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A Review of Medicinal Properties of *Ginkgo biloba* L.

Ginkgo *biloba* L.'nin Tıbbi Özelliklerinin İncelenmesi

Demet DİNCEL[1] Göktuğ Gürkan AYDEMİR[2] Onur ALTINBAŞAK[3]
Betül BÜYÜKKILIÇ ALTINBAŞAK[4] Pelin YÜKSEL MAYDA[5]

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ABSTRACT

The history of the *Ginkgo biloba* L. species' history dates back to very ancient times. It can live for approximately a thousand years and it is quite resistant to adverse conditions. Its leaves contain important components that make them useful for medicinal purposes. In addition, its seeds have also been used as a therapeutic agent in traditional Chinese medicine. *G. biloba* extracts are usually used in standardized dosage forms in medicinal preparations. Today, the preffered form is a standardized extract of *G. biloba* called Tebonin Egb761.

Studies have shown that *G. biloba* leaf extract is effective in treating symptomatic relief of mild to moderate cerebral insufficiency in humans. It provides effective treatment in both Alzheimer's and vascular dementia patients. The herbal extract can also have positive effects on the quality of life in healthy individuals. *G. biloba* is effective against inner ear disorders and provides protection against endothelial damage. Besides, scientific studies have demonstrated that it has antioxidant, anti-inflammatory, antiviral, antibacterial, antidiabetic, anticancer, neuroprotective, cardioprotective, and many other effects. *G. biloba* is considered an important nutraceutical due to its scientifically proven effects. There is a growing interest in the scientific community regarding this plant.

In this study, a review was made by compiling the data obtained from the literature on the "botanical characteristics", "history", "bioactive components", and "biological activities" of the *G. biloba* species.

Keywords: Ginkgo Biloba, Ethnobotany, Biological Activity

1. *Bezmi Alem Foundation University, Faculty of Pharmacy, Asst. Prof., dinceldmt@hotmail.com ORCID ID: 0000-0001-8319-9307*
2. *- aydemirgurkan@hotmail.com, ORCID ID: 0009-0001-9730-200X*
3. *Kocaeli Health and Technology University, Avrupa Vocational School, Lecturer, onur.altinbasak@kocaelisaglik.edu.tr, ORCID ID: 0000-0002-7167-7663Kocaeli Health and Technology University, Faculty of Pharmacy, Asst. Prof., betul.altinbasak@kocaelisaglik.edu.tr, ORCID ID: 0000-0002-9250-776X*
4. *Kocaeli Health and Technology University, Faculty of Pharmacy, Asst. Prof., betul.altinbasak@kocaelisaglik.edu.tr, ORCID ID: 0000-0002-9250-776X*
5. *Kocaeli Health and Technology University, Faculty of Pharmacy, Prof. Dr., pelin.mayda@kocaelisaglik.edu.tr, ORCID ID: 0000-0002-6998-5421*

ABSTRACT

Ginkgo biloba L. türünün geçmişi çok eskilere dayanmaktadır. Yaklaşık bin yıl yaşayabilmekte olup, olumsuz koşullara karşı oldukça dayanıklıdır. Yaprakları bitkiyi tıbbi açıdan faydalı kılan önemli bileşenler taşımaktadır. Ayrıca tohumları geleneksel Çin tıbbında terapötik bir ajan olarak da kullanılmıştır. *G. biloba* ekstraktları genellikle tıbbi müstahzarlarda standartlaştırılmış dozaj formlarında kullanılır. Günümüzde, *G. biloba* türünün standartlaştırılmış bir özü olan Tebonin Egb761 tercih edilmektedir.

Çalışmalar, *G. biloba* yaprağı ekstraktının insanlarda hafif ila orta dereceli serebral yetmezliğin semptomatik tedavisinde etkili olduğunu göstermiştir. Alzheimer ve vasküler demans hastalarında da etkin tedavi sağlamaktadır. Bitki ekstresi ayrıca sağlıklı bireylerde yaşam kalitesi üzerinde olumlu etkilere sahip olabilir. *G. biloba*, iç kulak rahatsızlıklarına karşı etkilidir ve endotel hasarına karşı koruma sağlar. Ayrıca bilimsel çalışmalar antioksidan, antienflamatuar, antiviral, antibakteriyel, antidiyabetik, antikanser, nöroprotektif, kalp koruyucu ve daha birçok etkiye sahip olduğunu göstermiştir. *G. biloba*, bilimsel olarak kanıtlanmış etkileri nedeniyle önemli bir nutrasötik olarak kabul edilir. Bilim camiasında bitkiye artan bir ilgi vardır.

Bu çalışmada *G. biloba* türünün "botanik özellikleri", "tarihçesi", "biyoaktif bileşenleri" ve "biyolojik aktiviteleri" ile ilgili literatürden elde edilen veriler derlenerek bir inceleme yapılmıştır.

Anahtar Kelimeler: Ginkgo Biloba, Etnobotanik, Biyolojik Aktivite

Introduction

All living things in nature are in balance. In mythology, plants are seen as the most precious gift given to man by the gods. Plants have been an integral part of human existence since the beginning of time, with a longstanding relationship between humans and plants. According to archeological findings from ancient times, people benefited from plants to obtain food and to eliminate health problems (Balkaya & Yanmaz, 2001; Faydaoğlu & Sürücüoğlu, 2011; Gezgin, 2006; Koçyiğit, 2005). *G. biloba* L. has gained the attention of researchers due to its medicinal importance.

G. biloba is called 'Tapınak ağacı, Fosil ağaç, Çin yelpazesi, Fil kulağı, Kız saçı, Mabet ağacı, Gümüş kayısı' in Turkish and 'Maidenhair tree, Living fossil, Temple balm, Duck foot tree, Silver apricot, Ginkgo balm, Kew tree' in English (Barnes et al., 2007; Demirezer et al., 2012; WHO, 1999).

