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Revisión / Review

The dietary supplement of *Ginkgo biloba*: a comprehensive review of its potential interactions based on pre-clinical and clinical evidences

[El suplemento dietético de *Ginkgo biloba*: una revisión exhaustiva de sus posibles interacciones basada en evidencias clínicas y preclínicas]

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Abstract: This review present *Gingko biloba* (GB) interactions, based on clinical and pre-clinical presentations. Literature was retrieved using databases; ScienceDirect, PubMed, Google scholar, Web of Science, Scopus etc. 14/45 interactions were found with clinical presentations. More interactions (80%) were reported with drugs followed by herbs (11.1%), and nutraceuticals (6.7%) with major mechanisms of interaction observed as; inhibition of Cytochrome metabolizing enzymes (44.4%) and platelet-activating factor (PAF) i.e. 15.6%. Major clinical features were; increased bleeding (eye, parietal), hematomas (subdural), and seizures as well as increased blood pressure, priapism, loss of infection/antiviral failure, and coma. Drugs with major interactions belonged to anti-platelet/anti-coagulant and NSAIDs. Synergistic effects were observed for GB vs herbs (except cannabis which showed rhabdomyolysis), foods, and nutraceuticals (except pyridoxine where neurotoxicity was seen). GB use should be monitored and the patient may seek proper advice from a healthcare professional.

Keywords: *Ginkgo biloba*; Interactions; Self-medication; Alzheimer; Astaxanthin

Resumen: Esta revisión presenta las interacciones de *Gingko biloba* (GB), basadas en presentaciones clínicas y preclínicas. La literatura se recuperó utilizando bases de datos; ScienceDirect, PubMed, Google Scholar, Web of Science, Scopus, etc. Se encontraron 14/45 interacciones con presentaciones clínicas. Se informaron más interacciones (80%) con fármacos seguidos de hierbas (11,1%) y nutracéuticos (6,7%) con los principales mecanismos de interacción observados como; inhibición de las enzimas metabolizadoras del citocromo (44,4%) y factor activador de plaquetas (PAF), es decir, 15,6%. Las principales características clínicas fueron; aumento de sangrado (ojo, parietal), hematomas (subdural) y convulsiones, así como aumento de la presión arterial, priapismo, pérdida de infección / insuficiencia antiviral y coma. Los fármacos con interacciones importantes pertenecían a los antiplaquetarios / anticoagulantes y los AINE. Se observaron efectos sinérgicos para GB frente a hierbas (excepto cannabis que mostró rabdomiólisis), alimentos y nutracéuticos (excepto piridoxina donde se observó neurotoxicidad). Se debe controlar el uso de GB y el paciente puede buscar el asesoramiento adecuado de un profesional de la salud.

Palabras clave: *Ginkgo biloba*; Interacciones; Automedicación; Alzheimer; Astaxantina

INTRODUCTION

Ginkgo biloba (GB) belongs to the family Ginkgoaceae, whereas Gingko is derived from a Chinese word "yin-kuo or Sankyo" which means a "silver fruit or hill apricot" (McKenna *et al*., 2001). It's the nuts and leaves of GB, implicated in different traditional treatment systems of China, Indonesia, and Japan, which imparts important medicinal and pharmacological properties to GB, to be used as food or dietary supplement (Kumar Singh *et al*., 2017). The food chemistry shows the presence of various components responsible for the unique pharmacological activities of GB dietary supplement such as ginkgolides (A, B, C, M, K, L and Q), flavonoids (quercetin, luteolin, kaempferol, apigenin etc.), bilobalide and proanthocyanidins (van Beek & Montoro, 2009; Liao *et al*., 2011). The dietary supplement finds therapeutic applications in the treatment of Alzheimer's, dementia (Kandiah *et al*., 2019), cardiovascular diseases (Tian *et al*., 2017), stress and memory enhancement (Raju *et al*., 2019), geriatric complaints i.e. vertigo, age-related macular degeneration (Gil-Martínez *et al*., 2020), psychiatric disorders (schizophrenia), and to improve blood circulation (Benzie & Wachtel-Galor, 2011). Though the nuts are more known for folkloric uses, the last 20 to 30 years witnessed a sudden raise for the therapeutic applications of GB leaves extract. The first standardized product EGB 761 (24% flavone glycosides and 6% terpene trilactones) is one of the examples with regular use worldwide for neurodegenerative and cerebral diseases (Omidkhoda *et al*., 2019). The increased attention for GB may be estimated with an annual market value of $840 M in the US and Europe (Chen *et al*., 2020). The global market value for GB extract is expected to rise with a CAGR of 4.1% by 2028, which makes a value of 2379.2M USD compared to a value of 1590.5M USD in 2018 (USM, 2020). Keeping in view the huge market value, it is noteworthy to mention the frequent practice of self-medication for GB used. Self-medication refers to the selection and use of medicines without any advice or prescription form a health care professional. Self-medication poses the risk of interactions with other drugs, foods, or herbal products leading towards a decrease or increase in the effectiveness of therapy, which may lead to life-threatening conditions. GB is amongst the top self-medicated dietary supplements, particularly in chronic venous insufficiency patients (Rubio *et al*., 2018; Damnjanovic *et al*., 2020). A prevalence with 52% concurrent use of GB with other prescription drugs has been reported (Agbabiaka *et al*., 2017). Alternative medicine is being widely used these days, in the US, 25% of American people use herbal products for preventive and therapeutic reasons, where only 70% of these people inform their physicians. It may lead to medical issues or fatal toxicities sometimes (Kleijnen & Knipschild, 1992; Borrelli *et al*., 2007).

Interestingly, the components in GB account for its anti-oxidant and platelet aggregation inhibition property hence, GB products are frequently used for improving blood flow and cognitive function (Cupp, 1999; Benzie & Wachtel-Galor, 2011). This poses a significant concern regarding GB safety with regard to its potential interactions, particularly when used concomitantly with drugs of narrow therapeutic index such as warfarin or herbal products with alike properties such as garlic. More chances of pharmacokinetics and pharmacody-namics interaction do exist and bleeding may occur which may be severe in most cases (Cupp, 1999; Borrelli *et al*., 2007). GB may have interactions with other drugs, herbs and foods which may either diminish or boost its effect in the body. Few such interactions may lead to fatal results even.

Figure No. 1
Gingko biloba

The current review aims to accurately report the interactions of GB when used concomitantly with other drugs, herbs or foods etc. The review focuses individually on all such interactions based on the evidence i.e. pre-clinical or clinical cases reported for these interactions. Besides, a proper conclusion will be established to report the significant adverse effects and mechanisms observed during GB interactions.

LITERATURE REVIEW

Strategy for study selection

The titles and abstracts were thoroughly studied for individual literature, and the articles relevant to the research question were collected and cross-verified by the coauthor. Independent reviewers resolved any disagreement about a study as per the inclusion and exclusion criteria as below.

Inclusion criteria: literature reporting interaction at any level i.e. clinical or pre-clinical as well as *in vitro* and *in vivo*. The articles mentioning interaction of GB with any herb, drug, food as well as lab tests/procedures were searched and included. The literature search was restricted to the English language.

Exclusion criteria: literature reporting uses, side effects, phytochemical studies and pharmacological activities only was excluded from the study. In addition, the clinical cases due to overdose, adverse effects, or associated with prolonged use of GB were not included.

Databases and resources utilized: databases; EMBASE, MEDLINE, Web of Science, Google Scholar, PubMed, Scopus, and online digital library of Imam Abdulrahman Bin Faisal University. Journals; Journal of food science, British Journal of Clinical Pharmacology, Journal of Clinical Pharmacy and Therapeutics, Trends in Food Science and Technology, Frontiers in Pharmacology etc. Furthermore, books and published theses were used as resources to collect information.

Keywords searched: "Ginkgo biloba", "*Ginkgo biloba* interactions", "Ginkgo-drug interaction", "Ginkgo-herb interaction", "Ginkgo-food interaction", "Ginkgo with anti-coagulants", "Dementia", "Alzheimer's", "*Ginkgo biloba*-Ginseng", "Astaxanthin", "Sodium aescinate", "Ginkgo-Ephedrine".

Time period: the literature was searched without any time limitation. Any literature available with regard to GB interactions and resulted in clinical cases was gathered, irrespective of its publishing year. The data was collected and kept updated starting October 2019 till July 2020.

