DERLEME REVIEW

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Therapeutic Applications of *Ginkgo biloba* L. Tree: Systemic Review

Ginkgo biloba L. Ağacının Terapötik Uygulamaları: Sistematik Derleme

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ABSTRACT *Ginkgo biloba* L. is considered one of the oldest trees in the world and has been used for thousands of years for its variety of pharmacological effects. It is commonly known as ginkgo. Leaf extracts of this fossil tree have been standardized and patented under the name EGb761. EGb761 mainly consists of terpene trilactones which are unique to this species and flavone glycosides. It is supported by scientific research that these chemical components are responsible for the pharmacological effects of the tree. *G. biloba* L. has gained interest as a therapeutic plant for its favorable effects in cognitive impairment and neurodegenerative disorders like dementia. Its beneficial impacts on a wide range of pathological conditions, including cardiovascular health, asthma, psychiatric disorders, skin problems, and glaucoma as well as antioxidant, anti-inflammatory, anticancer and hepatoprotective activities, have been reported through experimental and clinical research. Ginkgo is generally well tolerated but when combined with warfarin or other antiplatelet medications, it can increase the risk of bleeding. This review mainly focuses on recent studies of pharmacological effects of *G. biloba* L. and indicates that *G. biloba* L. might be beneficial in the prevention and improvement of neurological, cardiovascular, pulmonary, ocular, metabolic, mental disorders also have anticancer and antimicrobial properties however further studies and clinical trials are necessary to confirm the safety and efficacy of *G. biloba* L. in order to guide medical use.

Keywords: *Ginkgo biloba*; EGb761; ginkgolides; ginkgolic acid; pharmacological activity

ÖZET *Ginkgo biloba* L., dünyanın en eski ağaçlarından biri olarak kabul edilir ve çeşitli farmakolojik etkileri nedeniyle binlerce yıldır kullanılmaktadır. Genellikle ginkgo olarak bilinmektedir. Bu fosil ağacın kendine has yapraklarının ekstreleri standardize edilmiş ve EGb761 adı ile patent almıştır. EGb761 esas olarak terpen trilaktonlar ve flavon glikozitlerinden oluşur, *G. biloba* ağacının farmakolojik etkilerinden bu kimyasal bileşenlerin sorumlu olduğu bilimsel araştırmalarla desteklenmektedir. *G. biloba L.*, bilişsel bozulma ve bunama gibi nörodejeneratif bozukluklarda olumlu etkileri nedeniyle terapötik bir bitki olarak ilgi görmüştür. Kardiyovasküler sağlık, astım, psikiyatrik bozukluklar, cilt sorunları ve glokom dâhil olmak üzere çok çeşitli patolojik durumlar üzerindeki yararlı etkilerinin yanı sıra antioksidan, antiinflamatuar, antikanser ve hepatoprotektif aktiviteleri deneysel ve klinik araştırmalar yoluyla rapor edilmiştir. *G. biloba* L. genellikle iyi tolere edilir, ancak varfarin veya diğer antiplatelet ilaçlarla birlikte kullanıldığında kanama riskini artırabilir. Bu derleme, temel olarak *G. biloba* L. bitkisinin farmakolojik etkilerine ilişkin son çalışmalara odaklanmaktadır ve *G. biloba* L. bitkisinin nörolojik, kardiyovasküler, pulmoner, oküler, metabolik, zihinsel bozuklukların önlenmesinde ve iyileştirilmesinde faydalı olabileceğini, ayrıca antikanser ve antimikrobiyal özelliklere sahip olduğunu, ancak *G. biloba* L. bitkisinin güvenliğini ve etkinliğini doğrulamak ve tıbbi kullanıma geçebilmek için daha fazla araştırma ve daha ileri klinik çalışmaların gerekli olduğunu ortaya koymaktadır.