G. biloba has been used by humans for various benefits since ancient times. It was mainly used in traditional Chinese medicine for asthma, cardiovascular disorders, cough, and expectorant remedies (Barnes et al., 2007).

G. biloba is widely used worldwide for age-related memory impairment and dementia, due to its effects on cerebral blood vessels, thanks to its components such as flavonoids and terpenic lactones (Bikram et al., 2008; Escop & Phytotherapy, 2003; Fei et al., 2008). It is also used as a therapeutic agent for memory loss, concentration problems, depression, dizziness, tinnitus, headache, Raynaud's disease, peripheral arterial occlusive disease such as post-phlebitic syndrome, improving pain-free walking distance, and treating cardiovascular disorders (WHO, 1999).

This study compiles information from the literature on the "botanical characteristics," "historical use," "bioactive components," and "biological activities" of *G. biloba* species.

1. General Information About the Plant

1.1. The Distribution of *Ginkgo biloba* L.

G. biloba belongs to the family Ginkgoaceae and is the only genus in this family. The only species in this genus is *G. biloba*. It is native to China and grows in a temperate coastal climate. Also, it grows naturally in Japan, Asia, Europe, and America (Barnes et al., 2007; Demirezer et al., 2012; WHO, 1999). It has no natural distribution in Turkey. It is grown for landscaping in parks and gardens.

1.2. Botanical Features

G. biloba trees can reach heights of approximately 30-40 meters, can extend up to 70 m and their branches can spread up to 8 meters. The stem up to 500 cm wide in diameter (Lin et al. 2022). Its leaves are fan shaped, feathery and have a soft texture G. biloba is named after its two-lobed leaves **(Figure 1)**. It is a deciduous tree with long-stalked, bilobed, 6-9 cm wide leaves that turn yellow in autumn (Barnes et al., 2007). The bark of trees appears in shades of light grey or greyish brown, with a distinctive longitudinal fissured texture, particularly noticeable on mature trees. When young, the long shoots of trees have a pale brownish-yellow color that gradually transforms into a grey hue as they mature. The internodes of these shoots range from 1.5 to 4 cm in length. The short shoots of trees are characterized by a blackish-grey coloration and feature dense, irregularly shaped leaf scars that are elliptic in form. Additionally, certain branches of the Ginkgo tree have a unique growth pattern resembling stalactites, which are commonly referred to as 'chichi' (Lin et al., 2022). The tree exhibits a dioecious nature, meaning that it has separate male and female individuals. The male cones of the tree are ivory-colored and measure approximately 1.2 to 2.2 cm in length. Within these cones, the pollen sacs take the shape of boats and have widely gaping slits, allowing for the release of pollen (Zhou et al., 2020).

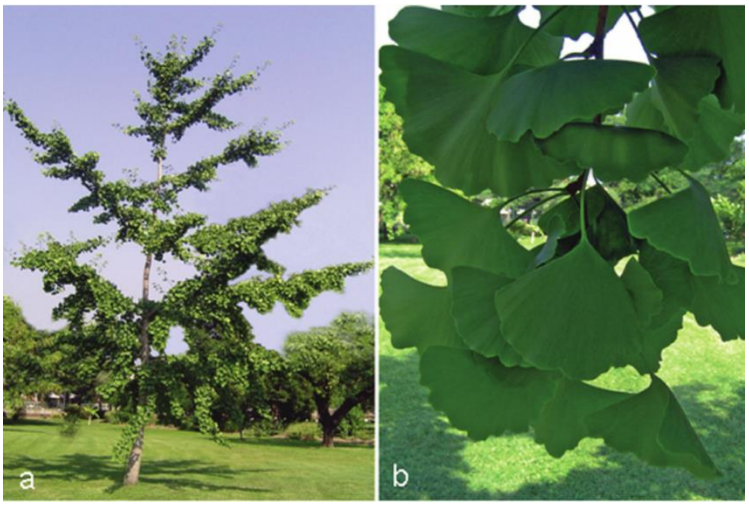

Figure 1: G. biloba tree (a) and leaves (b) (Iriti et al., 2010).

1.3. Registered Pharmacopoeias and Monographs

- American Herbal Pharmacopoeia
- British Herbal Pharmacopoeia
- Martindale 35th edition
- European Pharmacopoeia
- WHO Monographs

- Commission E Monographs
- ESCOP Monographs
- British Pharmacopoeia
- German Pharmacopoeia
- United States Pharmacopeia (Barnes et al., 2007; Demirezer et al., 2012).

1.4. The Distribution of *Ginkgo biloba* L.

The traditional use of *G. biloba* for medicinal purposes dates back to 2800 BC. In traditional Chinese medicine, the seeds and leaves are used for therapeutic purposes. The seeds of G. biloba have been used in traditional Chinese medicine as a cough suppressant, expectorant, and for asthma and bladder inflammation. The leaves have been used for asthma and cardiovascular disorders. Also, Materia Medica contains information that the seeds of G. biloba are used to treat fungal infection wounds (Barnes et al., 2007; Liu et al., 2022).

1.5. Chemical Composition

The chemical structures of the major compounds contained in the plant are shown in **Figure 2.**

