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PHARMACOLOGICAL PROPERTIES AND CLINICAL EFFICACY OF *Ginkgo biloba* IN COGNITIVE DECLINE AND ALZHEIMER'S DISEASE

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ABSTRACT

Alzheimer's disease is a progressive neurodegenerative disease in patients aged 60-65 years. It is defined by memory impairment, cognitive change, and disturbances in behavior. It is the leading cause of dementia, with increasing global prevalence, and has become a serious public health issue. *Ginkgo biloba*, a plant used as an herbal medicine for a long time, has been extensively researched for its neuroprotective effects. Its pharmacologically active compounds, flavonoids, and terpenoids exhibit antioxidant, anti-inflammatory, and anti-amyloid activities that may play a role in treating AD. Various studies have shown that GB extract can improve cognitive function, inhibit neuroinflammation, and induce neuronal survival. Furthermore, GB combined with acetylcholinesterase inhibitors has improved treatment efficacy in AD patients. Nevertheless, conflicting results and heterogeneity of clinical trials complicate the conclusion of its effectiveness. A systematic search of English and Chinese databases was performed to search for relevant literature on GB and AD. The current review presents the results of 30-plus studies, including clinical trials, meta-analyses, and preclinical studies. The dosage, treatment duration, and

patient characteristics affect GB's efficacy. Due to promising results, various limitations of current evidence must be overcome. Most studies have small sample sizes, short follow-up periods, and methodological heterogeneity. The lack of large-scale, high-quality, randomized controlled trials restricts the validity of current evidence. Future research needs to perform long-term clinical trials on standardized dosages to establish the optimal application of GB in treating AD. Further investigation of the mechanisms of GB, especially its interaction with AD-related genetic factors and potential combination with current therapies, is also needed. Correcting these shortcomings will assist in presenting a better picture of GB's place in AD management and its promise as an adjunctive treatment.

INTRODUCTION

According to the World Health Organization (WHO), Alzheimer's Disease (AD) is a neurodegenerative disease that leads to permanent deterioration of cognitive functions. It is a common form of dementia. It usually occurs at 65 years, the most common in older adults (Matej, Tesar et al. 2019, Assi, Farrag et al. 2023). More than 80 million people are affected by AD, and the number may increase beyond 115 million by 2050 (Babazadeh, Vahed et al. 2023). Initially, senile plaques appear in the body due to the accumulation of β-amyloid protein (βA) and Tau proteins at the cellular level (Băjenaru, Prada et al. 2021). This accumulation of βA and Tau proteins leads to the loss of cholinergic synapses and axon stability, resulting in dementia and memory loss (Das, Lami et al. 2022). Accumulation of βA is the only cause of AD. Mitochondrial dysfunction as another significant contributor to Alzheimer's disease. Energy production is essential for neuroprotection and repair. Impaired mitochondrial function leads to excessive free radical production, reduced calcium buffering, and neuronal degeneration. Additionally, it promotes abnormal processing of amyloid-β precursor protein (APP), resulting in toxic amyloid-beta fragments. These disturbances collectively drive cognitive decline. These changes decrease learning abilities, memory loss, and thinking powers (Mitra, Tallei et al. 2022).

The exact cause of Alzheimer's disease is still unknown. However, the studies by (de Souza, Leite et al. 2024) have shown a loss of acetylcholine (a neurotransmitter for memory). These results in Oxidative stress (OS) and toxic signaling pathways that lead to brain cell damage. Amyloid-beta (Aβ) proteins interact with metals like copper and zinc, producing free radicals. These free radicals increase oxidative stress, damaging brain cells and worsening Alzheimer's disease. Additionally, Aβ proteins may trigger an immune response, further contributing to brain damage and AD. Some pharmacological treatments can reduce the progression of the disease, such as galantamine and rivastigmine, Acetylcholinesterase inhibitors (AChEI), donepezil, and memantine, a non-competitive N-methyl-D-aspartame glutamate receptor antagonist (García-Alberca, Gris et al. 2022). However, there is always a need to develop natural remedies for cognitive decline and AZ. There are no effective treatment methods, but all are based on delaying the progression of the diseases. Many researchers reviewed how bioactive compounds in food can help with

