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Review Article

Ginkgo biloba: A review of its phytoconstituents and pharmacological activities

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ABSTRACT

Ginkgo biloba L. is one of the world's most famous medicinal herbs, it has been used for centuries for treating many diseases. This review article aims to provide an updated overview of the reported active constituents in *Ginkgo biloba* and its biological activities. *G. biloba* has existed for 2,000 years and is known as a "living fossil". Its native environment is China, Korea, and Japan. Numerous secondary metabolites, containing terpenoids, allyl phenols, and polyphenols have been identified in *G. biloba*. However, it is believed that flavonoids and terpene trilactones are the essential bioactive ingredients. *G. biloba* leaf extract is recognized as the most commonly sold phytomedicine in Europe. *G. biloba* extract is used to treat the symptoms of peripheral claudication, early-stage Alzheimer's disease, vascular dementia, and tinnitus of vascular basis. Additionally, *G. biloba* extract is extensively used to protect from and/or cure cardiovascular disorders, and numerous substances produced from Ginkgo are presently undergoing preclinical and clinical trials across the globe. The structures and bioactivities of the secondary metabolites of *G. biloba* are described in this review article, along with an overview of the pharmacological significance of the *Ginkgo biloba* plant.

Keywords: *Biological activities; Ginkgo biloba; Ginkgolides; secondary metabolites; terpene lactones*.

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Introduction

1. Introduction

The family Ginkgoaceae encompassed a total of ten genera in its history which were very numerous as forest communities across the Northern Hemisphere. Now, it includes only one genus; *Ginkgo*, with the only species *Ginkgo biloba* **[1]**. *Ginkgo biloba* L. (synonym *Salisburia adiantifolia* Sm. or *Salisburia biloba* (L.) Hoffmanns), commonly known as the maidenhair tree, has been a valued plant for humanity for over 2000 years **[2]**. It is estimated that *G. biloba* tree has flourished in forests for over 150 million years representing one of the best-known examples of a “living fossil” **[3]**. Due to phylogenetic divergence from other plants, *G. biloba*'s morphology has somewhat changed from that of its extinct relatives **[4]**. Though its original environment is Japan, China, and Korea, its native land is believed to be eastern China’s Zhejiang Province isolated mountain valleys. Today, Ginkgo trees are widely grown in Asia,

Europe, North America, Argentina, and New Zealand. More than 350 years ago, the availability of this plant resource was restricted to China **[5]**. Over 100 trees of *G. biloba* still live around the temples in China for more than 1000 years due to the use of Ginkgo nuts in religious traditions. Ginkgo originated around 200 million years ago, however, its floating sperms (spermatozoids) were detected about 100 years ago **[6]**. The tree is known for its inordinate beauty and long lifespan, with extreme resistance to viral and bacterial infections, insects, and air contamination. *G. biloba* displays an extended juvenile stage, normally not reaching sexual maturity until 20 years **[7]**.

The leaf has been suggested for treatment since 1509 and is still used as a tea. Currently, extracts of Ginkgo leaves formulated as tablets with film coats or syrups can be acquired in Europe and America **[8]**. *G. biloba* contains numerous unique metabolites that have favored to expansion of the chemical variety of the extract as an herbal medicine **[4]**. These constituents with distinctive structures belong to many classes such as terpenoids, flavonoids (acylated flavonol and biflavones), and alkyl phenolic acids **[9]**. However, the chief bioactive compounds are terpene trilactones and flavonoid glycosides which seem to be accountable for the pharmacological actions of its leaf extract **[6]**. Because of its broad pharmacological usefulness, all the parts of *G. biloba* have gone under extensive chemical analysis. The most common solvents for extracting leaves are methanol, water, or combinations of the two. Pressurized water extraction and supercritical fluid extraction are also feasible **[10]**.

G. biloba is extensively used in the cosmetics, medicinal sectors, and functional foods all over the world **[4]**. More than 7 billion dollars are yearly spent on herbal medicines and Ginkgo comes in first among them **[6]**. The extract of *G. biloba* (EGb) may act through many mechanisms, and the supposed beneficial effects of EGb could be through the interplay of one or more of the main modes of action. Active principles in EGb enhance blood flow, reduce clot formation, and protect nerve cells against oxygen depletion-induced damage **[11]**. The leaf extracts are used in the treatment of dementia disorders, such as difficulties in concentration, memory impairment, and Alzheimer's disease. Besides its neuroprotective properties, the extract also acts as anti-asthmatic and improves wound healing **[12]**. Ginkgo flavonoids are believed to protect against capillary fragility by their anti-inflammatory and antioxidant dual mechanism, reduce edema resulting from tissue injury, and have a free radical scavenger effect **[8]**. All these activities of EGb hold promise for patients receiving cancer chemotherapy who frequently report cognitive dysfunction, which is a critical aspect of health-related quality of life **[13]**.

This review article's objective is to present a current summary of *Ginkgo biloba* bioactive secondary metabolites and biological activities. It is founded on a thorough literature search using Google Scholar, SciFinder, and Pubmed databases. We examine the articles published between 1992 and 2022 using the keywords (*Ginkgo biloba,* EGb, Ginkgo pharmacology, Ginkgo terpene lactones, and Ginkgolides).

2. Taxonomy

Ginkgo biloba is a survivor species and the Ginkgoaceae family's sole surviving member in the Ginkgophyta plant lineage **[4]**. As of right now, there are no near relatives of *G. biloba* in the plant kingdom. As a result, it belongs to a separate section called the Ginkgophyta. The reproductive features of this taxon set it apart from the conifers **[6]**.

Domain: Eukaryota

Kingdom: Plantae

Division: Spermatophyta

Subdivision: Gymnospermae

Class: Ginkgopsida

Order: Ginkgoales

Family: Ginkgoaceae

Genus: *Ginkgo*

Species: *biloba* **[14]**

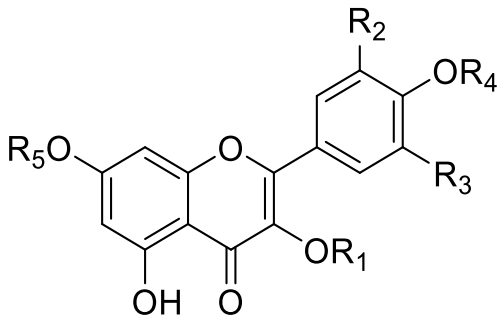
3. Phytochemical review of *Ginkgo biloba*

Phytochemical research carried out on *G. biloba* led to the isolation of a diverse array of secondary metabolites including isoflavonoids, flavones, anthocyanidins, terpenes, steroids, phytosterols, carotenoids, polyphenols, and other types of secondary metabolites from its different parts. Phenolic compounds, particularly flavonoids, are present in almost all the parts of *G. biloba*.