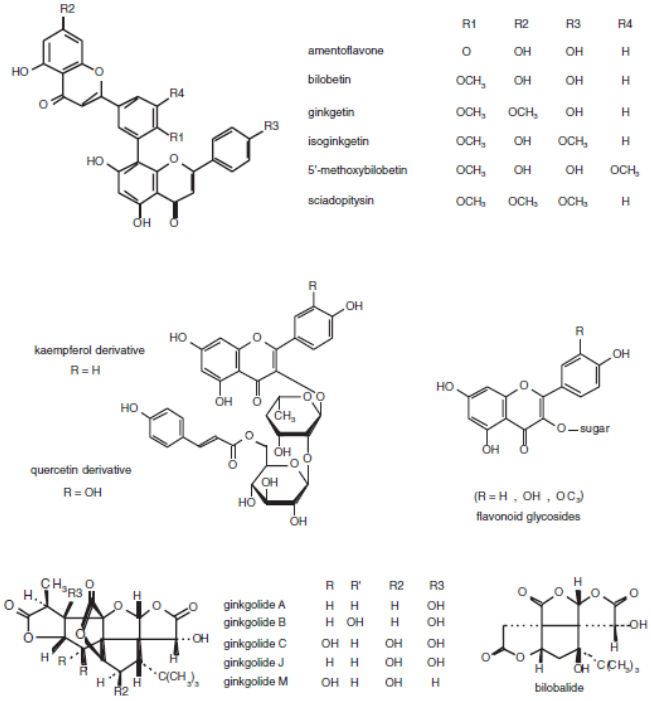

Figure 2. Representative structures of the major and characteristic components of G. biloba (WHO, 1999)

Major compounds found in the seeds of the plant:

- Alkaloids: Ginkgotoxin.
- Aminoacids: Cyanogenic glycosides, ginkgolic acids, ginkbilobin.

Major compounds found in the leaves of the plant:

- Amino acids: 6-Hydroxykynurenic acid, a tryptophan metabolite.

- Flavonoids: Dimeric flavones (e.g. amentoflavone, bilobetin, ginkgetin, isoginkgetin, sciadopitysin); Flavonols (e.g. quercetin, kaempferol) and their glycosides and coumaroyl esters.
- Proanthocyanidins: Terpenoids Sesquiterpenes (e.g. Bilobalide), diterpenes (e.g. Ginkgolides A, B, C, J, M) and triterpenes (e.g. Sterols).
- Other compounds: Benzoic acid, ginkgolic acids, 2-hexenal, polyprenols (e.g. di-trans-poly-cis-octadecaprenol), sugars, waxes, peptides (Barnes et al., 2007; Demirezer et al., 2012; WHO, 1999).

1.6. Effects and Medical Uses

According to investigations, *G. biloba* has effects on cerebral circulation disorders, lack of concentration, memory problems, energy deficiency, fatigue, anxiety, depressive symptoms, headaches, and dizziness. Additionally, it is also used for the treatment of degenerative or multi-infarct dementia. *G. biloba* is also used in the treatment of tinnitus due to its vasodilator and blood viscosity-reducing effects (Blumenthal et al., 2000; Çekkayan et al., 1996; Çelik & MB, 2002; Escop & Phytotherapy, 2003; Le Bars et al., 1997; Schulz, 2003; Singh et al., 2008).

Tebonin Egb761 (*G. biloba* extract) is also used in vertebrobasilar insufficiency due to its ability to reduce vertigo symptoms. It is known that *G. biloba* also has effects on vascular structures, blood elements, and body fluids. *G. biloba* can regulate blood flow and viscosity, leading to vasoregulatory effects. Ginkgolide B, one of the components of *G. biloba*, acts as an anti-aggregant especially by antagonizing the platelet-activating factor (PAF). Additionally, *Ginkgo* has high antioxidant activity (Demirezer et al., 2012; Kızkın et al., 2003; Kleijnen & Knipschild, 1992; McKenna et al., 2001; WHO, 1999). Also, observations have shown that the plant extract used for a short period of time has positive effects in improving the quality of life on healthy individuals. It has been determined that it leads to an increase in both motor functions and emotional development. It also improves painless walking distance in individuals with peripheral artery occlusive diseases such as intermittent claudication, Raynaud's disease, acrocyanosis, and post-phlebitic syndrome. Clinical studies have confirmed the effectiveness of *Ginkgo* in treating patients with Alzheimer's and vascular dementia (WHO, 1999).

1.7. General information: Preparations Containing *G. biloba* Extract

Film-coated tablets and oral drops containing *G. biloba* extract are commonly used for cerebral performance disorders, memory loss, tinnitus, and concentration disorders (Demirezer et al., 2012; WHO, 1999)

1.7.1. Contraindication

G. biloba extract should not be used in cases of hypersensitivity to any of the ingredients present in the extract (Blumenthal et al., 1998; Demirezer et al., 2012).

1.7.2. Warnings and Precautions.

Children under the age of 12 are not recommended to use it because there is a lack of sufficient clinical studies for this age group. The underlying cause of the cerebral symptoms should be identified before using *G. biloba* for treatment. (Demirezer et al., 2012; Escop & Phytotherapy, 2003). The use of *G. biloba* is not recommended in pregnant and lactating women due to limited

clinical studies (Demirezer et al., 2012; WHO, 1999). It should be discontinued at least 3 days before surgical and dental procedures in case of postoperative bleeding (Demirezer et al., 2012). If side effects occur, dosage should be reduced or use should be stopped directly (Blumenthal et al., 1998; Demirezer et al., 2012).

1.7.3. Side Effects

G. biloba should not be used in individuals taking blood clotting-inhibiting drugs at high doses due to the increased risk of bleeding (WHO, 1999). It can cause allergic reactions. When administered intravenously, it can cause allergy to the skin and irritation in the veins (Bressler, 2005). If *G. biloba* seeds are consumed excessively, tonic-clonic seizures and loss of consciousness may occur due to the ginkgotoxin present only in the seeds. There is a possibility of experiencing side effects such as nausea, diarrhea, vomiting, restlessness, and headache (Blumenthal et al., 1998; Bressler, 2005).

1.7.4. Dosage, Usage Form, and Duration of Use

Standardized extracts are generally used as dosage forms. It contains 22-27% flavone glycosides and 5-7% terpene lactones. These compounds comprise approximately 2.8-3.4% ginkgolides A, B, C, and 2.6-3.2% bilobalide. The level of ginkgolic acid is below 5 mg/kg. It is recommended to use the patented standard extract, Tebonin Egb761, in most preparations (WHO, 1999).

