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"GINKGO BILOBA" A COMPREHENSIVE REVIEW OF ITS THERAPEUTIC POTENTIALS

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Abstract

The "living fossil," Ginkgo Biloba has long been used in medicine. Both leaves and nuts are frequently given to treat a variety of illnesses, including as alcoholism, dementia, pulmonary disease, Alzheimer disease heart and bladder malfunction, dementia and lung infections. containing extracts and separated substances such organic acids, bioflavonoids, and flavonoids. Anxiety, stress, and depression are psychological disorders that are so prevalent that they will become the second most significant risk factor for morbidity and sociodemographic burden. to offer a range of health advantages to living things and is rich in bioactive substances, making it a chemically diverse plant with a number of pharmacological and therapeutic qualities, such as anti-lipidemic and anti-dementia effects. the most common herbal medicines in Europe is ginkgo biloba leaf extract, which is used to treat vascular dementia, early-stage Alzheimer's disease, peripheral isolation, and the condition of vascular origin. Additionally, it is among the top ten herbal remedies in several states. The quality life for healthy people can also be improved by the herbal extracts. In addition to producing against endothelial damage, G. biloba is useful against inner ear disorders. In addition, scientific research has shown that it contains antiviral, antibacterial, and antioxidant properties. Many effects, including anti-diabetic, anti-cancer, and cardioprotective Ginkgo properties have been scientifically verified, making it a significant nutraceutical. The scientific community is becoming more interested in this plant.One of the the main causes of dementia in older adults globally is Alzheimer's disease, a neurodegenerative condition. People with Alzheimer's disease experience disorientation, social marginalisation, and isolation as a result of the loss of neuronal structure and function in many brain regions. The utilisation of natural bioactive chemicals to treat neurodegenerative illnesses, such as Alzheimer's disease, has received increasing interest in recent years. The most widely used standardised extract of G. biloba.

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Introduction

All living things nature is in balance in mythology plants are seen as the most precious gift given to Man by the God plants have been an integral part of the human existence in the beginning of the time with the long-lasting relationship between the humans and the plant according to the archaeological findings from the ancient times people benefited from plants to obtain the food and to eliminate health problems [1].

Ginkgo biloba widely used worldwide for age related memory impairment and dementia due to its effects on cerebral blood vessels thanks to its components such as a flavonoid and terpenic and lactones.

it is also used as therapeutic agent for memory loss concentration problem depression, dizziness, headache, Raynaud's disease peripheral arterial occlusive disease post-phlebitis syndrome improving pain free walking distance, and treating cardiovascular disorders. This study compiles information from the literature on the botanical character-

istics, “historical use”, and “bioactive components” of ginkgo biloba species [5-6].

Anxiety and depression are universal brain disorder 7.3% and 7% prevalence. This disorder a characterised by stress linked mood problems and may cause early death. Surprisingly and prevalence of depression is 3 times higher in young people and women are 1.5 times to 2 times more susceptible to anxiety and depression, sleep disorder, weight loss or gain, retardation, fatigue, concentration and decision-makingchallenges and even tenderness of suicide are the most reported depression symptoms. Furthermore, this complication caused a significant number of 5 years of life lost to disability in multiple countries [7].

Botanical Features

G. biloba trees can grow to a height of 30 to 40 meters, with branches that can spread up to 8 meters and a maximum length of 70 meters. The diameter of the stem can reach 500 cm (Lin *et al.,* 2022). Its fluffy, fan-shaped leaves are pleasant to the touch. The two-lobed leaves of G. biloba are the source of its name (Figure 1). According to Barnes *et al.* (2007), it is a deciduous tree with long-stalked, bilobed leaves that are 6 to 9 cm wide and turn yellow in the fall. Tree bark is light grey or greyish brown in colour and has a characteristic longitudinal fissured texture that is especially apparent on mature trees.

These shoots have internodes that are 1.5–4 cm long. Trees with short shoots have elliptic, thick, irregularly formed leaf scars that are blackish-grey in colour. Furthermore, some ginkgo tree branches exhibit a distinctive growth pattern that resembles stalactites, which are known as "chichi”. Because of its dioecious nature, the tree has distinct male and female individuals. The tree's male cones are ivory in colour and range in length from 1.2 to 2.2 cm. Pollen is released from the pollen sacs, which are shaped like boats and have widely gaping openings inside these cones.