Anahtar Kelimeler: *Ginkgo biloba*; EGb761; ginkgolidler; ginkgolik asit; farmakolojik etkiler

Ginkgo biloba L., commonly known as ginkgo, is one of the oldest trees in the world that it often referred as "living fossil" and is the only species survived from *Ginkgoaceae*.[1] *G. biloba* L. is a plant that originated in China and has been cultivated in Asia. Ginkgo thrives in full sun and moderate, medium-moisture soil.[2] One of the most notable aspects is the leaves of *G. biloba* L., they are distinguished by their fan form and dichotomous venation.[3] *G. biloba* L. female plants produce orange apricot-like structures that are not technically fruits. They are seeds that have a soft, fleshy shell section called sarcotesta and a hard section called sclerotesta. The odor of the sarcotesta is powerful and foul-smelling, and most peo-

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ple find it unpleasant.[4] *G. biloba* L. leaf extracts have been utilized in traditional Chinese medicine for over 5,000 years. It is currently widely grown for its leaves and nuts. The Materia Medica, a Chinese herbal encyclopedia written around 2800 BC, mentions ginkgo's medicinal benefits. Ginkgo leaves were used in traditional Chinese medicine to treat circulatory abnormalities, asthma, vertigo, fatigue, tinnitus, and respiratory ailments. Ginkgo nuts have long been used to treat fever, sputum, and cough, as well as toothaches and diarrhea, gonorrhea, and skin problems, and to reduce micturition frequency.[5]

Standardized *G. biloba* extract (GBE), EGb761, developed by Beaufor-Ipsen Pharma in France and Dr. Willmar Schwabe Pharmaceuticals in Germany, contains 24 percent flavonoid glycosides, 6 percent terpene trilactones (TTL), and less than 5 ppm ginkgolic acid.[6] The antioxidant and free radical scavenging properties of EGb761 are thought to be aided by flavonoids. TTLs, or ginkgolides and bilobalides, are unique to *G. biloba* and can only be found in the *G. biloba* tree. TTLs are linked to platelet activating factor (PAF) antagonistism. PAF causes inflammation, contracts smooth muscles, and increases the permeability of vessel walls.[7]

Ginkgo is one of the most studied medicinal plants since its is used for ages and marketed widely all around the world.[8-11] As ginkgo has remarkable therapeutic indications, it has been the subject of many research.[7,13-15] Current therapeutic indications of GBE include dementia, memory and cognitive function improvement, dyscirculatory encephalopathy, neurosensory disorders such as tinnitus, vertigo, diabetic retinopathy, dizziness, hypacusia and senile macular degeneration, peripheral circulation and microcirculation disturbances such as diabetic microangiopathy, Raynaud's syndrome, arteriopathy of lower limbs, atherosclerosis, retinopathy and chronic ischemia of peripheral tissues.[11] Bioactive compounds of EGb761 and their therapeutic effects are summarized in Table 1.

PHARMACOLOGICAL EFFECTS

EFFECTS ON NEUROLOGICAL DISORDERS

Several research have aimed to determine whether EGb761's neuroprotective impact against various forms of injury also leads in enhanced neurological outcome.[16-18] Passive avoidance tests were used to measure changes in behavior, learning, and memory ability in most cases, both before and after injury.[8]

In Vitro Studies

EGb761 has been shown to improve neuronal cell metabolism, antioxidant activity, cerebral circulation, and the muscarinic cholinergic system. In vitro, EGb761 protected neurons against toxicity caused by Abeta and nitric oxide (NO), and it decreased apoptosis both in vitro and in vivo. In hippocampal neural cells, it was discovered that EGb761 can prevent Abeta1-42-induced Ca^{2+} dyshomeostasis that are caused by toxic mediators such H_2O_2 and PAF.[19]

In Vivo Studies

The impaired behavior of streptozotocin-treated rats was slowed considerably by EGb761. Furthermore, rats treated with EGb761 showed considerably better memory after bilateral carotid artery closure as well as scopolamine-induced amnesia. Stoll et al. found that EGb761-treated aged rats learned passive avoidance better than vehicle-treated rats.[8] After treatment with GBE, rats showed less scopolamine-induced amnesia, enhanced cognitive performance in young and old rats, and boosted short-term memory in mice.[19] Due to the neuroprotective effects of the quercetin, kaempferol and isorhamnetin, and the terpene lactones ginkgolides A, B, C, J and bilobalide, *G. biloba* seed extract improves recognition memory, short- and long-term recall and spatial working memory in naive rats, and may be as promising as *G. biloba* leaf extract in phytopharmacy. The hippocampus and medial prefrontal cortex are thought to be involved in the reported effect.[20] In animal research it is proved that GBE improves vestibular compensation. However, the usual problems of transferring data from animal models to humans should be taken into account in this context, particularly in symptoms with a significant subjective component.[14]

When behavioral signs of tinnitus were investigated in mice, studies revealed that EGb761 treatment resulted in a decrease in tinnitus.[21,22] In a study it is reported that prophylactic treatment of GBE dramatically lowers noise-induced hearing loss and tin-

TABLE 1: Summary of bioactive compounds of EGb761 and their therapeutic effects/functions.