G. biloba dry extract can be used orally, 1 tablet (120-240 mg) 2-3 times a day. *G. biloba* liquid extract can be taken in oral drop form, 0.5 mL (1 mL approximately 20 drops, equivalent to 120-240 mg extract 1:1) 3 times a day. The duration of treatment with *G. biloba* depends on the severity of symptoms and should be used for a minimum of 6-8 weeks in chronic patients (Demirezer et al., 2012; WHO, 1999).

In case of cognitive impairment: 120–240 mg dry extract of the leaf extract is given orally in two or three divided doses. Clinical trials of standardized extracts of *G. biloba* leaves have used oral doses ranging from 120-240 mg per day, usually for 8-12 weeks, although some studies have continued treatment for up to 24 or 52 weeks.

In case of peripheral arterial occlusive disease and vertigo/tinnitus: The recommended oral dosage of the dried leaf extract is divided into two or three doses, with each dose containing 120-160 mg of the extract. It has been determined that in clinical studies related to peripheral artery occlusive disease, 120-160 mg of extract has been used in oral doses for 3-6 months.

The effect on the central nervous system: The decrease in membrane fluidity in synaptic cells occurs through neural membrane peroxidation, which leads to a decrease in the efficiency of the dopamine transporter. The reduction in membrane fluidity can be prevented by the application of GBE (*G. biloba* extract) at doses ranging from 2 to 16 mg/mL (Ramassamy et al., 1993).

Effect of apoptosis on cancer cells: Treatment with GBE at a dose of 10 µg/mL for 30-60 minutes on cancer cells reduced apoptosis by 20% (Ergun et al., 2005).

2. Biological Activities of *G. biloba*

2.1. Antioxidant Activity

In a study by Dong et al. the effects of *G. biloba* extract on EPC (Endothelial Progenitor Cell), aging was investigated. The results suggest that *G. biloba* extract may increase Akt (protein kinase B) phosphorylation in EPCs which could lead to increased TERT (Telomerase Reverse Transcriptase) phosphorylation. It has been demonstrated that increased phosphorylation of TERT can prevent the onset of EPC aging by increasing telomerase activity (Dong et al., 2007).

A study by Chen et al. investigated the effects of *G. biloba* extract on EPC aging. As a result, Chen et al. demonstrated that *G. biloba* extracts increased EPC numbers in a dose- and time-dependent manner, as seen in the study by Dong et al. They also found that the extract increased cell proliferation, migration, and in vitro angiogenesis capacity (Chen et al., 2004).

In a study by Ren et al., crude GBPS (*G. biloba* polysaccharides) were obtained from GBL (*G. biloba* leaves) using various methods. When examining their ability to scavenge superoxide and ABTS radicals, it was found that they exhibited significant antioxidant activity. Additionally, it has been found that GBPSs stimulate the production of nitric oxide, tumor necrosis factor (TNF)-α, interleukin (IL)-1β, and IL-6 (Ren et al., 2019).

In a study by Ellnain-Wojtaszek et al., different antioxidant compounds were extracted from *G. biloba* leaves using various solvents such as flavonoids, proanthocyanidins, and flavonoid derivatives. The most effective phenolic compound among these is quercetin. On the other hand, catechin has the longest radical scavenging time. The different groups and bonds on the compounds affect their antioxidant properties (Ellnain-Wojtaszek et al., 2003).

Di Meo et al. conducted an analysis to identify the molecules responsible for the antioxidant effects of Tebonin Egb761 by examining its ability to protect SK-N-BE cells against apoptosis induced by oxidative stress. Neurons have a limited capacity for renewal, so they are very sensitive to oxidative stress. Therefore, reducing oxidative stress and preventing apoptosis are thought to potentially prevent neurodegeneration. (Di Meo et al., 2020).

Chao et al. investigated the effects of *G. biloba* extract on cytoprotective factors in rats with duodenal ulcers. As a result, *G. biloba* extract improved the repair of the duodenal mucosa in duodenal ulcer rats. It increased PGE2 levels and SOD activity through cytoprotective and antioxidant actions. Thus, the antioxidant and free radical scavenging activity of *G. biloba* has been demonstrated once again (Chao et al., 2004).

In a study by Sadowska et al., they aimed to test the effects of a six-week supplementation of a standardized *G. biloba* extract at 160 mg/day with a placebo on aerobic performance, blood antioxidant capacity, and brain-derived neurotrophic factor (BDNF) level. Six weeks of GBE supplementation may improve endurance performance and offer slight neuroprotection through exercise-induced BDNF production and increased blood antioxidant capacity. (Sadowska-Krępa et al., 2017).

Naik et al. investigated the antioxidant activity of *G. biloba* pyrosomes in rat brains through a study. *G. biloba* phytosomes were administered to Wistar rats at 50 mg/kg and 100 mg/kg for 7 and

14 days respectively. The *G. biloba* phytosome treatment increased the activities of superoxide dismutase, catalase, glutathione peroxidase, and glutathione reductase in all brain regions. Thus, it has been determined that it exhibits antioxidant activity (Naik et al., 2006).

2.2. Anti-inflammatory Activity

In a study by Chu et al., the anti-inflammatory activity of the *G. biloba* plant was investigated, and it was found that Ginkgolide B is a potent anti-inflammatory agent. It is also known to inhibit thromboxane A2, an important factor in the pathogenesis of asthma. Treatment with ginkgolide B leads to a significant decrease in eosinophil count. As a result, treatment with ginkgolide B leads to a significant decrease in eosinophil count, which effectively inhibits the increase of T-helper 2 cytokines such as interleukin (IL)-5 and IL-13 in bronchoalveolar lavage fluid. Furthermore, Ginkgolide B has significantly inhibited ovalbumin-induced eosinophils in lung tissue and excessive mucus secretion by goblet cells in the respiratory tract. These results suggest that Ginkgolide B may be beneficial for asthma treatment (Chu et al., 2011).

