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MEDICINE INTERACTIONS WITH GINKGO BILOBA

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Summary. Worldwide, Ginkgo biloba is one of the commonly used plant in the production of food supplements. The earliest evidence of use of leaves of Ginkgo biloba in clinical practice is found in the Chinese Materia Medica (Shen Nung Pen Tsao Ching), 2800 BC. In the 50 years of last century western medicine began to study the clinical application of Ginkgo biloba, and interest in nutritional supplements with Ginkgo biloba intensively increased in the late 70's. Today, many medical professionals recommend Ginkgo biloba products to counteract chronic, age-related neurological disorders, but there are also studies focusing on the Ginkgo biloba adverse events and interactions with prescription and non-prescription medications. The aim of our present study was to conduct a review of literature on interactions between Ginkgo biloba extract and conventional medicines based on descriptions of the clinical consequences, case series and case reports. We have reviewed 47 publications on Ginkgo interactions in the scientific literature. We selected studies performed with Ginkgo biloba and focused on interaction with medicines and analyses of medical records. The information about interactions is summarized according to the pharmacological groups of medicines, level of interaction and effects. Specific examples are given with anticonvulsant agents, antidepressants, antihypertensive medications, blood-thinning and blood sugar lowering medications, diuretics etc. The knowledge of herb-medicine supplements interactions is an important tool for rational use of medicinal products and dietary supplements.

Key words: Ginkgo biloba, food supplements, interactions, medicines, rational use

ВЗАИМОДЕЙСТВИЯ НА GINKGO BILOBA С ЛЕКАРСТВЕНИ ПРОДУКТИ

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Резюме. В световен мащаб, Ginkgo biloba е едно от най-често използваните растения, включвани в хранителни добавки. Най-ранните данни за приложението на листата на Ginkgo biloba в клиничната практика са намерени в Chinese Materia Medica (Shen Nung Pen Tsao Ching), 2800 пр.н.е. През 50-те години на миналия век западната медицина започва да проучва възможностите на Ginkgo biloba, а интересът към хранителни добавки с Ginkgo се увеличава значително. Днес много медицински специалисти препоръчват продуктите с Ginkgo biloba при редица хронични заболявания, вкл. и такива на нервната система. Все повече нарастват данните, фокусирани върху нежелани реакции и взаимодействията с лекарствени продукти, отпускани без и по лекарско предписание. Целта на настоящото ни проучване е да направим преглед на литературата, касаеща взаимодействието на Ginkgo biloba с лекарства. В прегледа са включени 47 публикации. За целта са подбрани проучвания, проведени с Ginkgo biloba, фокусирани върху взаимодействията с лекарства и анализи на информация за предписването на лекарства. Информацията за взаимодействията е обобщена по фармакологични групи, лекарствени вещества и взаимодействия. Дадени са конкретни примери с антиконвулсанти, антихипертензивни лекарства, антидиабетни, диуретици и др. Знанията за взаимодействията между хранителни добавки и лекарствени продукти са от съществено значение за рационалната употреба на лекарствата и хранителните добавки.

Key words: Ginkgo biloba, хранителни добавки, взаимодействия, лекарства, рационална употреба

Introduction

Alternative therapy including herbal medicines and complementary medicine is becoming increasingly popular. However, the rise in the incidence of herb-medicine interactions is causing concern, especially in the absence of warning labels addressing potential adverse effects and/or interactions [2, 5, 24]. Worldwide, Ginkgo biloba is one of the commonly used plants in the production of food sup-

plements.[7, 26, 39, 40, 48, 52] *Ginkgo biloba* is one of the oldest of living plants. The earliest evidence of use of leaves of Ginkgo biloba in clinical practice are found in the Chinese Materia Medica (Shen Nung Pen Tsao Ching), 2800 BC [12, 15, 18, 32].

