devices, can enter the bloodstream and bind to transferrin proteins and nitrate compounds. This binding facilitates aluminum's transport to the brain. Research confirms its accumulation in three critical brain regions: the cortex, hippocampus, and cerebellum. It disrupts normal protein structures, causing them to misfold, and triggers abnormal phosphorylation of tau proteins. Lead poses another threat through competition with essential metals. It mimics calcium and occupies binding sites in biological systems. More alarmingly, lead can easily cross the blood-brain barrier (BBB), the brain's protective shield. Once inside, it impairs two key neural processes: nerve cell differentiation and synaptogenesis. Studies have directly linked lead exposure to the development of AD, showing increased β-secretase production and accelerated amyloid-beta (Aβ) accumulation. These findings establish toxic metals as significant drivers of Alzheimer's disease progression (Huat et al. 2019).

3.2.4 Infections

In the central nervous system (CNS), persistent infections may contribute to the accumulation of Aβ plaques and neurofibrillary tangles (NFTs). Dr. Ruth Itzhaki indicates that individuals carrying the ApoE-ε4 gene often harbor DNA from the herpes simplex virus (HSV-1) in their brains. When HSV-1 proliferates in brain tissue, it triggers two primary issues: First, it induces inflammation. Second, it accelerates the aggregation of Aβ proteins. Both effects damage nerve cells and may precipitate the onset of AD. Other researchers have identified bacterial infections as contributing factors as well. For instance, the syphilis-causing bacterium Treponema pallidum induces brain damage resembling neurofibrillary tangles (NFTs). Another example is Chlamydia pneumoniae which activates two harmful cell types: astrocytes and cytotoxic microglia. This activation disrupts the brain's calcium balance regulation and interferes with normal cell death processes (Breijyeh & Karaman 2020).

3.3 Medical Factors

Medical factors such as cardiovascular diseases (CVDs) and metabolic disorders, particularly obesity and diabetes, are significant contributors to the development and progression of Alzheimer's disease (AD).

3.3.1 Cardiovascular Disease

Cardiovascular diseases (CVDs) significantly elevate the risk of Alzheimer's disease. Strokes directly damage brain tissue, accelerating the accumulation of amyloid plaques and tau tangles. Atrial fibrillation generates blood clots that can obstruct cerebral vessels, impairing memory networks. In heart failure, weakened blood pumping leads to chronic brain hypoperfusion, causing neuronal oxygen deprivation. Hypertension induces arterial thickening, reducing blood flow and potentially causing cerebral edema. Most importantly, these vascular abnormalities also disrupt amyloid clearance mechanisms. Therefore, targeting CVD management could provide protection against both cardiovascular and neurological deterioration (Santos et al. 2017).

3.3.1 Obesity and Diabetes

Obesity, defined as excessive body fat accumulation (BMI $\geqslant$ 30), disrupts brain function through interconnected metabolic processes. Excess fat reduces cerebral blood flow, increasing the risk of stroke-related memory loss and vascular dementia. Recently, it has been shown that obesity often leads to elevated blood sugar levels due to impaired glucose metabolism. Over time, this condition damages blood vessels and promotes amyloid plaque accumulation through three key mechanisms: oxidative stress, mitochondrial dysfunction, and chronic brain inflammation. Adipose tissue releases inflammatory signals that overactive immune cells, triggering systemic inflammation. This inflammation reduces

insulin sensitivity, creating a vicious cycle where elevated blood sugar further exacerbates fat accumulation. Importantly, obesity-related inflammation directly impacts brain cells. Overactive microglia—the brain's immune cells—interfere with insulin signaling by disrupting IRS-1 proteins, which are crucial for neuronal survival (Lee et al. 2018).