Yao et al. conducted a study to examine the preventive effects of *G. biloba* extract on LPS-induced ALI in mice. Pre-treatment with *G. biloba* extract in these mice significantly reduced MPO activity and neutrophil infiltration. In addition, *G. biloba* extracts successfully prevented lung tissue damage. It is known that pro-inflammatory cytokines, especially TNF-α, IL-1β, and IL-6, contribute to the early development of inflammation.
LPS (lipase) induces a significant increase in their levels. *G. biloba* extract down-regulated the secretion of TNF-α, IL-1β, and IL-6. In the LPS-induced group, increased NF-κB p65 activity was subjected to pretreatment with *G. biloba* extract. As a result, it was observed that NF-κB p65 expression was inhibited. In addition, COX-2 plays a role in lung damage. *G. biloba* extract also prevented the increase in COX-2 activity caused by LPS in the mouse ALI model. These results demonstrate that *G. biloba* extract has a protective effect on LPS-induced ALI (Xin et al., 2015).

Tao et al. conducted studies to evaluate the anti-inflammatory active compounds in *G. biloba* and elucidate the associated molecular mechanisms. The biological effects of different *G. biloba* extracts were evaluated in an ovalbumin-induced allergic mouse model. It has been observed that anti-inflammatory compounds are present in the ethyl acetate phase of the extract analyzed by HPLC-MS. The biflavonoids suppressed abnormal expression of the Akt and p38 pathways in HNE-stimulated A549 cells. They reduced inflammatory cells and cytokines. The results indicate that biflavones contained in *G. biloba* can inhibit leukocyte elastase activity. This indicates that *G. biloba* may be a functional food for the treatment of respiratory inflammation (Tao et al., 2019).

2.3. Antiviral Activity

In a study by Haruyama & Nagata, the infectivity of influenza viruses was investigated in Madin-Darby canine kidney (MDCK) cells treated with *G. biloba* leaf extract (Egb). Egb was applied to the cells before exposure to viruses, and their infectivity was significantly reduced. Egb inhibited viral infection in a dose-dependent manner. The inhibitory effect of Egb has been observed against influenza A (H1N1 and H3N2) and influenza B viruses. These findings indicate that Egb inhibits the initial stage of influenza virus infection before the virus enters the cytoplasm. According to all these findings, Egb contains an anti-influenza virus substance that directly affects influenza virus particles and disrupts the hemagglutinin function in adsorption to host cells (Haruyama & Nagata, 2013).

In a study by Liu et al. EGb 50, an herbal agent, possesses potential anti-inflammatory properties by inhibiting the activation of microglia induced by the NLRP3 inflammasome. Therefore, EGb has the potential to contribute to the reduction of inflammatory and oxidative stress disorders caused by SARS-CoV-2, while also helping to mitigate the deregulation of the renin-angiotensin system (RAS) (Liu et al., 2018). The peptides derived from EGb can inhibit the ACE activity effectively, and the extract can lower blood pressure by reducing the vasoconstrictive effects of Ang II levels. This discovery provides evidence for the beneficial effect of EGb in protecting against acute lung injury (ALI) mediated by Ang II during COVID-19 (Liskova et al, 2021).

2.4. Activity on Antidepressant-Induced Sexual Dysfunction

Cohen et al. investigated the activity of *G. biloba* on antidepressant-induced sexual dysfunction. Sexual dysfunction is a significant problem for patients taking antidepressant drugs, particularly SSRIs. This study found that *G. biloba* was 84% effective in alleviating antidepressant-induced sexual dysfunction. This study showed that *G. biloba* was 84% effective in alleviating antidepressant-induced sexual dysfunction. The sensitivity of women to the sexually enhancing effects of *G. biloba* was found to be higher than that of men. This rate is 76% in men and 91% in women. *G. biloba* has been shown to have a positive effect on all four stages of the sexual response cycle: excitement, plateau, orgasm, and resolution. No side effects have been reported with the use of *G. biloba* and it appears to be compatible with antidepressant treatment. In addition, many patients have reported an improvement in their mental clarity and memory with the use of *G. biloba* (Cohen & Bartlik, 1998).

2.5. Antibacterial Activity

The antibacterial activity of *G. biloba* methanol, ethanol, chloroform, and hexane extracts against microorganisms was investigated by Sati et al. According to the results, the methanol extract showed the highest activity among all tested extracts and inhibited the growth of all bacterial strains. Furthermore, it was observed that there was no uniform response among bacterial species in terms of sensitivity in different extracts. It is observed that small amounts of crude extracts of *G. biloba* leaves have inhibitory activity against Gram-positive and Gram-negative bacteria (Sati & Joshi, 2011).

2.6. Antidiabetic Activity

The effect of GBE on hyperglycemia, lipid profile, enzymatic and non-enzymatic antioxidants in STZ-induced diabetic rats was studied by Cheng et al. According to the results, GBE has the potential to prevent insulin resistance and is a promising antidiabetic drug was also supported. Diabetes is often accompanied by dyslipidemia, which is characterized by elevated levels of hyperglycemia, TC, LDL, VLDL, and TG, and decreased levels of HDL. The altered serum lipid profile had returned to normal after treatment with GBE. Additionally, hyperglycemia is the main cause of high levels of free radicals. Tissue MDA content is the final product of lipid breakdown caused by oxidative stress. After GBE treatment, the decreased MDA level also demonstrated the antioxidant activity of GBE (Cheng et al., 2013). In another study conducted by Wang et al., the effectiveness of *G. biloba* was assessed in patients with early-stage DN. It has been proven that *G. biloba* can reverse the increase in fasting blood glucose, 24-hour urine protein, blood urea nitrogen, and creatinine, and improve the changes in kidney histology in rats with DN. Furthermore, *G. biloba* can reduce the expression of E-cadherin, alpha smooth muscle actin, and snail in diabetic renal cortex and decrease