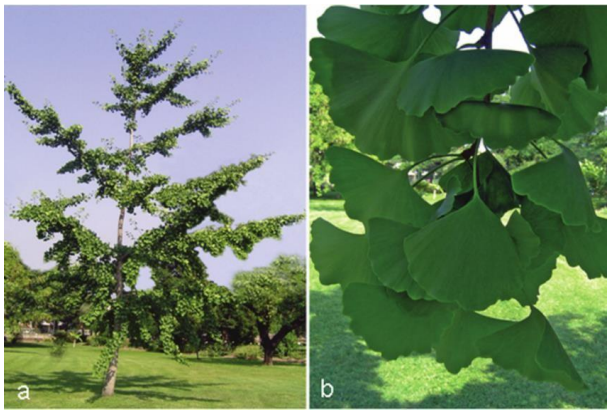

Figure 1: (a) Ginkgo biloba tree (b) ginkgo biloba leaves [8-9]

Chemical Composition

The chemical structures of the major compounds contained in the plant are shown in

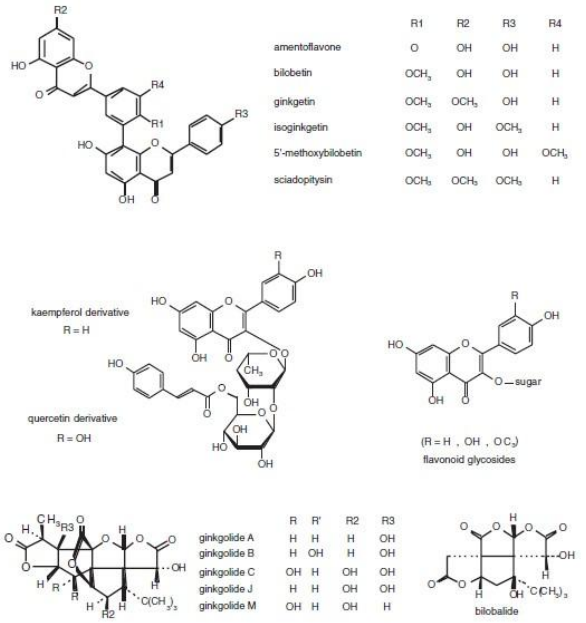

Figure 2. Representative structures of the major and characteristic components of G. biloba

Major compounds found in the seeds of the plant

1) Alkaloids:Ginkgo toxin
2) Amino acids: cytogenic glycosides, ginkgoid acids, ginkbilobin.

Major compounds found in the leaves of the plant

1) amino acids: 6 hydroxy kynurenic acid, a tryptophan metabolite.
2) Flavonoids: Dimeric flavones (e.g.Amentoflavone, bilobentin,ginkgeton, glycosides,kaempferol
3) proanthocyanidins: terpenoids sesquiterpenes (e.g. Bilobalide) diterpenes (e.g. Ginkgolides A, BC, J, M)
4) agar compounds: benzoic acid, ginkgoid acids, sugars,waxes,peptides

Alzheimer’s Disease

Ginkgo biloba L. is used as a neuroprotective agent. Alzheimer's disease: One of the most prevalent causes of dementia in older adults worldwide is Alzheimer's disease, a neurogenerative condition. Alzheimer's disease. results in the loss of neuronal structure and function in many brain regions, which causes people to become alienated and excluded from social and professional life. Natural bioactive substances that are beneficial in treating neurogenerative diseases, such as Alzheimer's disease, have been used to treat AD illness. For many years, gingko biloba L. and its most widely used standardized extract (EGb 761) have been employed in cognitive disorder prevention and supportive therapy. Ginkgo biloba extract and how it affects potential disease-causing bacteria. By learning as much as possible about the diseases [10].

Dementia in Alzheimer's disease (AD) can range from mild to severe. In the early stages, memory loss and personality changes are common, along with symptoms like depression, lack of interest, and guilt. As the disease progresses, patients may experience hallucinations, sleep disturbances, and need for constant support. In the final stages, muscle stiffness and slow motor functions make it difficult for patients to move, and they require round-the-clock care.

