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Review Article

Potential Role of Phytochemicals in Attenuating Alzheimer's Disease: A Comprehensive Review

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Abstract

Modern pharmacotherapy encourages the use of phytochemicals to combat Alzheimer's Disease (AD). This review aims to summarize the clinical findings and recent advances in the use of flavonoids, alkaloids, galantamine, and *Ginkgo biloba* against AD. Quercetin contains flavonoids that inhibit BACE-1 enzyme activity, which is responsible for the formation of the amyloid beta (Aβ) peptide. Quercetin also increases AMPK activity. Alkaloids inhibit acetylcholinesterase activity. Moreover, *Ginkgo biloba* produces antioxidant effects by scavenging free peroxyl radicals. Phenylethanoid glycosides exert neuroprotective properties by improving neuronal apoptosis impairment. All these claims have been supported through *in vivo* and *in vitro* studies. Our review of the literature shows that phytochemicals possess enormous potential for the treatment of AD. They possess antioxidant, anti-inflammatory, and specific neuroprotective properties, which make them ideal for the treatment of AD. Furthermore, the delivery of these agents can be achieved through nanocomposites to ensure they cross the blood-brain barrier and produce a therapeutic response.

Keywords: Alzheimer's Disease, Phytochemicals, Flavonoids, Alkaloids, Quercetin, *Ginkgo Biloba*, Naringin, Apigenin, Antioxidants

1. Introduction

Alzheimer's disease (AD) is the most common kind of dementia in the world, affecting a significant number of people, especially those 65 years of age and older. From modest memory lapses to severe cognitive decline, the illness causes memory loss, confusion, language difficulties, behavioral changes, and personality changes. The pathological features of AD include the build-up of tau protein tangles within neurons and amyloid-β (Aβ) plaques around them, which cause neuronal degeneration and brain shrinkage. According to current theories, a complex interplay of genetic, environmental, and lifestyle factors contributes to the onset and progression of the illness, with neuroinflammation being a key component. The inflammatory response that the central nervous system (CNS) has in response to an infection, trauma, or disease is known as neuroinflammation. This process includes the recruitment of immune cells, the release of inflammatory mediators, and the activation of glial cells (microglia and astrocytes). Long-term or severe neuroinflammation, while initially helpful, can worsen neuronal injury, accumulate Aβ plaque and tau pathology, and impair cognitive function. Understanding the function of neuroinflammation in neurodegenerative diseases, such as AD, is of increasing interest (Kim, Lim, and Oh 2024).

2. Epidemiology of AD

In a 2005 study employing the Delphi consensus methodology, projections indicated a global dementia prevalence of approximately 24.3 million individuals. Furthermore, the study

highlighted a significant annual incidence of 4 to 6 million new cases. Notably, the data suggested an exponential growth trajectory, with a projected doubling of affected individuals every two decades, culminating in an estimated 81.1 million cases by 2040. A striking demographic feature revealed that 60% of dementia cases are concentrated within developing nations. Specifically, Asian countries, including China, India, Japan, and Indonesia, were identified as possessing some of the highest dementia prevalence rates globally (Catindig et al. 2012).

According to estimates, the prevalence of dementia in adults 60 years of age and older was 3.9% globally. Regional prevalence rates were 1.6% in Africa, 4.0% in China and the Western Pacific, 4.6% in Latin America, 5.4% in Western Europe, and 6.4% in North America (Qiu, Kivipelto, and Von Strauss 2009).

According to estimates, there were 36.5 million dementia sufferers in 2010; 7.7 million new cases are reported each year, or one every four seconds. Every 20 years, the number of people with dementia will almost double. The majority of these people will reside in low- and middle-income nations (Sosa-Ortiz, Acosta-Castillo, and Prince 2012).

For a variety of reasons, including the significant presymptomatic neuronal damage brought on by the buildup of the Aβ peptide and tau protein abnormalities, deleterious side effects of drug candidates, and inadequate clinical trial design, recent conventional drug development efforts targeting AD have failed to produce effective disease-modifying agents. To identify and address early pathogenic occurrences, there is a critical need for novel molecular targets, biomarkers, and diagnostic methods in addition to nonpharmacological alternatives (Tatulian 2022).