3.1. Flavonoids

Flavonoids are a broad class of secondary metabolites found in plants. They are low-molecular-weight polyphenolic constituents that have a variety of functions in plant safeguarding and growth. These include proanthocyanidins, flavones, flavonol and its glycosides, acylated flavonol glycosides, biflavonoids, and flavan-3-ols **[15]**. Several flavonol glycosides illustrated in **Table 1** are derivatives of the aglycones quercetin (**1**), kaempferol (**2**), and isorhamnetin (**3**) among these flavonoids **[6]**. Among the flavones that have been separated from *G. biloba* are (**23-28**) shown in **Table 2 [4]**. Other classes were identified in *G. biloba* such as favan-3-ols **(Table 3)**. Three isoflavones were isolated from *G. biloba* (**33-35**) as depicted in **Table 4 [10]**. Biflavones (**36-48**) and flavanones (**49-51**) displayed in **Tables 5 and 6**, respectively, have been also reported **[16, 17]**. Baker and Simmonds discovered the first biflavone in Ginkgo **[18]**. Bioflavonoids are structurally made up of two flavonoid units that are either identical or non-identical and are connected symmetrically or asymmetrically by an alkyl or alkoxy-based linker of different lengths **[4]**. Additionally, several anthocyanidins have been reported **(Table 7)**.

Table 1. Flavonols and their glycosides reported in *Ginkgo biloba*

No.	Compound name	Structure	Part	Reference
				

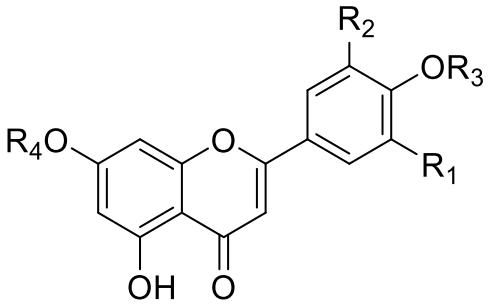
No.	Compound name	R_1	R_2	R_3	R_4	R_5	Part	Reference
1	Quercetin	H	OH	H	H	H	Root, bark, wood, and leaves	**[4]**

2	Kaempferol	H	H	H	H	H	Root, bark, wood, and leaves	**[4]**
3	Isorhmnetin	H	OCH_3	H	H	H	Root, bark, wood, and leaves	**[4]**
4	Quercetin-3-*O*-*α*-L-rhamnoside	Rha	OH	H	H	H	Leaves and flower	**[3]**
5	Quercetin-3-*O*-*β*-D-glucoside	Glc	OH	H	H	H	Leaves and flower	**[3]**
6	Rutin	Glc-(6→1)-Rha	OH	H	H	H	Leaves and flower	**[3]**
7	Isorhamnetin-3-*O*-rutinoside	Glc-(6→1)-Rha	OCH_3	H	H	H	Leaves and flower	**[3]**
8	Isorhamnetin-3-*O*-*β*-D- glucoside	Glc	OCH_3	H	H	H	Leaves and flower	**[3]**
9	Kaempferol-3-*O*-*α*-L-rhamnoside	Rha	H	H	H	H	Leaves and flower	**[3]**
10	Kaempferol-3-*O*-rutinoside	Glc-(6→1)-Rha	H	H	H	H	Leaves and flower	**[3]**
11	Kaempferol-7-*O*-*β*-D-glucoside	H	H	H	H	Glc	Leaves and flower	**[3]**
12	Kaempferol-3-*O*-*β*-D-galactoside-4′-*O*-*β*-D-glucoside	Gal	H	H	Glc	H	Leaves and flower	**[3]**
13	Kaempferol-4′-*O*-*β*-D-glucoside	H	H	H	Glc	H	Leaves and flower	**[3]**
14	Kaempferol-3-*O*-glucoside	Glc	H	H	H	H	Leaves	**[56]**
15	Kaempferol-3-*O*-glucorhamnoside	Rha-(1→6)-Glu	H	H	H	H	Leaves	**[56]**
16	Myricetin	H	OH	OH	H	H	Whole plant	**[6]**

17	Tamarixetin	H	H	OH	CH_3	H	Whole plant	**[6]**
18	3′-Methylmyricetin	H	CH_3	OH	H	H	Root, bark, wood, and leaves	**[6]**
19	Syringetin	H	OCH_3	OCH_3	H	H	Leaves	**[56]**
20	Syringetin-3-*O*-rutinoside	Glc-(6→1)-Rha	OCH_3	OCH_3	H	H	Leaves	**[56]**
21	Dimethoxyflavonol-3-*O*-*α*-L-rhamnopyranosyl-(1→6)-*β*-D-glucopyranoside	Glc-(6→1)-Rha	OCH_3	OH	CH_3	H	Leaves	**[57]**
22	Quercetin-3-*O*-*β*-D-glucopyranosyl-(1→2)-*α*-L-rhamnopyranoside	Rha-(2→1)-Glc	OH	H	H	H	Leaves	**[57]**

Table 2. Flavones and their glycosides reported in *Ginkgo biloba*

No.	Compound name	Structure	Part use	Reference



No.	Compound name	R_1	R_2	R_3	R_4	Part use	
23	Apigenin	H	H	H	H	Leaves	**[56]**
24	4′-Methoxy apigenin	H	H	CH_3	H	Leaves	**[56]**
25	Apigenin-7-O-β-D-glucopyranoside	H	H	H	Glc	Flower	**[3]**
26	Luteolin	H	OH	H	H	Leaves	**[6]**
27	Luteolin-3′-O-(β-D-glucopyranose)	H	O-Glc	H	H	Leaves	**[56]**
28	Genkwanin	H	H	H	CH_3		**[58]**

Table 3. Flavan-3-ols reported in *Ginkgo biloba*

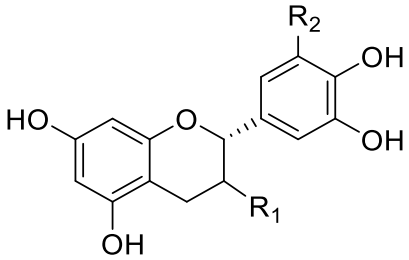
No.	Compound name	Structure		Part use	Reference
					
No.	**Compound name**	**R_1**	**R_2**	**Part use**	
29	Catechin	β-OH	H	Root, bark, wood, and leaves	**[6]**
30	Gallocatechin	β-OH	OH	Root, bark, wood, and leaves	**[6]**
31	Epicatechin	α-OH	H	Root, bark, wood, and leaves	**[6]**
32	Epigallocatechin	α-OH	OH	Root, bark, wood, and leaves	**[6]**

Table 4. Isoflavonoids reported in *Ginkgo biloba*

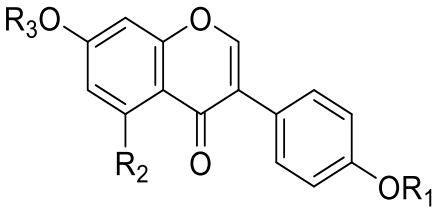
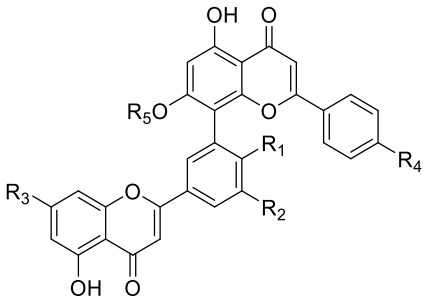
No.	Compound name	Structure			Part use	Reference
						