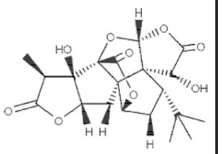
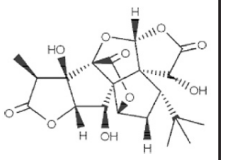
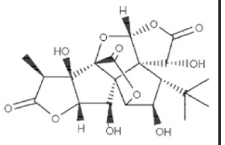
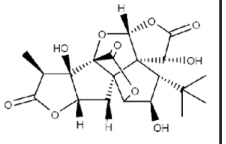
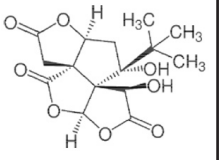
Class	Bioactive compounds	Molecular structure	Effects/Functions	References
Triterpene lactones	Ginkgolide A		• Improves recognition memory, short- and long-term recall and spatial working memory • PAF antagonistism • Antidepressant effects	7, 14, 35, 63
	Ginkgolide B		• Improves recognition memory, short- and long-term recall and spatial working memory • PAF antagonistism • Treatment of neurological disorders • Treatment of bronchial asthma by decreasing the activation of human peripheral blood mononuclear cells • Reduction of cervical cancer cell proliferation • Triggers cell cycle arrest and accelerates cell death by influencing the mitogen-activated protein kinase signaling system • Lowers plasma triglyceride levels and body weights • Antidepressant effects • SARS-CoV-2 3CLpro inhibitory effects	7, 14, 28, 35, 42, 47-49, 58, 63
	Ginkgolide C		• Improves recognition memory, short-and long-term recall and spatial working memory • PAF antagonistism • Reduces lipid aggregation by activating the sirtuin 1-AMP-activated protein kinase cascade • Improves triglyceride breakdown via boosting the phosphorylation of hormone-sensitive lipase and the synthesis of adipose triglyceride lipase • Antidepressant effects	7, 14, 35, 63
	Ginkgolide J		• Improves recognition memory, short- and long-term recall and spatial working memory • PAF antagonistism • Antidepressant effects	7, 14, 35, 63
	Bilobalide		• Improves recognition memory, short- and long-term recall and spatial working memory • PAF antagonistism	7, 14

TABLE 1: Summary of bioactive compounds of EGb761 and their therapeutic effects/functions *(continued)*.

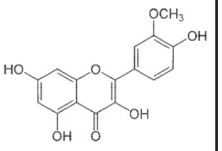
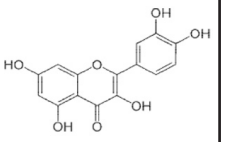
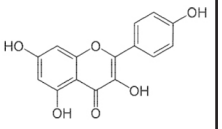
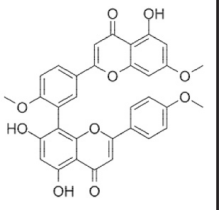
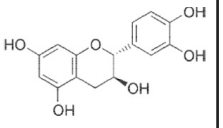
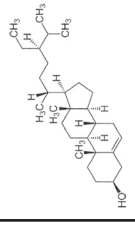
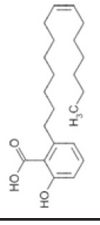
Class	Bioactive compounds	Molecular structure	Effects/Functions	References
Flavonoid	Isorhamnetin		• Improves recognition memory, short- and long-term recall and spatial working memory • Lower total cholesterol, triglyceride, and low-density lipoprotein levels in the blood • Enhance high-density lipoprotein levels • Prevent vascular endothelial cell disintegration • Prevent plaque formation	14, 36, 37
	Quercetin		• Improves recognition memory, short-and long-term recall and spatial working memory • Treatment of neurological disorders • Lower total cholesterol, triglyceride, and low-density lipoprotein levels in the blood • Enhance high-density lipoprotein levels • Prevent vascular endothelial cell disintegration • Prevent plaque formation	14, 28, 36, 37
	Kaempferol		• Improves recognition memory, short- and long-term recall and spatial working memory • Treatment of neurological disorders • Lower total cholesterol, triglyceride, and low-density lipoprotein levels in the blood • Enhance high-density lipoprotein levels • Prevent vascular endothelial cell disintegration • Prevent plaque formation	14, 28, 36, 37
	Sciadopitysin		• SARS-CoV-2 3CLpro inhibitory effects	48, 49
	Catechin		• Treatment of neurological disorders • Lower total cholesterol, triglyceride, and low-density lipoprotein levels in the blood • Enhance high-density lipoprotein levels • Prevent vascular endothelial cell disintegration • Prevent plaque formation	28, 36, 37