In the 50 years of last century western medicine began to study the clinical application of Ginkgo biloba, and interest in nutritional supplements with Ginkgo biloba intensively increased in the late 70's. Today, many medical professionals recommend Ginkgo-products in peripheral vascular disease, cerebral insufficiency, intermittent claudication and others, although concerns remain for its safety [26]. There are studies that ginkgo-containing food supplements can influence human metabolism, as well as the effectiveness of some prescription and non-prescription medicinal products (anticoagulants, anticonvulsants, thiazide diuretics, antihypertensives, antidepressants, etc.), but systematical analysis is still lacking [4, 5, 16, 17, 24, 33, 35, 37, 54, 56].

The aim of this study was is to systematize the literature on interactions between Ginkgo biloba extract (GBE) and conventional medicines.

Materials and Methods

It was reviewed publications in Scopus, Science Direct and Google Scholar with key words ginkgo biloba, medicine-herb interations, ginkgo biloba interaction with medicines. 47 publications during 2005–2010 were selected and systematized according to the medicines used, type of publication (controlled trial, review, case control, case records, interview etc.), described interaction, level of interaction and effects.

Results and Discussion

Special attention in the current publication is paid to articles announcing the results from studies of Ginkgo-herb interactions in humans.

The highest publication activity is recorded in 2005 (Fig. 1). [9, 11, 14, 20, 27, 30, 37, 38, 43, 44, 49, 50, 64] 78.57% of publications in 2005 are either reviews or case reports and studies in humans were lacking (Fig. 2). One publication was concerning the results of an open label, three-way crossover randomized study in 12 healthy male subjects, who received a single 25 mg dose of warfarin alone or after 7 days pretreatment with recommended doses of ginkgo or ginger from herbal medicine products. The results showed that international normalized ratio of prothrombin time and platelet aggregation were not affected by administration of ginkgo or ginger alone.

Glintborg et al. [27] reviewed the medical records of 83 surgical and 117 medical patients (n = 200) in order to identify potential interactions. 476 potential interactions were identified (126 patients); none were class 1 (always avoid medicines combination) and 25 were class 2 (usually avoid combination; 24 patients). 11 of the potential class 2 interactions involved aspirin. Of the 52 medicines involved in potential class 2 interactions, 50 had been used for more than 1 month. According to the hospital case notes, none of the potential class 2 interactions had actually caused adverse effects.

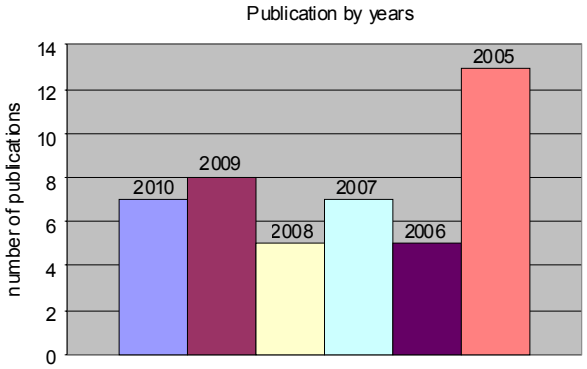

***Fig. 1**. Ginkgo-medicines' interactions publications 2005-2010*

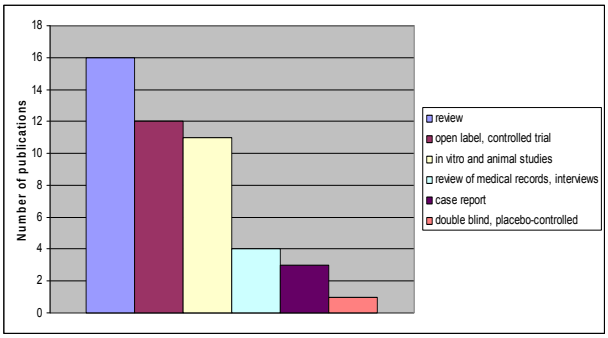

***Fig. 2**. Types of Ginkgo-medicines' interaction publications*

2 case reports [36, 44] were published in 2005: a fatal breakthrough seizure of 55-years old male on anticonvulsant therapy with no evidence of non-compliance with his anticonvulsant medications, concomitantly taken with GBE (the authopsy revealed subtherapeutic plasma levels of anticonvulsant medication) and post-operative haemorrhage in 65-years old male.

