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Review

Ginkgo biloba L.: An Updated Review on the Pharmacological Activities, Pharmacokinetics and Drug Interactions

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Abstract

Medicinal herbs have recently received considerable public attention for their therapeutic properties. Traditional healing systems such as Ayurveda, traditional Chinese medicine, and traditional Persian medicine highly rely on medicinal plants to treat many diseases. However, herbal medicines are usually not standardized and despite their widespread use, there is limited scientific evidence on their safety and interactions. L. is a medicinal plant whose biological properties have been confirmed in previous studies. Its leaf extract exhibited anti-inflammatory, antioxidant, neuroprotective, and anti-apoptotic properties. Nevertheless, *G. biloba* contains various pharmacologically active components, such as terpene lactones and flavonoids that could cause drug interactions through multiple mechanisms, including the effect on cytochrome isozymes and p-glycoprotein (P-gp). Thus, conducting studies to evaluate this plant's safety profile and drug interactions seems necessary. In the current paper, we reviewed the pharmacokinetics, drug interactions, and pharmacological properties of *G. biloba* plant. According to the included studies, bioactive compounds found in *G. biloba* extract have antagonistic activity against platelet aggregation and could inhibit human thrombin, thereby increasing the risk of severe bleeding. We also identified several other potential drug interactions for *G. biloba*, including risperidone, thiazides, mycophenolic acid, and diltiazem. Data on drug interactions between *G. biloba* and digoxin, simvastatin, nicardipine, and midazolam were less consistent. Therefore, caution should be taken in consuming this plant with anticoagulants or platelet inhibitors such as warfarin, ticlopidine, clopidogrel, and aspirin. However, patients' age, gender, and dosage forms of medicine seem to play an essential role in drug interactions. In summary, further clinical and laboratory research is necessary to elucidate the risk of *G. biloba* drug interactions. Also, the use of technologies such as genomics, metabolomics, and transcriptomics can provide a more comprehensive understanding of how *G. biloba* interacts with drugs at the molecular level.

Keywords: *Ginkgo biloba;* Herb–drug interaction; Cytochrome P450; Phytochemicals; Neurodegenerative disorders; Pharmacokinetics

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Introduction

Herbal remedies have traditionally been used for treating numerous illnesses [1]. In recent years, such medicines have gained considerable popularity globally; however, there is a shortage of robust evidence supporting their effectiveness and a lack of sufficient data concerning their safety profile [2,3]. Herbal medicinal products are easily accessible for purchase without consulting a healthcare professional in many countries. Self-medication through interactions with foods, herbal medicines, and synthetic drugs can lead to reducing, enhancing, or neutralizing the therapeutic effects of drugs, which may be life-threatening [4]. However, some believe that, unlike conventional medicines, herbal remedies are used for general purposes and do not have to meet the same safety standards. Herbal medicines contain various bioactive compounds that may exhibit therapeutic properties, and their composition can vary based on the plant part used, the season, and the growing conditions. The complexity is increased when multiple natural products are combined into a single formulation [5].

Ginkgo biloba L. is among the most ancient species of trees which is extensively used as dietary supplements and herbal medicine in traditional medical systems, with a specific emphasis on Chinese medicine [6]. The specific medicinal properties of ginkgo can be attributed to a range of phytochemical substances, including flavonoids (apigenin, kaempferol, quercetin, luteolin), terpene lactones (bilobalide and ginkgolide A, B, C,) and proanthocyanidins [7]. A majority of flavonoids, over 95%, are present as glycosides [8]. Flavonoids possess several physiological functions such as antioxidative properties, immunological modulation, and reduction of blood lipid levels, hepatoprotective effects, and adjustment of blood glucose levels [9]. Terpene lactones exhibit potent antagonistic properties against platelet-activating factor (PAF), hence exerting a supportive function on the cerebrospinal nervous system as well as lowering ischemia impairment [8]. These compounds also protect the cells against mitochondrial dysfunction and amyloidogenesis and modulate ion homeostasis and tau protein phosphorylation [7]. The clinical application of this plant has been observed in the therapeutic management of a range of disorders, particularly severe ischemic stroke, cognitive impairment and dementia, tinnitus, intermittent claudication, and age-related macular degeneration [7,10]. *G. biloba* inhibits PAF and improves blood flow, making it a therapeutic option for peripheral artery occlusive disease, tinnitus, and vertigo of vascular origin [11-13].

In patients with intermittent claudication, *G. biloba* can protect against post-ischemic oxidative damage and promote recovery, possibly through vasoregulation and antagonistic activity against platelet aggregation factor [14]. In vascular dementia, *G. biloba* is believed to improve blood flow and reduce ischemic damage [15]. Similar neuroprotective effects have been reported for this plant in Alzheimer's disease (AD) [16,17]. *G. biloba* could be administered to treat diabetic nephropathy and psychological disorders [18, 19]. EGB 761, the first standardized product made from ginkgo leaves, is employed for managing the symptoms of cerebral and neurodegenerative illnesses. It contains 6% terpene trilactones and 24% flavone glycosides [20]. The standardized leaf extract of *G. biloba* is presently available in different shapes as a medicinal herb in Europe, as well as in the United States as a nutritional supplement [21]. In Norway, *G. biloba* leaf extract has received approval from the Norwegian Medicines Agency for the treatment of cold hands and feet by improving blood circulation [10].

Ginkgo, due to its antiplatelet and antioxidant activities, is widely administrated to enhance blood flow and cognitive performance. However, possible interactions between ginkgo and medications of the narrow therapeutic indices, for instance, warfarin, as well as natural medicines with similar biological activities like garlic raise substantial concerns over the safety of ginkgo. As a result of pharmacodynamic and pharmacokinetic interactions, the occurrence of severe and dangerous bleeding in some cases may be increased [22].

Self-medication involves taking medicines without a physician's advice and prescription. Self-medication through interactions with foods, herbal medicines, and synthetic drugs can lead to reducing, enhancing, or neutralizing the therapeutic effects of drugs, which may be life-threatening. Ginkgo is often regarded as one of the most sought-after botanical remedies used for self-medication, especially for individuals with neurodegenerative conditions [23].

To conduct a comprehensive examination of the medication and dietary interactions associated with ginkgo, it is essential to explore the absorption of biologically active substances into the bloodstream and their subsequent concentration within the plasma. Hence, it is imperative to consider the oral absorption of potent compounds, such as flavonoid glycosides, which exhibit significant levels of efficacy [24].

Considering the increasing use of *G. biloba* as a medicinal herb and mounting evidence confirming its various medical properties, conducting studies to evaluate this plant's safety profile and drug interaction, as well as clarifying the effects of gender and dosage form on the pharmacokinetics of ginkgo compounds, seems necessary. Drug interactions generally occur due to the combination and simultaneous use of two or more drugs and are among the most common causes of unwanted drug side effects [25]. While herbal medicines are usually considered safe, they can have harmful, sometimes life-threatening interactions with

other drugs and alter their biological effects. More importantly, the elderly, who comprise the majority of individuals consuming herbal medicines, often take several drugs for various health problems, putting them at even greater risk for drug interactions [26]. Despite the clinical significance associated with possible interactions between medicinal herbs and other medications, studies in this field are limited, and the prevalence of such interactions is not well-documented [5,27]. This review focuses on the evidence-based interactions of ginkgo with plants, medicines, and foods, with a focus on preclinical studies and clinical cases. The pharmacokinetics of the active components and their pharmacological effects have also been reviewed.

Materials and Methods

Electronic databases including Scopus, PubMed, Science Direct and Cochrane Library were searched for *in vivo*, *in vitro*, and human studies with the following keywords: “Ginkgo or *Ginkgo biloba* ” in title/abstract along with “drug interaction”, “toxicity”, “pharmacokinetics”, and “biological activity” in the whole text from inception until January 2023. Only papers published in the English language were included.

Results

Botany of G. biloba

Ginkgo biloba L. is a member of the Ginkgoceae plant family. As a living fossil, the ginkgo tree is one of the world's earliest extant species and has flourished in forest ecosystems for more than 150 million years. The reproductive organs of the male and female of this dioecious tree are distinct. Their trunks are massive with a circumference of approximately 7 m and a height of approximately 30 m. Young ginkgo plants show branch dimorphism and are similar to conifers. In autumn, the clustered leaves of this plant change a golden yellow color. Its leathery, two-lobed leaves resemble the vein pattern and shape of a maidenhair fern. Pollination occurs when female pendulous pairs of ovules borne on the shoots are fertilized by male microstrobili harboring male gametophytes. After around 20 years, these trees begin to reproduce by producing nuts (bare seeds) with an exterior fleshy coating. The fleshy outer layer of the fruit contains a significant concentration of butanoic and hexanoic acids, which play a crucial role in both the rotting process and the olfactory perception of fermentation [28].