Articles found: a total of 45 GB interactions, including 14 clinical cases, were finalized based on eligibility criteria. The interactions with evidence of its pre-clinical or clinical reports are mentioned in detail in **Table No. 1**;

Table No. 1
Interactions for GB vs drugs, herbs, nutraceuticals and food

Interacting agent	Level of study	Mechanism of action	Outcome	Reference
GB Vs drugs interactions				
Ticlopidine	Preclinical	-	↑ bleeding	Cupp, 1999; Abebe, 2002; Coxeter *et al*., 2003; Bebbington *et al*., 2005; Greenblatt *et al*., 2006; Aruna & Naidu, 2007; Kim *et al*., 2010; Tarn *et al*., 2020
Warfarin		CYP2C9 inhibition		
Ticlopidine	Clinical	PAF inhibition		
Aspirin		↑ AUC		
Acetaminophen and ergotamine-caffeine		PAF inhibition		
Clopidogrel				
Cilostazol		CYP2C9 inhibition		
Flurbiprofen		-	No interaction	
Apixaban	-	-	↑ bleeding	
Trazodone	Clinical	CYP3A4 induction	Suspected coma	Coxeter *et al*., 2003; Diamond & Bailey, 2013; Meng & Liu, 2014
Nicardipine	Preclinical	CYP3A2 induction	↓ effectiveness	
Sodium valproate	Clinical	CYP2C19 induction	Seizures	Granger, 2001; Kupiec & Raj, 2005
Thiazide diuretic		-	↑ blood pressure	

Theophylline	Pre-clinical	CYP1A2 induction	↑clearance and metabolism	Tang *et al*., 2007
Omeprazole	Clinical	CYP2C19 induction	↓ renal clearance	Yin *et al*., 2004
Talinolol		P-glycoprotein inhibition	↑ talinolol AUC and C_{max}	Fan *et al*., 2009a
Efavirenz		CYP3A4 or P-gp inhibition	Virologic failure	Wiegman *et al*., 2009
Raltegravir			↑ AUC and C_{max}	Blonk *et al*., 2012
Voriconazole		CYP2C19 induction	loss of infection control	Lei *et al*., 2009
Bupropion	Pre-clinical	CYP2B6 inhibition	↓ hepatic or renal function	Lau & Chang, 2009
Ritonavir	Clinical	-	No interaction	Blonk *et al*., 2012
Risperidone		CYP enzyme inhibition	Priapism	Lin *et al*., 2007
Nifedipine		↑ plasma concentration	headaches, dizziness, ↑ heart rate	Yoshioka *et al*., 2004
Mycophenolic Acid		glucuronosyltransferase inhibition	↑immunosuppressive effect	Mohamed & Frye, 2010
Diltiazem		CYP3A inhibition	↑serum level	Ohnishi *et al*., 2003
Diazepam		CYP2C19 inhibition	Same bioequivalence	Zuo *et al*., 2010
Alprazolam		alteration in CYP3 A4	↓serum level	Markowitz *et al*., 2003
Midazolam		CYP3A4 inhibition	↑serum level	Zadoyan *et al*., 2012
Haloperidol		-	↓ superoxide dismutase	Coxeter *et al*., 2003
Sodium aescinate		↓ CYP2C9, CYP3A4 activity	↑ serum creatinine and BUN	Ji *et al*., 2017
Ephedrine		-	Seizures	Cupp, 1999; Spinella, 2001
Simvastatin		-	↑ AUC	Dai *et al*., 2013
Tolbutamide		CYP2C9 alteration	↑ AUC and Cmax	Uchida *et al*., 2006
Metformin		-	No interaction	Kudolo *et al*., 2006
Amoxetine		-	Eye pain and headache	Mazhar *et al*., 2020
GB vs herbs interactions				
Ginseng	Clinical	-	↑ cognitive performance	Kennedy *et al*., 2007
Bacopa monnieri		PAF inhibition	↑ cognitive function	Nathan *et al*., 2004
Cannabis		-	rhabdomyolysis	Strain *et al*., 2019
Devil's claw, green tea	-	-	Mild interaction	Persson *et al*., 2004
Silybum marianum	Pre-clinical	anti-oxidant and antiangiogenic	Chemo preventive role	El Mesallamy *et al*., 2011
GB vs nutraceuticals interactions				
Phosphatidylserine, vitamin-E/pyridoxine.	Preclinical	Synergistic effect	↑ cognitive function	Araujo *et al*., 2008
Phosphatidylserine		PAF inhibition/neuroprotective		Kennedy *et al*., 2007
Pyridoxine		-	Neurotoxicity	Arenz *et al*., 1996

GB vs food interactions				
GB bioflavones	Clinical	Inhibition of PAF, COX-2, cAMP phosphodiesterase	↓ asthma associated inflammation	Haines *et al*., 2011

***Ginkgo biloba*-drugs interactions**

Extracts of GB has shown serious effect when combined with some drugs. Aspirin, warfarin, and other anti-coagulant drugs are examples of serious GB-drug interactions (Diamond & Bailey, 2013).

Ginkgo and anti-platelet drugs interactions

Ginkgo-ticlopidine interaction

A clinical study in twenty-four healthy Korean men confirmed that GB increases bleeding time, platelet aggregation and an increase in ticlopidine AUC (6.1%) if taken together (Kim *et al*., 2010). Similarly, ticlopidine (50 mg/kg) when administered in a thrombosis-induced-rats model in combination with EGb761 (20-40 mg/kg), an agonistic effect was observed with prolonged bleeding time and a delay in thrombotic recovery (Coxeter *et al*., 2003).

Ginkgo-warfarin interaction

Warfarin is one of the most widely observed drugs that can interact with GB, and the combination may lead to an increase in the warfarin effect. A case report for a 78-year-old female patient with coronary bypass surgery, who was taking warfarin for five years, experienced left parietal bleeding after using GB product for two months. In addition, intracerebral bleeding was reported for a woman using warfarin and GB extract together. Terpenoids ginkgolide can inhibit platelet-activating factor (PAF), and this leads to prolonged bleeding time and spontaneous bleeding. The *in vitro* study for warfarin and GB suggests an inhibition of 7-hydroxylation of (S)-warfarin by CYP2C9 (Cupp, 1999; Mohutsky *et al*., 2006; Ge *et al*., 2014).

Ginkgo-clopidogrel interaction

A case reported for a 74 years-old woman manifested bruising, haematuria and vaginal haemorrhage following the use of GB along with clopidogrel in menopausal symptoms. The suspension of GB consumption for one week showed good laboratory results and the haemorrhage ceased (Darnborough, 2014).

Ginkgo-cilostazol and clopidogrel interaction

A randomized open-labeled crossover study was performed in ten healthy male volunteers where GB (120 mg) with cilostazol (100 mg) (CYP3A4 and CYP2C9 substrate) was compared to GB (120 mg) administered with clopidogrel (75 mg), for possible anti-platelet interaction. A measurement for platelet aggregation, platelet count, bleeding time and clotting time at 0 and 6 hours revealed; prolongation in bleeding time with cilostazol combination in comparison to individual doses (Aruna & Naidu, 2007).

Gingko-apixaban interaction

GB has been reported to increase the risk of bleeding if used, along with apixaban oral anti-coagulant (Tarn *et al*., 2020).

Ginkgo-NSAIDs interactions

Ginkgo-acetaminophen interaction

A case was reported for 33-years-old women using acetaminophen and ergotamine-caffeine preparation with GB. The combination of these medications resulted in bilateral subdural hematomas and prolonged bleeding time. Upon discontinuation of GB the bleeding time returned to normal. The presence of ginkgolide-B in GB is suggested to be responsible for anti-platelet aggregation (Cupp, 1999; Abebe, 2002).

Ginkgo-flurbiprofen interaction

A study by Greenblatt *et al*., in twelve healthy volunteers showed no significant interaction of GB and flurbiprofen; however, further studies are needed to confirm the effect (Greenblatt *et al*., 2006).

Ginkgo-aspirin interaction

A 70 years-old man suffered bleeding in the eye after one week of GB ingestion. The medical history showed coronary artery bypass surgery, and the patient was using aspirin. The discontinuation of concomitant use resulted a stable condition for the patient (Rosenblatt & Mindel, 1997). A case report of 77 years-old female patients with total hip arthroplasty (THA), using aspirin, suffered from bleeding and oozing. The in-depth investigation revealed the use of GB 120 mg daily; hence, GB was discontinued further and the patient conditions

improved. Ginkgolide-B is suggested to be responsible as it reduces platelet aggregation by preventing the binding to receptors of platelet activating factor (PAF) (Park *et al*., 2013). Another study for human volunteers who took a single dose of mixed ginkgolides resulted in platelet aggregation inhibition and bleeding was reported with and without NSAIDs administration (Cupp, 1999; Abebe, 2002; Bebbington *et al*., 2005).

Ginkgo and calcium channel blockers interactions

Ginkgo-nicardipine interaction

The combination of GB and nicardipine produced a reduced hypotensive effect for nicardipine. The suggested mechanism is the involvement of CYP3A2 metabolizing enzymes. (Diamond & Bailey, 2013).

Ginkgo-nifedipine interaction

Simultaneous administration of GB with nifedipine results in an increased plasma concentration level for nifedipine. The patients feel severer and long lasting headaches and may experience dizziness, flushes and accelerated heart rate. The mechanism though, is not clear (Yoshioka *et al*., 2004).

Ginkgo-diltiazem interaction

The flavonoids in GB (quercetin and kaempferol) inhibit CYP3A activities and diltiazem needs CYP3A to be converted to its active metabolite of diltiazem N-demethylase. An increased plasma level for diltiazem is observed, which may produce toxicity (Ohnishi *et al*., 2003).