3. Pathophysiology of AD

AD is the most common neurodegenerative disease. It is categorized into various stages according to the degree of cognitive decline and the level of disability that individuals experience. AD is a complex condition linked to a variety of known risk factors, e.g., age, obesity, diabetes, family history of dementia, head injury, and so on (Kumar et al. 2024). It is caused by the accumulation of abnormal neuritic plaque, neurofibrillary tangles, and the degeneration of cortical neurons. Oxidative stress is one of the major contributing factors in AD pathogenesis, which plays a critical role in the initiation and progression of these pathological changes. It leads to an imbalance between antioxidants and oxidants in favor of oxidants, which leads to excessive free radical production. Particularly, free radicals are reactive oxygen species (ROS), which are generated through the reduction of molecular oxygen into superoxide radicals, which further produce hydrogen peroxide. Progressive reduction of hydrogen peroxide produces highly reactive hydroxyl radicals that interact with lipids, proteins, and nucleic acids, causing structural and functional damage. High oxygen consumption and lipid-rich composition increase the brain's vulnerability to oxidative damage (Huang, Zhang, and Chen 2016).

These oxidative stress-induced changes contribute to the abnormal processing of the Amyloid precursor protein (APP), which leads to the formation of an Aβ peptide. Usually, APP is cleaved by enzymes α-, β-, and γ-secretase. In a normal individual, first the amyloid precursor protein is cleaved by α-secretase and then by γ-secretase. Cleavage by α-secretase reduces the formation risk of an Aβ peptide. In patients with AD, the β- secretase enzyme acts and cleaves the APP into $A\beta_{42}$. The increased concentration of $A\beta_{42}$ promotes the formation of oligomers, which have neurotoxic properties. These oligomers form clusters around the meningeal, cerebral clusters, and gray matter. These deposits lead to the formation of miliary structures, which are known as plaques. Concerning neurofibrillary tangles, they are thread-like structures found inside neurons, made up of a protein called Tau. Medically, the primary function of tau is to stabilize the microtubules (Calabrò et al. 2020).