History and traditional uses of G. biloba

The ginkgo tree is the sole remaining species in the family Ginkgoaceae, class Ginkgoatae, which was found again in 1670 in the gardens of an Asian shrine. There are about fifteen genera in the Ginkgoatae class, the three most significant of which are Ginkgo, Baiera, and Ginkgoites [29]. The term "Ginkgo" originates from its Chinese name, namely Sankyu or Yin Kuo, which translates to "hill apricot" or "silver fruit." This nomenclature is attributed to the yellow-colored, apricot-like appearance of ripe ginkgo fruits. Engelbert Kaempfer, a German surgeon, originally introduced the term “ginkgo” in 1712. However, it was not until 1771 that Linnaeus officially classified and identified the species as *G. biloba* [21,30]. Ginkgo tree nuts and leaves have therapeutic properties according to traditional Chinese medicine, with evidence dating back several centuries. Indeed, it is worth noting that the nuts possess a significantly extensive historical record of utilization, as they were initially documented in herbal texts during the Yuan dynasty, which spanned from 1280 to 1368 AD [31]. For thousands of years, it has been recognized that the seeds (often referred to as nuts) have therapeutic properties for various pulmonary ailments such as asthma, cough, and enuresis, in addition to curing bladder irritation and alcohol misuse. Conversely, the application of leaves is mainly observed in the management of cardiovascular and respiratory disorders, as well as for the treatment of skin infections [32,33].

The utilization of EGb 761, a standardized extract formulation of the ginkgo leaf, gained prominence in Germany during the past two to three decades [34]. Presently, it has become the predominant form of supplement utilized in the United States for addressing cognitive disorders [35]. The fruit of this tree, which is cooked and fermented, is also utilized as a delicacy at marriage ceremonies and celebrations. In Korea, Japan, Malaysia, and China, ginkgo seeds that have been roasted or boiled are highly regarded as a culinary delicacy. Additionally, it is also grown as an ornamental tree in many European and American countries [30,36].

Phytochemical components of G. biloba

The most important compounds found in *G. biloba* leaves include but are not limited to terpenoids and flavonoids. Variation in flavonoid amounts in ginkgo leaves has been observed to be season-dependent, with higher concentrations occurring during autumn compared to spring. The ginkgo leaf extract contains various types of flavonoids, including flavonols, flavones, and biflavones such as bilobetol, ginkgetin, amentoflavone, 5-methoxybilobetol, sciadopitysin, and isoginkgetin. Additionally, it contains glycosides of quercetin, isorhamnetin, and kaempferol [8]. *G. biloba* has been found to have several terpene lactones, which consist of several derivatives of 20-carbon diterpene lactones (specifically ginkgolides A, B, C, J, and M) as well as a 15-carbon sesquiterpene called bilobalide [37]. The chief physiologically active

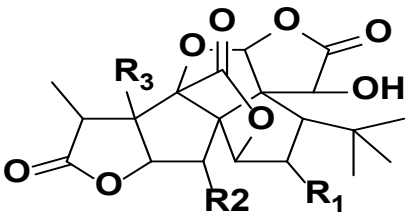
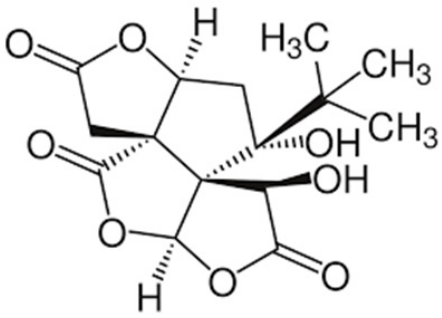
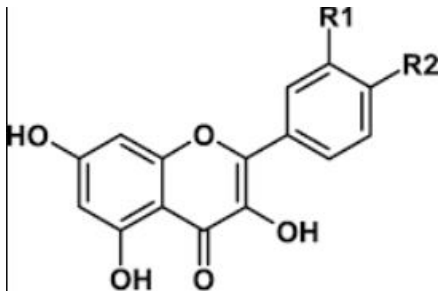
chemicals of *G. biloba* are described in table 1.

Pharmacological activity and clinical uses of *G. biloba*

Anti-inflammation activity

The potential anti-inflammatory properties of *G. biloba* are generally related to the biologically active compounds in *G. biloba*, including flavonoids, terpene trilactones, and polysaccharides. Ginkgo's inhibitory effects are demonstrated by the suppressing of inflammatory mediators and nuclear factor-κB (NF-κB), modulation of immune responses as well as antioxidant effects [38,39]. Numerous studies have shown that polysaccharides, such as those in *G. biloba*, exhibit anti-inflammatory activities [40]. It has been demonstrated that polysaccharides suppress the formation of inflammatory factors, suppress cytokine secretion, and interfere with the relationship between P-selectin protein, its ligands, and HL-60 cell adhesion. Purified polysaccharides of *G. biloba* leaves have demonstrated anti-inflammatory properties *in vivo*, decreasing the overexpression of nitric oxide (NO), increasing the level of cytokines such as interleukin-10 (IL-10), and reducing the levels of IL-1β and tumor necrosis factor-alpha (TNF-α). These observations suggest that polysaccharides of *G. biloba* leaves could potentially be used as an anti-inflammatory therapy [41-44]. Additionally, according to an *in vitro* study, ginkgo flavonoid O-glycosides inhibited lipopolysaccharide-induced NO release in RAW 264.7 macrophages in a dose-dependent manner [45]. An-

Table 1. Chemical structures of the major bioactive compounds found in *G. biloba*

Terpene lactones	R1	R2	R3
			
Ginkgolide A	H	OH	H
Ginkgolide B	H	OH	OH
Ginkgolide C	OH	OH	OH
Ginkgolide J	OH	OH	H
Ginkgolide M	OH	H	OH
			
Bilobalide			
Flavonoids			
			
Quercetin	OH	OH	___
Kaempferol	H	OH	___
Isorhamnetin	OCH3	OH	___

other study investigated the anti-inflammatory properties of EGb 761's water-soluble component in *Candida albicans*-induced inflammation in mice. The findings indicate that edema was decreased by intraperitoneal injection of this extract fraction at a dose of 2 mg once every three days for 15 days. According to a further investigation, terpenes were responsible for these beneficial anti-inflammatory effects. The administration of terpenes (7.4 µg/dose) via liposomal delivery technique produced results comparable to those of indomethacin (30 µg/dose) [46].

Antioxidant activity

Oxidative stress plays a significant role in various disorders. It occurs when there is an imbalance between the formation of reactive oxygen species (ROS) or free radicals and the body's potential to neutralize or detoxify them. Numerous diseases, including cancer, inflammatory disorders, metabolic disorders, autoimmune diseases, cardiovascular diseases, and neurodegenerative diseases are influenced by oxidative stress. The chemical components in ginkgo extract stimulate multiple signaling pathways in cells, one of which is the Nrf2 pathway. This pathway serves as the primary mechanism for exhibiting antioxidant benefits by neutralizing ROS through detoxification [47]. *In vitro* experiments have shown that EGb 761 can scavenge oxygen radicals and inhibit xanthine oxidase activity. Polysaccharides of *G. biloba* leaves are a rich source of antioxidants that can scavenge hydroxyl, 2,2-diphenyl-1-picrylhydrazyl (DPPH), 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid (ABTS), and superoxide radicals. Two polysaccharides in *G. biloba* leaves exert high ABTS scavenging capacities. *G. biloba* leaves polysaccharides also demonstrate DPPH and hydroxyl radical-scavenging activities [8,48-50].