4 ROLE OF PHYTOCHEMICALS IN THE PREVENTION OF AD

Currently, available methods for preventing and treating Alzheimer's disease (AD), such as synthetic medications, are only effective for a short period. However, phytochemicals that are safe and reasonably priced have shown encouraging potential for their use in AD. In China, traditional Chinese medicine (TCM) has demonstrated unique therapeutic advantages in AD prevention due to its diverse components, multi-target approach, and holistic nature. Concurrently, patients with AD in China have begun to incorporate medicinal plants and herbal formulations into their preventive and treatment regimens (Li et al. 2016). Phytochemicals protect against both internal stressors (free radicals, ROS) and external challenges (UV radiation, predators, and pathogens) (Gao et al. 2020). Since oxidative stress is a key contributor to AD, plants rich in antioxidants can help mitigate its harmful effects. To name just a few, coffee, blueberries, garlic, apples, green tea, olives, golden root, fennel, sage, coconut, walnuts, figs, pumpkin, spinach, and ginger have shown efficacy in managing AD progression. While the exact mechanisms vary, animal studies have consistently shown three benefits: (1) blocking amyloid clumping through enhanced α-secretase activity, (2) slowing tau protein damage by 40-60% in mouse models, and (3) improving maze navigation speed by 18% in aged rats. However, real-world effectiveness faces two significant obstacles: less than 5% of ingested phytochemical compounds reach the brain, and optimal doses vary widely—from 50 mg/day for curcumin to 500 mg/day for resveratrol. Despite these challenges, this multi-target approach, which simultaneously addresses protein misfolding and inflammation, could reshape preventive strategies for Alzheimer's disease (Gao et al. 2020).

4.1 Polyphenolic Compounds

Polyphenols, which are widely found in grapes, Salvia miltiorrhiza, tea, Gastrodia elata, and other medicinal plants, have antitumor, antioxidant, anti-inflammatory, and anti-oxidative stress properties, all of which demonstrate the potential of these compounds to combat Alzheimer's disease (AD). For example, proanthocyanidins—compounds found in red wine and cocoa—exhibit three biological actions: counteracting inflammatory pathways, enhancing cellular insulin responsiveness, and scavenging harmful free radicals. These effects have been shown to decelerate pathological markers in transgenic AD mice (Naik 2025). Resveratrol's therapeutic profile stands out due to its ability to cross the blood-brain barrier and directly inhibit the formation of amyloid precursor protein. Additionally, its impact on gut microbial populations provides another layer of protection (Xu 2023). Similarly, gastrodin regulates the gut-brain axis by preserving intestinal epithelial tight junctions, reducing systemic endotoxin leakage, and lowering neuroinflammation. Pterostilbene highlights its mitochondrial stabilizing properties, which inhibit the pathways of programmed cell death typical of AD development. Meanwhile, ferulic acid simultaneously promotes amyloid-beta clearance and inhibits tau phosphorylation, though its precise mechanism remains unclear (Sun et al. 2021). The spectrum of polyphenolic compounds continues to expand. While curcumin's efficacy depends on its formulation due to absorption issues, salidroside's cognitive improvement is associated with amyloid-beta phagocytosis. This mechanistic diversity helps scientists develop specific combinatorial treatments targeting different AD subtypes.

4.2 Flavonoids

Flavonoids, plant-based compounds, show promise for treating Alzheimer's disease (AD) by targeting key processes like oxidative stress, neuroinflammation, and protein aggregation. Rose flavonoids, in particular, have shown potential in combating AD, especially when circadian rhythms are disrupted. Studies indicate they reduce inflammation and support neuroprotective proteins like GRIN2B.

4.2.1 Flavonoid Compounds

Flavonoids are natural molecules present in plants that show potential for treating Alzheimer's disease

(AD). For instance, Nobiletin and Luteolin can slow down AD-induced damage by decreasing oxidative stress and enhancing mitochondrial function. They also reduce neuroinflammation, a major determinant of the disease's progression. Rutin stands out for its ability to inhibit tau protein aggregation and protect against its detrimental effects (Sun 2021). Recent studies have also shown that flavonoids can alleviate endoplasmic reticulum stress, a condition linked to memory loss in AD. These compounds appear to rejuvenate neurons, thereby improving memory and cognitive function (Gao 2022). Additionally, the gut-brain axis is emerging as an important therapeutic target. Quercetin-3-O-Glucuronide, for example, helps modulate gut microbiota and reduce brain inflammation by regulating short-chain fatty acids. This effect has been confirmed in both gut studies and cerebrospinal fluid analyses. Another flavonoid, like Amentoflavone, exerts its effects by activating the AMPK/GSK-3β pathway, which reduces inflammation and prevents amyloid-beta accumulation, thereby improving memory (Minocha 2022). Trilobatin reduces cognitive deficits, clears amyloid plaques, and inhibits tau protein accumulation by regulating the TLR4-MYD88-NF-κB pathway. In conclusion, flavonoids target several key processes in AD, including amyloid accumulation, tau protein changes, and inflammation, offering broader benefits than traditional treatments that focus on a single aspect of the condition.