Alzheimer's disease and other neurodegenerative disorders (NDDs). Certain foods or ingredients may positively impact brain health, making this an important area of pharmacology and food science study (Rangel-Huerta, Aguilera et al. 2012, Klyucherev, Olszewski et al. 2022). Synthetic drugs commonly cause insomnia, sickness, hepatotoxicity, and diarrhea. This concern has elevated the need for alternative medication and treatment plans. Here, the role of medicinal plants cannot be ignored. These plants help in the treatment of Alzheimer's disease by reducing inflammation, blocking harmful proteins, and improving antioxidant levels in the brain of the patient (Apetz, Munch et al. 2014, Amato, Terzo et al. 2019). Moreover, they affect important cell pathways that protect against damage. Herbs like Ginkgo (*Ginkgo biloba*) help prevent brain-related symptoms.

Ginkgo biloba is a deciduous ornamental tree from Japan and China. It is valued for its medicinal properties and used in landscaping. It is highly resistant to pollution, pests, diseases, and harsh weather conditions, with a lifespan of up to 2000 years. Despite taking 25–30 years to bear fruit, its wide variety of cultivars has led to research on better propagation methods, such as stem cuttings (Zhang, Zhang et al. 2023). *G. biloba* can thrive well in warm, humid environments but withstand extreme conditions, including drought, freezing, and pollution. Even in Japan, Ginkgo trees survived the atomic bombing of Hiroshima during World War – II (Egziabher 2017, Bidak, Heneidy et al. 2022). Ginkgo is a living fossil. Its extracts have numerous health benefits. When used as medicine, the water extract has antioxidant, anticancer, antihypertensive, and neuroprotective effects. It has been used in traditional Chinese medicine for thousands of years, with its leaves, seeds, and stems valued for their healing properties. In recent years, scientific interest in *Ginkgo biloba* has surged, driven by a global shift toward natural remedies and the search for new treatments for various health conditions. Researchers have extensively studied its pharmacological effects, considering the composition of bioactive compounds for its therapeutic potential. These compounds are mainly flavonoids, terpenoids, ginkgolides, and bilobalides as shown in Figure 1 (Shrinet, Singh et al. 2021, Ogbuagu, Mbata et al. 2022).

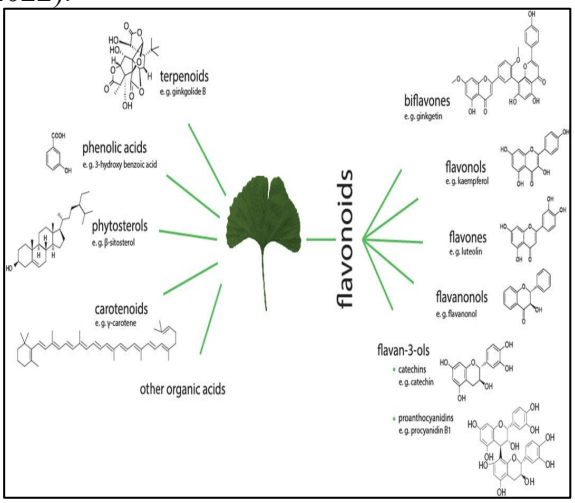

Fig. 1: Groups of active compounds contained in *G. biloba* leaves.

This review aims to provide a comprehensive analysis of the pharmacological properties and clinical efficacy of *Ginkgo biloba* in cognitive decline and Alzheimer's disease (AD). This paper evaluates the therapeutic potential and clinical outcomes of *Ginkgo biloba* in managing cognitive disorders. The objectives are to examine the phytochemical composition of *Ginkgo biloba*, focusing on its bioactive compounds that contribute to its pharmacological effects. The main focus will be to explore the pharmacological mechanisms through which *Ginkgo biloba* extracts can provide antioxidant and anti-inflammatory benefits to help with cognitive decline and Alzheimer's disease.