No.	**Compound name**	**R_1**	**R_2**	**R_3**	**Part use**	
33	Genistein	H	OH	H	Leaves	**[9]**
34	Genistein-7-O-glucoside (Genistin)	H	OH	Glc	Leaves	**[9]**
35	Formononetin	CH_3	H	H	Leaves	**[9]**

Table 5. Biflavones reported in *Ginkgo biloba*

No.	Compound name	Structure	Part use	Reference
				

No.	Compound name	R_1	R_2	R_3	R_4	R_5	Part use	
36	Amentoflavone	OH	H	OH	OH	H	Root, bark, wood, and leaves	**[6]**
37	7-Methoxyamentoflavone	OH	H	OCH_3	OH	H	Root, bark, wood, and leaves	**[6]**
38	Bilobetin	OCH_3	H	OH	OH	H	Root, bark, wood, and leaves	**[6]**
39	5′-Methoxybilobetin	OCH_3	OCH_3	OH	OH	H	Root, bark, wood, and leaves	**[6]**
40	Sequoiaflavone	OH	H	OCH_3	OH	H	Root, bark, wood, and leaves	**[6]**
41	Ginkgetin	OCH_3	H	OCH_3	OH	H	Leaves	**[9]**
42	7"-O-β-D-glucosyl-ginkgetin	OCH_3	H	OCH_3	OH	Glc	Leaves	**[9]**
43	Isoginkgetin	OCH_3	H	OH	OCH_3	H	Leaves	**[9]**
44	7"-O-β-D-Glucosyl-isoginkgetin	OCH_3	H	O-Glc	OCH_3	H	Leaves	**[9]**
45	2,3-Dihydroisoginkgetin	OCH_3	H	OH	OCH_3	H	Leaves	**[9]**
46	2,3-Dihydrosciadopitysin	OCH_3	H	OCH_3	OCH_3	H	Leaves	**[9]**
47	Podocarpusflavone A	OH	H	OH	OCH_3	H	Leaves	**[9]**
48	Sciadopitysin	OCH_3	H	OCH_3	OCH_3	H	Root, bark, wood, and leaves	**[6]**

Table 6. Flavanones and their glycosides reported in *Ginkgo biloba*

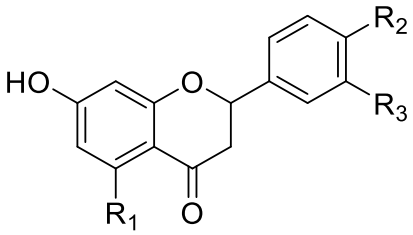
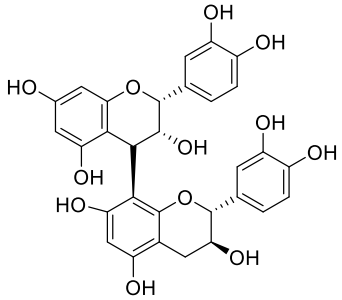
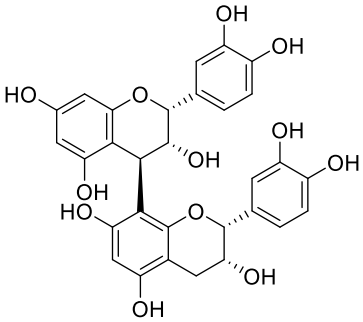
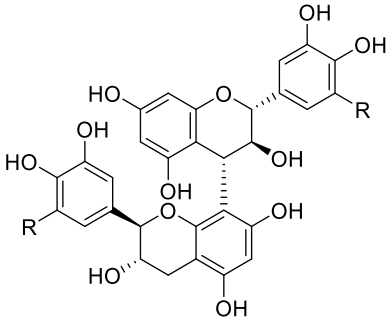
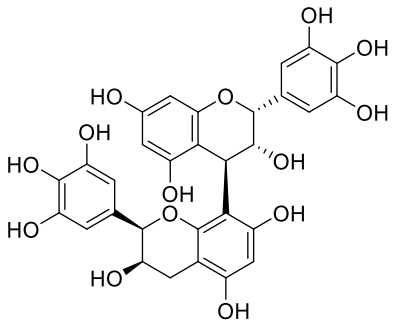
No.	Compound name	Structure	Part use	Reference
				
No.	Compound name	R_1	R_2	R_3	Part use	
49	Eriodictyol	OH	OH	OH	leaves	**[17]**
50	Liquiritin	H	O-Glc	H	Leaves	**[9]**
51	Naringenin	OH	OH	H	leaves	**[9]**

Table 7. Anthocyanidins reported in *Ginkgo biloba*

No.	Compound name	Structure	Part use	Reference
52	Procyanidin B_1		Root, bark, wood, and leaves	**[59, 60]**
53	Procyanidin B_2		Root, bark, wood, and leaves	**[59, 60]**
54	Procyanidin B_3		Root, bark, wood, and leaves	**[59, 60]**

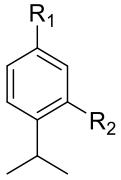
55	Prodelphinidin B_3		Root, bark, wood, and leaves	**[61]**

3.2. Terpenes

Table 8 shows Monoterpenes reported in *Ginkgo biloba* **(55-60)**. The two primary terpenoids that have been discovered and isolated from *G. biloba* are diterpenes and sesquiterpenoids **[6]**. The most distinctive components of *G. biloba* are diterpenes, also referred to as ginkgolides. The six rings that make up the ginkgolide skeleton include three lactones, a tetrahydrofuran, and a spiro[4.4]nonane carbocyclic ring. Ginkgolides have a caged skeleton and are incredibly stable even when they contain several oxygen functionals. The only differences between ginkgolides are the number and arrangement of hydroxyl groups **[4, 19]**. Ten ginkgolides (**61-70**) illustrated in **Table 9** were isolated from *G. biloba* to date. Ginkgolide A (GA, **61**), B (GB,**62**), C (GC, **63**), J (GJ, **64**), M (GM, **65**) P (GP, **66**), and Q (GQ, **67**) were different in the C-1, C-3, and C-18-hydroxyl substitution, while ginkgolide K (GK,**68**), L (GL, **69**), and N (GN, **70**) are dehydration derivatives (between C-3 and C-14) of 38, 37 and 41, respectively. A related 15 carbons compound with a sesquiterpenoid skeleton, bilobalide (BB, **71**), was detected in 1971 and is present in various *G. biloba* parts **[20, 21]**. Ginkgolides and BB are altogether known as terpene trilactones (TTLs). In 2020, a new sesquiterpene was isolated with two lactone rings from *G. biloba* leaf extract, and discovered to be a BB isomer (**72**) **[22]**. In contrast to (**71**), this isomer has one missing lactone ring and one more hydroxyl group exposed **(Table 10)**. Ursolic acid **(Table 11)** was also reported from *G. biloba*.

G. biloba is the source of a family of potential terpenoids called polyphenols **(Table 12)**. In *G. biloba*, polyprenols are composed of 15–22 linearly connected isoprene units. Up until recently, not many studies have looked at these alcohols, mostly because of the drawbacks of Ginkgo polyprenol extraction techniques. However, due to the application of silver thiol chromatographic materials, the purity of Ginkgo polyphenol extract increased to 99.8% in 2019 **[23]**.