Currently, there is no single drug to treat all AD symptoms, which makes developing effective treatments a significant challenge. This has led to increased interest in natural remedies, such as herbal medicines, which have been used for thousands of years and may offer fewer side effects than synthetic drugs. One promising plant is Ginkgo biloba (G. biloba), which contains bioactive compounds like flavonoids and terpenes. G. biloba is often used to treat cognitive issues in AD, as it can improve memory and brain function. However, more research is needed to fully understand its effects, especially when combined with other AD treatments [11-12].

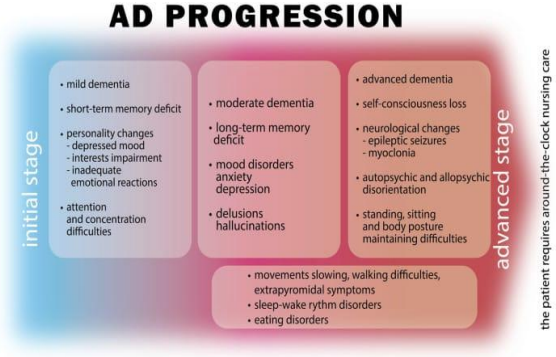

Figure3: -Alzheimer's disease (AD) progresses in stages, starting with the initial stage where individuals experience short-term memory loss, personality changes, and difficulty with attention or concentration. As the disease progresses, memory loss becomes more pronounced and mood disorders, delusions, and hallucinations may develop. Patients may also begin to have difficulties with movement, as well as problems with sleeping and eating. In the advanced stage, individuals lose self-awareness, become confused about time and place, and experience significant neurological changes such as seizures, muscle jerks, and balance problems. Dementia progresses from mild to moderate and eventually to an advanced stage, where the patient is no longer able to live independently [13].

The Factors Influencing AD

The development of Alzheimer's disease (AD) is influenced by both health conditions and genetic factors. Hypertension, obesity, and diabetes have all been shown to increase the risk of AD. Genetic factors play a major role, contributing to about 70% of AD cases. A key gene involved is apolipoprotein E (APOE), which has three variants: ε2, ε3, and ε4. Among these, the APOE ε4 variant is most strongly associated with an increased risk of developing AD. The risk related to the APOE genotype is thought to depend on how different APOE variants affect the buildup of β-amyloid proteins in the brain, which is a key factor in the development of AD.The risk factors influencing Alzheimer's disease (AD) are varied and complex. Genetic factors play a significant role, as abnormalities in lipid homeostasis, often linked to gut microbiota imbalances, can affect the gut-brain axis, leading to neuronal signalling disruptions and blood-brain barrier (BBB) breakdown. These issues may contribute to inflammation, oxidative stress, and mitochondrial dysfunction, all of which worsen AD progression. Specific gene mutations also contribute to AD development, such as HLA-DRB5-DRB1, INPP5D, MEF2C, PTK2B, CELF1, NME8, CASS4, and FERMT2, which are involved in immune response, synaptic function, and the metabolism of tau and beta-amyloid proteins.Age is another critical risk factor; the likelihood of developing AD doubles every five years after age 65, and it is more common in women than in men. By 2030, the global number of people with dementia is expected to reach 82 million, with AD accounting for 60% of these cases. Additionally, postmenopausal women are particularly at risk, with their incidence of AD being 2-3 times higher than men's, possibly due to the protective role of estrogen. Disturbances in sleep-wake rhythms before the onset of clinical symptoms are also linked to a higher risk of developing AD [14-15].

Treatment of AD

The main goals of Alzheimer's disease (AD) treatment are to stabilize the condition, slow its progression, reduce mental and behavioural symptoms, and improve the patient's quality of life. Currently, there is no cure or treatment that can permanently reverse the changes in the brain caused by AD. The focus of medication is to manage symptoms and slow the progression of the disease [16].