Neuroprotective effects

G. biloba extract has been demonstrated to have neuroprotective effects in several studies, including *in vitro* studies that exhibited its ability to protect against neuronal death and *in vivo* studies that showed a reduction of neuronal damage after exposure to different stressors. The ginkgolides, bilobalide, and flavonoid fractions of *G. biloba* have been identified as the main contributors to its neuroprotective properties. Additionally, *G. biloba*'s ability to affect the transcription of genes that regulate oxidative stress may help protect neuronal cells against oxidative damage. This is particularly relevant to neurodegenerative disorders such as Alzheimer’s disease and Parkinson’s disease, which are commonly associated with oxidative stress [51-53]. Several pre-clinical studies indicate that *G. biloba* polysaccharides can prevent cerebral ischemia in rat brains. Additionally, pre-treating neuronal cells with ginkgolide can protect them from synaptic damage and amyloid beta (Aβ) toxicity. Additionally, ginkgolide B and A protect against Aβ-toxicity and can improve cognitive and learning functions. Bilobalide can also decrease Aβ-induced degeneration of the hippocampus. For instance, ginkgolide J reduces neuronal death by inhibiting Aβ in the hippocampus [54].

Autism

Autism Spectrum Disorder (ASD), commonly referred to as autism, is a neurodevelopmental disorder distinguished by a range of impairments related to social interactions, communication abilities, and adherence to routines. The intensity of manifestations of ASD can be diverse considerably from individual to individual, which makes it a highly variable disease. The treatment of this condition usually involves a multidisciplinary approach, which may involve behavioral therapies, educational interventions, or prescription medications.

In a research employing an observational design, three volunteers were administered a dosage of 2 × 100 mg *G. biloba* EGb 761 for 28 days. The patients exhibited signs of progress as shown by the Symptom Checklist and Aberrant Behavior. The findings of this study indicate that *G. biloba* may have efficacy as an adjunctive treatment [55]. In contrast, findings from a double-blind clinical research including 47 outpatients diagnosed with autism revealed that the co-administration of ginkgo (at doses of 80 and 120 mg/day adjusted according to patient weight) alongside risperidone (at doses ranging from 1-3 mg/day) did not significantly impact the outcomes measured by the Aberrant Behavior Checklist, compared to a control group receiving only risperidone [56].

Anti-platelet activity

Administration of *G. biloba* leaf extract is claimed to reduce platelet aggregation. Indeed, ginkgolide has strong antagonistic activity against PAF and may increase peripheral blood flow [57,58]. Vasodilation properties of ginkgo dilate blood vessels. This may decrease the risk of blood vessel constriction, which can help improve blood flow and potentially avoid platelet aggregation [59-61]. Additionally, flavonoids in *G. biloba* inhibit cyclooxygenase, which in turn reduces the production of thromboxane A2, a potent platelet aggregator [62].

Nephroprotective effects

The term "nephroprotective" describes medications or procedures that have the ability to preserve the kidneys from injury, thereby alleviating the negative effects of specific nephrotoxic pharmaceuticals and detrimental conditions such as diabetes and hypertension on renal function. Medications that regulate blood pressure,

anti-inflammatories, and antioxidants comprise the conventional list of nephroprotective substances.
From a clinical perspective, *G. biloba* has been observed to provide several biological benefits, such as the removal of free radicals, antiapoptotic properties, as well as anti-inflammatory and antioxidant activity. The nephroprotective effect of ginkgo has been examined in several animal models. In a study conducted on rat models of nephrotoxicity induced by vancomycin, the administration of ginkgo at a dosage of 100 mg/kg/day for a duration of 10 days had a significant preventive effect on renal impairment [63]. A further *in vivo* study confirmed that concurrent administration of *G. biloba* extract and pentoxifylline resulted in a notable improvement in severe renal damage [64].

Metabolic Syndrome and Cardiovascular Diseases

G. biloba has been investigated for its potential role in addressing metabolic syndrome, a group of health issues that boost the chances of heart disease, diabetes, and stroke. Some studies suggest that *G. biloba* may have a positive impact on factors of metabolic syndrome, for instance, insulin resistance and lipid profile. The antioxidant properties of *G. biloba*'s bioactive compounds may contribute to mitigating oxidative stress associated with metabolic syndrome. *G. biloba* extract demonstrates a potentially significant antidiabetic effect. *G. biloba* may decrease plasma glucose levels by potentially increasing glycogen levels in both liver and muscle tissue. Furthermore, research has demonstrated that the implementation of this intervention can result in reductions in visceral adiposity index, HbA1c levels, insulin concentrations, body weight, and waist circumference [65]. Previous research has suggested that consuming *G. biloba* may be useful for reducing inflammation and insulin resistance. Numerous processes are thought to be involved in mediating these effects, including the suppression of IRS-1 receptor serine phosphorylation, the attenuation of NFκB/JNK activation, the elevation of adiponectin secretion, and the consequent decrease in the production of inflammatory adipokines. Additionally, *G. biloba's* effectiveness has been shown in lowering absorption of cholesterol, blocking 3-hydroxy-3-methylglutaryl–coenzyme A (HMG-CoA), an enzyme that is essential in controlling the creation of cholesterol and reducing hyperglycemia brought on by a high-fat diet [66]. Treatment with *G. biloba* notably reduced the triglyceride and cholesterol levels in rabbits; while elevating the content of high-density lipoprotein cholesterol (HDL-c). Furthermore, the administration of *G. biloba* resulted in a reduction in malondialdehyde content as well as an augment in antioxidant enzyme concentration. Research has indicated that the *G. biloba* extract has the potential to reduce both body weight and weight gain. Furthermore, it has been observed to upregulate IL-10 expression; while downregulating TNF-α and NF-κB expression. Additionally, studies have demonstrated that it stimulates the insulin receptor and facilitates the activation of protein kinase B (Akt), thereby augmenting the insulin signaling cascade. Because *G. biloba* inhibits the angiotensin-converting enzyme (ACE) and causes vasodilation, it also has hypotensive effects. Further research has demonstrated that *G. biloba* increases the synthesis of endothelial nitric oxide synthase (eNOS) [67]. *G. biloba* reduced the occurrence of cardiomyopathy, a prominent factor in heart failure and a determinant of cardiac mortality. Because the mechanism of cardiomyopathy is unknown, there is no proven treatment; hence, novel approaches must be developed. *G. biloba* and its bioactive components are beneficial in this medical state because they promote blood circulation and activate many pathways that regulate pro-survival, anti-inflammatory, and antiapoptotic effects via PI3K-AKT and NF-κB signaling [68]. Moreover, several studies suggest that ginkgolide A may function as an antithrombotic medication, used to prevent or treat thrombosis. In addition to suppressing collagen-stimulated platelet aggregation, it activates matrix metalloproteinase (MMP)-9 and generate cAMP and cGMP intracellularly. By blocking COX-1 and preventing the movement of intracellular Ca^{2+}, this diminishes the secretion of thromboxane A2 [69]. Vascular conditions associated with aging are strongly correlated with impaired endothelial function and increased arterial rigidity, both of which contribute to the development of cardiovascular disease (CVD). Vascular damage results from inflammation and oxidative stress, as this paper has already covered. *G. biloba* extract's antioxidant and anti-inflammatory characteristics effectively ameliorate age-related vascular diseases. The primary mechanism by which this plant influences conditions associated with vascular aging likely involves the modulation of longevity signaling pathways and the attenuation of vascular aging in diabetes, as its ability to regulate blood sugar and lipid metabolism has been proven [61]. A study assessed the effects of plant extracts with antioxidant properties on the psychological health and glycemic control of individuals diagnosed with type 2 diabetes mellitus (T2DM). The participants were administered either placebo capsules, a dry extract of green tea, or a standard dry extract of ginkgo leaves. The antioxidant status, HbA1c levels, and glucose control were evaluated at the beginning of the research and nine and eighteen months following the administration of antioxidant supplements or a placebo. Patients with T2DM responded moderately to ginkgo leaf extract. Research has demonstrated that the concurrent use of ginkgo as a supplementary medication with metformin enhances the therapeutic

efficacy of metformin in individuals diagnosed with T2DM. However, the limitations of this study include the short duration of the study, the small sample size, and the absence of information regarding the dose-response relationship of ginkgo extract when integrated with standard antidiabetic medication, which necessitates the need for further studies on a larger scale [70]. In addition, a clinical study showed that in patients with metabolic syndrome treated with ginkgo extract, the formation and size of plaques in blood vessels, as well as biomarkers of oxidative stress and inflammation, decreased. The results of the study showed that ginkgo could lessen CVD risk variables by lowering homeostasis model assessment of insulin resistance (HOMA-IR), hs-C reactive protein, and IL-6 [71].