TABLE 1: Summary of bioactive compounds of EGb761 and their therapeutic effects/functions *(continued)*.

Class	Bioactive compounds	Molecular structure	Effects/Functions	References
Phytosterols	Beta-sitosterol		• Treatment of neurological disorders	28
Organic acids	Ginkgolic acid		• SARS-CoV-2 3CLpro inhibitory effects • Antiviral effects by disrupting viral replication • Antimicrobial effects on Gram-positive bacteria such as *Bacillus amyloliquefaciens*, *Rhodococcus jostii*, *Staphylococcus aureus*, *Streptococcus thermophilus*, and vancomycin-resistant *Enterococcus* spp. • Antifungal effects • Acaricidal action	13, 48, 49, 65, 66

PAF: Platelet activating factor.

nitus development of Mongolian gerbils. In a guinea pig model of lipopolysaccharide-induced otitis media with labyrinthitis, GBE greatly reduces cochlear damage and exerts neuroinflammatory actions in lipopolysaccharide-activated primary microglial cells, suggesting a role in neurodegenerative diseases.[21]

The major components of GBE are flavonoid glycosides and terpene lactones, which have biological features include improving PAF receptor antagonism, vascular blood flow and protecting the cochlea from free radicals. GBE may be useful for sensorineural hearing loss (SSNHL) because of its antioxidant and vascular properties. The protective effects of GBE on the inner ear have been demonstrated in several animal models of ototoxicity, hearing loss related with aging, and noise damage.[23]

Recent research in animal Parkinson' disease (PD) models have shown that EGb761 may be useful in the treatment of PD because it slows the loss of striatal dopamine levels and prevents nigrostriatal pathway neurodegeneration.[24,25] The toxicity of levodopa was similarly reduced after therapy with EGb761. *G. biloba* dropping pill (GBDP) is a Chinese-made *G. biloba* leaf extract having antioxidative and neuroprotective properties in a variety of disorders. The researchers discovered 12 different compounds in EGb761 and GBDP, largely from the organic acid and flavonol families. Furthermore, quantitative study of these compounds revealed that EGb761 included more organic acids than GBDP, although GBDP contained more flavonoids. However, the chemical components of GBDP have yet to be identified, it is unknown whether GBDP is an effective PD medication or how it varies from EGb761 in terms of mechanism and treatment impact. Between GBDP and EGb761, GBDP had greater anti-PD effects than GBE, particularly in a 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced mouse PD model. The findings provided new information about the possible use of GBDP in the treatment of PD.[26]

Clinical Studies

EGb761 increased memory, in asymptomatic human volunteers.[8]

Researchers examined the efficacy of cholinesterase inhibitors and EGb761 in Alzheimer's disease (AD) from published placebo-controlled trials and revealed no significant difference in symptom progression in patients who were treated with metrifonate, donezepil, rivastigmine, or EGb761, implying that all medications are equally beneficial in the treatment of mild to moderate Alzheimer's dementia.[27] The findings imply that catechin, quercetin, beta-sitosterol, kaempferol, and ginkgolide B, which are active components of GBE are important in the treatment of neurological disorders. GBE regulate oxidative stress, apoptosis, and other complex mechanisms through, multi-target, multi-pathway, multi-component and synergistic action, providing a reference and scientific guide for future research on neurological disorder treatment using GBE or their bioactive components.[28]

The studies demonstrated that EGb761 once-daily formulation in the treatment of dementia in patients with neuropsychiatric symptoms was safe and preferable to the use of a placebo in this population in a randomized, double-blind, multicenter trial with a considerable number of participants and adequate follow-up.[10] Although EGb761 was found to be ineffective in preventing dementia, the clinical data for its usage in slowing the progression of dementia is promising and warrants additional clinical investigation.[17,29-31]