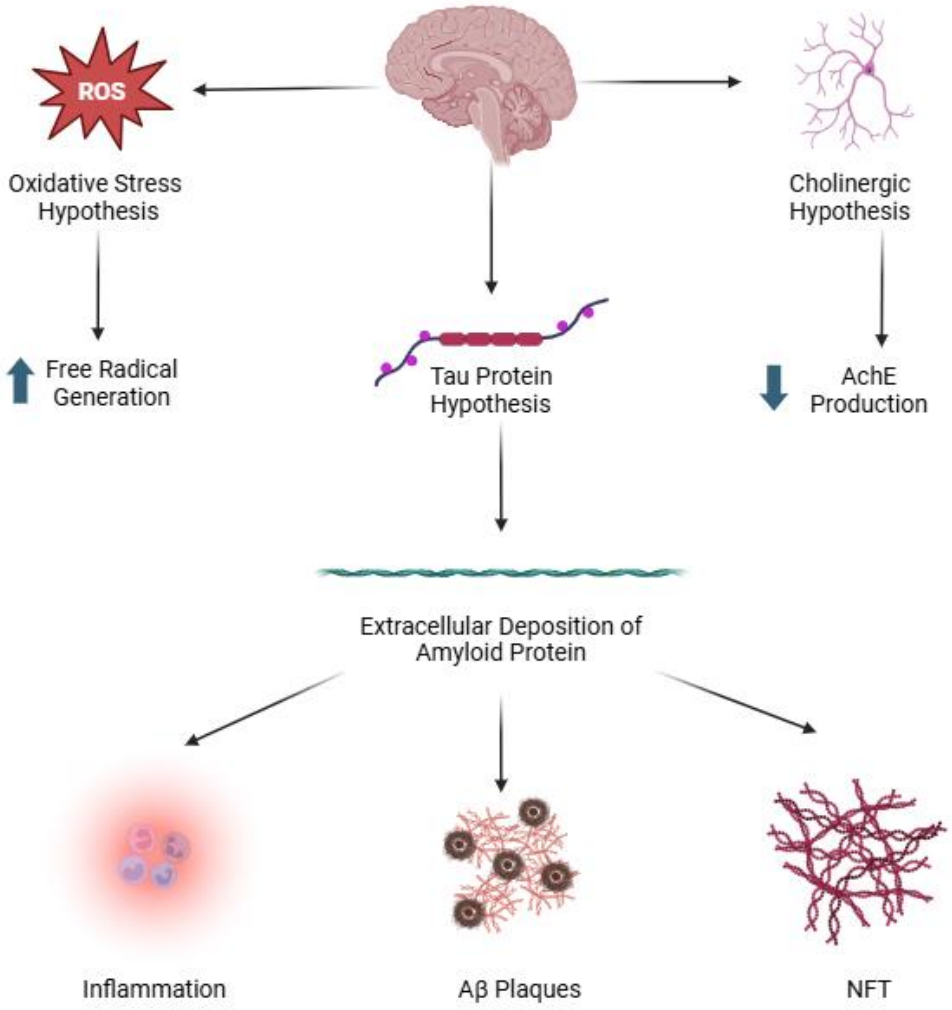

Figure 1. Pathophysiology of Alzheimer's Disease.

Microtubules extend along the axons of neurons and play a crucial role in transporting materials within the cell. Tau protein also helps in maintaining the integrity of microtubules (Kumar et al. 2024).

Physiologically, the tau protein is bound to microtubules and also contains a specific number of phosphate molecules attached to it. The phosphorylation mechanism of tau is abnormal in AD patients, but the exact reason remains unclear. This change results in an excessive increase in phosphorylation, which causes Tau molecules to detach from the microtubules. Hyper-phosphorylated Tau proteins, once detached, tend to assemble into filamentous structures called paired helical filaments. These filaments then cluster together, forming insoluble neurofibrillary tangles (NFT) (Calabrò et al. 2020). They first develop in the transentorhinal cortex, then spread to the hippocampus, and eventually extend to the cerebral cortex in the later stages (Calabrò et al. 2020). These NFTs cause abnormal communication between the neurons and signal processing, and ultimately, this leads to apoptosis in neurons (Tiwari et al. 2019). Figure 1 shows the pathophysiology of AD.

Another characteristic feature in AD is granulovacuolar degeneration observed in the

pyramidal cells of the hippocampus. This degeneration is likely linked to cognitive decline (memory formation, learning ability, spatial navigation). Changes in cognitive processes are related to a reduction in the number of presynaptic terminals from pyramidal neurons in layers III and IV of the cortex. The reduction in synaptic terminals is likely connected to vascular degeneration. In fact, the risk of dementia increased by four times with the presence of subcortical lesions.

Additionally, cerebrovascular disease can aggravate both the severity of dementia and the speed at which it progresses. However, the underlying mechanisms are not completely understood (Calabrò et al. 2020).

4. The Potential Health Benefits of Phytochemicals

The anti-inflammatory, neuroprotective, and antioxidant qualities of phytochemicals are well-recognized. These substances, which include sulfides, terpenoids, flavonoids, and polyphenols, are essential for shielding plants from environmental stressors and pathogens. Phytochemicals have garnered interest in the setting of AD because of their capacity to modulate the activity of different cell types and cytokines implicated in inflammatory responses, hence regulating distinct biological pathways linked to neuroinflammation.

Additionally, they influence signaling pathways that support neuronal survival, which helps them to perform a neuroprotective role. As prebiotics and postbiotics, phytochemicals also modify the community of gut microbiota, improve intestinal barrier integrity, and reduce the synthesis of harmful metabolites and pro-inflammatory factors.

Targeting the gut microbiota may be a therapeutic approach for treating neuroinflammation and slowing the course of AD, given the function that gut–brain axis (GBA) plays in bridging the gut health and neurodegenerative diseases (Tatulian 2022).

5. Effects of Phytochemicals Attenuating AD

5.1. Quercetin

One of the most powerful plant-derived antioxidants, quercetin, is a major flavonoid commonly found in many food plants (Khan et al. 2019). A flavonoid is generally a diphenyl propane, which has 15 carbon atoms in its structure. It has two benzene rings and a nearby heterocyclic pyran ring. Distinct variations exist among individual compounds within certain groups due to substitutions in the benzene rings of flavonoid structures (Khan et al. 2019; de la Rosa, Alvarez-Parrilla, and González-Aguilar 2009; Aherne-Bruce and O'Brien 2002). An OH group may be found in quercetin at positions 3, 5, 7, 3′, and 4′ (Khan et al. 2019). The plant families Compositae, Passiflorae, Rhamnaceae, and Solanaceae are high in quercetin (Khan et al. 2019; Alok et al. 2014). Berries, apples, capers, red leaf lettuce, onions, asparagus, and strawberries all have comparatively high quercetin contents (Costa et al. 2016).