Table 8. Monoterpenes reported in *Ginkgo biloba*

No.	Compound name	Structure	Part use	Reference
				

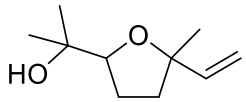
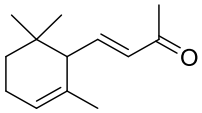
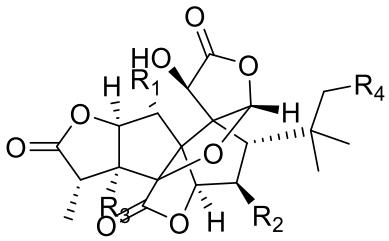
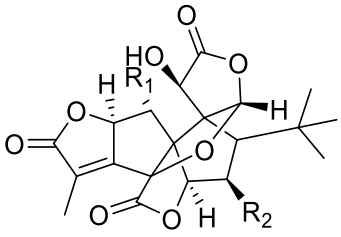
No.	Compound name	R_1	R_2	Part use	
56	*p*-Cymene	CH_3	H	Root, bark, wood, and leaves	**[6]**
57	Isopropyl-phenol	H	OH	Root, bark, wood, and leaves	**[6]**
58	Thymol	CH_3	OH	Root, bark, wood, and leaves	**[6]**
59	Linalool oxide			Root, bark, wood, and leaves	**[6]**
60	Ionone			Root, bark, wood, and leaves	**[6]**

Table 9. Diterpenes reported in *Ginkgo biloba*

No.	Compound name	Structure	Part use	Reference
				

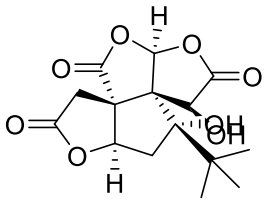
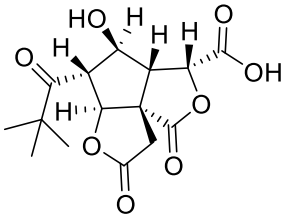
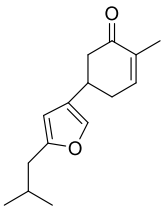
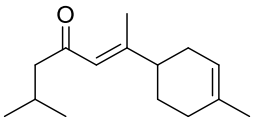
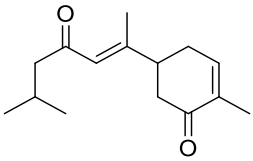
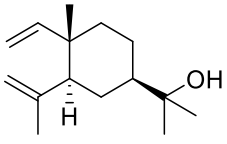
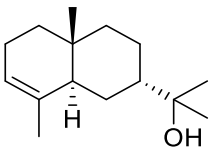
No.	Compound name	R1	R2	R3	R4	Part use	
61	Ginkgolide A	H	H	OH	H	Leaves	**[4]**
62	Ginkgolide B	OH	H	OH	H	Leaves	**[4]**
63	Ginkgolide C	OH	OH	OH	H	Leaves	**[4]**
64	Ginkgolide J	H	OH	OH	H	Leaves	**[4]**
65	Ginkgolide M	OH	OH	H	H	Leaves	**[4]**
66	Ginkgolide P	H	H	OH	OH	Leaves	**[4]**
67	Ginkgolide Q	OH	H	OH	OH	Leaves	**[4]**

No.	Compound name	Structure	Part use	
				

No.	Compound name	R_1	R_2	Part use	
68	Ginkgolide K	OH	H	Leaves	**[4]**

69	Ginkgolide L	H	H	Leaves	**[4]**
70	Ginkgolide N	OH	OH	Leaves	**[4]**

Table 10. Sesquiterpenes reported in *Ginkgo biloba*

No.	Compound name	Structure	Part use	Reference
71	Bilobalide		Root, bark, wood, and leaves	**[62]**
72	Bilobalide isomer		Leaves	**[22]**
73	Bilobanone		Root, bark, wood, and leaves	**[4]**
74	*E*- and *Z*- forms of 10-11-Dihydroatlantone		Root, bark, wood, and leaves	**[6]**
75	*E*-10-11-Dihydro-6-oxoatlantone		Root, bark, wood, and leaves	**[6]**
76	Elemol		Leaves	**[4]**
77	α-Eudesmol		Leaves	**[4]**

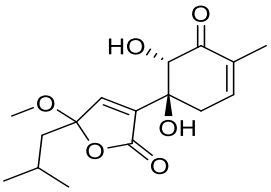
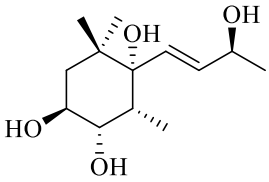
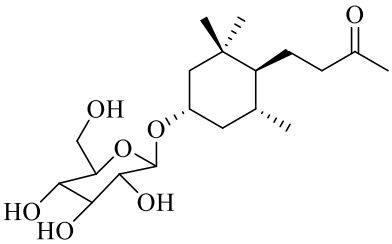
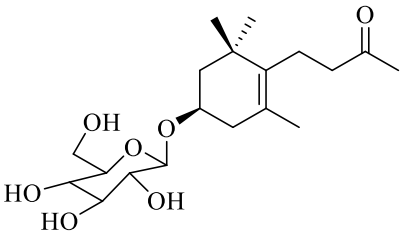
78	Bilobanol		Leaves	**[4]**
79	Wilsonol A		Leaves	**[63]**
80	Alatoside E		Leaves	**[63]**
81	Icariside B6		Leaves	**[63]**

Table 11. Triterpene reported in *Ginkgo biloba*

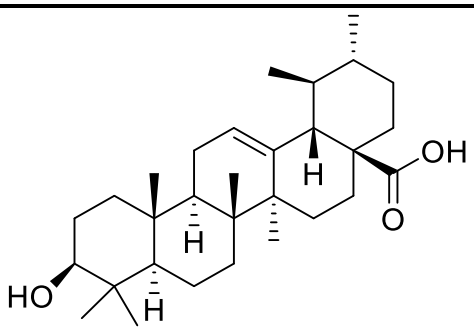
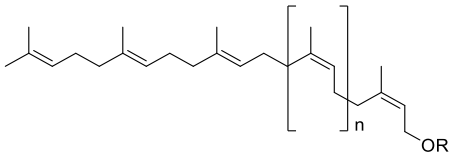
No.	Compound name	Structure	Part use	Reference
82	Ursolic acid		Leaves	**[4]**

Table 12. Polyprenols reported in *Ginkgo biloba*

No.	Compound name	Structure	Part use	Reference
				
No.	**Compound name**	**R**	**N**	**Part use**	
83	Ginkgo polyprenols	H	(10-20)	Root, bark, wood, and leaves	**[6]**
84	Ginkgo polyprenol acetates	$OCOCH_3$	(10-20)	Root, bark, wood, and leaves	**[6]**

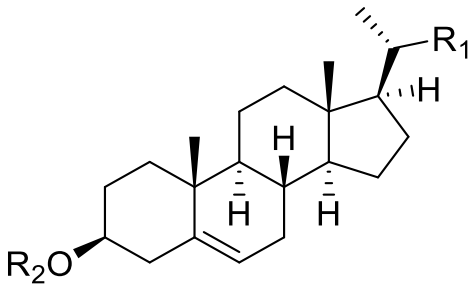
3.3. Sterols

Numerous steroids/phytosterols have been found in different parts of *G. biloba* illustrated in **Table 13**. Among them are β-sitosterol (**85**), stigmasterol (**86**), campesterol (**87**), daucosterol (**88**) **[4]**. stigmast- 3,6-dione (**89**), stigmast-4-ene-3,6-dione (**90**) **[6]** and ergosterol (**91**) **[24]**.