the phosphorylation levels of AKT, mTOR, and p70S6K. Blocking the Akt/mTOR signaling pathway can prevent renal fibrosis in rats with DN. It has been found that *G. biloba* can also alleviate albuminuria impairment in type 2 diabetes patients. Thus, it has been demonstrated that *G. biloba* is promising for the early stage of DN. Zhou et al. investigated the effect of *G. biloba* extract (GBE) on glucose intolerance caused by hyperinsulinism in hepatocytes. In this study, a control group treated with thiazolidinedione (TZD), specifically rosiglitazone, was also included to better understand the effectiveness. The data showed that GBE suppressed glucose uptake under normal conditions, but significantly improved glucose tolerance under insulin-resistant conditions. Additionally, after gene expression analysis, it was found that the effects of GBE were mainly manifested by stimulating the transcription of IRS-2. It has been suggested that GBE treatment can prevent drug-induced obesity. Because TZDs can cause weight gain. According to the data, it has been demonstrated that GBE has the potential to prevent insulin resistance and is a promising anti-diabetic drug (Zhou et al., 2011).

2.7. Neurological Activity

A study to confirm whether the alpha-2 adrenergic activity is involved in the facilitating effects of *G. biloba* extract on prefrontal cognitive function by Zhang et al. The data demonstrate that a single dose of Egb reverses yohimbine-induced working memory impairment, and this effect is associated with the stimulation of prefrontal postsynaptic alpha-2 adrenoceptors. Age-related deficits in working memory are associated with decreased activation of these adrenoceptors. Therefore, using *G. biloba* extract may improve working memory performance in elderly animals and patients with Alzheimer's disease (Zhang & Cai, 2005).

Spiegel et al. evaluated the effects of Tebonin Egb761 at a daily dose of 240 mg on tinnitus and vertigo associated with dementia. It has been demonstrated that Tebonin Egb761 is clearly superior to a placebo in reducing both tinnitus and dizziness. As a result of using Tebonin Egb761, a significant decrease in tinnitus severity, ranging from 27% to 40% above the placebo effect, was observed. The effects of dizziness are less pronounced. In conclusion, it has been proven that Tebonin Egb761 in daily doses of 240 mg can reduce both tinnitus and dizziness in dementia patients through various mechanisms (Spiegel et al., 2018).

Zheng et al. investigated the activity of *G. biloba* extract for tardive dyskinesia. According to the data, Egb is a potent antioxidant with neuroprotective effects mediated by increasing BDNF levels. Possible mechanisms of *G. biloba* in treating TD may include direct scavenging of free radicals and indirect inhibition of free radical formation. Thus, it can reduce oxidative stress. Also It can increase BDNF levels and reduce the possibility of neurotoxicity. In conclusion, it has been shown that 240 mg/day of *G. biloba* may be effective and safe in improving TD symptoms in patients with schizophrenia (Zheng et al., 2016).

In a randomized controlled trial involving 157 patients with TD, a standardized *G. biloba* leaf extract known as Egb-761 has been found to be effective in the treatment of TD. Compared to the placebo, treatment with Egb-761 at week 12 significantly reduced the involuntary movement score (Liang et al.).

Two separate studies conducted by Rabiei et al. and Tanaka et al. examined the effects of *G. biloba* extract on Parkinson's disease. The positive effect of Tebonin Egb761 on PD may be attributed to its ability to inhibit MAO activity, which is a potential mechanism for this effect. This MAO enzyme

triggers the formation of free radicals that damage nigrostriatal neurons by metabolizing DA. Pre-treated with Tebonin Egb761, preventive effect was also observed against MPP+ that increases MAO activity in mice. As a result, *G. biloba* demonstrates its effect on PD by preventing oxidative stress and mitochondrial dysfunction (Rabiei et al., 2019; Tanaka et al., 2013).

When examining the studies of Zhang, Liu, DeKosky, and Singh related to Alzheimer's disease in 4 separate ways, some contradictory results have been reached. Treatment with GBEs in combination with drug therapy has shown improvement in cognitive and daily activities, and the effect has been dose-dependent. Significant efficacy has only been observed when high daily doses (240 mg) are used. In patients treated with GBE, adverse effects related to dizziness, tinnitus, headache, and angina pectoris symptoms were reduced compared to placebo. *G. biloba* extracts have been reported to improve cognitive function and quality of life, but some studies have also reported that they cannot prevent the progression of Alzheimer's disease. According to various studies, the results are variable. Most of the studies that resulted in positive outcomes in Alzheimer's disease have used GBE doses above 240 mg/day and a long-term treatment period of 22-24 weeks. Negative results have generally been observed with a dose of 120 mg/day or shorter treatment duration in studies (DeKosky et al., 2008; Liu et al., 2022; Singh et al., 2019; Zhang et al., 2016).

Beck et al. investigated the effects of Tebonin Egb761 on prefrontal dopamine-dependent cognitive functions. In addition to cognitive control, it is assumed that stress responsivity is related to prefrontal dopamine and decreases with age. In conclusion, according to this study, Tebonin Egb761 enhances cognitive flexibility and processing efficiency without causing changes in brain activation. These effects are consistent with a mild increase in prefrontal dopamine (Beck et al., 2016).

Cho et al. aimed to investigate the neuroprotective effect of GBE against hypoxic damage in retinal ganglion cells (RGC). Oxidative stress due to hypoxia and impaired microvascular circulation is associated with the pathogenesis of glaucoma. The results have shown that GBE has a neuroprotective effect on retina ganglion cells against both in vitro and in vivo hypoxic damage (Cho et al., 2019).

Yang et al. investigated the neuroprotective effects of GBE and one of its important components, Ginkgolide B (GB), against oxygen-glucose deprivation and glucose damage. The results showed that GBE has preventive effects on neuronal cell death and improves the function of brain capillary endothelial monolayers after in vitro OGD/R (oxygen-glucose deprivation/reoxygenation) injury. Therefore, GBE can be used as an effective neuroprotective agent for acute ischemic stroke (Yang et al., 2018).