Ginkgo-benzodiazepines interactions

Ginkgo-diazepam interaction

The effect of GB upon CYP2C19 was studied. Diazepam is a substrate for CYP2C19, whereas GB inhibits this enzyme. The pharmacokinetic parameters for diazepam and its metabolite (N-desmethyldiazepam) upon exposure to GB were changed; however, the results were still in the bioequivalence interval. It suggests a safe use of diazepam with GB without any dose adjustment (Zuo *et al*., 2010).

Ginkgo-alprazolam interaction

A study in twelve healthy volunteers showed alteration in CYP3 A4 and CYP2D6 activities with a 17% decrease in alprazolam AUC when administered with GB (Markowitz et al., 2003).

Ginkgo-midazolam interaction

The effect of GB (360 mg/day) with midazolam (8 mg) was observed in ten healthy individuals. The results showed a significant increase (25%) for midazolam $AUC_{0-\infty}$ and a decrease (26%) in oral clearance. Midazolam is a substrate for CYP3A4, which is inhibited by GB (Uchida *et al*., 2006). However, another study in eighteen healthy Caucasian volunteers using GB with a cocktail (midazolam, caffeine, dexamethasone, tolbutamide and omeprazole) showed no change in the CYP enzymes activities (Zadoyan *et al*., 2012).

Ginkgo-antiepileptic's interactions

A case reported seizures episodes for two epileptic patients following concomitant use of sodium valproate and GB, which attacks relieved upon discontinuation of GB. In another case, a 78-years old man, suffering from epilepsy was presented to the hospital with tonic-clonic seizures in the past 12 hours. The patient already using sodium valproate (1200 mg) was found to add GB in his regime. Soon after GB discontinuation, seizure was diminished. A similar case of an 84-years old female patient diagnosed with dementia was admitted to the hospital with a seizure episode. The patient was using sodium valproate for two years until the psychiatrist gave her GB (120 mg daily). Immediately after twelve days of GB intake, seizures were observed, whereas discontinuation of GB resulted in a lack of seizures (Granger, 2001; Kupiec & Raj, 2005). The interaction between GB and antiepileptic's drugs was due to the induction of CYP2C19 by GB, which results in catabolism induction of phenytoin and valproic acid (Kupiec & Raj, 2005).

Ginkgo-diuretics interactions

A case report for an old female patient showed an elevated blood pressure, which was sorted due to combined dose of thiazide and GB. The cessation of GB corrected the blood pressure to the pre-treatment level (Kupiec & Raj, 2005).

Ginkgo-theophylline interaction

GB affects the pharmacokinetic profile for theophylline. A study in rat's model revealed that GB combined with theophylline, increases theophylline clearance. In addition, GB induces CYP1A2 activity whereby the metabolism for theophylline is increased (Tang et al., 2007).

Ginkgo-omeprazole interaction

A study in 18 years-old healthy Chinese patients, revealed that co-administration of GB with omeprazole led to hydroxylation of omeprazole via CYP2C19. Moreover, renal clearance of omeprazole was induced, and consequently, the effect of omeprazole was reduced (Yin *et al*., 2004).

Ginkgo-antiretroviral drugs interactions

GB along with antiretroviral drugs (nevirapine, rilpivirine, doravirine and elvitegravir) may effect CYP3A4 (induction or inhibition) whereas, abacavir and tenofovir may exert an effect on P-gp. For raltegravir, no significant pharmacokinetic interactions were found *in vitro* studies. Protease inhibitors (efavirenz, dolutegravir, bictegravir and maraviroc) may inhibit or induce CYP3A4 and P-gp both (Yale & Glurich, 2005; Hellum & Nilsen, 2008; Robertson *et al*., 2008; Wiegman *et al*., 2009; Blonk *et al*., 2012; Naccarato *et al*., 2012).

Ginkgo-efavirenz interaction

A patient with human immunodeficiency virus (HIV) disease using efavirenz developed a new medical illness with the use of GB (300 mg/day). The clinical tests showed a decrease in antiviral activity for efavirenz due to GB upregulation of enzymes responsible for efavirenz metabolism. GB accelerated the hepatic clearance with a decrease serum level; hence, a reduced antiviral activity for efavirenz (Wiegman *et al*., 2009; Naccarato *et al*., 2012).

Ginkgo-raltegravir interaction

The effect of GB on raltegravir was studied in an open-label, randomized clinical trial using eighteen healthy volunteers. The bioavailability and maximum plasma concentration (Cmax) for the drug were increased, which suggests an inhibitory effect of GB upon raltegravir metabolizing enzymes of P-GP (Blonk *et al*., 2012).

Ginkgo-antipsychotics interactions

Ginkgo-risperidone interaction

A schizophrenia patient on risperidone therapy started to take GB, developed priapism with the prolonged and persistent erection of the penis (not due to sexual stimulation). It was suggested due to GB inhibition of risperidone metabolizing enzyme, leading to an increased serum level (Lin *et al*., 2007).

Ginkgo-haloperidol interaction

A placebo-controlled clinical trial in schizophrenic patients administered GB alongwith haloperidol as a co-treatment for schizophrenia. A significant decrease in superoxide dismutase (SOD) levels was found in these patients, thus reducing the extrapyramidal symptoms of haloperidol (Coxeter *et al*., 2003; Hu *et al*., 2005).

Ginkgo-antidepressant interactions

Ginkgo-bupropion interaction

A recent study showed that GBE with bupropion (CYP2B6 drug substrate) leads to chronic illness or compromised hepatic and renal function. The effect was due to decreased bupropion hydroxylation catalyzed by recombinant CYP2B6 (Lau & Chang, 2009).

Ginkgo-trazodone interaction

An 80 years old female patient with Alzheimer's disease was found in a coma, was suspected of using trazodone alongwith GB. The active metabolite of trazodone i.e. 1-(m-chlorophenyl) piperazine (mCPP) is increased by GB, which in turn releases γ-aminobutyric acid (GABA) at presynaptic serotonin 5-HT2 and α2-adrenergic receptors via an agonistic action. In addition, it increases cytochrome-P450 (CYP3A4) activity, which metabolizes trazodone to mCPP. The GABAergic activity is further reinforced through flavonoids via acting on the biding sites of benzodiazepine (Coxeter *et al*., 2003; Diamond & Bailey, 2013; Meng & Liu, 2014).

Ginkgo-mycophenolic acid interaction

The combination of mycophenolic acid and GB increases the concentration of mycophenolic acid, leading to many adverse effects. This is due to GB flavone aglycone, which inhibits glucuronosyltransferase-UGT-mediated metabolism of mycophenolic acid in human intestinal and liver microsomal systems. Hence, the systemic concentration of mycophenolic acid is raised due to inhibition of first-pass metabolism and an increased immunosuppressive effect is observed (Mohamed & Frye, 2010).

Ginkgo-talinolol interaction

Talinolol is a substrate for P-glycoprotein in humans, which is likely to interact with GB. The flavonoids in GB inhibit P-glycoprotein function and may lead to an increased AUC for talinolol. A study in ten healthy volunteers revealed an increased talinolol AUC along with C_{max}, following the ingestion of GB (Fan *et al*., 2009b). In another similar study, a 24%

increase in talinolol AUC was observed in twelve healthy individuals when GB was coadminstered with *Schisandra chinensis* and talinolol (Fan *et al*., 2009b).

Ginkgo-voriconazole interaction

Voriconazole is extensively metabolized by CYP2C19 and CYP3A4. A study revealed a powerful inductive effect for GB on CYP2C19 activity, where the stimulation of this enzyme decreased the efficacy of the antifungal drug and loss of infection control (Lei *et al*., 2009).

Ginkgo-sodium aescinate interaction

GB with sodium aescinate may produce acute kidney injury and they are avoided to be coadminstered. A 58-year old patient was diagnosed with left phalangeal fractures. The ant-inflammatory and anti-edematous agent sodium aescinate and anti-coagulant GB were administered to improve microcirculation and promote wound healing. However, the patient serum creatinine (SCr) and blood urea nitrogen (BUN) levels were found significantly elevated and the treatment was immediately discontinued. The patient's renal function returned to normal. It is suggested due to downregulation of CYP2C9 and CYP3AA produced by amentoflavone in GB. In addition, the high protein-binding capacity of both drugs may contribute to an interaction (Demarin *et al*., 2017).

Ginkgo-ephedrine interaction

GB administered with ephedrine leads to seizure in some special cases, prone to various factors of older adults and that undergoing drug withdrawal. This is due to a direct effect on the central nervous system. Thus prescription containing GB with ephedrine needs to be avoided (Cupp, 1999; Spinella, 2001).

Ginkgo-simvastatin interaction

GB and simvastatin coadminstered in fourteen healthy volunteers resulted a 36% decrease in AUC for simvastatin while no significant change was observed in the level of cholesterol (Dai *et al*., 2013).

Ginkgo-antidiabetic drugs interactions

Ginkgo-tolbutamide interaction

A study of GB use with tolbutamide (substrate for CYP2C9) in ten healthy individuals showed an alteration of CYP2C9 activity, which is evident from a lower (16%) $AUC_{0-\infty}$ for tolbutamide (Uchida *et al*., 2006).

Ginkgo-metformin interaction

GB concurrently used with metformin resulted in no significant change in pharmacokinetics and efficacy was observed for metformin (Kudolo *et al*., 2006); however, further studies are required to know the interactive effects of higher doses of GB.