Many *in vitro* studies have proved that quercetin significantly inhibits beta-secretase-1 (BACE-1) enzyme activity through the formation of hydrogen bonds. The OH group at position C-3 has a prominent role in BACE-1 inhibition (Khan et al. 2019). After using standard experimental protocols (Shimmyo et al. 2008), the study demonstrated that a higher quantity of flavonoids resulted in a higher inhibition of BACE-1 activity. These results imply that flavonoids may be useful as powerful BACE-1 inhibitors, which may be important for future studies regarding AD. The calculated 50% inhibitory concentrations (IC50) were as follows: (2.8 μM) < quercetin (5.4 μM) < kaempherol (14.7 μM) < morin (21.7 μM) <apigenin (38.5 μM) (Shimmyo et al. 2008).

Quercetin also protects neuronal cells from oxidative stress (Khan et al. 2019; Costa et al. 2016). Quercetin improves memory, learning, and cognitive functions, and all these effects have been associated with its antioxidant properties (David, Arulmoli, and Parasuraman 2016). Studies using mice as animal models have shown that quercetin

Table 1. Core findings of the study by (Konrath et al. 2013).

Alkaloid	Type	IC50 (μM)	Key Structural Features	Key Findings
Galantamine	Galantamine	9.60	Hydroxyl group	Potent acetylcholinesterase (AChE) inhibitor due to hydrogen bonding capabilities.
11a-Hydroxygalantamine	Galantamine	0.10	Additional hydroxyl group	More potent than galantamine due to stronger binding.
Ungeremine	Lycorine	0.35	Quaternary nitrogen atom, aromatic ring	Very potent inhibitor, similar to other isoquinoline alkaloids.

increases spatial memory by increasing AMP-activated protein kinase (AMPK) activity (Khan et al. 2019; Wang et al. 2014; Sabogal-Guáqueta et al. 2015). In one study, the effect of quercetin consumption on the prevention of memory loss, Ab-induced neurotoxicity, and mitochondrial dysfunction were studied in the APPswe/PS1dE9 transgenic mouse model of AD as previously described (Wang et al. 2014; Zong et al. 2011). Five groups of mice were created: one for low-dose quercetin (20 mg/kg/day), another for high-dose quercetin (40 mg/kg/day), a group treated with Aricept (2 mg/kg/day), a group for transgenic control (no medication), and a group for wild-type (WT) control. Prior to tissue collection and examinations of cognitive function, the therapies were given for 16 weeks (Wang et al. 2014).Their findings suggest that AMPK is a proline-directed ser/thr kinase that is associated with Ab and mitochondrial function in AD. As phosphorylated AMPK Thr172 (pAMPK172) is a marker of AMPK activation, total AMPK and pAMPK172 were measured by Western blot to evaluate the activation of AMPK. Quercetin treatment increased the pAMPK172 level by 53.1 % compared with control APPswe/PS1dE9 mice. In contrast, Aricept treatment did not obviously affect the activity of AMPK (Wang et al. 2014). Quercetin increased the activity of AMPK *in vivo*.

5.2. Galantamine

Alkaloids are widely known because of their therapeutic properties, being anti-inflammatory, antinociceptive, antitumoral, antioxidant, and antimicrobial (Zong et al. 2011). Despite many uses of alkaloids, only a few are marketed as drugs. One of the three anticholinesterase agents approved by the FDA for the treatment of AD, galanthamine is an *Amaryllidaceae* alkaloid (Lima and Hamerski 2019). Galantamine (also called galanthamine) belongs to the isoquinoline alkaloid family (Ng, Or, and Ip 2015). Galantamine is a tetracyclic compound with three asymmetric centers and a quaternary benzylic carbon (Janssen and Schäfer 2017; Scott and Goa 2000). It is isolated from Narcissus spp. (daffodil), Leucojum spp. (snowflake), and Lycoris, including Lycoris radiata (red spider Lily), in industrial production (Ng, Or, and Ip 2015).