EGb761, has been demonstrated to have therapeutic efficacy such as modest improvements in cognitive function in number of studies, after it is administered to AD and non-AD patients. Once-daily 240 mg of EGb761, improved psychiatric symptoms, cognitive functioning and functional capacities in 404 outpatients with AD and vascular dementia in a 24-week randomized controlled trial (RCT). According to the Ginkgo Evaluation of Memory study, which is a doubleblind, placebo-controlled, randomized clinical trial with 3,069 community-dwelling participants at the age of 72 to 96 years, taking 120 mg twice daily of GBE did not reduce cognitive impairment in older adults with normal cognition or mild cognitive impairment.[19]

The effect of EGb761 on cognitive impairment and memory loss related with disease and aging is a great interest. GBE's ability to modify excitotoxic glutamatergic neurotransmission, reduce amyloid aggregation and toxicity, and act as a radical scavenger suggests that it could be used to treat a variety of dementias. Clinical trials of 240 mg daily EGb761 administration to dementia patients show that it is effective in stabilizing or reducing mental function decline, especially in patients with neuropsychiatric symptoms. The European studies included AD patients with a composite score of >4 on the Neuropsychiatric Inventory (NPI) and found significant improvements in the NPI as well as reductions in anxiety and depression Furthermore, a clinical trial combining EGb761 and a regularly prescribed cholinesterase inhibitor, donepezil, reveals that the combination of the two medicines is more effective than using only either one.[17]

Tinnitus, acute cochlear deafness, vertigo, and abnormalities in equilibrium are the most common clinical applications of EGb761.[14,21,22] RCTs demonstrate GBE has clinical efficacy in both vestibular and non-vestibular vertigo, but due to a lack of standardized research methodology among the trials, no clear conclusions can be formed based on this limited data.[14]

The self-perception of tinnitus loudness and intensity improved significantly 90 days following hearing aid fitting in a study. GBE showed significant improvement on hearing, in the pre-treatment and post-treatment comparisons, but not significantly in the improvement of tinnitus in comparison to the group that used either a hearing aid or EGb761 alone. Regardless of tinnitus onset time of patient, the results showed that using EGb761 alone or in combination with a hearing aid was beneficial. EGb761 may have a potential therapeutic effect on tinnitus by controlling neuromodulation in the central auditory pathway. On the other hand, there are inconclusive research about the link between GBE and tinnitus in the literature, and some studies have revealed no differences following GBE treatment. The lack of standardization of the extracts, no standard rigorous techniques for evaluating therapeutic effectiveness, and no ideal dosages and pharmaceutical forms can all be blamed for the contradictory therapeutic results of GBE as tinnitus treatment.[21]

GBE has been proven to compare favorably with pentoxifylline, nicergoline and naftidrofuryl in the treatment of SSNHL in clinical trials. *G. biloba* may have an additive therapeutic impact in individuals with SSNHL when used in combination with corticosteroids, but there is no firm proof of its efficacy.[23]

CARDIOVASCULAR PROTECTIVE EFFECTS

In Vivo Studies

G. biloba has been shown to have antihypertensive properties in a range of animal models.[32-35] EGb761 inhibited renal NO overproduction and reduced tumor necrosis factor-α and interleukin-6 levels in kidney tissue in rats with damaged kidneys, resulting in hypotensive and renoprotective effects. The hypotensive impact of GBE could be related to enhanced endothelial NO synthase expression and NO generation, which reduces blood pressure through dilating blood vessels. GBE also causes hypotension via increasing endothelial intracellular Ca^{2+} levels and endothelium-dependent vasodilation.[35]

Researchers discovered that EGb761 and ginkgo flavonoids can lower total cholesterol, triglyceride, and low-density lipoprotein levels in the blood, enhance high-density lipoprotein levels, and prevent vascular endothelial cell disintegration and plaque formation.[36,37] EGb761 can lower blood lipid levels in patients with coronary artery disease and slow the course of atherosclerosis. The degree of atherosclerosis and markers of oxidative stress were improved after therapy with EGb761 for patients with metabolic syndrome.[36]