Ginkgo-atomoxetine interaction

An eight-year child taking atomoxetine and GB complained about eye pain and headache, which later was diagnosed with glaucoma. Though psychiatrists of the child declared atomoxetine as a causative agent, such concomitant administration needs to investigate further for possible drug interaction (Mazhar *et al*., 2020).

***Ginkgo biloba*-herbs interactions**

Ginkgo-Devil's claw-green tea interaction

GB may lead to mild interaction when used along with green tea or devil's claw plant. In the event of GB allergy, it is risky to consume plants that contain the same constituents, such as fossil tree, Kew tree, or maidenhair tree. No study has explicitly reported the severe interactions of GB with herbs (Kennedy *et al*., 2001; Persson *et al*., 2004).

Ginkgo-ginseng interaction

GB has a synergistic effect when combined with ginseng. GB and ginseng improve cognitive performance and gained wide attraction as "a common prescription together" during the last few years. The positive results of this combination showed improved learning skills and memory in healthy volunteers and these findings were supported by many reliable studies. Few studies conducted in Alzheimer's patients also revealed excellent performance when these two herbs were administered concomitantly (Hartley *et al*., 2004; Persson *et al*., 2004).

Gingko-Bacopa monnieri interaction

GB and *Bacopa monnieri* produce a positive effect on cognitive function in healthy humans. It enhances a wide range of neuropsychological functions, including attention, short-term and working memory, verbal learning, memory consolidation, executive processes, planning and problem-solving speed. The two herbs produce platelet-activating factor (PAF) antagonistic effects and also inhibit monoamine metabolizing enzymes, which contribute to its free-radical scavenging activity. Furthermore, it modulates the cholinergic system via a direct effect

upon muscarinic receptors, which affects choline uptake and acetylcholine release (Nathan *et al*., 2004).

Ginkgo-Silybum marianum interactions

GB and *Silybum marianum* have an anti-cancer property through inhibition of oxidative DNA damage and enhancing DNA repair. It regulates cells proliferation, induces apoptosis, and kills hepatic cancer cells. The combination of GBE and *Silybum marianum* showed protective effects against hepatocarcinoma and minimized the damage to liver cells. They have a positive chemo preventive effect against hepatocellular carcinoma through anti-oxidant, antiangiogenic and antigenotoxic activities (El Mesallamy *et al*., 2011).

Ginkgo biloba-cannabis interactions

A case report of rhabdomyolysis in a twenty-six year old female was reported as she was using GB supplement and cannabis (Strain *et al*., 2019).

Ginkgo-nutraceuticals interactions

Gingko and nutraceutical supplement (phosphatidylserine, vitamin-E, and pyridoxine)

GB, vitamin-E and pyridoxine can improve cognitive functions and memory where a synergistic action is suggested. The supplement has been licensed in Italy, and it is used to treat elderly dogs and cats with pathophysiological brain aging. The mechanism of action is not known and further research is required in order to elucidate this mechanism (Araujo *et al*., 2008).

Ginkgo-phosphatidylserine interaction

Administration of phosphatidylserine or phosphatidylcholine has a synergistic effect with GB and enhances the bioavailability of GB with an increase in its effect. Chronic administration of GB and phosphatidylserine potentiates secondary memory performance and increases the speed of memory task performance. The mechanism of action for such a combination is believed due to the antagonism of platelet-activating factor and neuroprotection (Kennedy *et al*., 2007).

Ginkgo-pyridoxine interaction

GB containing ginkgotoxin (4-O-methyl pyroxine) interacts with pyridoxine metabolites and results in neurotoxicity, seizures and loss of consciousness (Arenz *et al*., 1996). However, more studies are required.

Ginkgo-food interactions

For GB-food interactions, very limited data is available. Only one study was found where food containing Astaxanthin and vitamin-C were observed to have a pronounced effect in the suppression of respiratory inflammation when combined with GB. Astaxanthin is usually found in seafood (salmon, trout, lobster and shrimp), which acts as a cytoprotective agent by eliminating toxic reactive oxygen compounds. For asthmatic patients, PAF is responsible for inflammation associated processes and administration of GB with Astaxanthin interrupts the pathogenesis of asthma by blocking PAF receptor. In addition, bioflavones present in GBE inhibits COX-2 and cAMP-phosphodiesterase. This probably leads to increased cyclic nucleotide levels in lung tissues; thus, increasing the cAMP and cGMP which are involved in relaxing the airway and contributes to lessening the severity of disease by decreasing airway muscle contractility. Vitamin-C is a water-soluble dietary anti-oxidant. It facilitates urinary elimination of reactive oxygen metabolites as well as increases the activity of Astaxanthin in the suppression of oxidative damage secondary to *Helicobacter pylori* infection. Vitamin-C has a significant role, when combined with GBE and Astaxanthin, in the suppression of asthma-associated inflammation (Haines *et al*., 2011).

Statistical analysis

The descriptive statistics revealed (**Table No. 2**), a frequency of 45 interaction cases for GB. A high percentage (80%) of the interactions was observed for GB vs drugs followed by 11.1% for GB vs herbs and 6.7% for GB vs nutraceuticals. Only one interaction (2.2%) was found for food vs GB. With regard to mechanisms of interactions, almost half (44.4%) of the interactions were observed at the level of Cytochrome metabolizing enzymes followed by the next major (15.6%) interaction of PAF inhibition i.e. increased antiplatelet activity. All these cases of interactions were observed at the clinical level, which makes one-third of the total cases (575.6%). For 31.1% of the cases, no mechanism of interactions was reported. Likewise, 20.0% of the cases were pre-clinical oriented data, followed by 4.4% of the cases where no clinical or pre-clinical level was reported. A three-dimensional representation for the GB interactions, its mechanisms along with level of study is also shown in Figure No. 2.

Table No. 2
Descriptive statistics for the GB interactions, mechanisms and level of study observed

Type of GB Interaction		
	Frequency	Percentage
GB-drug interactions	36	80.0
GB-herb interactions	5	11.1
GB-nutraceuticals interactions	3	6.7
GB-food interactions	1	2.2
Total	**45**	**100.0**
Mechanisms of interaction		
Cytochrome-P450/P-gp inhibitor/inducer	20	44.4
PAF inhibition (increased anti-platelet and anticoagulant activity)	7	15.6
Other (anti-oxidant, nueroprotective, increase/decrease AUC etc.)	4	8.9
Not determined	14	31.1
Total	**45**	**100.0**
Level of study		
Clinical	34	75.6
Pre-clinical	9	20.0
Not determined	2	4.4
Total	**45**	**100.0**

DISCUSSION

Gingko biloba is an ancient herb used for years to treat many diseases. The current literature review focuses on interactions for GB, related to drugs, herbs, nutraceuticals and food. Among different interactions, more cases were reported for GB vs. drugs. As shown in Table No. 1, GB exhibited the most frequent and potential interactions with anticoagulant and anti-platelet drugs warfarin, aspirin, clopidogrel, ticlopidine and cilostazol, where an increase in bleeding incidences was recorded. This implicates not to use surgery preparing drugs with GB, as it may increase bleeding time and pose difficulty for the appropriate surgery conditions of the patient. Pharmacokinetics interaction for GB involved either hepatic cytochrome-P450 enzyme system induction or inhibition. For instance, GB increased the clearance and metabolism for theophylline due to CYP1A2 induction, however, decreased the renal clearance and therapeutic effect of; omeprazole due to hydroxylation via CYP2C19 genotype (Yin *et al*., 2004; Tang *et al*., 2007), efavirenz through upregulation of metabolizing enzymes, increased serum diltiazem due to CYP3A inhibition as well as increased C_{max} and AUC for Talinolol due to enzyme inhibition as reported (Engelsen *et al*., 2003; Ohnishi *et al*., 2003; Naccarato *et al*., 2012) Notwithstanding, it is safe to use GB with several drugs such as diazepam (Zuo *et al*., 2010).

Concerning clinical cases, GB has been attributed to several rare but treacherous hemorrhagic events (Benjamin *et al*., 2001; Hu *et al*., 2005). For instance, concomitant use of GB and warfarin results in severe bleeding (Matthews, 1998). It is suggested due to flavonoids in GB, which inhibits CYP2C9 (Mohutsky *et al*., 2006; Numa *et al*., 2007), especially amentoflavone (von Moltke *et al*., 2004). For the majority of the cases, it is CYP2C9 inhibition, which is involved in potentially harmful GB-drug interactions such as GB vs. anti-platelet drugs, trazodone, diuretics, and NSAIDs (Sørensen, 2002; Valli & Giardina, 2002).