3.4. Carotenoids

Carotenoids displayed in **Table 14** were reported in *G. biloba* leaves. Carotenoids are categorized as either carotenes (that contain pure hydrocarbons without oxygen) such as *α*-carotene (**92**), or xanthophylls which contain oxygen, such as lutein (**94**) and zeaxanthin (**95**) **[6, 25]**.

Table 13. Sterols reported in *Ginkgo biloba*

No.	Compound name	Structure	Part use	Reference
				

.

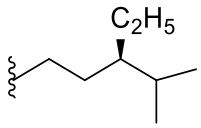
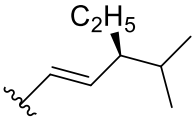
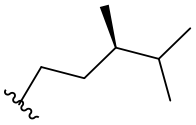
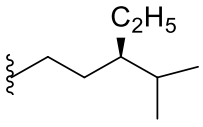
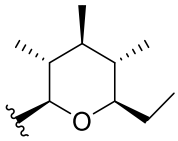
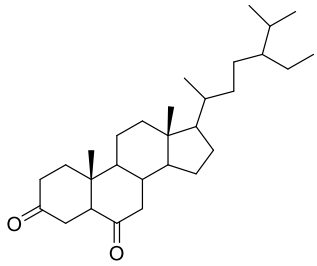
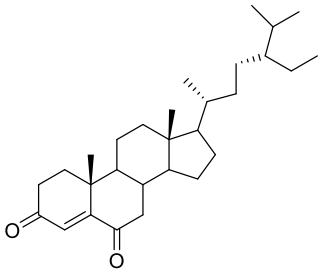
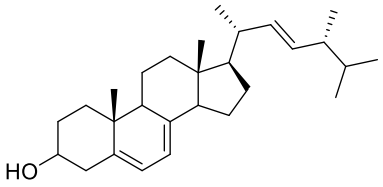
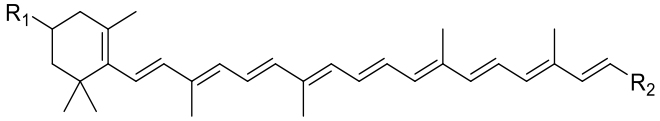
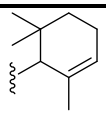
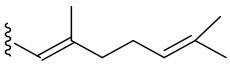
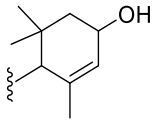
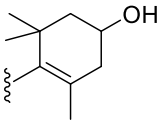
No.	Compound name	R_1	R_2	Part use	
85	β-Sitosterol		H	Root, bark, wood, and leaves	**[6]**
86	Stigmasterol		H	Root, bark, wood, and leaves	**[6]**
87	Campesterol		H	Root, bark, wood, and leaves	**[6]**
88	Daucosterol			Root, bark, wood, and leaves	**[6]**
89	Stigmastane-3,6-dione			Leaves	**[4]**
90	Stigmast-4-ene-3,6-dione			Leaves	**[4]**
91	Ergosterol			leaves	**[24, 64]**

Table 14. Carotenoids reported in *Ginkgo biloba*

No.	Compound name	Structure	Part	Reference
				

No.	Compound name	R_1	R_2	Part	Reference
92	*α*-Carotene	H		Root, bark, wood, and leaves	**[6, 25]**
93	*γ*-Carotene	H		Root, bark, wood, and leaves	**[6, 25]**
94	Lutein	OH		Root, bark, wood, and leaves	**[6, 25]**
95	Zeaxanthin	OH		Root, bark, wood, and leaves	**[6, 25]**

4. Biological review of *Ginkgo biloba*

4.1. Neuroprotective activity

4.1.1. Anti-Alzheimer's Disease (anti-AD)

An Extract standardized from *G. biloba* leaf (EGb) has been employed for its useful benefits on brain functioning in clinical research, especially concerning Alzheimer's disease (AD) and age-related dementias. EGb showed significant experimental evidence about its protective effect against several injuries that cause neuronal malfunction. In a neuroblastoma cell line that was stable in expressing an AD-associated double mutation, this extract prevent the production of amyloid-β (Aβ) fibrils, which are the diagnostic, and likely casual feature of AD **[26]**. This reduction in Aβ fibrillogenesis was shown in both the *in vitro* solution and the conditioned medium of this Aβ-secreting cell line. Additionally, EGb reduced the activity of caspase 3, an essential enzyme in the apoptosis cell-signaling cascade, and dramatically slowed mitochondrion-initiated apoptosis. Another study **[27]** also reported that EGb lowered the level of the precursor protein of β-amyloid in PC12 cells. In an interesting transgenic APP/PS1 mouse model, supplementation with EGb daily for six months enhanced cognitive ability and greatly reduced the development of amyloid plaque. After EGb was administered, the amount of soluble Aβ remained unchanged, despite a drop in the quantity of insoluble Aβ was observed. Since hippocampal plasticity is believed to be a crucial component of memory, both acute and long-term effects of EGb on synaptic transmission and plasticity in hippocampus slices from C57Bl/6 mice were assessed **[28]**. The quick impacts of EGb on plasticity indicate a direct relationship with the glutamatergic system and evoke important questions concerning a mechanism underlying its impacts on cognitive improvement in dementia patients.

4.1.2. Anti-Parkinson's disease

The neuroprotective effects of *G. biloba* L. graded extract (EGb) were examined in this study

on 6-hydroxydopamine (6-OHDA)-induced neurotoxicity in the rat brain's nigrostriatal dopaminergic system **[12]**, based on body weight mice were split into four groups at random. Mice in the model, (EGb groups) were given intraperitoneally MPTP (30 mg/kg/day) for five consecutive days, whereas mice in the vehicle control group received the same volume of saline. From day 6 to day 19, mice in the EGb groups were given EGb at 50 mg/kg orally every day. Other groups of mice received 0.1 mL/10 g body weight from carboxymethyl cellulose sodium every day for 14 days. On day 19, motor coordination was assessed using a pole test. After four days of training, the mice's ability to remember and recall information was assessed using the Morris water maze (MWM) test from day 20 to day 24. Three mouse brains from each group were chosen at random, dissected, and preserved in 10% neutral buffered formalin following the MWM test. Following paraffin embedding, brain slices were stained with hematoxylin and eosin (HE), these experiments showed that EGb safeguarded dopaminergic neurons from 6-OHDA and MPTP/ MPPþ-induced neurotoxicity. Also, in different studies, rats received an injection of 6-OHDA before receiving EGb treatment. Rats receiving large doses of EGb (100 mg/kg daily) had noticeably greater contralateral forepaw adjustment steps. A behavioral deficiency was correlated with a decrease in striatal dopamine and a loss of dopamine neurons in the substantia nigra. These findings imply that EGb's neuroprotective properties reduce the behavioral deficit in rats with 6-OHDA lesions and point to a possible use of the extract in the management of Parkinson's disease **[29]**.