Background study of Ginkgo biloba

The plant *Ginkgo biloba*, commonly known as the maidenhair tree, is one of the

oldest living tree species, often referred to as a "living fossil" because it has survived for more than 200 million years with minimal evolutionary changes. It belongs to its own distinct division, *Ginkgophyte*, and is the only extant species within this group. Native to China, *Ginkgo biloba* has long been revered in traditional medicine and is widely cultivated for its medicinal, ornamental, and ecological value (Habib, Pirro et al. 2022).

Table 1: The detailed profile of *Ginkgo biloba*

Category	Details
Common Name	Ginkgo, Maidenhair Tree
Scientific Name	*Ginkgo biloba*
Family	Ginkgoaceae
Class	Ginkgoopsida
Order	Ginkgoales
Kingdom	Plantae
Phylum	Ginkgophyta
Genus	*Ginkgo*
Species	*Ginkgo biloba*
Origin	Native to China
Habitat	Temperate regions, well-drained soils, urban environments
Growth Habit	Deciduous tree, slow-growing, can live for over 1,000 years
Medicinal Uses	Neuroprotection, cognitive enhancement, antioxidant, anti-inflammatory

The researchers explain the biotic profile of *Ginkgo biloba.* According to them, Ginkgo contains many bioactive compounds like Flavonoids, Terpenoids, Phenolics, Carboxylic acids, lignans, etc. These compounds have significant therapeutic potential (Lin, Lou et al. 2019). Flavonoids have been identified, including kaempferol, quercetin, and isorhamnetin, which exhibit strong antioxidant properties. *Ginkgo biloba* is also rich in terpenoids such as diterpenoid lactones (ginkgolides A–Q) and sesquiterpene lactones (bilobalide). These compounds contribute to the neuroprotective and cerebrovascular benefits. Some other biological compounds, such as alkylphenols and alkyl phenolic acids, are present in Ginkgo's extracts. While some of these compounds have potential pharmacological effects, ginkgolic acids are known to be toxic (Shehata, Ragupathy et al. 2021, Gu, Lin et al. 2022). Ginkgo exhibits antioxidant and anti-inflammatory properties due to the presence of carboxylic acids. Moreover, lignans and Proanthocyanidins from the roots, seeds, and extracts also have antioxidant activities and have been studied for their potential health benefits (Zhang, Fang et al. 2023). Among some other compounds, Polysaccharides – Composed of glucose, mannose, rhamnose, and galactose, play a role in immunomodulatory and antioxidant activities. All these bioactive compounds collectively contribute to the medicinal properties of *Ginkgo biloba*, including its antioxidant and anti-inflammatory benefits (Zhang, Wu et al. 2018).

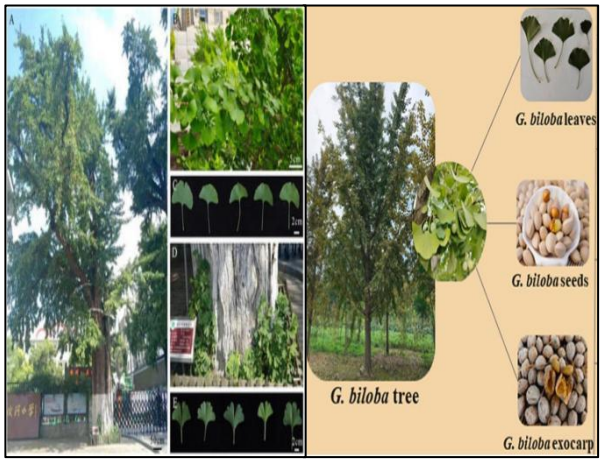

Fig.2: The visualization of *FiGinkgo biloba Plant* and *Ginkgo biloba plant parts.*

Ginkgo biloba has been used in traditional Chinese medicine. In the 1970s, scientists developed a standardized extract (GBE) containing beneficial compounds like flavonoids and terpenoids. These compounds support brain health by acting as antioxidants, reducing inflammation, and preventing brain cell damage (Nyulas, Simon-Szabó et al. 2024). Additionally, GBE protects mitochondria, the energy-producing structures in cells. Healthy mitochondria also help prevent the buildup of harmful amyloid plaques directly linked to the occurrence of Alzheimer's disease. Research has shown that GBE improves memory and learning abilities. Since 1985, clinical trials have been conducted to test its effectiveness in humans. Despite these limitations, GBE remains a promising natural option for slowing cognitive decline and supporting brain functions in Alzheimer's patients (Bhattacharya, Soares et al. 2022).