An et al. aimed to investigate the changes in Bax and Bcl-2 expression levels in brain regions associated with TD and the effects of Tebonin Egb761 on Bax and Bcl-2 levels in their study. Teeth grinding disorder (TD) is found to be associated with increased empty chewing movements (VCM), increased proapoptotic Bax protein expression, decreased antiapoptotic Bcl-2 protein expression, and increased Bax/Bcl-2 ratio. Tebonin Egb761 treatment reversed the increase in empty chewing movements, reduced Bax expression, increased Bcl-2 expression, and decreased the Bax/Bcl-2 ratio. These results indicate that long-term haloperidol administration may affect Bcl-2 expression and promote neuronal apoptosis in the basal ganglia. The antiapoptotic effects of Tebonin Egb761 through Bcl-2 pathway can explain the symptom improvement observed in rats with haloperidol-induced TD (An et al., 2016).

Yuan et al. investigated the effectiveness of *G. biloba* extract in the treatment of dementia. According to current evidence, GbE at doses higher than 200 mg/day (mostly 240 mg/day) administered for 22 weeks or longer, may have potentially beneficial effects on cognitive performance and activities of daily living in dementia treatment compared to placebo. There is insufficient evidence to support the positive effects of GbE administered for less than 22 weeks. Current evidence shows that consistently using a GbE dose lower than 200 mg/day may not be sufficient to provide clinically significant effects in the treatment of dementia. In conclusion, GbE has potentially beneficial effects for individuals with dementia when administered at doses higher than 200 mg/day for at least 5 months (Yuan et al., 2017).

Hilton et al. investigated the effectiveness of *G. biloba* in patients with tinnitus. There is no evidence to support the effectiveness of *G. biloba* in patients with primary tinnitus. In patients with vascular dementia and Alzheimer's disease who received *G. biloba*, a small but statistically significant reduction of 1.5 and 0.7 points was observed, respectively. In conclusion, *G. biloba* has been found effective for tinnitus in people with vascular dementia and Alzheimer's disease (Hilton et al., 2013).

2.8. Anticancer Activity

Bai et al. has investigated the effects of *G. biloba* extract on cell apoptosis and G0/G1 cycle in gastric cancer cells. The anticancer activity of Tebonin Egb761 is widely used in the treatment of various cancers. According to this study, after 48 hours of treatment, the data revealed that Tebonin Egb761 significantly suppressed the proliferation of human gastric cancer AGS cells in a dose-dependent manner. Tebonin Egb761 at a concentration of 80 mg/L increased the number of cells in the G0/G1 phase and decreased the cells in the G2/M and S phases. In addition, Tebonin Egb761 treatment significantly increased the apoptosis rate of AGS cells. In conclusion, Tebonin Egb761 can induce apoptosis in human gastric cancer cells through various mechanisms and exhibit anticancer activity by causing cells to remain in G0/G1 phase (Bai et al., 2015).

Cao et al. investigated the activity of *G. biloba* exocarp extracts on inducing apoptosis in Lewis Lung Cancer Cells (LLC) involving MAPK signaling pathways. This study has shown that GBEE (50-200 mg/kg) has dose-dependent inhibitory effects on the growth of LLC-transplanted tumors. As a result, GBEE induces apoptosis in LLC cells through the mitochondrial-mediated intrinsic pathway and the death receptor-mediated extrinsic pathway, which may be closely related to the regulation of MAPK signaling pathways by various mechanisms (Cao et al., 2017).

Wang et al. have investigated the anticancer effect of Tebonin Egb761 on hepatocellular carcinoma (HCC) cell lines in their study. They found that Tebonin Egb761 inhibited cancer cell growth, reduced cell viability, and supported apoptosis in hepatocellular carcinoma cells. Additionally, Tebonin Egb761 dose-dependently reduced the proliferation of human hepatocellular carcinoma (HepG2) cells and increased their apoptosis.
In addition, it has been observed that Tebonin Egb761 exerts an anticancer effect on HepG2 cells by activating p53 and inhibiting nuclear factor (NF)-κB signaling pathways. In conclusion, Wang et al. determined that Tebonin Egb761 inhibited the proliferation and induced apoptosis of hepatocellular carcinoma cells through the NF-κB/p53 signaling pathway (Wang et al., 2020).

DeFeudis et al. investigate the activity of *G. biloba* extracts on cancer in their study. In this study, ginkgolide B inhibited the growth of a highly aggressive human breast cancer cell line in mice.

In addition, exposure of bladder cancer cells to a Ginkgo extract has elicited an adaptive transcriptional response that prevents DNA damage. In humans, Ginkgo extracts also inhibit the formation of oxidative stress effects caused by radiation-induced clastogenic factors and ultraviolet light, which may be associated with anticancer activity (DeFeudis et al., 2003).

Liu et al. investigated the anti-metastatic effect of Tebonin Egb761 on colorectal cancer cells in their study. The treatment of colorectal cancer cells with Tebonin Egb761 has been shown to induce inhibition of cell migration and invasion ability in a concentration-dependent manner. As a result, Tebonin Egb761 has been shown to upregulate LincRNA-p21 expression in a dose- and time-dependent manner. Therefore, Tebonin Egb 761 may be a promising treatment regimen for colorectal cancer (Liu et al., 2017).

Pretner et al. aimed to determine the role of PBR in cancer and the possible anticancer effects of Tebonin Egb761 against it in their study. Treatment with Tebonin Egb761 reduced PBR mRNA levels and inhibited the proliferation of breast, glioma, and hepatocarcinoma cell lines. As a result, treatment with Tebonin Egb761 is believed to be beneficial in preventing or treating cancer metastasis by reducing PBR overexpression (Pretner et al., 2006).