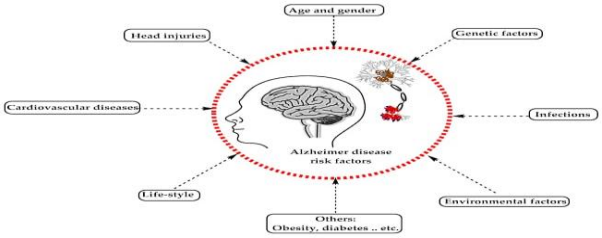

Figure 4: Factors influencing the development of AD–the most common type of dementia. Genetic and environmental factors are mentioned as the main risk factors for developing AD. Apolipoproteins E lead to irregular amyloid β aggregation. Mutations of genes such as HLA-DRB5-DRB1, INPP5D,MEFLC, PTK2B, CELF1,NME8, CASS4 and FERMT2 may induce the dysfunctions of brain physiological processes. Other factors such as hypertension, obesity, diabetes, blood circulationdisorders, oxidative stress and inflammation, also influence AD progression. People over the age of 65 years, especially postmenopausal women, are morepredisposed to AD development [17].

Applications of Synthetic Treatments in AD

In treating Alzheimer's disease (AD), the main drugs used are acetylcholinesterase inhibitors (AchEIs) like donepezil, galantamine, and rivastigmine. These are first-line treatments that work well for patients with mild to moderate AD symptoms by increasing levels of acetylcholine, which helps improve cognitive function. Tacrine, an older drug for AD, is used less now due to its side effects.

Another group of drugs, N-methyl-D-aspartate receptor (NMDAR) antagonists like memantine, is used for moderate to severe AD.For psychiatric symptoms such as depression, selective serotonin reuptake inhibitors (SSRIs) are commonly used. In addition, atypical antipsychotic drugs like olanzapine, quetiapine, and risperidone may be added for behavioural symptoms. However, conventional antipsychotics can cause more side effects, and using these medications in AD may increase the risk of death [18-19].

Applications of natural treatment in AD

In Alzheimer's disease (AD) treatment, natural drugs are being explored as possible alternatives or supplements to synthetic medications. Many plants are being studied for their potential to provide new treatments, especially since multipurpose drugs-those that can help with several aspects of the disease-are highly desired. Plants contain many bioactive compounds that could play a significant role in treating neurological disorders like AD [20].

The use of ginkgo biloba in treatment and prevention of AD

Ginkgo biloba, often referred to as a "living fossil," is a unique plant with a rich history and distinctive characteristics. This species is the sole surviving member of the genus Ginkgo, which was widespread during the Mesozoic era. Remarkably, it was not found in its natural habitat until the mid-20th century in southeastern China. However, Ginkgo biloba has long been cultivated in East Asia, particularly at temples, where it was revered as a sacred tree. Its cultivation spread to temperate climates, where it is valued both for its aesthetic appeal and its medicinal properties [21].

Ginkgo biloba is a dioecious gymnosperm tree, meaning it has separate male and female reproductive structures. The leaves are one of its most distinctive features, with a fan-shaped structure and seasonal shedding in winter. The leaf blade is leathery and often has a dissected edge with primitive dichotomous veins. The seeds, which are encased in a fleshy, fruit-like structure called the aril, are yellow and attached to long stalks. The aril contains butyric acid, contributing to its characteristic rancid butter smell, though roasted seeds are edible.

For over 600 years, Ginkgo biloba has been an important component of traditional Chinese medicine, where it was used to treat a wide range of ailments, including bronchitis, asthma, renal dysfunction, bladder diseases, and inflammation. While the seeds were initially the primary part used for medicinal purposes, the leaves have also been recognized for their therapeutic potential. The first recorded uses of the leaves for medicinal purposes appear in ancient Chinese texts. Today, Ginkgo biloba leaf extracts are primarily employed in the treatment of cognitive decline associated with aging and neurodegenerative disorders like dementia, including Alzheimer's disease.

The plant's medicinal benefits are believed to stem from its ability to improve blood circulation, protect against oxidative stress, and support cognitive function. The bioactive compounds found in Ginkgo biloba, such as flavonoids and terpenoids, are thought to enhance neuronal activity and provide neuroprotective effects, which are essential for managing age-related cognitive decline [22-23].

Extraction of Ginkgo biloba

In 1965, Dr. Willmar Schwabe III, a German physician and pharmacist, developed the standardized extract of dried Ginkgo biloba leaves for pharmaceutical use. This extract was first used to treat blood flow issues, particularly in the brain and peripheral areas, and was later registered in France in 1974 under the name EGb 761. EGb 761 is now a widely used herbal supplement made by extracting active compounds from Ginkgo biloba leaves using acetone. It is enriched with beneficial ingredients like flavonoids and terpene lactones while being free of toxic components like ginkgolide acids.