Gingko biloba-herb interactions (Table No. 1) revealed a safe use for GB along with other herbs; however, the chances of interaction still do exist. A notable example is the use of ephedrine and GB, where seizures were observed with concomitant usage. In addition, some mild interactions may occur when used with green tea or devil's claw plant, further details studies are required to elucidate these interactions. Synergistic interaction with ginseng was also found for GB where a positive effect on human health was observed. The phenomenon of synergism was observed for GB-nutraceuticals, also where beneficial therapeutic outcomes were achieved. For

example, GB and Bacopa monnieri enhanced the cognitive function in healthy people, and GB with Silybum marianum enhanced the recovery rate in cancerous patients with hepatocarcinoma. Another study showed an improvement in short term memory performance for GB with phosphatidylserine, vitamin-E and pyridoxine (Cupp, 1999; Spinella, 2001; Kennedy *et al*., 2007). A beneficial GB-food interaction was observed for GB with food containing Astaxanthin and vitamin-C (Table No. 1). The use of GB with these foods inhibits COX-2 and cAMP-phosphodiesterases and increases cyclic nucleotides hence, resulting in increased cAMP and cGMP with the end effect of the airway relaxation (Haines *et al*., 2011).

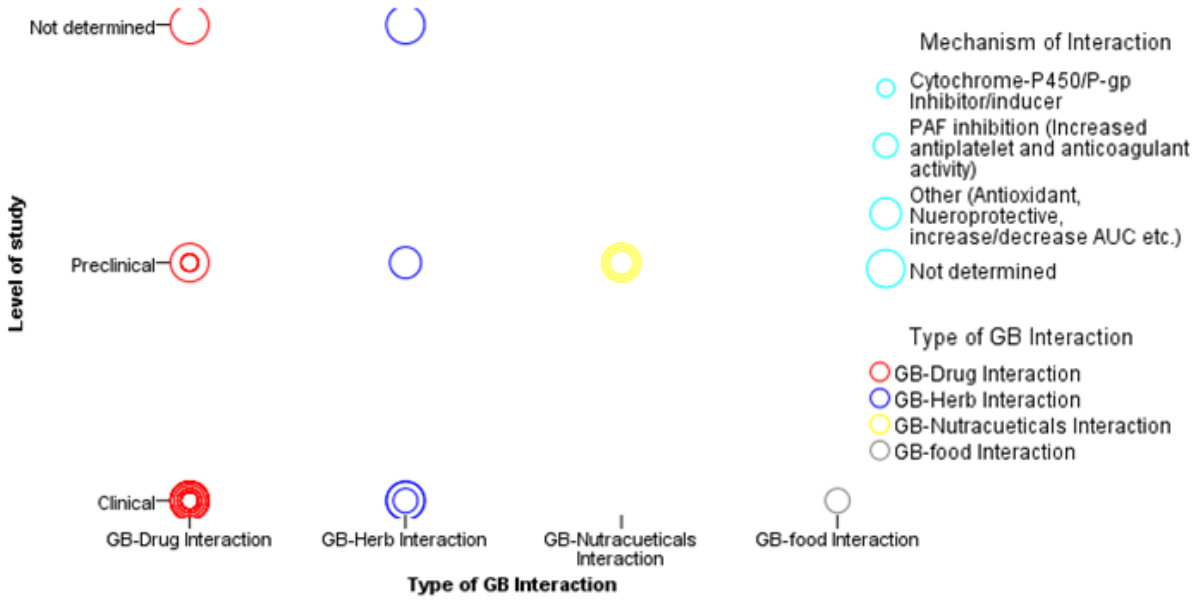

Figure No. 2
A three dimensional representation for GB-interactions, mechanisms and level of study

For GB-interactions, more incidences were observed in females; however, there is no proper evidence that a certain gender will be at more risk of interactions. Sex-related differences may be the cause, which is a multifactorial issue that requires information on different study fields (Miller, 2001). The frequency of interactions was found more in elderly patients compared to other age groups. It may be linked with more usage of GB in geriatric diseases of dementia, Alzheimer's, headache, and sexual weakness. The more important reason is a lack of dialogues between patients and health professionals (Cupp, 1999; Spinella, 2001; Silva *et al*., 2014).

Future perspectives

The review provides useful insight regarding the GB-interactions, mechanisms, and clinical cases. Numerous cases have been reported for GB interactions, but a major deficiency of lack of proper in-depth mechanisms do exist. The reported mechanisms need to be updated at molecular or biochemical level. Clinical trials at early stages are conducted; however, a gap for advanced level (P-III to V) studies with more sample size and multi-center studies is there. Much attention is needed for GB and food interactions as very little information is available. The patients mostly use drugs or supplement along with food for the sake of avoiding gastric problems. It necessitates detailed study for GB with different food types (fat, protein, carbohydrates, and fiber containing foods). It is worthy of mentioning that the quality in terms of the active ingredient and its quantity, adulteration with extraneous matter, and standardization of products available in the market should be evaluated and maintained.

Clinical cases reported (symptoms and drugs)

A total of fourteen clinical cases were reported to hospitals or healthcare clinics where a severe

interaction for GB with various drugs was found. More cases were observed with patients' medical history of; an increased or abnormal bleeding (parietal and eye) and platelet aggregation, bruising, hematuria, vaginal hemorrhage and hematomas such as subdural hematomas. In addition, seizures attacks and priapism like conditions were also experienced by patients with concomitant use of GB with other drugs. The drugs with more interaction in these clinical cases were anticoagulant and anti-platelet, NSAIDs and acetaminophen. This conclusion of major symptoms due to the most commonly involved drugs in these interactions may help the healthcare professionals regarding the use of GB and its interaction with other drugs as well as to identify the specific clinical presentations as mentioned for GB and anticoagulant/NSAIDs.

Patient counselling, warnings and role of healthcare professionals

A number of interactions have been reported for GB however, most of the frequent cases observed are related to warfarin and NSAIDs. Hence, these drug classes require special precautions. Bleeding episodes may occur when used along with NSAIDs and may decrease the activity of antiepileptic drugs (phenytoin and valproic acid). Avoid GB with aspirin and ibuprofen. Do not take GB while using warfarin due to an increased risk of bleeding. Take care to use skullcap and GB together, as it may produce hepatotoxicity (Dasgupta, 2013).

The authors evaluated the factors behind these interactions where a number of interesting findings were observed, the major among these reason was the phenomenon of GB self-medication (Rosenblatt & Mindel, 1997). Lack of drug interactions knowledge and self-medication were the main cause for these interactions and unsafe use of GB. Previous studies have reported a link of self-medication with serious side effects and even death (Montastruc *et al*., 1997; Bebbington *et al*., 2005; Ruiz, 2010; Albusalih *et al*., 2017; Al Rasheed *et al*., 2017). This implies a huge responsibility on the part of healthcare professionals including physicians and pharmacists to avoid GB toxicity. The patients prefer herbal products due to many reasons, its the sole responsibility of the clinician is to dig deeper the history of medication, drugs in-use by patient, any herbal product suggested for use by family, friends or any health care provider. The clinician needs to discuss the uses, side and adverse effects, and potential interactions of the herbal product with the patient current medications. Pharmacists do possess a vital role as health providers to achieve the goal of the pharmaceutical care model. As a responsible health care provider, they may play a role via patient counseling in order to highlight the risks associated with GB-drugs interaction (Ansari, 2010; Ismail, 2009; Ge *et al*., 2014; Al Laif *et al*., 2017). The pharmacist may need to investigate the proper use/purpose of using GB, and warn the patient regarding potential health consequences that may result due to such interactions. Patient awareness and education is another key to successfully achieve the goal of treatment, while reducing the burden of side/adverse effects (Longtin *et al*., 2010; Al-Qanbar *et al*., 2017). More importantly, the patients should be educated to discourage the idea of self-medication, as it may produce fatal outcomes at times. In continuation to these adoptations, uniform regulatory directives are required to be applied and strictly folloed across the globe for a drug to be declared fit for self-medications, such as (i) must have a low level of toxicity (ii) the product owes quality and standardization protocol (Ahmad *et al*., 2020a; Ahmad *et al*., 2020b) (iii) poses a low risk of misuse (iv) provided with a full and clear informative leaflet about its use, strength, and risks associated (v) the drug should have more than 5-years history of prescription record of safe use (Bergmann, 2003).

CONCLUSION

GB owes a very significant therapeutic effect. Using it for specific conditions and diseases such as Alzheimer's related dementia, mental depression, tinnitus, and cardiovascular diseases is considerable. Nevertheless, for the sake of avoiding potential interactions, the use of GB should come from an authorized healthcare professional. Its self-medication may be discouraged and health practitioner may play a positive role while prescribing GB products i.e. keeping in view an appropriate medical history of the patient. Otherwise, uniform regulatory directives about self-medication shall be adapted across the globe.