In vitro studies have demonstrated that *Amaryllidaceae* alkaloids, particularly those from the galantamine and lycorine groups, exhibit significant acetylcholinesterase (AChE) inhibitory activity. Structural features, such as the presence of hydroxyl groups and quaternary nitrogen atoms, appear to enhance binding affinity and inhibitory potency. For instance, galantamine and its derivatives, including hydroxygalantamine, showed potent AChE inhibition, attributed to additional hydrogen bonding. In contrast, isomers like chlidanthine, with altered stereochemistry, displayed reduced activity. Lycorine-type alkaloids such as assoanine and ungeremine also exhibited strong AChE inhibition due to their aromatic rings and quaternary structures.

Alkaloids with other skeleton types, however, showed much weaker cholinesterase inhibition,

highlighting the critical role of structural characteristics in determining efficacy (Konrath et al. 2013). With IC50 values ranging from 0.10 to 9.60 μM, this study demonstrated that a number of alkaloids, including galantamine, hydroxygalantamine, and ungeremine, efficiently inhibited AChE activity. These results are consistent with the theory that molecular structures, such as the existence of aromatic rings and a quaternary nitrogen atom, significantly increase inhibitory efficacy. Because of stereochemical differences, the galantamine isomer chloridanthine was significantly less powerful, which validated the study's findings. Overall, the study's findings validate the validity of the findings by agreeing with the hypothesised association between structural characteristics and AChE inhibition (Konrath et al. 2013). Table 1 summarizes the core findings of the study.

In a separate study (Saito et al. 2019), a substantial decrease in platform latency and an increase in spatial bias in the probing test showed that galantamine administration enhanced cognitive function in the APPswe/PS1dE9 mice, especially in the Morris water maze test. Mice administered with galantamine had improved identification of unfamiliar items in the NOR test, indicating improved memory retention. Mice treated with galantamine had lower levels of oxidative stress in their brains, especially in the cortex, according to EPR imaging. Galantamine therapy preserved synaptic integrity as seen by synaptophysin staining, but it also decreased Aβ plaque formation and inflammatory markers, including Iba1 (Ionized calcium-binding adaptor molecule 1) and GFAP (Glial fibrillary acidic protein, according to immunohistochemical research. These results imply that in this AD model, galantamine reduces neuroinflammation, oxidative stress, and cognitive deterioration (Saito et al. 2019).

5.3. Naringin

Many citrus fruits, especially grapefruit, contain naringin, which is a flavonoid glycoside having many health advantages. It is made up of the disaccharide neohesperidose and the flavone naringenin and contains many properties like antioxidant, anti-inflammatory, and anti-cancer, which can help reduce the risk of many chronic diseases. The chemical structure of naringin consists of a flavonoid backbone, two phenolic rings, and a heterocyclic pyran ring. Its molecular weight per mole is 580.54 g, and its chemical formula is $C_{27}H_{32}O_{14}$ (Shilpa et al. 2023). This study demonstrates that naringin improves long-term memory in an AD transgenic mouse model. The enhancement of CaMKII activity appears to be a key mechanism underlying its cognitive benefits.

5.4. *Ginkgo Biloba*

Ginkgo biloba leaves extract (EGb761) contain 24% flavonoid glycosides (containing quercetin, kaempferol, isorhamnetin), 6% terpenoids (in which 3.1% are ginkgolides A, B, C, and J and 2.9% is bilobalide), and 5–10% organic acids (Serrano-García et al. 2013). The flavonoids and terpenoids are suggested to be the active constituents. The action of Ginkgo is believed to be produced by its functions as a neuroprotective agent, an antioxidant, a free-radical scavenger, a membrane stabilizer, and an inhibitor of platelet-activating factor via the terpene ginkgolide B. Other pharmacologic effects include endothelium relaxation mediated by inhibition of 3',5'-cyclic GMP (guanosine monophosphate) phosphodiesterase; inhibition of age-related loss of muscarinic cholinoreceptors and α-adrenoceptors; and stimulation of choline uptake in the hippocampus. Ginkgo extract has also been shown to inhibit beta-amyloid deposition.