Review of another 15 case reports suggested Ginkgo's role in spotaneus bleedings. [9] However, only 6 reports clearly described that ginkgo was stopped and that bleeding did not recur.

In 2006 there are only 5 publications focused on GBE-medicines interactions [13, 29, 55, 61, 63]. 2 of them involved studies performed in total of 21 health volunteers [29, 61] and one publication revealed the results of the screening of medical records of 250 patients for potential interactions. [55] The rest 2 publications in 2006 involved experiments in rats. [13, 63] Uchida et al. [61] studied the GBE effect on orally administrated CYP2C9 probe (tolbutamide, 125 mg) and CYP3A4 probe (midazolam, 8 mg) in 10 male healthy volunteers. Plasma

medicine concentrations and blood glucose levels were measured. The area under concentration versus time curve (AUC0-infinity) for tolbutamide after GBE intake was slightly but significantly (16%) lower than that before GBE intake. Concomitantly, GBE tended to attenuate AUC0-2 of blood glucose-lowering effect of tolbutamide. AUC0-infinity for midazolam was significantly (25%) increased by GBE intake and oral clearance was significantly (26%) decreased. This study results suggested that the combination of GBE and medicines should be cautious in terms of the potential interactions, especially in elderly patients or patients treated with medicines exerting relatively narrow therapeutic windows.

In another study, Greenblatt et al. [29] assessed the effect of GBE on the activity of CYP2C9, the isoform responsible for S-warfarin clearance, in 11 healthy volunteers who received single 100-mg doses of flurbiprofen, a probe substrate for CYP2C9. Subjects also received a standardized Ginkgo biloba leaf preparation (3 doses of 120 mg) or matching placebo in a randomized, double-blind, 2-way crossover study. Mean kinetic variables for flurbiprofen with either placebo or GBE were elimination half-life, 3.9 versus 3.5 hours; total AUC, 57 versus 55 microg/mL h; and oral clearance, 32.9 versus 31.6 mL/min. None of these differences was significant.

Saw et al. [55] performed a cross-sectional survey evaluating the use of herbal medicines in medical wards patients that may interfere with the effect of antiplatelet or anticoagulant therapy. Among the 250 patients participated, 42.4% (n = 106) were taking herbs with 76 patients (71.7%) using herbs for the past 12 months. Overall, almost 31% (n = 23, N = 76) of patients were taking one or more of the specified herbal medicines [ginseng (Panax ginseng), garlic (Allium sativum), ginkgo (Gingko biloba) thought to interact with antiplatelet or anticoagulant therapy. The study showed that 21% of patients co-ingested specified herbs with antiplatelet or anticoagulant therapy, of which half of them were at risk of potential medicine-herb interactions. A large proportion of respondents involved in potential medicine-herb interaction were elderly people. However, more than 90% of herbal users did not disclose the use of herbal medicine to their health professionals. The study results suggested that all health care givers should be aware of the possibility of medicine and herb interaction and inquire about herbal use from patients.

Out of the 7 studied scientific articles published in 2007 [6, 8, 19, 21, 25, 28, 60], 1 was a review article, 3 publications revealed the results of concomitant Ginkgo plus medicine administration in humans, 1 was a retrospective analysis of prescriptions and the rest 2 – in vitro studies in rats. In randomized, double-blind, placebo-controlled, parallel design trial of 4-week duration Gardner et al. [25] examined the potential adverse effects of concomitant aspirin and GBE on platelet function. GBE (300 mg/day) was compared with placebo for effects on measures of platelet aggregation among adults consuming 325 mg/day aspirin. Outcome measures included platelet function analysis (PFA-100 analyzer) using ADP as an agonist (n = 26 placebo; n = 29 ginkgo), and platelet aggregation using ADP, epinephrine, collagen and ristocetin as agonists (n = 21 placebo; n = 23 ginkgo). There were no clinically or statistically significant differences between treatment groups for any agonists, for either PFA-100 analysis or platelet aggregation. Reports of bleeding or bruising were infrequent and similar for both study groups. Beckert at al. [8] studied 5 commercially available herbal agents, including GBE, garlic, Asian ginseng, St. John's wort, and Saw palmetto and their effect on *in vivo* platelet function. In a blinded fashion, one of the agents was administered to 10 adult volunteers at the manufacturer's recommended dose for 2 weeks. At the end of the 2-week period, in vivo platelet function was quantified using the PFA-100 assay. After a 2-week "washout" period, the protocol was repeated using a different agent. This 4-week cycle was repeated for each of the five herbal agents, as well as the control agent aspirin. The study confirmed that the platelet function was not affected by the administration of any herbal agent.