Pharmacokinetic

The ADME factors, including absorption, distribution, metabolism, and excretion, are critical in determining the pharmacokinetic properties of medications. Pharmacokinetic medicine interactions are most commonly related to changes in one or more of these parameters caused by medicines that affect the movement of the gastrointestinal system or modify drug transport in the intestine, liver, or kidney. Among the metabolic enzymes present in these organs, cytochrome proteins (CYPs) are chiefly involved in the oxidative metabolism of xenobiotics. The most important CYP450 enzymes involved in the metabolism of drugs include CYP1A2, CYP2C8, CYP2D6, and CYP3A4. The CYP3A4 isozyme exhibits the highest level of expression in both the intestine and liver. Medications, especially their metabolites that have undergone hydroxylation or dealkylation, are combined with glucuronic acid through the activity of uridine 5'-diphosphate-glucuronosyltransferase (UGTs) in the liver or intestine. The water-soluble metabolites are subsequently eliminated through either the biliary or urinary excretion pathways. Drug metabolism and elimination are significantly influenced by transporters like P-gp and the organic anion-transporting polypeptides (OATPs), which play a crucial role in drug take-up and efflux within the intestine and liver [72].

The pharmacokinetics of *G. biloba* involves the processes of absorption, distribution, metabolism, and excretion, which directly contribute to the bioavailability and duration of action of its principal constituents. The major medicinally active substances of *G. biloba* are flavonoids and terpenoids, and these substances are assimilated into the digestive system following oral consumption. For an extended period, the limited technological advancements and methodologies limited the detection of prototype flavone glycosides in blood or urine. Consequently, it was widely believed that the absorption of flavone glycosides into the bloodstream through the small intestine was exceedingly challenging. Advances in science and technology have provided major developments in the investigation of flavonoid glycoside oral absorption in recent years. Studies have shown that orally administered naturally occurring substances rutin, quercetin-3-O-glucoside, and quercetin-3-O-rhamnoside are effectively absorbed into the circulatory system [73-75]. The pharmacokinetics of these compounds are outlined as follows:

Pharmacokinetics of the flavonol glycosides

Cytosolic β-glucosidase in the small intestine plays a major role in the hydrolysis of ginkgo flavonoids. After passing through the epithelial cells of the intestinal wall, the resulting aglycone flavonoids reach the liver through the portal vein. Then they are affected by different phases of metabolism. Unlike phase II, phase I has little role in the metabolism of flavonoid aglycones. Phase II metabolic enzymes, such as uridine 5'-diphospho-glucuronosyltransferase, catechol-O-methyltransferase, and sulfotransferase, convert flavonoid aglycones into sulfate, methyl, and glucuronide metabolites [76].

Researchers administered EGb 761 to Wistar rats and analyzed the pharmacokinetics of flavonol glycosides and aglycones in blood, feces, and urine using LC-DAD, HPLC, and Mass spectrometry. Before EGb 761 administration, rats were given a diet without flavonoids for 15 days. The results showed that the samples did not contain any flavonol glycosides or aglycones; however, degradation products such as homovanillic acid, 3,4-dihydroxyphenylacetic acid, hippuric acid, and benzoic acid were identified. Benzoylglycine (II) was present in the blank sample and the corresponding peak increased only in the first urine fraction (0-24 h); whereas benzoic acid (VII) was present only in the second urine fraction (24-48 h) [77]. Rangel-Ordo´n˜ez et al. investigated the levels of ginkgo flavonol aglycones in the plasma and their distribution in the brain of rats following the oral administration of single or repeated doses of EGb 761. Administration of a single dose resulted in peak plasma levels of kaempferol, quercetin, and isorhamnetin/tamarixetin; while only kaempferol and isorhamnetin/tamarixetin were identified in the brain. In comparison, repeated dosing increased the level of kaempferol and isorhamnetin/tamarixetin in the blood plasma and brain. About 90% of the determined flavonoids were distributed in the hippocampus, frontal cortex, striatum, and cerebellum, which together represent only 38% of the whole brain [78].

Two studies investigated the metabolism of ginkgo flavonol glycosides in humans and animals. The first study measured the concentration of aglycones in healthy volunteers who took 50, 100, or 300 mg of *G. biloba* leaf extract (GLE) orally. It was found that

the highest concentration of aglycones was reached approximately 2-3 hours after taking the highest dose. The second study, conducted on six participants who took 4 g of EGb 761, demonstrated that the glycosides were broken down into aglycones and then processed in the gut and liver. However, the study did not provide any data on the levels of derivatives of flavonols in the bloodstream or urinary excretion [79]. Overall, it can be concluded that the metabolism of ginkgo flavonol glycosides is extensive. Thus, even moderate to high doses do not result in high levels of aglycones in the bloodstream.

Pharmacokinetics of the terpene lactones

The terpene lactones ginkgolide A, B, C, J, and bilobalide are explicitly found in *G. biloba* leaf extracts [80]. Pharmacokinetic investigations of terpene lactones are thought to be reliable as their concentrations in plasma, urine or feces remain unaffected by the consumption of food [81]. Early investigations in the bioavailability of terpene lactones disclosed that ginkgolide C was undetectable in plasma, likely attributed to the process of methylation. However, ginkgolide A and B and bilobalide were found following intravenous administration or oral consumption of EGb 761 to human volunteers and rats [81-83]. The oral administration of EGb 761 to rats revealed linear pharmacokinetics with C_{max} values for ginkgolide A and B and bilobalide [82]; while the observed T_{max} values were between 0.5 and 1.0 hours. Ginkgolide C was not measurable in blood plasma, most probably because of extensive methylation. Three metabolites of ginkgolide B in rat urine were identified [83].

Researchers used the human colon adenocarcinoma cell monolayer (Caco-2) to study bilobalide absorption, intestinal permeability, and transport mechanisms. Additionally, they tested blood-brain barrier permeability using an MDR1-MDCK monolayer. This research found that bilobalide crosses Caco-2 cell monolayers by active efflux at physiological pH (7.4) and has pH-dependent characteristics. Due to bilobalide's ability to permeate the Caco-2 and MDR1-MDCK monolayers, it exhibits the potential to penetrate both the blood-brain and intestinal barriers. Furthermore, bilobalide could be able to modify the blood-brain barrier's permeability in a reversible manner. The process involves promoting the phosphorylation of the actin-binding protein via the adenosine A1 receptor, which modifies the ultrastructure of cell tight junctions and facilitates bilobalide's passage into the brain. Following the oral ingestion of ginkgo extract, the gastrointestinal tract typically absorbs bilobalide as a monomer. The bioavailability ranges of ginkgolide A, B, and bilobalide were found to be 32.82–41.87%, 30.15–39.12%, and 57.09–62.69%, respectively. Another study demonstrated that the bioavailability of ginkgolide A, ginkgolide B, and bilobalide in rats was found to be 61.2%, 27.2%, and 56.2%, respectively. The aforementioned studies demonstrated that the bioavailability of bilobalide was considerably greater in comparison to ginkgolide A and B. Several studies investigated the pharmacokinetics of bilobalide following consumption of *G. biloba* extract (GBE) tablets at doses of 120 or 240 mg. The findings of the experiment indicate that bilobalide exhibits a high oral bioavailability of 79%, a quick absorption rate ($T_{max} < 2$ hours), and a biological half-life varying between 2.08 and 6.04 hours. Furthermore, it should be noted that bilobalide has a short peak time, high bioavailability, and fast absorption in comparison to ginkgolides A, B, C, and J [84,85].

An investigation on the distribution of bilobalide in animals revealed that it exists in plasma and erythrocytes, showing that it is distributed in different tissues and organs. Bilobalide mainly has a high excretion rate and is eliminated from the kidney by OATPs. The process of bilobalide excretion is unknown; however, it does not involve enterohepatic circulation. As compared to other terpenoids of ginkgo, bilobalide has a relatively slower plasma clearance. The results of an animal study state that after administering 600 mg/kg to rats, bilobalide quickly penetrates the central nervous system after crossing the blood-brain barrier. Then it is excreted through the kidneys within 24 hours, but despite the fact that its excretion is very slow, it still does not accumulate in the body [86].

The effect of route of administration and dosage form on the pharmacokinetics of G. biloba main compounds

The delivery of drugs by the oral route is widely prevalent in clinical practice. The majority of pharmaceutical substances are absorbed within the gastrointestinal system after oral administration, and then enter the bloodstream to elicit their therapeutic effects. Several factors can influence the oral absorption of medications, including the physicochemical features and dosage forms of the drugs, as well as the physiological circumstances in the gastrointestinal system. The disintegration or dissolution time of oral medications can be influenced by the preparation processes or excipients used to create the dosage forms. This, in turn, may potentially affect the effectiveness of the drugs. In clinical practice, it is common for drugs to be administered orally following meals. However, the consumption of food can potentially alter the acidity capacity of the gastrointestinal tract and also change the rate at which drugs are emptied from the stomach. Additionally, food may interact with drug molecules, thereby influencing the absorption of drugs within the body. Consequently, these interactions have the potential to impact the overall effectiveness of drugs.