Clinical Studies

In patients with coronary heart disease (CHD), GBE raised NO, endothelin, and endothelin ratio, and the increase in left anterior descending artery blood flow was strongly linked with the increases in NO and endothelin. The left ventricular systolic and diastolic meaning of the left ventricular expulsion portion's overall effective rate. The early diastolic phase and late diastolic filling ratios were both improved significantly.[36]

G. biloba is thought to help prevent strokes by decreasing the formation of blood clots and improving blood flow to the brain.[36,38-41] It is also hypothesized that the herb protects brain cells from free radical damage after a stroke. Flavonoids of GBE inhibited lipid peroxidation and oxidative modification of superoxide anion radical scavenging, and the quantity of vitamin C increased greatly, achieving the therapeutic effect of CHD.[36]

EFFECTS ON PULMONARY DISORDERS

In Vitro Studies

PAF, an inflammatory mediator capable of generating persistent inflammation of the airways and bronchial hyperreactivity, has been demonstrated to be inhibited by Ginkgolide B in *G. biloba*.[42-46] GB believed to have a contribution in the treatment of bronchial asthma by decreasing the activation of asthmatic patients' human peripheral blood mononuclear cells.[42,47] Protein kinase C (PKC) activation is required for PAF activation on asthma, and GB, a natural PAF antagonist, can prevent PAF-mediated inflammatory reactions.[48]

EGb761 is found to be responsible for severe acute respiratory syndrome-coronavirus-2 3-Chymotrypsin-like protease (SARS-CoV-2 $3CL^{pro}$) inhibition. The bioflavones and ginkgolic acids were discovered to have effective SARS-CoV-2 $3CL^{pro}$ inhibition activities after evaluating the inhibitory potentials of twenty phytochemicals extracted from EGb761 against SARS-CoV-2 $3CL^{pro}$. Two ginkgolic acids and a bioflavone (sciadopitysin) showed the most powerful SARS-CoV-2 $3CL^{pro}$ inhibitory effects among all phytochemicals evaluated in EGb761. Natural bioflavones could be useful as lead chemicals in the development of anti-coronavirus disease-2019 (COVID-19) or broad-spectrum anti-CoVs drugs but they should be substantially modified to improve both inhibitory potency and drug-like features in order to develop more effective orally administered $3CL^{pro}$ inhibitors. Another method is to develop nasal administration systems for delivering bioactive bioflavones to the lungs, so blocking COVID-19 viral replication at this target organ and thereby reducing COVID-19's primary symptoms. Ginkgolic acids have been shown to have a wide spectrum of antiviral actions by disrupting viral replication, according to growing evidence. In general, toxic ginkgolic acids

levels in marketed *G. biloba* preparations are strictly monitored to be less than 5 ppm, since these agents could lead to serious allergic reactions. Ginkgolic acids should not be administered orally but could be administered as disinfection or cleaning preparations for external usage. The ginkgolic acids isolated from EGb761 have a hydrophobic long chain structure, and these compounds could be easily modified to behave as surfactants. It is suggested that new antiviral surfactants could be produced and developed in the future utilizing ginkgolic acids as starting materials, and they could be utilized in combination with current commercial disinfectants to prevent and disinfect a wide range of coronaviruses in vitro.[48,49]

Clinical Studies

In one study, minor variations in eosinophil, PKCα positive expression rate, and lymphocytes were found between two asthma patient groups, one treated with glucocorticoids (GS) and the other with GS plus GBE. In the second group, eosinophils, the positive expression ratio of PKCα, and lymphocytes were all lower. This found that GBE may reduce future airway inflammation in asthmatic patients treated with GS, and that this effect is time-dependent. As a result, GBE and glucocorticosteroids have complimentary effects in the treatment of asthma.[48]

EFFECTS ON OCULAR DISORDERS

In Vitro Studies

GBE has the potential to treat retinal diseases with its ability to induce lysosomal autophagy, which promotes the clearance of neurodegenerative aggregates.[50-52] Extensive potential of the active compounds of GBE in resolving glaucomatous damage on a molecular level, tests were conducted to investigate if GBE could leverage its neuroprotective capabilities in cases of normal tension glaucoma.[50,51,53-55]