The standardized extract contains 22-27% flavonoids and 5-7% terpene lactones, including specific ginkgolides and bilobalide, and has less than 5 parts per million of ginkgolic acid. EGb 761 is commonly used to treat hearingand balance disorders, such as tinnitus and dizziness, which are related to poor blood circulation. It is also used to improve cognitive function, especially in age-related memory problems [24].

Oxidative stress in AD

Oxidative stress occurs when the body produces too many reactive oxygen species (ROS), which are harmful molecules that can damage cells. This stress is linked to various health problems, including heart disease, tissue damage, and DNA damage. In neurodegenerative diseases like Alzheimer's disease (AD), oxidative stress plays a major role in the damage to brain cells. The excess ROS can harm neurons, causing irreversible damage that leads to cell death. This damage is often seen in the form of advanced glycation end products (AGEs), lipid peroxidation, and nitration products. In Alzheimer's, a protein called hemoxygenase-1 (HO-1) is elevated as a marker of cellular stress. Oxidative stress is also associated with the buildup of senile plaques in the brain, which worsen the condition by increasing harmful enzyme activity, contributing to further cell damage and disease progression [25].

Microglia function in AD

Microglial cells are important non-neuronal cells in the brain that help maintain homeostasis (balance) and are involved in immune responses. They become activated in

response to brain damage, and while they can protect the brain, they can also cause tissue damage if overactive. In Alzheimer's disease (AD), activated microglia release harmful substances like amyloid beta (Aβ), which contributes to the formation of senile plaques.

Microglia also secrete pro-inflammatory molecules, such as interleukin-1 (IL-1), which can increase the production of amyloid precursor protein (APP) and other components involved in plaque buildup. Inflammation plays a key role in the development of AD, and studies have shown that anti-inflammatory drugs can slow down the disease's progression. Microglia can both harm and help the brain: while they can cause neuron loss by releasing pro-inflammatory substances, they also aid in neuron repair.The proper function of microglia is crucial for maintaining balance in the brain. If microglia are not working well, it can lead to problems with the brain's ability to clear amyloid plaques and maintain healthy nerve cells. Research is ongoing to explore natural treatments that might help microglia perform these functions without increasing inflammation, which could potentially help treat or manage AD.

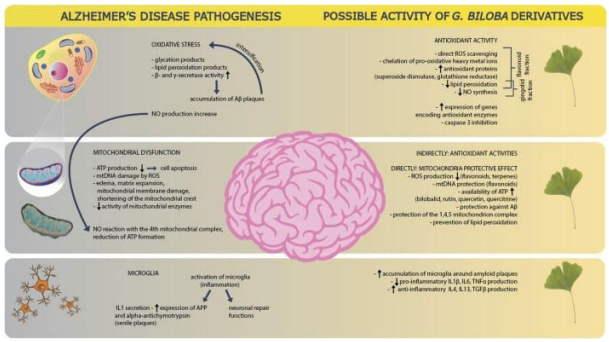

Figure 5: In Alzheimer's disease (AD), one of the main causes is oxidative stress, which leads to the formation of harmful substances like advanced glycation end products (AGEs) and lipid peroxidation products. This also increases the activity of certain enzymes, like beta and gamma secretases, and stimulates platelet activation, further increasing oxidative stress. Ginkgo biloba (GB) derivatives help reduce these effects by trapping reactive oxygen species (ROS), chelating metal ions, delivering antioxidant proteins, and reducing lipid peroxidation and nitric oxide (NO) production, mainly through the flavonoid and ginkgolide compounds. Another key issue in AD is mitochondrial dysfunction, which decreases ATP production and accelerates cell death. ROS can damage mitochondrial DNA and impair mitochondrial function. GB derivatives help protect against mitochondrial dysfunction by reducing ROS, protecting mitochondrial DNA, supporting ATP production, and protecting mitochondrial complexes. They also reduce lipid peroxidation.In AD, microglial cells, which are part of the brain's immune system, become activated due to inflammation, leading to an increase in pro-inflammatory cytokines. However, microglial activation also triggers repair mechanisms. GB derivatives support microglia in accumulating around amyloid plaques, reducing the production of harmful cytokines (like IL1β, IL6, TNFα), and increasing the production of anti-inflammatory cytokines (like IL4, IL13, TGFβ), helping to counteract inflammation in the brain.