Previous studies have predominantly focused on the absorption of medications *in vivo* through various oral dosage forms and in the presence of different foods, primarily within the context of Western medicine or formulations consisting of a single component. However, there is a paucity of research investigating the absorption characteristics of traditional medicine or its extracts in this regard. Researchers investigated the effect of different dosage forms on the pharmacokinetics of five flavonoid glycosides, three aglycones, and four terpene lactones of *G. biloba*. The findings on the content determination of GBE tablets, and tinctures indicate that the tincture exhibited higher levels of several components, particularly flavonoid glycosides, compared to the other two preparations. The pharmacokinetics analysis yielded disparate findings following the oral delivery of the three formulations. The tincture exhibited a higher bioavailability of flavonoid glycosides compared to the other two preparations.

This study examined the variations in the composition and oral bioavailability of active compounds in various oral formulations of GBE. It also elucidated the *in vivo* absorption of a prototype flavonoid glycoside and investigated the impact of diet on the pharmacokinetics of active compounds. These findings hold significant implications for the clinical utilization of GBE oral preparations [86].

Effects of food and gender on the pharmacokinetics of terpene lactones bilobalide

An animal study was conducted to examine the impact of gender and food on the pharmacokinetics of ginkgo terpene lactones, including bilobalide, ginkgolide A, B, and C. In this study, to examine the disparity in the pharmacokinetics of ginkgo terpene lactones between food consumption and fasting, a group of six rats had a 24-hour fasting period before the oral consumption of ginkgo terpene lactones extract. Conversely, another group of six rats was provided unrestricted access to food before the treatment. Following the oral administration of 6 mg/kg of ginkgo terpene lactones, blood samples were obtained over a period of 24 hours. The findings indicate that both half-time ($t_{1/2}$) values and area under concentration–time curve (AUC) values were considerably lower ($p < 0.05$), in the fasting group compared to the fed group; while a statistically significant increase was seen in the maximum plasma concentration (C_{max}) of all terpene lactones in the fasting group ($p < 0.05$). When comparing the male group to the female group, it was observed that the $t_{1/2}$ values and AUC values for terpene lactones in females were significantly higher ($p < 0.05$). However, there were no variations in T_{max} values across the aforementioned groups. In summary, the findings of this study indicate that the recommended oral dosages of ginkgo terpene lactones should be adjusted to be lower for individuals who are in a fasted state and for female participants, in comparison to those who are in a fed state and male participants, respectively [87].

The pharmacokinetic outcomes obtained from experiments conducted on individuals in a fasting state compared to those in a non-fasting state revealed that the administration of GBE tincture on an empty stomach resulted in enhanced absorption of a range of chemicals, with a particular emphasis on flavonoid glycosides. Nevertheless, the presence of meal remnants in the gastrointestinal tract resulted in a notable enhancement of the oral bioavailability of flavonoid glycosides [86].

Drug interactions of G. biloba

The active compounds of herbal medicines can affect the metabolism and transport of other drugs by inducing or inhibiting metabolic enzymes and transporters. Orphan nuclear receptors such as the nuclear receptors pregnane X receptor (PXR) and constitutive androstane receptor (CAR) play a crucial role in mediating the activities of drug-metabolizing enzymes and transporters. Furthermore, other nuclear receptors such as Farnesoid X receptor (FXR), Liver X Receptor Alpha (LXRα), Peroxisome Proliferator-Activated Receptor Alpha (PPARα), Retinoic Acid Receptor-Related Orphan Receptor Alpha (RORα), Retinoic Acid Receptor-Related Orphan Receptor Gamma (RORγ), and Aryl Hydrocarbon Receptor (AhR) also regulate genes linked to drug absorption, distribution, metabolism, and excretion. P-gp is widely expressed in various tissues and can influence drug absorption, elimination, and distribution. Inhibition of metabolic enzymes occurs mainly through competition for CYP binding sites, and reversible inhibition can be categorized into competitive, non-competitive, uncompetitive, and mixed-type. It is crucial to consider inter-species differences when extrapolating data obtained from cultured rodent cells or laboratory animals to humans [88-92].

G. biloba is a plant species known for its various bioactive compounds, including flavonoids, terpene trilactones, proanthocyanidins, ginkgolic acids, biflavone, polyflavones, and ginkgotoxin [93, 94]. Among these, flavonoids have been shown to inhibit CYP450 enzymes, responsible for metabolizing several drugs, and thus, could influence the efficacy and safety of such drugs [75, 93]. In particular, quercetin, kaempferol, and isorhamnetin have been identified as inhibitors of several CYP enzymes. Quercetin inhibits CYP3A, which metabolizes cyclosporine, nifedipine, and diltiazem. On the other hand, kaempferol inhibits CYP1A2 and CYP2C9, which are involved in the metabolism of theophylline and warfarin. Studies conducted on rats and human volunteers have demon-

strated that the coadministration of ginkgo extract and drugs metabolized by CYP enzymes can alter pharmacokinetics, leading to potentially harmful drug interactions. For instance, the simultaneous intake of ginkgo and nifedipine reduced the first-pass metabolism of nifedipine by inhibiting CYP3A, but not P-gp. Similarly, nifedipine can influence the metabolism of flavonoids from ginkgo extract, emphasizing caution when administering these medications together in a clinical context. Additionally, it has been suggested that quercetin can interfere with the effectiveness of cyclosporine by interacting at the absorption site. Moreover, studies on rats indicated that simultaneous administration of ginkgo extract and diltiazem resulted in increased diltiazem bioavailability, partially due to a mechanism-based inhibition of CYP3A. In conclusion, *G. biloba* contains various compounds that can inhibit CYP enzymes, leading to potential drug interactions. Therefore, caution should be exercised when co-administering ginkgo extract and drugs metabolized by CYP enzymes, and careful monitoring is essential to ensure patient safety. Further research is warranted to explore the mechanisms underlying these interactions and to identify strategies for mitigating their adverse effects [95-99].

Inhibitory effects of G. biloba biflavones on human thrombin

A study examined the antithrombotic properties of sixteen major ginkgo compounds on human thrombin, the primary coagulation and thrombosis-related enzyme. The results showed that four biflavones and five flavonoids inhibited thrombin activity (IC_{50} values ranging from 8.05 μM to 82.08 μM). The four biflavones were found to be mixed inhibitors of thrombin-mediated Z-GGRAMC acetate hydrolysis, with K (i) values ranging from 4.12 μM to 11.01 μM. According to molecular docking analysis, the four biflavones could bind to hydrogen atoms and fill the active site. Furthermore, according to the lysine-labeled reaction assay, biflavones can attach to human thrombin specifically at exosite I. These findings indicate that biflavones in *G. biloba* are natural inhibitors of human thrombin and may be useful in drug development after further studies [100].

Aspirin

The ginkgolides in *G. biloba* extract appear to inhibit PAF and, thus, could hinder PAF-induced platelet conglomeration. However, PAF has never been illustrated *in vivo* to play a part in physiological blood clotting. Moreover, the available evidence does not support the notion that *G. biloba* could cause meaningful changes in blood coagulation parameters [101].

In a randomized controlled trial with a double-blind design, sixty-seven adult volunteers with peripheral artery disease or risk factors for cardiovascular disease were allocated to either take EGb 761 or a placebo. All participants were directed to take a daily aspirin tablet (325 mg). According to the findings, the simultaneous daily intake of 325 mg aspirin and 300 mg EGb 761 in individuals with CVD or peripheral artery disease did not have any noticeable effect on platelet activity [102].