In Vivo Studies

GBE administration after light-induced injury or optic nerve hypoplasia crushing resulted in fewer apoptotic cells in the photoreceptor and outer nuclear layer, as well as higher retinal ganglion cell survival in animal studies. Studies also demonstrated that GBE could be used to treat retinitis pigmentosa caused by oxidative dysregulation. In addition, EGb761 therapy reduced the incidence of retinal detachment and inflammation of uveitis also prevented retinal disease related inflammation.[50-52]

Clinical Studies

Patients with glaucoma who were given GBE for two days had elevated ocular artery end-diastolic velocity, as determined by color Doppler imaging. GBE also increased blood flow velocity in the superior and inferior capillaries, retrobulbular vasculature. It also reduced vascular resistance in the central retinal and nasal short posterior ciliary arteries, according to a different study. Increased peripapillary blood flow, as well as increased blood volume and velocity, were observed in a study of normal tension glaucoma patients who were administered GBE for four weeks.[50]

ANTICANCER EFFECTS

In Vitro Studies

G. biloba polysaccharides inhibit the proliferation of human endometrial cancer cells and breast cancer cells. Capsules containing *G. biloba* polysaccharides can be used to treat gastric cancer by promoting apoptosis and inducing tumor cell differentiation. *G. biloba* leaves are high in selenium-containing polysaccharide, which has an anticancer effect in human bladder cancer cells by changing Bcl-2 expression, causing numerous alterations in the mitochondrial membrane, and releasing cytochrome c to the cytoplasm.[56]

GBE regulates E-cadherin expression level and affects invasion and migration of carcinoma. It is demonstrated that treating colorectal cells with EGb761 inhibited their capacity to invade by targeting lincRNA-p21. Furthermore, experiments indicated that nuclear lincRNA-p21 impacts fibronectin expression via binding to the promoter of the fibronectin gene. During EGb761 administration, cytoplasmic lincRNA-p21 inhibited the ubiquitination process, stabilizing E-cadherin protein.[57]

GB had influence on the reduction of cervical cancer cell proliferation. By influencing the mitogen-activated protein kinase signaling system, GB trig-

gered cell cycle arrest and accelerated cell death. As a result, it is suggested that GBE is a unique and promising anti-tumor medication for cervical cancer treatment.[58]

In a study twenty-five phytocompounds from the *G. biloba* nut were docked into the HER2 binding pocket for their HER2 inhibitory activities and cianidanol was the lead bioactive compound. It is possible that cianidanol could act as an antagonistic agent against HER2+ that is overexpressed in aggressive female breast cancer.[59]

GBE inhibits lung cancer cell proliferation, invasion, and colony formation, indicating that it acts as a tumor inhibitor. GBE triggered autophagy in lung cancer cells, but not apoptosis, and this was dependent on Beclin-1. Anticancer effect of GBE could be due to its ability to reduce NLRP3-related inflammation. GBE appears to be a promising therapeutic candidate for the treatment of lung cancer.[60]

In Vivo Studies

GBE reduced alpha-fetoprotein, glypican-3, and carcinoembryonic antigen levels and improved histological features in rats with hepatocellular carcinoma, implying that GBE's anti-cancer capabilities were produced by its anti-proliferative and apoptotic properties in the animal model.[61]

EFFECTS ON METABOLIC DISORDERS

In Vivo Studies

In overweight rats on a high-fat meal diet, the GBE was found to successfully reduce body weight. In a separate study, GBE treatment was found to lower both body weight growth and food/energy intake in high-fat diet-fed rats for 8 weeks after a 2-week injection of 500 mg/kg of GBE, compared to the untreated rats. The difference between the amount of meal served and the remaining volume after 24 hours was used to determine the food intake evaluation. Reduced food intake might be considered due to GBE consumption because the environmental variables were same.[32] The effects of Ginkgolide B on body weight in C57BL/6 male mice were investigated in a high-fat diet-induced model of obesity, ginkgolide B lowered plasma triglyceride levels and body weights. In an in vitro study of HepG2 liver cells, treatment with 3-100 M Ginkgolide C reduced lipid aggregation and improved triglyceride breakdown via boosting the phosphorylation of hormone-sensitive lipase and the synthesis of adipose triglyceride lipase. In an oleic acid-induced fatty liver model, ginkgolide C was discovered to increase lipolysis and decrease lipid aggregation by activating the sirtuin 1-AMP-activated protein kinase cascade.[35]