Impact of Ginkgo Biloba Leaf on Alzheimer's disease

In their study, (Wang, Chen et al. 2021) used network pharmacology methods to investigate how extracting *Ginkgo biloba* leaves might help treat Alzheimer's disease (AD). They analyzed gene expression data and identified 10 key genes linked to AD. Additionally, they gathered 729 AD-related genes from various databases. The study also screened *Ginkgo biloba's* active chemical components, identifying 27 bioactive compounds and linking them to 35 candidate genes associated with AD. The usage of Cytoscape software, the researchers mapped the relationships between *Ginkgo biloba* compounds, target genes, and AD. The analysis highlighted quercetin, luteolin, and kaempferol as the most significant compounds due to their strong interactions with AD-related genes. Since previous research has shown these compounds have neuroprotective properties, the findings provide strong evidence for *Ginkgo biloba's* potential in AD treatment. This study offers a scientific foundation for understanding *Ginkgo biloba's* role in alleviating AD and supports its clinical use (Liu, Yue et al. 2022, Zhi, Yin et al. 2024). Research done by (Bidak, Heneidy et al. 2022, Liu, Yue et al. 2022) has demonstrated that *Ginkgo biloba* extract (EGb 761) possesses potent antioxidant properties that may help protect against oxidative stress, a key factor in Alzheimer's disease (AD). The extract enhances cerebral blood flow, modulates the neurotransmitter system, and influences the cellular redox state and nitric oxide levels. EGb 761 can directly scavenge reactive oxygen species (ROS) and increase the expression of antioxidant enzymes. Studies on human brain tissues exposed to oxidative damage showed that EGb 761 effectively reduced the harmful effects of free radicals. Additionally, experiments on rat cerebellar cells indicated that the extract protected against oxidative damage induced by hydrogen peroxide, preventing apoptotic cell death (Heidari, Mahmoudzadeh-Sagheb et al. 2021). The antioxidant properties of *Ginkgo biloba* are primarily attributed to its flavonoids, particularly quercetin and kaempferol, which reduce ROS levels in both in vitro and in vivo models. These flavonoids act by scavenging ROS, chelating heavy metal ions, and increasing the expression of antioxidant proteins such as superoxide dismutase (SOD) and glutathione reductase (GSH). Furthermore, *Ginkgo biloba* inhibits lipid peroxidation in the hippocampus, reduces ROS formation via the cytochrome P-450 enzyme system, and prevents oxidative stress-induced cell apoptosis. Ginkgolides, another active component, are crucial in reducing oxidative damage by inhibiting platelet aggregation factor (PAF) and preventing blood-brain barrier permeability (Huang, Liao et al. 2024). Ginkgolide B has been identified as a potent ROS scavenger, significantly reducing oxidative stress in

neuroblastoma cells. Additionally, EGb 761 has been shown to block amyloid-beta-induced apoptosis, inhibit caspase three activation, and enhance angiogenesis, further supporting its potential in AD prevention and treatment (Pereira, Souza et al. 2017).

Research carried out by (Li, Liu et al. 2020) has shown that ginkgolides, key components of *Ginkgo biloba*, play an essential role in inhibiting inflammation associated with Alzheimer's disease (AD). These compounds suppress the TLR4-mediated inflammatory response by preventing the activation of adapter proteins such as MYD88, TRAM, and TIRAP, which are responsible for triggering nuclear factor kappa B (NF-κB) phosphorylation. Additionally, ginkgolides activate the JAK2/STAT3 and p38 MAPK signaling pathways, further influencing immune system function. AD is a neurodegenerative disorder marked by the accumulation of β-amyloid (Aβ) plaques. Ginkgolides have been found to inhibit the formation of toxic Aβ-derived diffusible ligands (ADDLs) and lower cholesterol levels dose-dependently. Furthermore, they enhance alpha-secretase activity, promoting the non-amyloidogenic processing of amyloid precursor protein (APP), which helps reduce Aβ production. They have demonstrated that pre-treatment with ginkgolides A or B successfully protected cortical and hippocampal neurons from this loss, unlike other *Ginkgo biloba* components such as myricetin and quercetin. Interestingly, ginkgolides may bind directly to Aβ1-42 peptides, promoting the formation of an inactive conformer (Niu, Yuan et al. 2022).