REFERENCES

Abebe W. 2002. Herbal medication: potential for adverse interactions with analgesic drugs. **J Clin Pharm Ther** 27: 391 - 401. **https://doi.org/10.1046/j.1365-2710.2002.00444.x**

Agbabiaka TB, Wider B, Watson LK, Goodman C. 2017. Concurrent use of prescription drugs and herbal medicinal products in older adults: a systematic review. **Drugs Aging** 34: 891 - 905. **https://doi.org/10.1007/s40266-017-0501-7**

Ahmad R, Ahmad N, Amir M, Aljishi F, Alamer MH, Al-Shaban HR, Alsadah ZA, Alsultan BM, Aldawood NA, Chathoth S, Almofty SA. 2020a. Quality variation and standardization of black pepper (*Piper nigrum*): A comparative geographical evaluation based on instrumental and metabolomics analysis. **Biomed Chromatograph** 34: e4772. **https://doi.org/10.1002/bmc.4772**

Ahmad R, Ahmad N, Amir M, Aljhisi F, Alamer MH, Al-Shaban HR, Alsultan BM, Alsadah ZA, Aldawood NA, Chathoth S, Khan A. 2020b. Variation in *Nigella sativa* quality and its standardization via instrumental analysis: A study based on geographical origin. **Notulae Bot Horti Agrobot Cluj-Napoca** 48: 1141 - 1154. **https://doi.org/10.15835/nbha48311957**

Albusalih FA, Naqvi AA, Ahmad R, Ahmad N. 2017. Prevalence of self-medication among students of pharmacy and medicine colleges of a public sector university in Dammam City, Saudi Arabia. **Pharmacy** 5: 51. **https://doi.org/10.3390/pharmacy5030051**

Al Laif FZ, Ahmad R, Naqvi AA, Ahmad N. 2017. Pharmacist perceived barriers to patient counseling; a study in eastern region of Saudi Arabia. **J Pharmaceut Res Int** 1 - 12. **https://doi.org/10.9734/jpri/2017/37705**

Al Rasheed F, Naqvi AA, Ahmad R, Ahmad N. 2017. Academic stress and prevalence of stress-related self-medication among undergraduate female students of health and non-health cluster colleges of a public sector university in Dammam, Saudi Arabia. **J Pharm Bioallied Sci** 9: 251. **https://doi.org/10.4103/jpbs.JPBS_189_17**

Anonymous. 2014. Clopidogrel/*Ginkgo biloba* interaction. **Reactions Weekly** 1490: 15.

Ansari J. 2010. Drug interaction and pharmacist. **J Young Pharmac** 2: 326 - 331.

Al-Qanbar FA, Ahmad R, Naqvi AA, Ahmad N. 2017. Pharmacists perception of physicians and patients responses towards suggested drug alternative. **J Pharmaceut Res Int** 1-13. **https://doi.org/10.9734/jpri/2017/37706**

Araujo JA, Landsberg GM, Milgram NW, Miolo A. 2008. Improvement of short-term memory performance in aged beagles by a nutraceutical supplement containing phosphatidylserine, *Ginkgo biloba*, vitamin E, and pyridoxine. **Can Vet J** 49: 379.

Arenz A, Klein M, Fiehe K, Groß J, Drewke C, Hemscheidt T, Leistner E. 1996. Occurrence of neurotoxic 4′-O-methylpyridoxine in *Ginkgo biloba* leaves, Ginkgo medications and Japanese Ginkgo food. **Planta Medica** 62: 548 - 551. **https://doi.org/10.1055/s-2006-957967**

Aruna D, Naidu M. 2007. Pharmacodynamic interaction studies of *Ginkgo biloba* with cilostazol and clopidogrel in healthy human subjects. **Brit J Clin Pharmacol** 63: 333 - 338. **https://doi.org/10.1111/j.1365-2125.2006.02759.x**

Bebbington A, Kulkarni R, Roberts P. 2005. *Ginkgo biloba*: persistent bleeding after total hip arthroplasty caused by herbal self-medication. **J Arthroplasty** 20: 125 - 126. **https://doi.org/10.1016/s0883-5403(04)00165-2**

Benjamin J, Muir T, Briggs K, Pentland B. 2001. A case of cerebral haemorrhage—can *Ginkgo biloba* be implicated? **Postgraduate Med J** 77: 112 - 113. **https://doi.org/10.1136/pmj.77.904.112**

Benzie IF, Wachtel-Galor S. (Eds.). 2011. **Herbal medicine: biomolecular and clinical aspects.** CRC Press/Taylor & Francis, Boca Raton, Florida, USA.

Bergmann JF. 2003. Self-medication: from European regulatory directives to therapeutic strategy. **Fundamental Clin Pharmacol** 17: 275 - 280. **https://doi.org/10.1046/j.1472-8206.2003.00141.x**

Blonk M, Colbers A, Poirters A, Schouwenberg B, Burger D. 2012. Effect of *Ginkgo biloba* on the pharmacokinetics of raltegravir in healthy volunteers. **Antimicrob Agents Chemother** 56: 5070 - 5075. **https://doi.org/10.1128/aac.00672-12**

Borrelli F, Capasso R, Izzo AA. 2007. Garlic (*Allium sativum* L.): adverse effects and drug interactions in humans. **Mol Nutr Food Res** 51: 1386 - 1397. **https://doi.org/10.1002/mnfr.200700072**

Chen Y, Huang C, Jin Z, Xu X, Cai Y, Bai Y. 2020. HPTLC-bioautography/SERS screening nifedipine adulteration in food supplement based on *Ginkgo biloba*. **Microchem J** 154: 104647. **https://doi.org/10.1016/j.microc.2020.104647**

Coxeter PD, Duke CC, Roufogalis B, McLachlan AJ. 2003. *Ginkgo biloba* interactions. **J Complement Med** 2: 62.

Cupp MJ. 1999. Herbal remedies: adverse effects and drug interactions. **Am Family Phys** 59: 1239.

Dai LL, Fan L, Wu HZ, Tan ZR, Chen Y, Peng XD, Shen MX, Yang GP, Zhou HH. 2013. Assessment of a

pharmacokinetic and pharmacodynamic interaction between simvastatin and *Ginkgo biloba* extracts in healthy subjects. **Xenobiotica** 43: 862 - 867. **https://doi.org/10.3109/00498254.2013.773385**

Damnjanovic I, Stefanovic N, Zlatkovic-Guberinic S, Damnjanovic Z, Catic-Djordjevic A, Velickovic-Radovanovic R. 2020. Self-medication practices among the patients with chronic venous disease. **Farmacia** 68: 225 - 231. **https://doi.org/10.31925/farmacia.2020.2.6**

Darnborough S. 2014. Clopidogrel/*Ginkgo biloba* interaction: Bruising, haematuria and vaginal bleeding in an elderly patient: Case report. **Reactions Weekly** 1490: 15-15. **https://doi.org/10.1007/s40278-014-9086-7**

Dasgupta A. 2013. **Effect of herbal remedies on clinical laboratory tests**. Accurate results in the clinical laboratory. Elsevier, The Netherland. **https://doi.org/10.1016/b978-0-12-415783-5.00007-4**

Demarin V, Kes VB, Trkanjec Z, Budišić M, Pašić MB, Črnac P, Budinčević H. 2017. Efficacy and safety of *Ginkgo biloba* standardized extract in the treatment of vascular cognitive impairment: a randomized, double-blind, placebo-controlled clinical trial. **Neuropsych Dis Treat** 13: 483 - 490. **https://doi.org/10.2147/ndt.s120790**

Diamond BJ, Bailey MR. 2013. *Ginkgo biloba*: indications, mechanisms, and safety. **Psychiatric Clin** 36: 73 - 83.

El Mesallamy HO, Metwally NS, Soliman MS, Ahmed KA, Moaty MMA. 2011. The chemopreventive effect of *Ginkgo biloba* and *Silybum marianum* extracts on hepatocarcinogenesis in rats. **Cancer Cell Int** 11: 38. **https://doi.org/10.1186/1475-2867-11-38**

Engelsen J, Nielsen JD, Hansen K. 2003. Effect of coenzyme Q10 and *Ginkgo biloba* on warfarin dosage in patients on long-term warfarin treatment. A randomized, double-blind, placebo-controlled cross-over trial. **Ugeskrift Laeger** 165: 1868 - 1871.

Fan L, Mao XQ, Tao GY, Wang G, Jiang F, Chen Y, Li Q, Zhang W, Lei HP, Hu DL, Huang YF, Wang D, Zhou HH. 2009a. Effect of *Schisandra chinensis* extract and *Ginkgo biloba* extract on the pharmacokinetics of talinolol in healthy volunteers. **Xenobiotica** 39: 249 - 254. **https://doi.org/10.1080/00498250802687657**

Fan L, Tao GY, Wang G, Chen Y, Zhang W, He YJ, Li Q, Lei HP, Jiang F, Hu DL. 2009b. Effects of *Ginkgo biloba* extract ingestion on the pharmacokinetics of talinolol in healthy Chinese volunteers. **Ann Pharmacother** 43: 944 - 949. **https://doi.org/10.1345/aph.1l656**

Ge B, Zhang Z, Zuo Z. 2014. Updates on the clinical evidenced herb-warfarin interactions. **Evid Based Complement Altern Med** 2014: 957362. **https://doi.org/10.1155/2014/957362**

Gil-Martínez M, Santos-Ramos P, Fernández-Rodríguez M, Abraldes MJ, Rodríguez-Cid MJ, Santiago-Varela M, Fernandez-Ferreiro A, Gómez-Ulla F. 2020. Pharmacological advances in the treatment of age-related macular degeneration. **Curr Med Chem** 27: 583 - 598. **https://doi.org/10.2174/0929867326666190726121711**