Memory and cognition in AD

Cognitive decline is recognized as one of the main symptoms of AD. In the elderly, the prefrontal cortex plays a key role in cognitive function, where prefrontal dopaminergic innervationdecreases with age. This results in a decrease in the control of cognitive functions, i.e., cognitive flexibility, goal retention,inhibition of habitual or impulsive reactions and prospectivememory.

Ginkgo Biloba Leaves Extract for the Treatment of Anxiety, Stress and Depression

Ginkgo biloba leaf extract has showed promise in treating anxiety, stress, and depression. Studies have discovered that Ginkgo biloba extract (GBE) possesses antidepressant, anxiolytic, and antistress qualities, making it a possible natural therapy for mental health conditions.

Anti-stress effects

Research has shown that GBE can reduce stress symptoms in both young and old mouse models. It has also been demonstrated to boost cognitive performance and decrease the harmful impact of stress on the brain. Antidepressant effects in several trials, GBE has been shown to have considerable antidepressant effects. Research indicates that it can boost mood, alleviate depressive symptoms, and supplement traditional antidepressants.

Anxiolytic effects

Ginkgo biloba extract has also been shown to have anxiolytic properties, lowering anxiety symptoms in both animal and human tests. Research suggests that GBE could be an effective treatment for anxiety disorders. While the existing evidence is encouraging, further research is required to completely understand the effects of Ginkgo biloba leaf extract on anxiety, stress, and depression. However, present research suggests that GBE could be an effective natural treatment for mental health conditions [26-27].

Antiviral Activity

Antiviral activity refers to the ability of a substance to prevent viruses from infecting cells or reproducing. In the study by Haruyama & Nagata, researchers tested the effect of Ginkgo biloba leaf extract (Egb) on influenza viruses using MDCK cells. They applied Egb to the cells before exposing them to the virus and found that Egb significantly reduced the virus's ability to infect the cells. The effect was stronger at higher doses of Egb.

The study showed that Egb works during the early stage of infection, preventing the virus from entering the cells. Egb disrupts the virus's hemagglutinin, a protein that helps the virus attach to host cells. This means Egb directly affects the virus particles and blocks their ability to infect cells.

In the study by Liu et al., EGb 50, an herbal extract, showed anti-inflammatory effects by preventing the activation of microglia (immune cells in the brain) through blocking the NLRP3 inflammasome, a key player in inflammation. This suggests that EGb 50 could help reduce inflammation and oxidative stress linked to SARS-CoV-2 (the virus that causes COVID-19).

Additionally, EGb 50 peptides can effectively block ACE (angiotensin-converting enzyme) activity, helping lower blood pressure and reducing the effects of Ang II, a molecule that causes blood vessel tightening. This makes EGb 50 potentially helpful in protecting against acute lung injury (ALI) caused by high Ang II levels during COVID-19.

Antibacterial

In a study by Sati et al., different extracts of Ginkgo biloba leaves (methanol, ethanol, chloroform, and hexane) were tested for their ability to stop bacteria from growing. The methanol extract was the most effective, inhibiting the growth of all tested bacteria. However, different bacterial species responded differently to the extracts. Overall, small amounts of Ginkgo biloba leaf extracts showed the ability to fight both Gram-positive and Gram-negative bacteria.

Neurological activity [28-30]

Cognitive Function and Memory

A study showed that Ginkgo biloba extract (Egb) improved working memory by stimulating alpha-2 adrenergic receptors in the brain, which are often less active with aging. This suggests Egb can help improve memory in elderly individuals and Alzheimer's patients.

Tinnitus and Vertigo

Using Tebonin Egb761 (240 mg/day) significantly reduced tinnitus (27-40% improvement) and dizziness in dementia patients compared to a placebo, though the effect on dizziness was less pronounced.

Tardive Dyskinesia

Egb was found to reduce symptoms of tardive dyskinesia (TD), a movement disorder, by acting as an antioxidant, reducing oxidative stress, and increasing BDNF (a protein supporting brain health). A daily dose of 240 mg Egb-761 was shown to improve TD symptoms safely in patients with schizophrenia.