4.2.2 Rose Flavonoids

Rose flavonoids show potential in preventing neurodegenerative diseases, particularly Alzheimer's disease (AD) linked to circadian rhythm disruption. In recent years, increasing work and study pressures have led to late-night activities and sleeplessness across various age groups, from teenagers to middle-aged individuals. Chronic disruption of circadian rhythms may accelerate AD development. Previous research using an AD mouse model demonstrated that rose flavonoids have a significant inhibitory effect on AD. By targeting neuronal cells and microglia, researchers replicate an in vitro AD model, identify specific genes and metabolites, and analyze protein expression levels and signaling pathways. This suggests that rose flavonoids could serve as a dietary intervention to slow AD progression in individuals with circadian rhythm disturbances (Li 2023). The study focused on extracting rose flavonoids from fresh roses. Researchers processed rose petals by washing, dehydrating, and crushing them, followed by extraction in a water bath with distilled water. After centrifugation, the supernatant's flavonoid concentration was measured to determine the total flavonoid content. Researchers constructed an AD cellular model by exposing PC12 and N2a cells to Aβ42 for 24 hours to induce damage, simulating Alzheimer's disease. Elevated levels of inflammatory markers, including NF-κB, TNF-α, and IL-1β, confirmed the successful establishment of the AD model. However, rose flavonoids significantly diminished these inflammatory components, suggesting their potential to reduce brain inflammation associated with AD. Transcriptomic analysis of Aβ42-exposed PC12 cells further revealed that rose flavonoids enhanced grin2b activity, a key gene in reducing inflammation and oxidative damage, suggesting their role in AD prevention.

The next phase analyzed protein expression in Aβ42-exposed cells treated with rose flavonoids using Western blot technique. Researchers measured GRIN2B and inflammatory markers (NF-κB, TNF-α, and IL-1β), relative to the control protein β-actin. The cells from the damage model were collected, lysed, and analyzed for the expression of key proteins. The results show that the Aβ42-treated group expressed these inflammatory markers far higher than the control group, whereas rose flavonoids markedly reduced them, reinforcing their anti-inflammatory potential in AD pathology. An overexpression study was conducted, to explore the neuroprotective role of GRIN2B. Considering that GRIN2B is a membrane protein, expression strategies for both mammalian and insect cells were evaluated. Functional proteins are generated and transformed into DH5α-competent cells by vector cloning. Plasmids from positive clones were extracted, sequenced, and purified before removing the protein for further analysis. Finally, they docked all molecules using 7KL0 as a template, established the molecular binding pockets, and identified the most plausible ones. Molecular dynamics studies showed that six main rose flavonoids interacted significantly with the GRIN2B protein, exhibiting varying affinities and stabilizing each other, further supporting their potential role in neuroprotection.

4.3 Alkaloids

Alkaloids, nitrogen-containing compounds from medicinal plants, protect against Alzheimer's disease (AD) by reducing inflammation, oxidative damage, and neuronal death. Matrine, from Sophora flavescens plant, can help address memory loss by

decreasing proteins that trigger brain inflammation and inhibiting the formation of amyloid-beta plaques. This occurs through interference with the RAGE pathway. Oxymatrine regulates the NF-κB pathway, which is responsible for inflammatory responses, and the MAPK pathway, which is involved in cellular stress reactions. This suggests their potential for AD treatment. Isorhynchophylline reduces amyloid-beta deposition, excessive tau phosphorylation, and neuroinflammation. Berberine, from Rhizoma coptidis, can diminish the accumulation of amyloid-beta deposits, excessive tau protein phosphorylation, and neuronal loss. Palmatine enhances cognitive performance and restores mitochondrial health, suggesting its potential to prevent Alzheimer's disease (Li 2023).

4.4 Terpenes

Terpenoids, found in medicinal plants, possess unique biological properties, including anti-inflammatory, anti-oxidant, and anti-apoptotic characteristics. These properties endow terpenoids with both preventive and therapeutic effects on Alzheimer's disease. For example, Huperzine-A, derived from the plant Huperzia serrata, protects brain cells by reducing the accumulation of Aβ proteins, supporting proper mitochondrial function, and maintaining balanced cellular iron levels (Friedli & Inestrosa 2021). Additionally, Paeoniflorin, prevents neuronal death via ferroptosis, mediated by the P53 pathway. Geniposidic acid improves cognitive performance, reduces Aβ accumulation, and decreases neuronal death and neuroinflammation. Ginkgolide B, from ginkgo biloba leaves, reduces the expression of the inflammasome NLRP3 and improves memory and cognitive functions. Patchouli oil suppresses Aβ plaque accumulation, excessive tau protein phosphorylation, neuroinflammation, and intestinal dysbiosis. By facilitating Aβ transport and reducing oxidative damage, neuroinflammation, and tau protein phosphorylation, these compounds provide defense against Alzheimer's disease.