According to (Kamat, Kalani et al. 2016), AD is caused by the buildup of harmful proteins amyloid beta (Aβ) plaques and hyperphosphorylated which lead to neuron damage, inflammation, and oxidative stress (Fig. 3). *Ginkgo biloba* can work to protect the brain from this degenerative disease. They referred to the following image (Fig. 4), where on the right side of the image, we see the amyloid precursor protein (APP) being cut by secretase enzymes. If beta-secretase and gamma-secretase work together, they form toxic Aβ plaques, which clump together and trigger inflammation. This leads to oxidative stress and the release of harmful inflammatory molecules like TNF-α, IL-1β, IL-6, and NF-κB, all contributing to neuron damage (Habotta, Ateya et al. 2023).

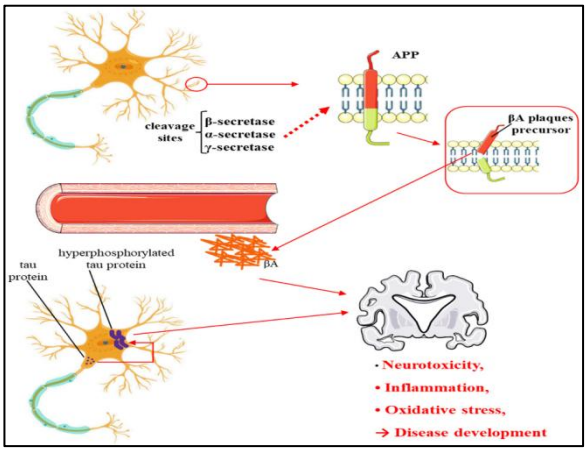

Fig. 3: Occurrence of AD by the buildup of harmful proteins.

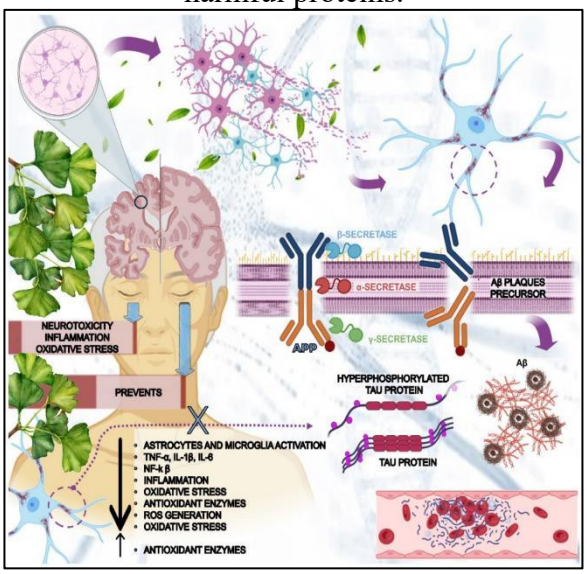

Fig. 4: The schematic visualization of the occurrence of AD Pagotto.

The *GB* extract (GbE) reduces neuroinflammation and oxidative stress. It inhibits inflammatory mediators like nitric oxide and prostaglandins while blocking NF-

κB, which is key in triggering inflammation. GbE also strengthens blood vessel walls, improves blood circulation, and prevents harmful immune cells from sticking to blood vessels and entering the brain. Moreover, GB promotes the production *of* antioxidant enzymes that neutralize reactive oxygen species (ROS), reducing oxidative stress, further protecting neurons from damage, and supporting memory and learning (Ojha, Javed et al. 2016). (Assi, Farrag et al. 2023) used Curcumin, a key compound in turmeric, and *Ginkgo biloba* extract (GBE) in their study. Curcumin is a natural substance known for its potential benefits in Alzheimer's disease (AD). However, Curcumin has trouble reaching the brain due to the blood-brain barrier (BBB). This necessitates using it with GB extract, as it helps improve BBB permeability. The results showed that the brain and blood curcumin levels were significantly higher when taken with *Ginkgo biloba* than when taken alone.