Clinical Studies

Decreases in fasting salivary glucose (FSG), were similarly associated with changes in blood hemoglobin A1c (HbA1c) in both the GBE and placebo-treated groups, indicating that GBE can help with glycemic management as a supplement to metformin. Only GBE-treated patients showed significant reductions in body mass index (BMI), waist circumference, and visceral adiposity index (VAI). Several active ingredients in the GBE, particularly polyphenols, are thought to be responsible for improving peripheral tissue sensitivity to insulin while lowering or eliminating insulin resistance (IR). When utilized as an adjuvant in type 2 diabetes mellitus (T2DM) patients who were poorly treated by metformin alone, GBE improved blood HbA1c and FSG concentrations, IR index, BMI, and VAI. This finding supports the use of GBE as a dietary supplement in T2DM patients' treatment regimens.[62]

EFFECTS ON MENTAL DISORDERS

In Vivo Studies

GBE appears to have favorable effects on ischemia, hypoxia, and stress reduction in cases of cognitive deterioration, according to the literature. Stress-induced depression is reduced by a water-soluble *G. biloba* polysaccharide, which also restores intestinal dysbiosis. In several brain locations, mice treated with *G. biloba* polysaccharides showed higher serotonin and dopamine levels than the unpredictably chronic mild stress mice. Polysaccharides produced from *G. biloba* leaves could be promising pharmaceutical candidates in the treatment of depression. In treatment of post-traumatic stress disorder, GBE resulted in a significant increase in venlafaxine. Many earlier investigations have revealed that diterpene

ginkgolides in GBE have neuroprotective properties. In mice, diterpene ginkgolides had antidepressant but not antianxiety effects, suggesting that GBE could be used to treat serious depressive disorders.[35,63]

Clinical Studies

In older adult patients with cognitive impairment, EGb761 enhances emotional function and stabilizes mood.[35,63,64] EGb761 has also been demonstrated to alleviate anxiety symptoms in adults with mental illness, even in younger patients with anxiety symptoms. The chemical structures and synergy of various chemical components found in EGb761 can produce neuroprotective effects, which are mediated by antioxidant effects and the regulation of neurotransmission, neuroendocrine signaling, and neurotrophic factors, resulting in the relief of anxiety symptoms. GBE can effectively reduce depressive symptoms and lower serum S100B expression, implying that GBE can restore neuronal activity in adults, who have been treated for depression. When GBE is used with antidepressant medicines, a synergistic effect is noticed, resulting in faster outcomes than when the antidepressant drugs are used alone.[35,63]

ANTIMICROBIAL PROPERTIES

In Vitro Studies

Ginkgolic acids have been showed antimicrobial affects on Gram-positive bacteria such as *Bacillus amyloliquefaciens, Rhodococcus jostii, Staphylococcus aureus, Streptococcus thermophilus*, and vancomycin-resistant *Enterococcus* spp. Ginkgolic acids have been shown to be more effective against Gram-positive bacteria than Gram-negative bacteria. Antifungal and acaricidal action are two more pharmacological properties of ginkgolic acids, which could explain the usage of seeds in traditional medicine, particularly for crab lice.[13,65,66]

CONCLUSION

The standardized Ginkgo leaf extract preparation has been discovered to have number of therapeutic effects on neurodegenerative diseases, cancer, cardiovascular diseases, tinnitus, pulmonary, ophthalmic, metabolic, and psychiatric disorders. The antioxidant activities of the extract have been the key underlying mechanism of action in all of these cases. Ginkgo leaf extract has therefore been demonstrated to be a potential herbal drug with established therapeutic advantages. When the requisite clinical investigations are conducted, it is expected that GBEs may be used in the treatment of several problems or may help discovery of medications that will improve the course of many diseases. However, its long-term safety must be addressed thoroughly.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Sena Öztürk, Aynur Sarı;* ***Design:*** *Sena Öztürk, Aynur Sarı;* ***Control/Supervision:*** *Aynur Sarı;* ***Data Collection and/or Processing:*** *Sena Öztürk;* ***Analysis and/or Interpretation:*** *Sena Öztürk, Aynur Sarı;* ***Literature Review:*** *Sena Öztürk;* ***Writing the Article:*** *Sena Öztürk;* ***Critical Review:*** *Sena Öztürk, Aynur Sarı.*

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