4.5 Polysaccharides

Plant-based polysaccharides have gained global attention for their antioxidant, anti-inflammatory, and oxidative stress-resistant properties, which are closely linked to Alzheimer's disease (AD). These polysaccharides mitigate AD risk factors by enhancing neuroplasticity, stimulating neuronal growth, restoring neurotransmission, and reducing neuroinflammation. For example, angelica polysaccharides can improve memory impairment by reducing oxidative damage, inflammation, and apoptotic cell death. Polysaccharides derived from Chinese Coptis species protect against Aβ-induced neurodegeneration, reduce phosphorylated tau accumulation, and alleviate oxidative stress. Polysaccharides from Lycium barbarum reduce Aβ plaque accumulation and improve cognitive function. In animal models induced with D-galactose, polysaccharides from Polygonatum sibiricum exhibit potent anti-inflammatory and antioxidant properties (Bian et al. 2022). Additionally, polysaccharides from Cistanche deserticola can enhance cognitive abilities by restoring equilibrium in the gut microbiota-brain axis.

5 RECENT STATUS OF PHYTOCHEMICALS IN AD PREVENTION ACROSS DIFFERENT REGIONS

Plant-derived bioactive compounds have been used for millennia, especially in China and other Asian countries like Korea, Japan, and Taiwan. The Chinese have accumulated extensive clinical experience in using phytochemicals to prevent neurodegenerative diseases, with herbal products accounting for approximately 40% of the pharmaceutical market (Naik 2025). Globally, the WHO (World Health Organization) reports that roughly 85% of the population relies on medicinal plants for healthcare.

5.1 Global Examples

Traditional medicine worldwide utilizes various plants to combat Alzheimer's disease (AD) in India, plants like Evalvulus alsinoides and Myristica fragrans inhibit acetylcholinesterase, enhancing cognitive function. In Europe, ethanolic extracts from medicinal herbs block acetylcholinesterase and amyloidogenic processes. Medicinal plants from the Australian rainforest reduce neuroinflammation. In West Africa, approximately 10,000 medicinal plants are used to treat neurological disorders, including Phyllanthus amarus, Rauwolfia vomitoria, and Abrus precatorius. In Japan, a traditional Kampo formula known as ninjin'yoeito (NYT) has been shown to benefit Alzheimer's disease (AD) patients experiencing symptoms of depression and cognitive impairment. Similarly, Ginkgo biloba extract, widely

recognized as a treatment for AD, is extensively used in Western countries. Additionally, galantamine, a selective reversible acetylcholinesterase inhibitor, has been approved for use in several countries, including the United States and Germany. Moreover, the U.S. Food and Drug Administration (FDA) has approved drugs such as donepezil, memantine, and rivastigmine for AD treatment (Varadharajan 2023). Plant-based medicinal compounds have shown significant potential in slowing the progression of Alzheimer's disease and alleviating symptoms.

5.2 Traditional Chinese Medicine Development in AD

Driven by government policies and collaborative research, Traditional Chinese Medicine (TCM) has emerged as a promising approach to Alzheimer's disease (AD) therapy in China. AD is a priority in China's 14th Five-Year Plan for TCM development, with studies funded by the National Natural Science Foundation of China (NSFC). Recent advancements highlight the potential of classic TCM formulas and single herbal ingredients. Key advancements include Huperzine A, a cholinesterase inhibitor that reduces AB plaques and enhances cognitive function, now in Phase III trials, and ginsenoside Rg1, which promotes autophagy to clear AB accumulation (Ma 2023). Traditional TCM formulas such as Huanglian Jiedu Decoction and Liuwei Dihuang Pill have been re-engineered using artificial intelligence and network pharmacology to elucidate their multi-target mechanisms, including NLRP3 inflammasome inhibition and regulation of the "kidney essence-brain axis." The Compound Sea Snake Capsule, the first TCM-approved medicine for AD, has demonstrated effective collaboration between policy and industry, showing a reduction in Aβ and Tau pathology in multicenter trials. Despite these advancements, challenges remain. Quality control of complex TCM formulas is inconsistent, and there is a lack of high-level evidence, such as long-term randomized controlled trials (RCTs). To address these issues, China is leveraging AI-driven medicine screening and forging international partnerships. For instance, the FDA granted orphan drug designation for Compound Danshen Dripping Pill in 2022, highlighting the growing global impact of TCM in AD therapeutics.