The combination treatment improved memory and learning in an AD-like rat model and reduced harmful proteins linked to AD (amyloid beta and tau). It lowered inflammation and oxidative stress more effectively than Curcumin alone. These findings suggest combining *Ginkgo biloba* with Curcumin could be a promising approach for preventing or managing neurological disorders like AD. The study highlights the need for further research on the combined effects of herbal treatments on brain health (Assi, Farrag et al. 2023). A review of clinical trials on *Ginkgo biloba* extract (EGb) by (Liu, Ye et al. 2020) examined its effects on cognitive *function* in healthy individuals and Alzheimer's patients. The analysis showed that EGb may help improve cognitive function in patients with mild dementia. It can only be effective with long-term use (more than 24 weeks). Moreover, an appropriate daily dose of 240 mg is required for its effectiveness. The studies show that many clinical trials on EGb were too short to assess its benefits fully. Alzheimer's is a long-term disease, and drug effects may change over time, affecting its control. (Huang, Tian et al. 2020) conducted a meta-analysis to evaluate the effectiveness and safety of combining *Ginkgo biloba* preparations with donepezil hydrochloride for treating Alzheimer's disease (AD) compared to donepezil alone. They searched three English databases (Cochrane Library, PubMed, EMBASE) and four Chinese databases (CKNI, CBM, Chongqing VIP, and WANFANG DATA) for randomized controlled trials (RCTs) published up to December 2022. A total of 18 RCTs involving 1,642 participants were included, with 842 in the experimental group (*Ginkgo biloba* and donepezil) and 800 in the control group (donepezil alone). Data from these studies were analyzed using the RevMan 5.3 software, and their quality was assessed based on the risk of bias.

The results showed that combining *Ginkgo biloba* and donepezil significantly improved clinical effectiveness, cognitive function (Mini-Mental State Examination, Hasegawa Dementia Scale, and Montreal Cognitive Assessment scores), and daily living activities compared to *donepezil* alone. However, the two groups had no significant difference in adverse reactions. Despite these promising findings, the study noted that the overall quality of the included RCTs was low due to risks related to blinding and allocation concealment. Therefore, while the combination therapy appears beneficial, further high-quality clinical trials are necessary to confirm these results (Maruthur, Tseng et al. 2016).

(Tian, Shi et al. 2019) conducted a meta-analysis to evaluate the effectiveness and safety of *Ginkgo biloba* in *treating* Alzheimer's disease (AD). They aimed to determine whether *Ginkgo biloba* could improve cognitive function and overall clinical outcomes in AD patients. To achieve

this, they systematically searched English (PubMed, Embase, Cochrane Library) and Chinese (WanFang, CNKI, VIP) databases for studies published until July 3, 2019. They included studies where AD patients were treated with *Ginkgo biloba* and assessed its effects on cognitive function and safety. Their analysis included seven studies with 939 participants. The results showed that *Ginkgo biloba* significantly improved cognitive function and overall clinical assessment compared to a placebo. Statistical analysis confirmed its effectiveness and adverse effects were mild. Liao et al. concluded that *Ginkgo biloba* is a reliable and safe option for improving cognitive function in AD patients. However, further research is needed to strengthen these findings. (García-Alberca, Mendoza et al. 2022) conducted a study to investigate whether combining *Ginkgo biloba* extract EGb 761 with acetylcholinesterase inhibitors (AChEIs) could provide additional benefits for patients with mild cognitive impairment (MCI). Since no approved treatment exists for MCI, the study aimed to explore the potential advantages of this combination therapy. They analyzed data from 133 patients with amnestic MCI who were attending a memory clinic to achieve this. Patients were divided into three groups: those receiving EGb 761, those on AChEIs (donepezil, galantamine, or rivastigmine), and those receiving a combination of both. Cognitive, functional, and behavioral assessments were conducted over 12 months using tests like the Mini-Mental State Examination (MMSE) and the Neuropsychiatric Inventory (Da Silva, Ordonez et al. 2021).