Granger AS. 2001. *Ginkgo biloba* precipitating epileptic seizures. **Age Ageing** 30: 523 - 525. **https://doi.org/10.1093/ageing/30.6.523**

Greenblatt DJ, von Moltke LL, Luo Y, Perloff ES, Horan KA, Bruce A, Reynolds RC, Harmatz JS, Avula B, Khan IA, Goldman P. 2006. *Ginkgo biloba* does not alter clearance of flurbiprofen, a cytochrome P450-2C9 substrate. **J Clin Pharmacol** 46: 214 - 221. **https://doi.org/10.1177/0091270005283465**

Haines DD, Varga B, Bak I, Juhasz B, Mahmoud FF, Kalantari H, Gesztelyi R, Lekli I, Czompa A, Tosaki A. 2011. Summative interaction between astaxanthin, *Ginkgo biloba* extract (EGb761) and vitamin C in suppression of respiratory inflammation: a comparison with ibuprofen. **Phytother Res** 25: 128 - 136. **https://doi.org/10.1002/ptr.3160**

Hartley D, Elsabagh S, File S. 2004. Gincosan (a combination of *Ginkgo biloba* and *Panax ginseng*): the effects on mood and cognition of 6 and 12 weeks' treatment in post-menopausal women. **Nutr Neurosci** 7: 325 - 333. **https://doi.org/10.1080/10284150400015557**

Hellum BH, Nilsen OG. 2008. In vitro inhibition of CYP3A4 metabolism and P-glycoprotein-mediated transport by trade herbal products. **Basic Clin Pharmacol Toxicol** 102: 466 - 475. **https://doi.org/10.1111/j.1742-7843.2008.00227.x**

Hu Z, Yang X, Ho PCL, Chan SY, Heng PWS, Chan E, Duan W, Koh HL, Zhou S. 2005. Herb-drug interactions. **Drugs** 65: 1239 - 1282. **https://doi.org/10.2165/00003495-200565090-00005**

Ismail MYM. 2009. Drug-food interactions and role of pharmacist. **Asian J Pharmaceut Clin Res** 2: 1 - 10.

Ji H, Zhang G, Yue F, Zhou X. 2017. Adverse event due to a likely interaction between sodium aescinate and *Ginkgo biloba* extract: a case report. **J Clin Pharm Therapeut** 42: 237 - 238.

https://doi.org/10.1111/jcpt.12500

Kandiah N, Ong PA, Yuda T, Ng LL, Mamun K, Merchant RA, Chen C, Dominguez J, Marasigan S, Ampil E, Nguyen VT, Yusoff S, Chan YF, Yong FM, Krairit O, Suthisisang C, Senanarong V, Ji Y, Thukral R, Ihl R. 2019. Treatment of dementia and mild cognitive impairment with or without cerebrovascular disease: expert consensus on the use of *Ginkgo biloba* extract, EGb 761®. **CNS Neurosci Therapeut** 25: 288 - 298. **https://doi.org/10.1111/cns.13095**

Kennedy D, Haskell C, Mauri P, Scholey A. 2007. Acute cognitive effects of standardised *Ginkgo biloba* extract complexed with phosphatidylserine. **Hum Psychopharmacol Clin Exp** 22: 199 - 210. **https://doi.org/10.1002/hup.837**

Kennedy D, Scholey A, Wesnes K. 2001. Dose dependent changes in cognitive performance and mood following acute administration of Ginseng to healthy young volunteers. **Nutr Neurosci** 4: 295 - 310. **https://doi.org/10.1080/1028415x.2001.11747370**

Kim BH, Kim KP, Lim KS, Kim JR, Yoon SH, Cho JY, Lee YO, Lee KH, Jang IJ, Shin SG. 2010. Influence of *Ginkgo biloba* extract on the pharmacodynamic effects and pharmacokinetic properties of ticlopidine: an open-label, randomized, two-period, two-treatment, two-sequence, single-dose crossover study in healthy Korean male volunteers. **Clin Ther** 32: 380 - 390. **https://doi.org/10.1016/j.clinthera.2010.01.027**

Kleijnen J, Knipschild P. 1992. Ginkgo biloba. **Lancet** 340: 1136 - 1139. **https://doi.org/10.1016/0140-6736(92)93158-j**

Kudolo GB, Wang W, Javors M, Blodgett J. 2006. The effect of the ingestion of Ginkgo biloba extract (EGb 761) on the pharmacokinetics of metformin in non-diabetic and type 2 diabetic subjects -a double blind placebo-controlled, crossover study. **Clin Nutr** 25: 606 - 616. **https://doi.org/10.1016/j.clnu.2005.12.012**

Kumar Singh S, Barreto G, Aliev G, Echeverria V. 2017. Ginkgo biloba as an alternative medicine in the treatment of anxiety in dementia and other psychiatric disorders. **Curr Drug Metab** 18: 112 - 119. **https://doi.org/10.2174/1389200217666161201112206**

Kupiec T, Raj V. 2005. Fatal seizures due to potential herb-drug interactions with *Ginkgo biloba*. **J Anal Toxicol** 29: 755 - 758. **https://doi.org/10.1093/jat/29.7.755**

Lau AJ, Chang TK. 2009. Inhibition of human CYP2B6-catalyzed bupropion hydroxylation by *Ginkgo biloba* extract: effect of terpene trilactones and flavonols. **Drug Metab Disposition** 37: 1931 - 1937. **https://doi.org/10.1124/dmd.109.028118**

Lei HP, Wang G, Wang LS, Ou-Yang DS, Chen H, Li Q, Zhang W, Tan ZR, Fan L, He YJ. 2009. Lack of effect of *Ginkgo biloba* on voriconazole pharmacokinetics in Chinese volunteers identified as CYP2C19 poor and extensive metabolizers. **Ann Pharmacother** 43: 726 - 731. **https://doi.org/10.1345/aph.1l537**

Liao HJ, Zheng YF, Li HY, Peng GP. 2011. Two new ginkgolides from the leaves of *Ginkgo biloba*. **Planta Medica** 77: 1818 - 1821. **https://doi.org/10.1055/s-0030-1271153**

Lin YY, Chu SJ, Tsai SH. 2007. Association between priapism and concurrent use of risperidone and *Ginkgo biloba*. **Mayo Clinic Proceed** 82: 1289 - 1290. **https://doi.org/10.4065/82.10.1289**

Longtin Y, Sax H, Leape LL, Sheridan SE, Donaldson L, Pittet D. 2010. Patient participation: current knowledge and applicability to patient safety. **Mayo Clinic Proceed** 85: 53 - 62. **https://doi.org/10.4065/mcp.2009.0248**

Markowitz JS, Donovan JL, DeVane CL, Sipkes L, Chavin KD. 2003. Multiple-dose administration of *Ginkgo biloba* did not affect cytochrome P-450 2D6 or 3A4 activity in normal volunteers. **J Clin Psychopharmacol** 23: 576 - 581. **https://doi.org/10.1097/01.jcp.0000095340.32154.c6**

Matthews MK. 1998. Association of *Ginkgo biloba* with intracerebral hemorrhage. **Neurology** 50: 1933 - 1933. **https://doi.org/10.1212/wnl.50.6.1933**

Mazhar H, Foster BC, Necyk C, Gardiner PM, Harris CS, Robaey P. 2020. Natural health product–drug interaction causality assessment in pediatric adverse event reports associated with attention-deficit/hyperactivity disorder medication. **J Child Adolescent Psychopharmacol** 30: 38 - 47. **https://doi.org/10.1089/cap.2019.0102**

McKenna DJ, Jones K, Hughes K. 2001. Efficacy, safety, and use of ginkgo biloba in clinical and preclinical applications. **Altern Ther Health Med** 7: 70 - 86.

Meng Q, Liu K. 2014. Pharmacokinetic interactions between herbal medicines and prescribed drugs: focus on drug metabolic enzymes and transporters. **Curr Drug Metab** 15: 791 - 807.

https://doi.org/10.2174/138920021666615022315234 8

Miller MA. 2001. Gender-based differences in the toxicity of pharmaceuticals—the food and drug administration's perspective. **Int J Toxicol** 20: 149 - 152. **https://doi.org/10.1080/109158101317097728**

Mohamed MEF, Frye RF. 2010. Inhibition of intestinal and hepatic glucuronidation of mycophenolic acid by *Ginkgo biloba* extract and flavonoids. **Drug Metabol Disposition** 38: 270 - 275. **https://doi.org/10.1124/dmd.109.030080**

Mohutsky MA, Anderson GD, Miller JW, Elmer GW. 2006. *Ginkgo biloba*: evaluation of CYP2C9 drug interactions *in vitro* and *in vivo*. **Am J Ther** 13: 24 - 31. **https://doi.org/10.1097/01.mjt.0000143695.68285.31**

Montastruc JL, Bagheri H, Geraud T, Lapeyre-Mestre M. 1997. Pharmacovigilance de l'automédication. **Therapie** 52: 105 - 110.