6 POTENTIALS AND CHALLENGES

Alzheimer's disease is a complex neurodegenerative condition influenced by multiple risk factors. With the rising incidence rate, it is highly important to identify the real problems and develop innovative ideas for both therapy and prevention. Recent discoveries highlight the pivotal role of phytochemicals in preventing and treating Alzheimer's disease. The use of plant-based alternatives offers a novel approach to Alzheimer's disease treatment, enabling millions of patients to overcome their unpleasant symptoms. Phytochemicals reduce the synthesis and accumulation of pathogenic proteins, enhance cognitive function, mitigate oxidative and inflammatory stress, and regulate mitochondrial activity. Many studies conducted over the years have shown that phytochemicals are quite effective in lowering the risk of Alzheimer's disease. Additionally, phytochemicals have shown promise in fighting several viral infections, such as Ebola, Hepatitis, and COVID-19 by reducing viral DNA replication and limiting systemic invasion. To explore the potential of phytochemicals in stopping epidemic viruses, researchers need to create a precise understanding of the mechanisms and activities of various components, guiding them to design therapies and treatments for combating diseases.

However, despite their promise in alleviating and mediating AD symptoms, several challenges need to be considered. These include safety issues, extraction methods, dosage, combination, and efficacy. Therefore, rigorous clinical trials are essential to guarantee their safety and efficacy. Questions also persist regarding the integration of phytochemicals and Traditional Chinese Medicine (TCM) in AD treatment. Advanced research techniques—such as network pharmacology, metabolomics, and gut microbiome analysis — are needed to clarify their physiological roles and mechanisms. Medicinal plant-based molecules face several challenges in practical application, including unstable chemical structures, limited bioavailability, and sensitivity to oxidation. Fortunately, techniques such as liposome encapsulation or nanoparticle formulations may help overcome these constraints. Furthermore, many bioactive substances derived from plants struggle to cross the blood-brain barrier (BBB) and reach the brain. Notably, modulating gut microbiota via the "gut-brain axis" presents a promising strategy for AD

prevention (Chen 2025). In conclusion, while challenges exist, medicinal plants offer significant potential in neurodegenerative disease treatment. With large-scale studies and clinical trials, phytochemicals have the potential to offer safe and effective therapeutic options for Alzheimer's disease.

7 CONCLUSION

Alzheimer's disease is the most common and demanding neurological disorder worldwide. While contemporary pharmaceutical treatments have evolved, phytochemicals from medicinal plants have shown promise in targeting key AD mechanisms, including amyloid-beta accumulation, neuroinflammation, and tau hyperphosphorylation. Because of their neuroprotective properties, phytochemicals offer a safe, cost-effective, and promising alternative to modern drugs. Flavonoid compounds, particularly rose flavonoids, stand out among other phytochemicals in their ability to mitigate oxidative stress and inflammation, reducing the risk of AD caused by disturbance of circadian rhythm These compounds increase the action of antioxidant enzymes and reduce the synthesis of harmful pro-inflammatory cytokines, protecting neurons from damage. The diverse mechanisms make them promising candidates for both therapy and prevention of Alzheimer's disease. Various countries use different approaches to phytochemical research. Traditional Chinese medicine (TCM) integrates modern scientific techniques with traditional methods. Traditional medicinal herbs are extensively used for AD treatment in India and Japan, developed in national research projects and clinical trials. Western nations, on the other hand, focused more on particular phytochemicals. Regardless of these differences, there is a worldwide agreement that phytochemicals have great potential for AD treatment, and cooperation between countries is necessary to speed up studies and handle problems. Still, challenges remain, including inadequate brain penetration, variable bioavailability, and insufficient clinical data. Fortunately, emerging solutions, such as liposome encapsulation, nanoparticles, and network pharmacology, are improving efficacy. Additionally, advancements in multi-omics and gut-brain axis research are expanding the role of phytochemicals in AD prevention and therapy. In conclusion, phytochemicals represent a unique frontline in the fight against Alzheimer's disease, supported by evidence of the efficacy of medicinal plants and their long-standing history in traditional medical systems. Unlocking the full potential of these natural compounds will depend on ongoing research, large-scale clinical trials, and the application of modern scientific technologies.

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