The results showed that patients receiving the combination treatment had significantly better cognitive and behavioral improvements than those who only took AChEIs or EGb 761. The combination therapy more effectively improved MMSE, memory tests, attention, and neuropsychiatric symptoms. The study concluded that EGb 761, especially when combined with *AChEIs*, could provide greater cognitive and behavioral benefits for MCI patients. These findings support further research on the combined use of *Ginkgo biloba* and dementia medications in managing MCI. Yang et al. (2025) *carried* out a study to examine whether adding *Ginkgo biloba* to donepezil provides additional benefits for Alzheimer's disease (AD) patients who tested positive for amyloid PET scans. In doing so, they also investigated changes in a plasma biomarker (MDS-Oaβ) related to amyloid buildup. They analyzed 101 newly diagnosed, drug-naïve AD patients with at least 12 months of follow-up. Patients were divided into two groups: one received only donepezil, while the other received both donepezil and *Ginkgo biloba*. Cognitive function was measured using the Korean version of the Mini-Mental State Examination (K-MMSE) and the Clinical Dementia Rating (CDR-SB). Plasma MDS-Oaβ levels were assessed at the start and after 12 months. The results showed that patients who took both donepezil and *Ginkgo biloba* had significant cognitive improvement (+2.4 on K-MMSE) and a greater reduction in MDS-Oaβ levels than those who took only donepezil. However, the two groups had no significant difference in the CDR-SB scores. Adverse events were mild and did not cause treatment discontinuation. Thus, adding *Ginkgo biloba* to donepezil may enhance cognitive function and reduce amyloid-related biomarkers in AD patients. However, more extensive trials are needed to confirm these findings and understand *Ginkgo biloba's* role in AD treatment.

All these studies have explored the effects of *Ginkgo biloba* on cognitive function in Alzheimer's disease (AD). *Ginkgo biloba* may improve cognitive function in mild dementia, but long-term use (over 24 weeks) at a dose of 240 mg daily is necessary. They also noted that many trials were too short to

assess its benefits fully. Significant improvements in cognitive function and daily activities with the combination therapy, though no significant difference in adverse effects was found. However, the study emphasized the need for high-quality clinical trials. Similarly, researchers who combined *Ginkgo biloba* with acetylcholinesterase inhibitors improved cognitive and behavioral outcomes in MCI patients (Özge, Ghouri et al. 2023).

Safety, Side Effects, and Drug Interactions

Ginkgo biloba has antioxidant and neuroprotective properties; its indiscriminate use can lead to serious health risks. These include cellular toxicity, neurotoxicity, and liver damage. It can also interact with other drugs, increasing potential harm. In his studies, (de Souza, Leite et al. 2024, Huang, Liao et al. 2024) evaluated the toxicity and possible dangers of the uncontrolled use of *Ginkgo biloba*. They conducted a systematic review of 23 scientific articles focusing on its toxicity, adverse effects, and drug interactions. The study found that commercial *Ginkgo biloba* products vary in composition, sometimes containing harmful substances that increase health risks. There is a need for strict regulation and quality control of *Ginkgo biloba* products to ensure safety. They concluded that the consumption of *Ginkgo biloba* should always be supervised by healthcare professionals. More stringent regulations are necessary to prevent potential dangers and ensure the safe use of this supplement (Berthier, Dávila et al. 2020).

To assess whether long-term use of EGb761 could improve cognitive function, memory, daily activities, and depression over 24 months, (Shen, Hu et al. 2022) conducted a study. They worked to evaluate the effectiveness and safety of standardized *Ginkgo biloba* extract EGb761® (Tanakan®) in patients with amnestic mild cognitive impairment (aMCI). More than 500 patients with aMCI were treated with 120 mg/day of EGb761®. They were assessed every six months using cognitive and functional tests, including the Mini-Mental State Examination (MMSE), Functional Activities Questionnaire (FAQ), Clinical Global Impression (CGI), and Hamilton Depression Rating Scale (HAM-D).