4.1.3. ADHD-like behavioral side effects

Among school-age children, attention-deficit/hyperactivity disorder (ADHD) is among the most prevalent neuropsychiatric conditions. Inattention, impulsiveness, and hyperactivity are the main signs of the condition. Most of the time, ADHD sufferers may need long-term medication, and the illness might persist in adulthood **[30]**. Thus, creating non-psychostimulant drugs that are safe to use and that can reduce ADHD symptoms may offer an alternate approach to the treatments that are now being used for the disorder. The neuroprotective and antioxidant properties of alternative medications may be helpful, at least partially, for the population with ADHD, as recent research has indicated that oxidative imbalance (oxidative stress) may be one of the etiological aspects of ADHD **[31]**. It has been suggested that *G. biloba* may help with ADHD. Animal studies have demonstrated that *G. biloba* extract increases brain dopaminergic activity, an area that may be deficient in ADHD patients. Thirty-six youngsters with ADHD were given a product containing *G. biloba* extract twice a day for four weeks as part of an open research. A shift in a single symptom or overall score of at least five points toward the normal range was considered an improvement **[32, 33]**.

4.2. Anticancer activity

4.2.1. Human hepatocellular carcinoma (HepG2 cells)

The anticancer impacts of *G. biloba* leaf extract and many of its ingredients were assessed in HepG2 cells **[34]** and the primary mode of action was assessed. Using a biochemical assay to investigate Topoisomerase II (Topo II) enzyme inhibition, compared to the other components of *G. biloba*, quercetin, a flavonoid, exhibited a greater propensity to interact with Topo II, according to molecular docking research. Furthermore, quercetin, kaempferol, and isorhamnetin were the most powerful DNA injury inducers in cells of HepG2, as determined by the Comet test and the initiation of γ-H2A.X. In Topo II knockdown cells, quercetin or *G. biloba* leaf extract greatly decreased DNA

damage, indicating a direct correlation between Topo II and DNA injury. DNA damage was additionally discovered when treating the cells with a *G. biloba* extract commercial product. According to their results, Topo II inhibition may be the cause of the *in vitro* genotoxicity brought on by quercetin and *G. biloba* extract in normal cells.

4.2.2. Pancreatic cancer

Different concentrations of *Ginkgo biloba* extract kaempferol (17.5, 35, and 70 μM) effectively prevent pancreatic cancer cell growth and trigger cancer cell apoptosis. The two concentrations were analyzed using two cell lines from pancreatic cancer (MIA PaCa-2 and Panc-1) **[35]**. Cell growth and apoptosis were investigated using a numerous technique. MIA PaCa-2 and Panc-1 proliferation was significantly inhibited by kaempferol; treatment with 70 μM kaempferol decreased growth to 21% and 53%, respectively. Additionally, the reduction of MIA PaCa-2 cell growth was enhanced by the combination treatment of low quantities of kaempferol and 5-fluorouracil.

4.2.3. Bladder cancer

The work done by Gohil et al (2000) using EGb, supports the idea that the flavonoid components of Ginkgo extracts influence gene expression in a manner that may be connected to chemo-preventive or anticancer potential **[36]**. They identified EGb-induced alterations in mRNA expression in the human bladder cancer cell line T-24, which carries an active c-Ha-ras oncogene that codes for the G-protein Ras, using high-density oligonucleotide microarrays. Indeed, this cell line was chosen because Ginkgo extracts have antioxidant qualities and because elevated Ras expression has been linked to increases in ROS and cellular proliferation that can be suppressed by certain antioxidants. According to their findings, EGb (100 μg/mL) caused a net stimulation of transcription, the most noticeable alterations taking place in the levels of mRNAs linked to transcription, intracellular vesicular transport, mitochondria, and antioxidant activity. This human cancer cell line has higher levels of the transcripts for mitochondrial Mn-superoxide dismutase (Mn-SOD), oxygenase-1 (HO-1), and the regulatory subunit of γ-glutamyl-cysteinyl synthetase (c-GCS), which is the enzyme that controls the rate of glutathione synthesis, as well as the proteins that are encoded by these enzymes. Additionally, the extract raised transcripts for DNA synthesis and repair as well as intracellular glutathione **[37]**.

4.2.4. Human breast cancer

A correlation was established in human breast cancer between the peripheral benzodiazepine receptor (PBR) expression and cell proliferation **[38]**. IPS200 (2–200 μg/mL), EGb preparation low in proanthocyanidins, plus one of the terpenoid constituents, Ginkgolide B, reduction in the concentration- and in a time-dependent way both cell proliferation and PBR expression in the PBR-enriched, extremely aggressive, lacks the estrogen receptor (ER) human breast cancer cell line MDA-231. This result was reversible and unrelated to GB or IPS200 antioxidant properties. However, the growth of the nonaggressive, estrogen-sensitive (ER-positive) human breast cancer cell line MCF-7, which has extremely low PBR levels, was unaffected by either IPS200 or GB. Additionally, it was noted that 48 hours of IPS200 (20 μg/mL) exposure to MDA-231 cells changed the expression of 36 genes, some of which are directly involved in the control of cell proliferation, differentiation, or apoptosis, in addition to PBR **[37]**.

4.3. Antimicrobial activity

4.3.1. Antibacterial activity

The ethanol extract of *G. biloba* leaves

cultivated in Nigeria exhibited some degree of antibacterial and antifungal activity. Gram-negative bacteria e.g., *Escherichia coli* (inhibition zone diameter of 10.5±1.41 mm) and *Pseudomonas aeruginosa* (no activity) showed less activity than gram-positive bacteria e.g., *Staphylococcus aureus* (15.5±0.71mm) **[39]**.

4.3.2. Antifungal activity

Antifungal activity was observed against the yeast *Candida albicans* (16.5±0.71 mm) and less activity against the molds *Aspergillus fumigatus* (no activity) and *Penicillium cyclopium* (9±1.41 mm). On both bacteria and fungi, the aqueous extract exhibited negligible antimicrobial action **[39]**.

4.3.3. Antiviral activity

4.3.3.1. Antiviral activity in COVID-19 treatment

Blocking SARS-CoV-2 3-chymotrypsin-like protease (SARS-CoV-2 3CL), which confers trans-variant efficacy, is one of the ways by which EGb mediates its antiviral activity **[40]**. At 100 μg/mL, EGb was able to block over 70% of the hydrolytic activity of SARS-CoV-2 3 CLpro *in vitro* tests [41]. The dose-inhibition curve of EGb on SARS-CoV-2 3CL was plotted using escalating dosages (from 1.25 to 100 μg/mL) to further characterize the inhibitory activity of EGb. With an estimated IC_{50} value of 6.68 μg/mL, EGb inhibited the target enzyme in a dose-dependent manner. This discovery implies that EGb has naturally occurring SARS-CoV-2 3CL inhibitors.