In an *in vitro* study, the antiplatelet effects of aspirin and ginkgo extract, and their drug mixture in equal proportions were evaluated by microplate strategy utilizing rabbit platelets. The results indicated that ginkgo can be used as a supplementary treatment for thrombotic disorders [103]. In contrast, in another study by Benjamin et al. on ten healthy adult volunteers (six male and four female), consumption of ginkgo for two weeks had no effects on platelet function [104]. This was consistent with a population-based retrospective study by Agnes et al. which showed that the simultaneous use of ginkgo extract with antiplatelet or anticoagulants has no significant relationship with the increased risk of bleeding [105]. However, there are multiple case reports documenting interactions between *G. biloba* and aspirin leading to bleeding. One such case involves a 70-year-old man who experienced spontaneous hyphema with a daily consumption of 40 mg of *G. biloba* [106], another case of a 61-year-old man who suffered from subarachnoid hemorrhage while taking 40 mg of *G. biloba* 3-4 times daily [107], a 33-year-old healthy woman who developed bilateral subdural hematoma after long-term use of *G. biloba* [108], and finally, a 72-year-old woman developed intracerebral hemorrhage while taking 50 mg of *G. biloba* thrice daily [109].

These cases of bleeding may have occurred due to the antagonism of PAF by ginkgolide B. It should be noted that most cases were at an advanced age. Consequently, the simultaneous prescription of *G. biloba* with aspirin and other antiplatelets might be a relative contraindication in older adults [110].

Warfarin

A randomized cross-over study on 24 outpatients supplemented with oral *G. biloba* extract (100 mg daily for four weeks) showed no changes in INR. It should be noted that the geometric mean dosage of warfarin did not change during the study period [111]. Similarly, Taki et al. observed that *G. biloba* extract (up to 1000 mg/kg) and ginkgolide B (up to 140 mg/kg) did not change the blood coagulation parameters in mice under treatment with warfarin. In contrast, *G. biloba* extract attenuated the anticoagulant effects of warfarin [112].

G. biloba leaf extract is prescribed to inhibit and cure thrombosis and heart and circulatory system disorders. However, its bioactive compounds and the underlying

mechanisms of antithrombotic activity have not been completely clarified. A research was designed to assess the inhibitory effects of the main compounds of *G. biloba* on human thrombin, an essential serine protease controlling the blood coagulation cascade and thrombosis mechanism. A biochemical assay based on fluorescence was employed to quantify the inhibitory effects of sixteen *G. biloba* compounds on human thrombin. The findings indicated that the biflavones in *G. biloba* are natural inhibitors of human thrombin and, thus, could regulate the blood coagulation cascade. The biflavones in *G. biloba*, such as bilobetin, ginkgetin, and amentoflavone, are relatively potent inhibitors of human thrombin. However, the antithrombin activity of these biflavones is not as strong as direct synthetic thrombin inhibitors such as dabigatran and bivalirudin [100].

In another study by Di Pierro et al., coadministration of ticlopidine or warfarin with *G. biloba* increased the antiplatelet effects and prolonged the bleeding time in rats. However, administering ticlopidine or warfarin with VR456 (a standardized deterpened *G. biloba* leaf extract) increased the antiplatelet effect without prolonging the bleeding time. The authors concluded that terpenoid was the main PAF-antagonist fraction of *G. biloba* and played a crucial role in increasing the risk of bleeding in patients taking anticoagulants. Thus, using deterpened *G. biloba* extract could mitigate the danger of bleeding in high-risk patients [113].

Digoxin

Using dynamic multiple reaction monitoring methods, Rao et al. demonstrated that co-administrating *G. biloba* extracts with digoxin could increase the plasma concentration, $AUC_{0-t,}$ and C_{max} of digoxin in rats [114]. In contrast, in a study by Mauro et al., *G. biloba*'s effects on digoxin's pharmacokinetics were evaluated. No significant changes in peak plasma drug concentration (C_{max}) and $t_{1/2}$ parameters were observed in healthy volunteers who received 0.5 mg of digoxin and 80 mg of *G. biloba* thrice daily. Thus, it was concluded that ginkgo had no significant effects on the pharmacokinetics of digoxin [115]. Further large-scale human studies are needed to validate these results.

Bupropion

In an *in vitro* study, Lau et al. reported that *G. biloba* extract and its flavonol aglycones could inhibit CYP2B6 catalytic activity and bupropion hydroxylation [116]. In a similar human study, Lei et al. investigated the effects of *G. biloba* extract on the pharmacokinetics of bupropion. Fourteen healthy male volunteers consumed 240 mg of *G. biloba* as two 60 mg tablets twice daily for fourteen days, concomitantly with 150 mg of bupropion. Treatment with *G. biloba* extract significantly reduced $t_{1/2.}$ It also increased the C_{max} of hydroxybupropion. However, no significant changes were noted in the area under the plasma drug concentration-time curve of bupropion or hydroxybupropion, suggesting that adjusting the bupropion dose was unnecessary [117].

Diltiazem

In an *in vivo* study on rats, pretreatment with oral administration of GBE (20 mg/kg) increased the bioavailability of diltiazem by inhibiting the intestinal and hepatic metabolism of diltiazem in CYP3A and decreasing the elimination rate [118].

Diuretics

A case report in an elderly patient showed increased blood pressure resulting from concomitant use of thiazides and *G. biloba*. Discontinuation of *G. biloba* reduced the blood pressure to pretreatment levels [118].

Risperidone

One study reported the possible interactions between risperidone and *G. biloba* in a 26-year-old man with new-onset priapism. He had previously been diagnosed with paranoid schizophrenia and had been under treatment with 3 mg of risperidone for three years. He had no other chronic diseases and denied using other medication or trauma. He also denied any complications caused by antipsychotic drugs. However, two weeks earlier, he had started consuming *G. biloba* 160 mg daily due to occasional tinnitus. Nevertheless, he experienced erectile dysfunction. Finally, the patient was treated with diluted epinephrine and advised to stop taking ginkgo. After six months of follow-up, the patient had a normal erection [119].

Risperidone is metabolized by CYP450 isoform 2D6 (CYP2D6) and CYP450 isoform 3A4 (CYP3A4), both inhibited by *G. biloba*. Thus, *G. biloba* can increase the serum concentration of risperidone and the risk of associated side effects. In addition, *G. biloba* causes vasodilation by increasing the activity of NO or directly affecting the endothelium, making it a potential treatment option for erectile dysfunction. Finally, priapism may be due to the synergistic effect of risperidone and *G. biloba* [119].

Ticlopidine

Both ticlopidine and ginkgo are OATP-B inhibitors. Lu et al. observed that concurrent consumption of ticlopidine and *G. biloba* did not change the AUC and C_{max} of ticlopidine [120]. In another study, the simultaneous administration of ticlopidine and *G. biloba* did not show an additional antiplatelet effect compared to ticlopidine alone, and it did not increase the bleeding time. An open-label, randomized, two-period, two-treatment, two-sequence, single-dose cross over

study by Kim et al. concluded that coadministration of *G. biloba* extracts with ticlopidine did not considerably affect the pharmacokinetic profile of ticlopidine [121]. Similarly, in another study, young and healthy volunteers were treated with 120 mg ginkgo extract daily for three days, then given 250 mg ticlopidine, and finally, a single dose of 40 mg ginkgo extract the next day. No changes in C_{max} and AUC were noted [75].

Clopidogrel

In vitro researches explained that *G. biloba* extract induces the conversion of clopidogrel into its active metabolite in rat liver microsomes. One study reported that pretreatment with high-dose *G. biloba* extract markedly elevated the C_{max} and $AUC_{0-\infty}$ of the clopidogrel active metabolite. However, this effect was not apparent at medium and low doses, indicating that biotransformation occurs only at high doses [122].

Statins

In a two-treatment, two-cycle, cross-over trial conducted on fourteen healthy volunteers, the interactions of *G. biloba* and simvastatin in therapeutic doses were evaluated. Study subjects were simultaneously treated with 40 mg of simvastatin and 120 mg of *G. biloba* or placebo. *G. biloba* significantly decreased simvastatin AUC and C_{max} but did not affect simvastatin acid PK or its cholesterol-lowering efficacy. This might be due to the fact that simvastatin and simvastatin acid are metabolized by the CYP3A isoenzyme, which is induced by *G. biloba*. However, because the induction of GBE on CYP3A was very weak compared to strong inducers such as rifampin, it may be that simvastatin acid does not have a statistically significant difference. However, other studies failed to show any effects of *G. biloba* on cytochrome 3A4; thus, further evaluation of the pharmacokinetics of this interaction is needed [123].