A study in which primary cultures of hepatocytes from rats were treated with EGb761 (50 mg/kg/day) for 8 days showed reduced cell viability and apoptosis when exposed to 2,2′-azobis (2-aminopropyl) propane (AAPH), a peroxyl radical-generator, compared to hepatocytes from control rats. This suggests that EGb 761 may have induced changes in liver cells, making them more resistant to the damaging effects of oxidants. Based on these findings, the effects of EGb 761 were investigated on the

Table 2. Summary of the findings of the *in vivo* study by (Shi, Xiao, et al. 2010).

Parameter	Effect of Age (SAMP8 Mice)	Effect of 12-Week EGb761 Treatment
COX activity in platelets and hippocampi	Decrease with age	**Young Mice:** Completely prevented decrease. **Old Mice:** Rescued decrease.
Mitochondrial ATP content in platelets and hippocampi	Gradual decrease, significant after 40 weeks	**Young Mice:** No significant effect. **Old Mice:** Protected against decrease.
Mitochondrial GSH content in platelets	Decreased with age	**Young Mice:** Completely prevented decrease. **Old Mice:** Rescued decrease.
Mitochondrial GSH content in hippocampi	Decrease with age	**Young Mice:** Failed to prevent a decrease. **Old Mice:** Rescued decrease.

viability and apoptosis of primary cultures of hippocampal nerve cells from rats treated with a dose of EGb 761 known to protect the hippocampus against ischemia (Rapin, Zaibi, and Drieu 1998). Additionally, they tested ginkgolide B and bilobalide at concentrations or doses relative to their respective percentages in EGb 761 and their bioavailability as pure substances found in rat plasma after oral administration of the total extract (Fourtillan et al. 1995). AAPH reduced cell viability, while EGb 761 improved it at concentrations of 5–20 μg/mL. Ginkgolide B also enhanced cell viability at lower doses and blocked glutamate-induced cell death, supporting neural stem cell growth in rats with cerebral ischemia. Bilobalide did not affect cell viability except at high concentrations.

Both EGb 761 and ginkgolide B protected against AAPH-induced cell death, while bilobalide did not (Pagotto et al. 2024). However, bilobalide promotes neurogenesis in the hippocampus and enhances alpha-secretase processing of amyloid precursor protein, reducing beta-amyloid production. It also improves cognitive function in AD models, making it a potential neuroprotective agent.

Mitochondrial function, assessed through cytochrome c oxidase (COX) activity, mitochondrial ATP levels, and glutathione (GSH) content, is found to decline with age. In SAMP8 (one of the nine substrains of SAMP) mice, a model of accelerated aging, mitochondrial function deteriorates earlier in SAMP8 compared to SAMR1. Additionally, six-month-old SAMP8 mice exhibited relative insensitivity to beta-amyloid protein, the key component of amyloid plaques found in AD brains (Shi, Fang, et al. 2010). EGb761 was administered orally to SAMP8 mice at 3 and 24 weeks of age for 12 weeks to test the preventive and rescue effects of this herb on age-associated mitochondrial dysfunction (Shi, Xiao, et al. 2010). Table 2 summarizes the key findings of the study.

EGb761 demonstrated protective effects against mitochondrial dysfunction in platelets in both young and old mice, suggesting it may have a peripheral role in combating age-related degeneration in AD patients. However, in the hippocampi, these protective effects were only observed in older mice, possibly due to age-related increases in blood-brain barrier (BBB) permeability. BBB permeability rises with age in humans and becomes even more pronounced in neurodegenerative conditions like AD compared to normal aging. As the BBB becomes more permeable with age, EGb761 may have better brain penetration, enhancing its effects on the CNS.

5.5. Phenylethanoid Glycoside

Phenylethanoid glycoside is a constituent of *Herba Cistanche.* It is composed of five major components, among which acteoside and echinacoside have proved to have a neuroprotective role in AD. It improves the impairment of neuronal apoptosis caused by