The results showed a significant improvement in cognitive function, with a 2-point increase in MMSE scores after 24 months. Patients also experienced better memory recall, improved ability to perform daily tasks, and reduced depression symptoms. However, those with additional cognitive disorders showed less improvement. More than 80% of patients had at least minimal improvement based on the CGI scale. The findings concluded that long-term use of EGb761® significantly benefits cognitive function, memory, and quality of life in aMCI patients, supporting its potential as a treatment for cognitive decline (García-Alberca, Mendoza et al. 2022). More research is needed to confirm whether ginkgolides can indeed delay Alzheimer's disease (AD) progression and effectively cross the blood-brain barrier. Future studies should investigate the relationship between *Ginkgo biloba* extract (EGb) and the APOE4 gene, a major risk factor for AD. They should also focus on longer treatment durations for more accurate results (Pramotton, Spitz et al. 2024). While *Ginkgo biloba* extract (GBE) has shown promise in animal models, more research is needed to evaluate its safety and effectiveness in human Alzheimer's disease (AD) patients through well-designed clinical trials. Further studies should focus on isolating and identifying the specific bioactive compounds in GBE responsible for its effects and understanding their mechanisms of action. Additionally, research should explore the potential benefits of combining GBE with existing AD medications. Future studies should use more reliable Alzheimer's disease (AD) mouse models, like 3xTg and 5xFAD, to better understand the effects of *Ginkgo*

biloba extract (GBE). More clinical trials should test GBE in early-stage AD patients or healthy older adults. Studies should focus on long-term use (over 24 weeks) and higher doses (more than 240 mg/day) to see if GBE can help prevent or slow down AD. More research is needed to enhance vascularization in brain organoids to prevent necrosis and allow more extended development. Developing 3D cerebral organoids and organ-on-a-chip systems can help create better models for studying Alzheimer's disease (AD) and testing treatments. Future studies should investigate how microfluidic chip systems can replicate actual brain conditions and improve AD research (Wan, Zhou et al. 2022).

CONCLUSION

Ginkgo biloba (GB) has been comprehensively researched for its possible therapeutic application in the treatment of cognitive impairment and Alzheimer's disease (AD). The pharmacology of GB is due to its antioxidant, anti-inflammatory, and neuroprotective properties, which amplify cognitive function and repress disease progression. Some improvement has been seen by some studies in memory, attention, and neuropsychiatric symptoms, especially in patients with mild to moderate AD. GB is likely to exert its effects via mechanisms involving decreases in oxidative stress, modulation of neurotransmitter functions, and modulation of important pathways such as PI3K/AKT/NF-κB. Some clinical trials have provided evidence for the efficacy of GB, but large trials have provided weak evidence that GB can delay or prevent dementia. The addition of GB as adjunct therapy with acetylcholinesterase inhibitors (AChEIs), e.g., donepezil, has been found to be modestly better in some, proposing a possible synergistic effect. In spite of positive outcomes achieved, the current evidence of research on GB and AD is marred by several limitations. Most studies are plagued by small populations, heterogeneous research designs, and short treatment durations, rendering it challenging to make final conclusions. In addition, although GB has shown cognitive benefits in animals, its efficacy in human volunteers remains unclear due to the absence of long-term high-quality clinical studies. Another critical limitation is heterogeneity of GB extract formulations, resulting in heterogeneity of effects of treatment. Moreover, genetic effects, e.g., APOE4 gene presence, have not been extensively investigated for their role in the effect of GB on AD. These methodological limitations highlight the need for well-designed studies, taking into account heterogeneity of patients, optimal dosing, and long-term effects of GB treatment. GB is an intriguing natural treatment for cognitive disease, but clinical efficacy is questionable. Although it has demonstrated promise for enhancing cognitive function and neuropsychiatric symptoms, more research is necessary to validate its effectiveness and to develop accepted treatment protocols. Subsequent research should emphasize long-term trials in larger groups of patients, explore the effects of GB on varying stages of AD, and investigate its interaction with genetic risk factors. The potential for combining GB with current AD therapies also might offer new insights into its therapeutic application. Supported by more robust clinical data, GB might have a valuable role in the treatment of cognitive deterioration and AD, either as monotherapy or as an adjunct to current therapies.

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