The researchers examined the impact of ginkgo leaf extracts on hepatocyte organic anion transporting polypeptide (Oatp) 1b2 in the context of non-alcoholic fatty liver disease through *in vivo* experimentation and investigated the pharmacokinetics of ginkgo active components. The levels of ginkgolides and flavonols in the plasma of rats exhibited a dose-dependent rise following oral administration. The half-lives of quercetin, kaempferol, and isorhamnetin were 2 to 3 hours longer than ginkgolides A, B, C, and bilobalide. Non-alcoholic fatty liver disease caused an approximate 50% reduction in plasma pitavastatin exposure in rats owing to elevated Oatp1b2 expression. As the concentration of ginkgo's active compounds increases (from 3.6 to 32.4 mg/kg) AUC_{0-t} and C_{max} of pitavastatin increase 1.3-3.0 and 1.8-3.2 times, respectively. The presence of kaempferol (IC_{50} values of 3.28 ± 1.08 μM) and isorhamnetin (46.12 ± 5.25 μM) resulted in the suppression of OATP1B1-mediated uptake of H-ES [124].

In a clinical trial, a group of sixteen participants was administered a single oral dosage of 40 mg of atorvastatin, following a five-day interval the participants were administered a daily dosage of 360 mg of GBE for 14 days, after which they received a single dose of 40 mg of atorvastatin. Blood samples were collected up to 48 hours post-atorvastatin administration to evaluate atorvastatin plasma concentration, cholesterol absorption markers (sitosterol), and cholesterol synthesis markers (lathosterol). According to the findings, following GBE consumption, atorvastatin's AUC_{0-48}, $AUC_{0-\infty}$, and C_{max} decreased by 14.27% ($p = 0.005$), 10.00% ($p = 0.03$), and 28.93% ($p = 0.002$), respectively. Atorvastatin's Volume of distribution (Vd/F) and clearance (CL/F) increased by 31.95% and 6.48%, respectively. It was discovered that 14 days of medication with GBE did not significantly affect the ability of atorvastatin to decrease cholesterol levels. In summary, it can be concluded that GBE has a minor impact on the plasma concentrations of atorvastatin; however, this effect does not significantly affect the ability of atorvastatin to lower cholesterol levels [125].

Mycophenolic acid

G. biloba can increase the serum concentration of mycophenolic acid since flavone aglycones of *G. biloba* inhibits the metabolism of mycophenolic acid in human intestinal and liver microsomal systems by glucuronosyltransferase-UGT. As the first-pass metabolism is inhibited, the systemic concentration of mycophenolic acid rises and its immunosuppressive effects increased [126].

Omeprazole

A group of healthy 18-year-old Chinese patients were studied, and it was found that taking GBE along with omeprazole caused hydroxylation of omeprazole through CYP2C19. This led to an increase in renal clearance of omeprazole, ultimately reducing the effectiveness of omeprazole [127].

Nicardipine

Kubota et al. evaluated the effects of oral *G. biloba* extract on the antihypertensive action of nicardipine in rats. They reported that ginkgo decreased the hypotensive effects of nicardipine and reduced the maximal nicardipine plasma concentrations [128]. Conversely, in a study by Mauro et al., an evaluation of the effects of *G. biloba* extract on the pharmacokinetics of nicardipine in healthy volunteers showed that *G. biloba* extract did not significantly influence the pharmacokinetics of nicardipine. However, the study was

limited by its small sample size and short duration [117]. Another study by Brantley et al. reported the case of an elderly patient who developed hypotension after taking *G. biloba* and nicardipine together. The authors hypothesized that the hypotensive effects of *G. biloba* may have been potentiated by nicardipine. However, the exact mechanism of this interaction and its true nature is not well understood [129]. Further trials seem necessary to draw definitive conclusions regarding the interactions between *G. biloba* extract and nicardipine.

Midazolam

In a clinical study, biochemical investigations revealed that ginkgo decreased midazolam plasma levels by inducing CYP3A4 [130]. However, other clinical trials, with the help of molecular investigations, failed to show any differences in CYP3A4 activity in patients taking *G. biloba* [93, 131,132]. This is also confirmed by a recent meta-analysis [133]. Table 2 summarizes some of the studies on the drug interactions of *G. biloba*.

Discussion

Nowadays, medicinal products containing dry *G. biloba* extract are widely used by the general population for different purposes [167]. Indeed, in a study on patients attending a geriatric care center, *G. biloba* was the most frequently used herbal medicine [168].

G. biloba seems to improve the quality of life and age-related cognitive disorders in the elderly; however, it has been shown that the dry extract of *G. biloba* leaves contains high amounts of ginkgolic acids, which are potent allergens that may have cytotoxic, genotoxic, and carcinogenic properties [169]. Moreover, case reports of seizures exist after commencing extract of *G. biloba*, possibly due to herb-drug interactions, ginkgo-induced Steven's Johnson syndrome, and ginkgo-induced post-operative hemorrhage [170-172]. Ginkgo is also suspected to increase the risk of bleeding in patients on anticoagulants or antiplatelet therapies [173]. Indeed, several studies have indicated that ginkgo interferes with platelet function and may be associated with an increased risk of bleeding when taken simultaneously with anticoagulants or platelet inhibitors such as warfarin, clopidogrel, or aspirin [108,111,174,175]. *In vitro* studies have also confirmed the inhibition of thrombin and platelet aggregation by substances extracted from *G. biloba* leaves [100,176-178].

Conversely, other studies have demonstrated different results, including a small randomized, double-blind, placebo-controlled trial which found no differences in platelet function or reports of bleeding and bruising in patients taking EGb 761 and aspirin [101]. Likewise, two clinical studies failed to show a considerable impact of *G. biloba* and its effective substance on blood clotting [179,180]. Finally, one meta-analysis could not confirm the increased risk of bleeding in patients taking *G. biloba* [101].

In a cross-sectional study aimed at analyzing the Taiwan National Health Insurance Research Database (NHIRD), Chan et al. reported no increased risk of bleeding with the concomitant use of *G. biloba* extract and antiplatelet/anticoagulant agents; however, univariate analysis of the relative risk of bleeding in elderly patients (65 years or older) was significant [105]. In another study, several drug interactions related to blood coagulation and platelet function were observed in elderly participants taking ginkgo [181]. Another study evaluated a medical database that included several thousand patients taking warfarin, with or without ginkgo. Results showed an increased risk of bleeding for concomitant use. Authors noted that the administration and regularity of herbal product consumption lack regulation and are seldom documented. Therefore medical records often exhibit information bias, with incomplete data more common in sicker patients [182].

These findings indicate a possible, albeit modest, increase in the risk of bleeding by *G. biloba* that might be influenced by physiological factors such as age. Indeed, drug interactions are known to be more common in old age [183]. Treatment monitoring is recommended for patients at risk, and discontinuing ginkgo before surgeries may be advisable.

More importantly, there exists a public misconception that herbal products and medicines are healthy and safe because they are derived from nature. This causes many patients to take medicinal plants in addition to prescribed drugs, which sometimes leads to dangerous drug interactions [184]. Thus, it is essential to consider the safety profiles and legal standards in prescribing and providing medicinal herbs.

Our study had some limitations. Firstly, many previous reviews focused on dietary supplements and excluded herbal medicinal products. Moreover, it should be noted that the legal status of products containing the same plant might vary significantly between countries [185].

One of the reasons for the difference between the results of the studies is the lack of standardization of the products and the change in the amount of active substances, which is different based on the various growing conditions of the plant and processing procedures. Pharmacokinetics also plays an important role in interactions. Pharmacokinetics is influenced by various factors such as gender, age, genetics, body weight, conditions of the gastrointestinal tract in terms of fullness and emptiness of the stomach, pH of the gastrointestinal tract, diet and pharmaceutical forms, drug administration methods, and various dis-