Parkinson's Disease

Studies indicated that Tebonin Egb761 may benefit Parkinson's patients by inhibiting MAO (monoamine oxidase), an enzyme involved in brain chemistry, helping to manage symptoms of the disease.

Summary

Ginkgo biloba extract shows potential in improving memory, reducing tinnitus and vertigo, managing tardive dyskinesia, and aiding Parkinson's disease due to its antioxidant, neuroprotective, and brain-regulating properties.

Other activities

Examined the impact of Tebonin Egb761 (a standardized Ginkgo biloba extract) on rat brain neurons. It focused on how it influenced normal and glutamate-stimulated activity, as well as the expression of tPA (a protein involved in excitotoxicity, which can damage neurons). The study found that Tebonin Egb761 provided protection against neural damage caused by excessive tPA. Investigated how Ginkgo biloba leaf extract affected liver damage in rats caused by thioacetamide (a toxic chemical). Results showed the extract could reduce liver fibrosis (scarring) and oxidative stress, highlighting its protective effects.

Found that Tebonin Egb761 protects melanocytes (pigment cells) in vitiligo patients from oxidative damage by activating the Nrf2-ARE signalling pathway, which boosts antioxidant defences. Studied GBE's effects on red blood cells under stress (caused by amyloid peptide, peroxide, or hypotonic conditions). GBE showed both protective and harmful effects depending on the type of stress.

Showed that rats pretreated with Tebonin Egb761 before brain injury (microinfarction) had better blood flow and higher brain energy levels, suggesting its potential in managing cerebral hypoxia. Demonstrated that GBE protects the heart in rabbits during myocardial ischemia-reperfusion injury by reducing oxygen-free radicals and enhancing antioxidant activity in heart cells Found that GBE prevents aortic rupture in mice with abdominal aortic aneurysms, but only in the early stages of the disease. Reviewed GBE's protective effects against natural toxins, chemical toxicity, and radiation. It was effective against toxins like scorpion venom and harmful chemicals like metals, ethanol, and pesticides. Showed that Tebonin Egb761 protected rats from cisplatin-induced hearing damage (ototoxicity).

Conclusion

Ginkgo biloba, one of the oldest living tree species, has demonstrated a wide spectrum of pharmacological properties, including antioxidant, anti-inflammatory, neuroprotective, and circulatory benefits. Extensive research supports its potential therapeutic applications in cognitive disorders, particularly in dementia and Alzheimer's disease, as well as in improving peripheral blood circulation and treating anxiety. However, the clinical efficacy of Ginkgo biloba remains a topic of debate due to variability in study designs, extract standardization, and dosage. While generally well-tolerated, its interactions with anticoagulants and potential side effects must be carefully considered. Further well-designed, large-scale clinical trials are essential to establish definitive therapeutic roles and safety profiles. In summary, Ginkgo biloba holds promise as a complementary herbal remedy, but its use should be based on evidence-based guidelines and under professional supervision

Ginkgo biloba, one of the oldest living tree species, continues to attract significant scientific and therapeutic interest due to its wide range of pharmacological properties. Rich

in flavonoids and terpenoids, the plant exhibits strong antioxidant, anti-inflammatory, neuroprotective, and vasodilatory activities. Numerous studies have supported its potential benefits in improving cognitive function, particularly in age-related disorders such as Alzheimer's disease and dementia, as well as in enhancing peripheral circulation and managing anxiety.

Despite promising preclinical and clinical findings, there remain challenges such as variability in extract standardization, inconsistent clinical trial results, and potential herb-drug interactions that must be addressed. Further research involving larger, well-designed randomized controlled trials and mechanistic studies is essential to validate its efficacy and safety across broader populations.

In conclusion, Ginkgo biloba holds significant therapeutic promise as a complementary medicine. However, a cautious and evidence-based approach must be adopted in its clinical use, especially considering individual patient profiles and concurrent medications. Standardized extracts like EGb 761 offer a reliable foundation for future pharmacological exploration and therapeutic applications.

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Conflicts of Interest

The authors declare no conflicts of interest.

Author Contribution

Both are contributed equally

Financial Support

None

Inform Consent and Ethical Statement

Not Applicable

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