$A\beta_{25-35}$ (Yang et al. 2017) via its antioxidant effects. Aβ is the major constituent of senile plaques of neuronal cells, which causes intracellular accumulation of ROS, leading to lipid and protein oxidation and DNA damage. Excessive amounts of H_2O_2 may lead to oxidative damage and induce apoptosis of PC12 cells in AD patients. Studies have proved that acteoside and echinacoside improve cognitive dysfunction caused by $A\beta_{1-42}$ (Ji et al. 2019). In a study that successfully developed an *in vitro* AD model using $A\beta_{1-42}$ and H_2O_2 to induce injury in PC12 cells, Phenylethanoid glycosides (PhGs) demonstrated significant neuroprotective effects by increasing the cell viability and reducing the release of lactate dehydrogenase (LDH) and malondialdehyde (MDA), markers of oxidative stress and cell damage. The results showed that PhGs at 75, 100, 125, 150, 175, and 200 μg/mL had a significant inhibitory effect on PC12 cells ($P<0.05$, $P<0.01$), while cell viability remained >80% at concentrations of 5, 25, and 50 μg/mL The safe doses of PhGs identified were 5, 25, and 50 μg/mL. It showed nontoxic and no adverse effects on cell growth. The study concluded that PhGs offer strong protection against $A\beta_{1-42}$ and H_2O_2-induced damage in PC12 cells, highlighting their therapeutic potential for AD (Yang et al. 2017).

5.6. Apigenin

Apigenin is a 4′,5,7-trihydroxyflavone, based on the skeleton of 2-phenylchromen-4-one (2-phenyl-1-benzopyran-4-one). In plants, apigenin is present in the form of aglycone and its C- and O-glycosides (detected as 6-C and 8-C-glucoside, and 7-O-glucoside), and glucuronides. One hypothesis concerning the origin of apigenin is that free apigenin is a product of the post-harvest degradation process. Apigenin belongs to the flavonoid class of polyphenols (Zhao et al. 2013).

In vivo studies of epigenin were performed in APP/PSI double transgenic mice. Apigenin was dissolved in distilled water containing 5% sodium carboxymethyl cellulose (CMC-Na) at a concentration of 10 mg/mL. The results showed that apigenin ameliorates learning and memory. It also restores the ERK/CREB/BDNF pathway of the cerebral cortex in APP/PS1 mice. Therefore, apigenin appears to offer an alternative medication for the prevention of AD. *In vitro* studies in a human induced pluripotent stem cell (iPSC) model of familial and sporadic AD, alongside healthy controls, demonstrated that iPSC-derived AD neurons increased calcium signaling, had higher nitrite levels, increased cell death, reduced neurite length, and greater vulnerability to inflammation from activated murine microglia compared to controls. Apigenin demonstrated significant anti-inflammatory effects, protecting neurites and cell viability by decreasing cytokine and nitric oxide release. Furthermore, apigenin reduced spontaneous calcium signals and significantly decreased caspase-3/7 mediated apoptosis, underscoring its wide-ranging neuroprotective impact against AD pathology in a human model (Balez et al. 2016). Figure 2 illustrates the structures of key neuroprotective phytochemicals, including quercetin, galantamine, naringin, and apigenin.

6. Opportunities and Challenges

The first and foremost challenge in translating phytochemicals into pharmaceuticals is the difficulty in extrapolating the dose required in humans from the dose that provides a therapeutic effect in in *vitro* or *in vivo* studies (Piccialli et al. 2022). Second, phytochemicals face many challenges in being bioavailable due to factors such as metabolism by gut microflora, stability due to gastric and colonic pH, absorption across the intestinal wall, active efflux mechanism, and first-pass metabolism. However, if we introduce the phytochemical as a co-delivery system with an agent that can modulate the glucuronidation activity or inhibit the CYP450-mediated clearance mechanism, we could potentially increase its bioavailability (D'Onofrio et al. 2017).

Nanotherapy could also be employed to deliver these phytochemicals to their targets, but unfortunately, they lack the potential in clinical settings. Due to their oral administration