4.3.3.2. Anti-Herpes simplex activity

A comprehensive study examined the antiviral properties of EGb and its phytochemical components such as flavonoids and terpene tri lactones against Human alpha Herpes virus 1 (HHV-1) and Human α-Herpes virus 2 (HHV-2) **[42]**. It was discovered that the antiviral action of EGb is caused by flavonoids, particularly isorhamnetin. The anti-HHV-1 and anti-HHV-2 actions of EGb were impressive. At non-cytotoxic doses, the extract impacted the viruses before their adsorption onto the cell surface. It seems that EGb interacted with the cell-free virions in a concentration-dependent way, producing irreversible changes that shielded from cell monolayer infection that followed. These findings showed that, at non-toxic concentrations, these free virus particles are directly impacted by EGb, which makes them inactive and less contagious. Even at 4 log TCID50 (median tissue culture infectious dose), EGb reduced viral titer, indicating a 99.99% reduction in virus infectivity. Lastly, EGb may complement existing treatments for genital herpes and herpes labialis. Additionally, EGb's possible application in multidrug therapy with artificial anti-herpes substances may be taken into consideration.

4.4. Anti-inflammatory activity

4.4.1. Inflammation in airways

An interesting study showed that *G. biloba* leaf extract (EGb) can inhibit gene expression of IL-1β-induced MUC5AC in human airway epithelial cells (NCI-H292) [43]. The NCI-H292 cells were treated with 10 ng/ml of IL-1β for a whole day. Pretreatment with 200 μg/mL of EGb dramatically reduced the expression of MUC5AC caused by IL-1β. In a kinase-specific inhibitor investigation, it was observed that expression of the MUC5AC gene was inhibited by EGb through both the extracellular (ERK) signal-regulated kinase and the p38 MAPK pathways. *G. biloba* extract may be considered as a possible anti-hyper secretory agent. Another study was conducted to recognize which constituents of EGb down-regulate IL-1β-induced MUC5AC gene expression in NCI-H292 cells and to discover which MAPKs are connected to each ingredient's MUC5AC gene suppression **[44]**. The findings demonstrated that

both quercetin and kaempferol significantly inhibited MUC5AC mRNA expression in a dose-dependent manner, beginning at 40 mM (about equivalent to the twelfth or thirteenth dose of EGb). Following pretreatment with kaempferol, quercetin, and EGb, MAPK proteins were identified using real-time PCR and western blot analysis. The phosphorylation of p38 and ERK kinases was inhibited by all three. Essential components of EGb, kaempferol, and quercetin, may be able to solve the drug's dosage issue and are therapeutically crucial in regulating mucin hypersecretion during airway inflammation.

4.4.2. Anti-arthritic activity

4.4.2.1. Reduction of cyclooxygenase COX-1 and COX-2

Ginkgetin and a bioflavonoid mixture (1–10 µM) and (10–50 µM) respectively, composed of a 1:1 combination of ginkgetin and iso-ginkgetin, from *G. biloba* leaf prevented lipopolysaccharide-induced RAW 264.7 cells from producing prostaglandin E_2 **[45]**. At least some of this suppression was caused by downregulating COX-2 instead of directly inhibiting COX-1 or COX-2 activity, which in turn inhibited COX-2 expression. Ginkgetin significantly reduced COX-2 expression and suppressed prostaglandin E2 production by 65.6% in the dorsal skin of ICR mice treated with 12-*O*-tetradecanoylphorbol 13-acetate (TPA). Additionally, when applied topically, ginkgetin and the bioflavonoid mixture reduced the skin inflammation of mice's ear edema caused by croton oil in a dose-dependent manner.

4.4.2.2. Inhibition of adhesion and inflammation in P-selectin-mediated leucocyte

Cleared polysaccharide from *G. biloba* leaf (p-PGBL) was tested for its anti-inflammatory properties in mice with acute peritonitis model and xylol-induced ear edema [46]. Using flow cytometry and a flow chamber, the impact of (p-PGBL) on blocking the binding between P-selectin and its substrate was examined. Acute inflammation in mice may be effectively reduced by p-PGBL, which may also interfere in a dose-dependent way with the adhesion of neutrophils to human endothelial cells in the umbilical vein and in ovary cells of Chinese hamsters that express human P-selectin, as well as the static adherence of neutrophils, HL-60 cells, or a human leukemia cell line to P-selectin.

4.5. Antioxidant and Anti-lipid peroxidation activity

4.5.1. Antioxidant activity

The antioxidant property of *G. biloba* extract was examined *in vitro* **[47]** using 33% Ginkgo flavone glycosides, primarily quercetin and kaempferol derivatives, and is terpene-free containing extract. Superoxide dismutase (SOD) was used as a positive control to examine the extract's potential free-radical scavenging effect. Ginkgo extract's two aglycones, quercetin and kaempferol, were tested for activity. Significant antioxidant effects were demonstrated by quercetin and ginkgo extract. In exchange, kaempferol acted as a pro-oxidant when its concentration was higher than the ideal antioxidant level. An anti-inflammatory model was used for the *in vivo* tests. The data validated the Ginkgo extract's ability to scavenge free radicals. Similar to SOD, the Ginkgo extracts markedly reduced (37%) cutaneous blood flow. In addition, Ginkgo extract's antioxidant qualities were established by the reduction of both the induced and baseline levels of ROS linked to H_2O_2 **[48]**.

4.5.2. Anti-lipid peroxidation activity

An in vivo study examined the mechanisms behind the effects of protection of EGb on the livers of elderly rats **[49]**. Samples of liver tissue were used to measure the levels of glutathione peroxidase (GPx), malondialdehyde (MDA),

SOD, and tissue inhibitor-1 of metalloproteinase (TIMP-1). Blood samples were tested for albumin, total bilirubin (TBIL), aspartate aminotransferase (AST), and alanine aminotransferase (ALT). Histopathologic analyses showed that aged rats had mild liver fibrosis, but the livers of older rats given EGb showed less fibrosis and accumulation of lipofuscin. Additionally, in rats treated with EGb, the activity of GPx increased whereas the TIMP-1 expression and the amount of MDA in the liver both dropped. The level of liver MDA, lipofuscin, and TIMP-1 expression was higher in aged rats than in the group treated with saline, but the activity of GPx and SOD was reduced in older rats. EGb has protective benefits on the aging liver; its antioxidant properties and suppression of TIMP-1 expression are potential mechanisms.

4.6. Anti-aging activity

By postponing the onset of endothelial progenitor-cell (EPC) senescence, *G. biloba* extract was found to enhance cellular activity, which in turn boosted cell proliferation **[50]**. Since telomerase and serine/threonine kinase Akt activation play a crucial role in cellular aging, *G. biloba* extracts significantly boosted telomerase activity. The mitogenic capacity of G. biloba extract-treated EPCs outperformed that of untreated (control) EPCs, which extend telomeres, according to an MTT experiment. The effect counteracted the decline in telomere length brought on by each cell division and was dose-dependent, peaking at 25 mg/L.

4.7. Cardioprotective activity

The potential effects of EGb on induced oxidative damage of Hg II in the aorta and heart tissues were assessed *in vivo* **[51]**. Glutathione (GSH), malondialdehyde (MDA), and tumor necrosis factor (TNF) levels were biochemically analyzed. The results showed that EGb therapy reversed the oxidative harm to tissue caused by HgCl2, indicating that EGb can shield the cardiovascular tissues from $HgCl_2$-induced oxidative damage. Rats who received mercury had significantly greater MDA levels and significantly lower GSH levels than rats given both EGb and Hg, which had dramatically lower MDA and much higher GSH levels in the aorta and serum samples than the group given Hg alone. Mice treated with Hg had significantly higher serum lactate dehydrogenase activity, a measure of widespread tissue damage, whereas mice treated with both Hg and EGb demonstrated much lower enzyme activity. In contrast to the group treated with both Hg and EGb, where TNF-α levels significantly fell, the Hg-treated group's TNF-α level significantly increased.