Park et al. investigated the anti-cancer effects of *G. biloba* extract in estrogen-independent breast cancer in their study. According to the results, it was shown that the cytotoxic effects of GBE in MDA-MB-231 led to DNA fragmentation at high concentrations (500 and 1000 µg/ml). It has been shown that GBE has chemopreventive effects in estrogen-independent breast cancer through anti-proliferative and apoptotic- inducing activities (Park et al., 2013)

Jiang et al. investigated whether *G. biloba* is an effective agent for reducing the risk of ovarian cancer associated with BRCA1 in their study. GB treatment has shown anti-cancer activities in BRCA1 mutant cells through numerous mechanisms. The results showed that GB found in *G. biloba* may have cancer preventive activities in BRCA1-mutant ovarian epithelial cells (Jiang et al., 2011).

2.9. Cardiovascular Activity

In a study by Koltermann et al., an activity analysis was performed on the effect of *G. biloba* extract on endothelial nitric oxide production. *G. biloba* extract caused acute relaxation of isolated aortic rings and a decrease in in vivo blood pressure dependent on NO in rats. These effects on eNOS are evidence for Tebonin Egb761's protective cardiovascular properties (Koltermann et al., 2007).

2.10. Other Activities

In this study by Cho et al., the effects of Tebonin Egb761 on basal and glutamate-induced activity, as well as tPA (Tissue plasminogen activator) expression in primary cortical neurons of rats were investigated. Given the neurotoxic role of excessive tPA during excitotoxic conditions, Tebonin Egb761 has been shown to provide protective roles in such neural insult situations (Cho et al., 2016).

Al-Attar et al. investigated the effect of *G. biloba* leaf extract on thioacetamide (TAA)-induced experimental liver fibrosis in male albino rats. This study showed that Ginkgo biloba leaf extract has a potential activity against TAA-induced liver fibrosis in male albino rats, and the chemical components of *G. biloba* are effective in modulating oxidative stress induced by TAA (Al-Attar, 2012).

Zhang et al. investigated the efficacy of *G. biloba* in vitiligo patients. It has been found that the antioxidant effect of Tebonin Egb761 on melanocytes is achieved by activating Nrf2. In conclusion, Tebonin Egb761 is able to protect melanocytes against oxidative stress damage by activating the Nrf2-ARE signaling pathway (Zhang et al., 2019).

The effects of *G. biloba* leaf extract on the human red blood cells in the presence of amyloid peptide (Abeta25-35), peroxide and hypotonic stress were investigated by He et al. The results show that *G. biloba* leaf extract has a dual effect on red blood cells, both protective and destructive, depending on whether exogenous stress is present (He et al., 2009).

Logani et al. investigated the potential beneficial actions of *G. biloba* in the treatment of conditions involving cerebral hypoxia. Rats pretreated with Tebonin Egb761 before microinfarction had better cerebral blood flow, higher brain glucose, and higher brain lactate levels than saline-injected controls before microinfarction (Logani et al., 2000).

Ran et al. examined the protective effects of *G. biloba* extract on myocardial ischemia-reperfusion injury in rabbits. In conclusion, this study demonstrated that *G. biloba* extract has myocardial protective effects by reducing the formation of oxygen-free radicals and increasing the antioxidant capacity of myocardial cells (Ran et al., 2014).

Huang et al. investigated the effects of GBE on aortic dilation and rupture rate of AngII-induced AAAs (abdominal aortic aneurysms). As a result, GBE prevented aortic rupture in hypercholesterolemic mice inoculated with AngII, but this effectiveness was observed only in the early stage of disease development (Huang et al., 2019).

Omidkhoda et al. conducted a comprehensive study to investigate the protective effects of *G. biloba* against natural toxins, chemical toxicity, and radiation. In conclusion, they examined the protective effects of *G. biloba* against natural toxins, chemical toxicities, and radiation. The protective activity of *G. biloba* leaves was found to be effective against some natural toxins such as LPS, LPC, scorpion venom, lantadenes, manyok, gossypol, and aflatoxinB1. It was also found to be significantly effective against the harmful consequences of substances such as metals, ethanol, pesticides, carbon tetrachloride, cigarette smoke, naphthalene, and monosodium glutamate (Omidkhoda et al., 2019).

In the study by Huang et al., the effect of Tebonin Egb761 on cisplatin-induced ototoxicity in rats was investigated. It was found that Tebonin Egb761 provided protection against cisplatin-induced ototoxicity in a rat model (Huang et al., 2007).

Discussion

G. biloba is a unique and entirely distinctive tree that continues to exist today without any close relatives or similar species. *G. biloba* is known to be effective in concentration problems, memory problems, lack of energy, anxiety, headaches, vertigo, tinnitus, depressive symptoms, dementia, Alzheimer's disease, cardiovascular distress, intermittent claudication, Raynaud's disease, as well as improving painless walking distance in people with peripheral artery occlusive disease. Furthermore, positive effects of short-term use of the plant extract to improve the quality of life in healthy individuals have also been observed. Clinical studies have shown that *G. biloba* has very high

antioxidant activity and various effects such as anti-inflammatory, antiviral, antibacterial, antidiabetic, anticancer, neuroprotective, cardioprotective, and many others.

Although only the leaf extract is used medicinally nowadays, in ancient Chinese medicine, the seeds of *G. biloba* were also used due to their antitussive, expectorant, asthma-preventative, and bladder inflammation-reducing effects.

As seen, the *G. biloba* plant is an important herb with many biological activities, versatile, with a relatively good side effect profile, and is highly demanded in the pharmaceutical industry due to its effects. The *G. biloba* plant has been researched for years and has been utilized for various effects since ancient times. The main components found in this plant are flavonoids and terpenic lactones, and its usage is becoming increasingly widespread, particularly in cases of age-related memory loss and dementia, due to its effects on brain blood vessels. Modern medicine places great emphasis on the use of herbal supplements such as *G. biloba* to improve the quality of life for individuals struggling with neurological disorders like Alzheimer's and dementia. Additionally, it is believed in the scientific community that *G. biloba*, which is one of the longest-living tree species in the world, has other biological activities waiting to be discovered.

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