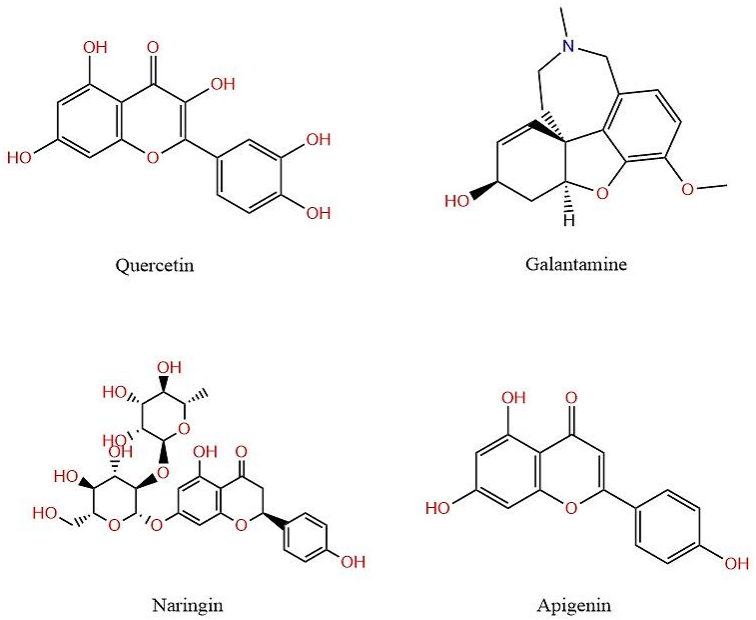

Figure 2. Structures of Phytochemicals known for attenuating Alzheimer's Disease.

route, these face challenges due to physiological barriers such as enzymatic degradation, pH, target specificity, and side effects observed when used at high doses (Vaiserman, Koliada, and Lushchak 2020).

Nevertheless, these challenges can be overcome by employing some modern techniques, such as the development of nanostructured materials at a size range of 1 to 1000 nm, including solid lipid nanoparticles, nanostructured lipid carriers, liposomes, emulsions, micelles, poly (lactic-co-glycolic acid) nanoparticles, etc., to deliver the phytochemicals (Vaiserman, Koliada, and Lushchak 2020). These nanosized particles can be modified as required. In particular, surface properties can be enhanced to determine the hydrophilicity, hydrophobicity, and biological responses induced by nanoparticles, including immune responses, interactions with plasma proteins, cellular uptake, and their removal (Ajdary et al. 2018). Lipid nanoparticles are specifically designed to combat the drawbacks of other nano-delivery systems because they show good release patterns and greater stability (Singh et al. 2021). Other techniques can also be employed, such as loading nano-delivery systems with phyto-bioactive compounds that have been confirmed to have the potential to overcome oxidative stress and inflammation, known to be the main factors in brain-associated pathological conditions (Liu et al. 2022). Since delivering therapeutic drugs to the brain is challenging due to the BBB, using nanocomposites that can penetrate the BBB seems to be the solution for the targeted delivery of CNS therapeutics (Harilal et al. 2019).

7. Conclusions

AD is a complex neurodegenerative condition characterized by abnormal amyloid–beta plaque formation, neurofibrillary tangles from hyperphosphorylated tau proteins, and neuronal loss. These pathological changes impair neuron communication, leading to dementia progression and cognitive impairment. This article covers various *in vivo* and *in vitro* studies that have shown the significant potential of quercetin, a flavonoid, and galantamine, an *Amaryllidaceae* alkaloid, as phytochemicals with therapeutic uses in AD due to their neuroprotective properties. They inhibit BACE-1 enzyme activity, AChE, and increase AMPK activity, which leads to a reduction in oxidative stress and neuroinflammation. Similarly, *Ginkgo biloba*, a free radical scavenger,

exhibits reduced cell viability and apoptosis when exposed to AAPH in hepatocytes from rats and hippocampus in young and old mice. They have a role in combating age-related AD as the BBB becomes more permeable with age. Phenylethanoid glycoside, a constituent of *H. Cistanche*, improves the impairment of neuronal apoptosis caused by $A\beta_{25-35}$ via its antioxidant effects in AD. These therapeutic agents, hence, alleviate AD symptoms and improve cognitive function. Lastly, encapsulating these therapeutic agents in the form of nanocomposites proves to be the future of drug delivery to the brain, as it can readily penetrate the BBB, thereby accommodating targeted and effective therapy for AD.

Conflict of Interest

The authors declare that they have no competing interests.

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Consent Forms

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Data Availability

Not Applicable

Author's Contribution

The study was conceptualized by MU; the literature was searched by MU, WI, JS, MA, and EF. Graphics were made by MU & JS. The initial draft was written by MU, WI, JS, MA, and EF. The final draft was written by MU and MA after critical review and refinement.

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