Table 2. *G. biloba* drug interactions

Drug group	Drug	Study Type	Mechanism	Potential Outcome	References
Alpha and beta-adrenergic agonist	Ephedrine	*In vivo*	Stimulation of the sympathetic nervous system	Increased blood pressure and heart rate	[134]
Analgesic	Acetaminophen and ergotamine-caffeine	*In vivo*	PAF inhibition	Increase the risk of bleeding	[134]
Antiviral	Sofosbuvir	*In vivo*	P-gp inhibition	Increased sofosbuvir $AUC_{(0-t)}$ & $t_{1/2}$	[135]
Antibiotic aminoglycoside	Amikacin	*In vivo*	____	Increased amikacin-induced ototoxicity	[136]
Anticoagulant	Warfarin	*In vivo*	Inhibition of hepatic metabolism of warfarin	Increased risk of bleeding	[137]
Anticoagulants	(heparin, enoxaparin)	*In vitro*	Inhibition of platelet aggregation	Increased risk of bleeding	[138, 139]
Anticonvulsants	Sodium valproate	Case report	CYP2C19 induction	Increase the incidence of seizures due to ginkgotoxin (4'-O-methylpyridoxine)	[140]
Anticonvulsants	Phenobarbital	*In vivo*	CYP2B induction	Reduced maximum serum levels of phenobarbital	[141]
Antidepressant Benzodiazepine	Midazolam	*In vivo*	CYP3A4 induction	Increased sedation	[142]
Antidepressant Benzodiazepine	Alprazolam	*In vivo*	CYP3A4 induction	17% decrease in alprazolam AUC	[143]
Antidepressant Benzodiazepine	Diazepam	*In vivo*	CYP2C19 inhibition	Same bioequivalence	[144]
Antidepressants as selective serotonin reuptake inhibitors (SSRIs)	Fluoxetine and Venlafaxine	*In vivo*	P-gp inhibition CYP3A4 inhibition	Dose dependently increase the serum level of venlafaxine	[145]
Antidepressant serotonin receptor antagonists and reuptake inhibitors (SARIs)	Trazodone	Case report	synergistic GABAergic effect	Ataxia, drowsiness, and coma in an elderly patient with Alzheimer's disease	[146]
Antifungal (triazoles)	Voriconazole	*In vivo*	CYP2C19 induction	Loss of infection control	[147]
Antiplatelet	Aspirin	*In vivo*	Inhibition of platelet aggregation	Increased risk of bleeding	[148]
Antiplatelet	Clopidogrel	*In vivo*	PAF inhibition	Increase the risk of bleeding	[149]
Antiretroviral (non-nucleoside reverse transcriptase inhibitors (NNRTIs)	Efavirenz	Case report	Induction of CYP2B6 & CYP3A4	Lower Efavirenz serum concentrations and virological breakthrough	[150]
Atypical antipsychotics	Risperidone	*In vivo*	CYP inhibition	Priapism	[119]
Beta-blockers	Propranolol	*In vivo*	Induction of CYP1A2, CYP2B1/2 & CYP3A1	Reduce the levels of propranolol	[151]
Beta1-selective adrenoceptor antagonist	Talinolol	*In vivo*	P-gp inhibition	Reduced hypotensive action	[152, 153]

Bronchodilator (xanthines)	Theophylline	*In vivo*	CYP1A2 induction	Increased clearance and metabolism	[154]
Calcium channel blocker	Nicardipine	*In vivo*	CYP3A induction	Reduce the levels of nicardipine	[155]
Calcium channel blocker	Nifedipine	*In vivo*	CYP450 3A4-inhibiting activity	Increasing nifedipine Levels	[99]
Calcium channel blocker	Diltiazem	*In vivo*	CYP450 3A4-inhibiting activity	Increasing Diltiazem levels	[95]
Diuretics	Thiazide diuretics	*In vivo*	Not known	Increased blood pressure	[156]
Immunosuppressant	Ciclosporin	*In vivo*	CYP3A inhibition	Reduced maximum serum levels and AUC of ciclosporin	[157]
Immunosuppressants	Tacrolimus	*In vivo & in vitro*	Inhibition of Tacrolimus Metabolism	Increased Tacrolimus AUC_{0-t} and C_{max}	[158]
Nonsteroidal anti-inflammatory drugs (NSAIDs)	Ibuprofen	Case report	Inhibition of platelet aggregation	Increased risk of bleeding	[139]
Proton-pump inhibitors	Omeprazole	*In vivo*	CYP2C19 induction	Decreased plasma concentration of omeprazole (about 40%)	[159]
Sulfonylureas	Tolbutamide	*In vivo*	Inhibition of CYP2C9 & CYP3A4	Hypoglycemia	[142]
Sulfonylureas	Tolbutamide	*In vivo*	CYP2C9 induction	Decreased hypoglycemic effects of tolbutamide	[160]
Herbal drugs	*Cannabis sativa* L.	*In vivo*	Not known	Rhabdomyolysis	[161]
Herbal drugs	*Panax notoginseng* (Burkill) F.H.Chen	*In vivo*	Inhibition of platelet aggregation	Increased risk of bleeding	[162]
Herbal drugs	*Bacopa monnieri* (L.) Wettst.	*In vivo*	PAF inhibition	Increased cognitive function	[163]
Herbal drugs	*Valeriana officinalis* L.	Case report	____	Fainting and psychotic symptoms	[164]
Herbal drugs	*Scutellaria baicalensis* Georgi	*In vitro*	____	Reduced neuroprotective effects of the herbs	[165]
Herbal drugs	Sodium Aescinate	Case report	Improved microcirculation and reduced capillary permeability	Acute kidney injury	[166]

eases. The physicochemical properties of a drug, such as solubility and lipophilicity, can affect its absorption, distribution, and metabolism. Circadian rhythms and biological variations over a 24-hour period can influence drug absorption, distribution, metabolism, and elimination [186]. The results of studies conducted on the pharmacokinetics of important ginkgo compounds, namely flavonoids and terpene lactones, have sometimes had controversial results.

The pharmacokinetics of flavonoids of *G. biloba* indicate that benzoylglycine or hippuric acid is present in the initial urine sample obtained within the first 24 hours, but benzoic acid is detected in the subsequent sample, possibly due to hepatic glycine conjugation system saturation. It can be inferred that within the chromone ring; besides the ether link, other bonds can also break, resulting in the formation of benzoic acid, phenylacetic acid, or 3-(phenyl) propionic acid. Addi-

tionally, the metabolism of other extract components, such as proanthocyanidins, might result in the creation of the 3-(phenyl) propionic derivatives [77,187].
Enterohepatic circulation is the cause of ginkgo flavonoids' characteristic bimodal behavior. Certain flavonoid glycosides entered the gut again and were quickly reabsorbed in the upper portion of the digestive tract. They can also be eliminated through the biliary tracts. This phenomenon will contribute to the prolongation of the half-life of flavonoids and an increase in their serum levels [188].
Terpene lactones have higher bioavailability than flavonoids because flavonoids have a very extensive first pass and undergo glucuronidation. Flavonoids are absorbed in the form of aglycone and are seen in the form of sulfate and glucuronate in urine and plasma. Ginkgo flavones are the substrate of P-glycoprotein. As a result, P-gp has a role in the low bioavailability of flavonoids. Extensive first-pass metabolism and P-gp-mediated efflux are the primary reasons for the limited bioavailability of flavonoids in *G. biloba* [76]. Terpene lactones are less soluble in water and also inhibit the activity of a number of P450 cytochromes, which causes the pharmacokinetic difference of these compounds due to food and gender [189-191].
Some properties of the *G. biloba* plant are related to the terpene lactones of this plant. Studies show that ginkgolides A, B, C, and J have different bioavailabilities despite their structural similarity [192]. Various factors are involved in these differences, as mentioned. These compounds have different membrane penetration abilities [84]. In addition, intestinal flow transmitters are ineffective on ginkgolides C and J, and bilobalide, and the bioavailability of medicinal compounds is directly related to intestinal absorption [193]. It also seems that the kinetics of ginkgolides A and B are flip-flop kinetics, where the speed of absorption of a compound is significantly slower than the speed of its removal from the body. Therefore, the persistence of this compound in the body depends on absorption rather than elimination processes [194]. Also, the permeation of ginkgolides, which usually takes place in the duodenum, is influenced by pH-dependent carboxylation, which leads to the opening of the lactone ring. Ginkgolides and bilobalide are present in plasma as both trilactone and carboxylated forms. Also, paraoxonase 1 plays an important role in the hydrolysis of lactone compounds [194]. The amount of paraoxonase varies in different people according to diet, lifestyle, and disease status [195]. Since the removal of ginkgo terpene lactones is done through the kidney, kidney diseases and changes in renal blood flow lead to changes in renal clearance [196].
In summary, personalized medicine, incorporating genetic information and patient-specific characteristics, is an evolving approach to optimize drug efficacy and safety.

Conclusion

In conclusion, the potential for drug interactions with *G. biloba* underscores the importance of a cautious and informed approach to its use in conjunction with other medications. While *G. biloba* is an herbal supplement widely known for its potential cognitive and circulatory benefits, its pharmacological effects and interactions with conventional medicines can vary among individuals. The complex composition of *G. biloba*, including flavonoids and terpene lactones, introduces the possibility of modulating drug metabolism and affecting pharmacokinetic profiles.

Conflict of Interests

Authors declare no conflicts of interests.

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