Naccarato M, Yoong D, Gough K. 2012. A potential drug–herbal interaction between *Ginkgo biloba* and efavirenz. **J Int Assoc Phys AIDS Care** 11: 98 - 100. **https://doi.org/10.1177/1545109711435364**

Nathan PJ, Tanner S, Lloyd J, Harrison B, Curran L, Oliver C, Stough C. 2004. Effects of a combined extract of *Ginkgo biloba* and *Bacopa monniera* on cognitive function in healthy humans. **Hum Psychopharmacol Clin Exp** 19: 91 - 96. **https://doi.org/10.1002/hup.544**

Numa AM, Abbott FS, Chang TK. 2007. Effect of *Ginkgo biloba* extract on oxidative metabolism of valproic acid in hepatic microsomes from donors with the CYP2C9* 1/* 1 genotype. **Can J Physiol Pharmacol** 85: 848 - 855. **https://doi.org/10.1139/y06-085**

Ohnishi N, Kusuhara M, Yoshioka M, Kuroda K, Soga A, Nishikawa F, Koishi T, Nakagawa M, Hori S, Matsumoto T. 2003. Studies on interactions between functional foods or dietary supplements and medicines. I. Effects of *Ginkgo biloba* leaf extract on the pharmacokinetics of diltiazem in rats. **Biol Pharmaceut Bull** 26: 1315 - 1320. **https://doi.org/10.1248/bpb.26.1315**

Omidkhoda SF, Razavi BM, Hosseinzadeh H. 2019. Protective effects of *Ginkgo biloba* L. against natural toxins, chemical toxicities, and radiation: A comprehensive review. **Phytother Res** 33: 2821 - 2840. **https://doi.org/10.1002/ptr.6469**

Park YJ, Kim MJ, Kim HR, Yi MS, Chung KH, Oh SM. 2013. Chemopreventive effects of *Ginkgo biloba* extract in estrogen-negative human breast cancer cells. **Arch Pharmacal Res** 36: 102 - 108. **https://doi.org/10.1007/s12272-013-0002-0**

Persson J, Bringlöv E, Nilsson LG, Nyberg L. 2004. The memory-enhancing effects of Ginseng and *Ginkgo biloba* in healthy volunteers. **Psychopharmacology** 172: 430 - 434. **https://doi.org/10.1007/s00213-003-1675-8**

Raju S, Sivanesan SK, Gudemalla K. 2019. Cognitive enhancement effect of *Ginkgo biloba* extract on memory and learning impairments induced by fluoride neurotoxicity. **Int J Res Pharmaceut Sci** 10: 129 - 134.

Robertson SM, Davey RT, Voell J, Formentini E, Alfaro RM, Penzak SR. 2008. Effect of *Ginkgo biloba* extract on lopinavir, midazolam and fexofenadine pharmacokinetics in healthy subjects. **Curr Med Res Opinion** 24: 591 - 599. **https://doi.org/10.1185/030079908x260871**

Rosenblatt M, Mindel J. 1997. Spontaneous hyphema associated with ingestion of *Ginkgo biloba* extract. **New Engl J Med** 336: 1108 - 1108. **https://doi.org/10.1056/nejm199704103361518**

Rubio C, Paz S, Tius E, Hardisson A, Gutierrez AJ, Gonzalez-Weller D, Caballero JM, Revert C. 2018. Metal contents in the most widely consumed commercial preparations of four different medicinal plants (aloe, senna, ginseng, and ginkgo) from Europe. **Biol Trace Element Res** 186: 562 - 567. **https://doi.org/10.1007/s12011-018-1329-7**

Ruiz ME. 2010. Risks of self-medication practices. **Current Drug Safety** 5: 315 - 323. **https://doi.org/10.2174/157488610792245966**

Silva JES, Souza CAS, da Silva TB, Gomes IA, Brito GC, Araújo AA, de Lyra-Júnior DP, da Silva WB, da Silva FA. 2014. Use of herbal medicines by elderly patients: A systematic review. **Arch Gerontol Geriat** 59: 227 - 233. **https://doi.org/10.1016/j.archger.2014.06.002**

Sørensen JM. 2002. Herb–drug, food–drug, nutrient–drug, and drug–drug interactions: mechanisms involved and their medical implications. **J Altern Complement Med** 8: 293 - 308. **https://doi.org/10.1089/10755530260127989**

Spinella M. 2001. Herbal medicines and epilepsy: the potential for benefit and adverse effects. **Epilepsy Behavior** 2: 524 - 532. **https://doi.org/10.1006/ebeh.2001.0281**

Strain ML, Yingling MN, Kraleti S, Thiessen KA. 2019. Rhabdomyolysis after *Ginkgo biloba* and cannabis. **J Pharm Pract Res** 49: 368 - 372. **https://doi.org/10.1002/jppr.1560**

Tang J, Sun J, Zhang Y, Li L, Cui F, He Z. 2007. Herb–drug interactions: Effect of Ginkgo biloba extract on the pharmacokinetics of theophylline in rats. **Food Chem Toxicol** 45: 2441 - 2445. **https://doi.org/10.1016/j.fct.2007.05.023**

Tarn DM, Barrientos M, Wang AY, Ramaprasad A, Fang MC, Schwartz JB. 2020. Prevalence and knowledge of potential interactions between over-the-counter products and Apixaban. **J Am Geriatrics Soc** 68: 155 - 162.

Tian J, Liu Y, Chen K. 2017. *Ginkgo biloba* extract in vascular protection: molecular mechanisms and clinical applications. **Curr Vasc Pharmacol** 15: 532 - 548. **https://doi.org/10.2174/1570161115666170713095545**

Uchida S, Yamada H, Li XD, Maruyama S, Ohmori Y, Oki T, Watanabe H, Umegaki K, Ohashi K, Yamada S, 2006. Effects of *Ginkgo biloba* extract on pharmacokinetics and pharmacodynamics of tolbutamide and midazolam in healthy volunteers. **J Clin Pharmacol** 46: 1290 - 1298. **https://doi.org/10.1177/0091270006292628**

USM. 2020. **Global *Ginkgo biloba* extract market by type, by application** (tablets, capsules, and liquid extracts), by region and key companies - industry segment outlook, market assessment, competition scenario, trends and forecast 2019–2028. **https://market.us/report/ginkgo-biloba-extract-market/request-sample/#overview** .

Valli G, Giardina EGV. 2002. Benefits, adverse effects and drug interactionsof herbal therapies with cardiovascular effects. **J Am Coll Cardiol** 39: 1083 - 1095. **https://doi.org/10.1016/s0735-1097(02)01749-7**

van Beek TA, Montoro P. 2009. Chemical analysis and quality control of *Ginkgo biloba* leaves, extracts, and phytopharmaceuticals. **J Chromatography A** 1216: 2002 - 2032. **https://doi.org/10.1016/j.chroma.2009.01.013**

von Moltke LL, Weemhoff JL, Bedir E, Khan IA, Harmatz JS, Goldman P, Greenblatt DJ. 2004. Inhibition of human cytochromes P450 by components of *Ginkgo biloba*. **J Pharm Pharmacol** 56: 1039 - 1044. **https://doi.org/10.1211/0022357044021**

Wiegman DJ, Brinkman K, Franssen EJ. 2009. Interaction of Ginkgo biloba with efavirenz. **Aids** 23: 1184 - 1185. **https://doi.org/10.1097/qad.0b013e32832c412b**

Yale SH, Glurich I. 2005. Analysis of the inhibitory potential of *Ginkgo biloba*, *Echinacea purpurea*, and *Serenoa repens* on the metabolic activity of cytochrome P450 3A4, 2D6, and 2C9. **J Altern Complement Med** 11: 433 - 439. **https://doi.org/10.1089/acm.2005.11.433**

Yin OQ, Tomlinson B, Waye MM, Chow AH, Chow MS. 2004. Pharmacogenetics and herb–drug interactions: experience with *Ginkgo biloba* and omeprazole. **Pharmacogen Genom** 14: 841 - 850. **https://doi.org/10.1097/00008571-200412000-00007**

Yoshioka M, Ohnishi N, Koishi T, Obata Y, Nakagawa M, Matsumoto T, Tagagi K, Takara K, Ohkuni T, Yokoyama T. 2004. Studies on interactions between functional foods or dietary supplements and medicines. IV. Effects of *Ginkgo biloba* leaf extract on the pharmacokinetics and pharmacodynamics of nifedipine in healthy volunteers. **Biol Pharmaceut Bull** 27: 2006 - 2009. **https://doi.org/10.1248/bpb.27.2006**

Zadoyan G, Rokitta D, Klement S, Dienel A, Hoerr R, Gramatté T, Fuhr U. 2012. Effect of *Ginkgo biloba* special extract EGb 761® on human cytochrome P450 activity: a cocktail interaction study in healthy volunteers. **Eur J Clin Pharmacol** 68: 553 - 560. **https://doi.org/10.1007/s00228-011-1174-5**

Zuo XC, Zhang BK, Jia SJ, Liu SK, Zhou LY, Li J, Zhang J, Dai LL, Chen BM, Yang GP, Yuan H. 2010. Effects of *Ginkgo biloba* extracts on diazepam metabolism: a pharmacokinetic study in healthy Chinese male subjects. **Eur J Clin Pharmacol** 66: 503 - 509. **https://doi.org/10.1007/s00228-010-0795-4**