4.8. Antiplatelet and anti-thrombus activity

Endothelial cells have a high-affinity thrombin receptor called thrombomodulin (TM) on their surface which by producing plasminogen tissue-type activators (t-PA, an anticoagulant) and plasminogen initiator inhibitors (PAI, procoagulant), endothelial cells control the activity of hemostasis and fibrinolysis. *G. biloba* extract (EGb) exhibits pharmacological effects that include peripheral and coronary vasodilation, improvement in coronary blood flow, suppression of thrombus formation, and antiplatelet activities **[52]**. A flow cytometer was used to assess the influence of EGb and quercetin (a key flavonoid component in EGb) on human umbilical vein endothelial cells (HUVECs') surface expression of TM *in vitro* and a gel imaging system to assess the effect of EGb and quercetin on t-PA secretion by HUVECs. At 10, 30, 50, and 100 µg/mL of EGb for 24 hours, the expression of TM on the surface of HUVEC cells increased in a dose-dependent manner. Indeed, EGb, but not quercetin, the expression of TM increased on the surface of HUVECs. Accordingly, the ability of endothelial cells to

produce TM and secrete t-PA may contribute to EGb's ability to improve blood circulation.

Ginkgolide A (GA) from *G. biloba* leaves was tested for its effects on collagen (10 µg/mL)-stimulated platelet aggregation **[53]**. Intracellular Ca^{2+} mobilization, thromboxane A2 (TXA2) generation, and platelet aggregation were all inhibited by GA concentration independently via suppressing the activity of COX-1 in platelets activated by collagen. Additionally, cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP), which suppress platelets both at rest and in response to collagen-stimulated platelets, were produced in greater quantities by GA.

4.9. Clinical trials on *Ginkgo biloba*

4.9.1. The effect of EGb on serum C-reactive protein (CRP) level

The weighted mean differences (WMD) of 7 trials with random-effects model analysis showed a significantly reduced effect of EGb on serum CRP level compared with the placebo with an intervention dose of <500 mg/day and baseline CRP levels of ≥3 mg/L **[54]**.

4.9.2 Fight against Alzheimer's Disease (AD)

Fifteen studies compared the outcomes of EGb treatment to a placebo in AD and dementia. The dosage ranged from 120 to 240 mg, with treatment periods ranging from 4-24 weeks. Four studies found no significant differences between groups treated with EGb and placebo. Eleven studies found that administering EGb improved cognitive function, neuropsychiatric symptoms, and functional abilities in both types of dementia. Significant differences were found in the Mini-Mental State Examination (MMSE), Short Cognitive Performance Test (SKT), and Neuropsychiatric Inventory (NPI) scores **[55]**.

Conclusion

This review summarizes the phytoconstituents reported in *G. biloba* and their bioactivities. *G. biloba* contains chemically diverse secondary metabolites including monoterpenoids, sesquiterpenoids, diterpenoids, triterpenoids, polyprenols, flavones, flavonols, isoflavonoids, biflavones, and allyl phenols. Terpene trilactones and flavonoids are considered the main bioactive compounds. *G. biloba* leaf extract is used in the treatment of many diseases particularly dementia conditions like memory loss, concentration issues, and Alzheimer's disease, strengthens capillary walls, increases blood flow, prevents clots formation, and preserves nerve cells from damage Additionally, the extract has anti-inflammatory, anti-oxidant, anti-asthmatic, radical scavenging, and wound-healing activities. The widespread use of *G. biloba* extract in managing various conditions prioritizes the evaluation of its pharmacokinetics and pharmacodynamics. Also assessing its potential side effects and toxicity would be an interesting research area.

List of abbreviation

6-OHDA, 6-hydroxydopamine; AD,Alzheimer's disease; ADHD, Attention deficit/hyperactivity disorder; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; Aβ, Amyloid-β; BB, Bilobalide; cAMP, Cyclic adenosine monophosphate; c-GCS, γ-glutamyl-cysteinyl synthetase; cGMP, Cyclic guanosine monophosphate; COVID-19, Coronavirus disease 2019; COX-1, Cyclooxygenase 1; COX-2, Cyclooxygenase 2; CRP, C-reactive protein; EGb, Extract of Ginkgo biloba; EPC, Endothelial progenitor-cell; ER, Estrogen receptor; ERK, Extracellular signal-regulated kinases; GA, Ginkgolide A; GB, Ginkgolide B; GC, Ginkgolide C; GJ, Ginkgolide J; GL, Ginkgolide L; GM, Ginkgolide M; GN, Ginkgolide N; GP, Ginkgolide P; GPx, Glutathione peroxidase; GQ, Ginkgolide Q;

GSH, Glutathione; HE, Hematoxylin and eosin; HHV-1, Human alpha Herpes virus 1; HHV-2, Human α-Herpes virus 2; HO-1, Oxygenase-1; HUVECs', Human umbilical vein endothelial cells; IL-1β, Interleukin-1 β; MAPK, Mitogen-activated protein kinases; MDA, Malondialdehyde; MMSE, Mini-Mental State Examination; Mn-SOD, Mitochondrial Mn-superoxide dismutase; MPTP 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine MTT, 3- [4,5-dimethylthiazol-2-yl]-2,5 diphenyl tetrazolium bromide; MUC5AC, Mucin gene; MWM, Morris water maze; NPI , Neuropsychiatric Inventory; PAI, Plasminogen initiator inhibitors; PBR, peripheral benzodiazepine receptor; PC12, cells Pheochromocytoma cells; PCR, Polymerase chain reaction; p-PGBL, Polysaccharide from G. biloba leaf; ROS, Reactive oxygen species; SARS-CoV-2 3CL Blocking, SARS-CoV-2 3-chymotrypsin-like protease; SKT, Short Cognitive Performance Test; SOD, Superoxide dismutase; TBIL, Total bilirubin; TCID50, Median tissue culture infectious dose; TIMP-1, Tissue inhibitor-1 of metalloproteinase; TM, Thrombomodulin; TNF, Tumor necrosis factor; Topo II, Topoisomerase II; TPA, 12-O-tetradecanoylphorbol 13-acetate; t-PA, Plasminogen tissue-type activators; TTLs, Terpene trilactones; TXA2, Thromboxane A2; WMD, Weighted mean differences; γ-H2A.X., Histone family member X;

Declarations

Consent to publish

The published version of the manuscript has been read and approved by all authors.

Ethics approval and consent to participate

Not applicable.

Availability of data and material

All data generated or analyzed during this study will be available upon request.

Conflict of Interest

The authors assert that there are no conflicts of interest.

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Authors' Contribution

All authors contributed to the study's conception, design, and analysis of the data. The first draft of the manuscript was written by Shimaa Gamal and all authors revised the manuscript. All authors read and approved the final manuscript.

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