Aruna et al. [6] studied in a randomized, open-label, crossover study of 10 healthy male volunteers the level of interaction between 120 mg Ginkgo biloba, 240 mg Ginkgo biloba, 100 mg cilostazol, 200 mg cilostazol, 75 mg clopidogrel, 150 mg clopidogrel, 120 mg Ginkgo biloba + 100 mg cilostazol and 120 mg Ginkgo biloba + 75 mg clopidogrel. Platelet aggregation, platelet count, bleeding time and clotting time were measured 0 and 6 h after medicine administration. The results showed that the co-administration of GBE either with cilostazol or clopidogrel did not enhance antiplatelet activity compared with individual agents. GBE potentiated the bleeding time prolongation effect of cilostazol. There was no significant correlation between prolongation of bleeding time and inhibition of platelet aggregation.

Only 1 of the 5 publications [3, 10, 53, 57, 62] on GBE interactions in 2008 was an open-label study [53] which evaluated the effect of 2 weeks of standardized Ginkgo biloba extract administration on the steady-state exposure of lopinavir and ritonavir in 14 healthy volunteers administered lopinavir/ritonavir to steady-state. In addition, single oral doses of probe medicines midazolam and fexofenadine were administered prior to and after 4 weeks of GBE (following washout of lopi-

navir/ritonavir) to assess the influence of ginkgo on CYP3A and P-gp activity, respectively. The study results suggested that GBE induces CYP3A metabolism, as assessed by a decrease in midazolam concentrations. However, there was no change in the exposure of lopinavir, likely due to ritonavir's potent inhibition of CYP3A4.

Amongst the 7 publications in 2009 [22, 23, 34, 45, 46, 47, 59], 3 revelead the results of studies on the effect of GBE on the efficacy of bupropion and talinolol in humans. Lei et al. [46] studied the interaction between bupropion (150 mg) and GBE 240 mg daily, received orally for 14 days by 14 healthy male volunteers. The results showed that GBE administration for 14 days does not significantly alter the basic pharmacokinetic parameters of bupropion in healthy volunteers. Fan et al. [22] investigated the effect of herbal medicine Schisandra chinensis extract and GBE on the oral pharmacokinetics of P-glycoprotein substrate talinolol in humans. Twelve healthy male volunteers took a single 100-mg oral dose of talinolol either alone or after pretreatment with 300 mg Schisandra chinensis extract twice daily or with 120 mg GBE three times daily for 14 days. On day 14, a single 100-mg oral dose of talinolol was administered. Plasma concentrations of talinolol from zero to 24 h were measured by high-performance liquid chromatography. The results of the trial suggested that both extracts significantly inhibited P-glycoprotein in humans. In another study Fan et al. [23] investigated the effects of single and repeated Ginkgo ingestion on the oral pharmacokinetics of talinolol in 10 healthy male volunteers. The results showed that single oral dose of GBE did not affect the pharmacokinetics of talinolol. Repeated ingestion of Ginkgo increased the talinolol maximum plasma concentration (C(max)) by 36%, the area under the concentration-time curve (AUC)(0-24) by 26% and AUC(0-infinity) by 22%, respectively, without significant changes in elimination half-life and the time to C (max). These findings confirmed that long-term use of Gingko significantly influence talinolol disposition in humans, likely by affecting the activity of P-glycoprotein and/or other medicine transporters.

In 2010 only 2 out of 7 publications in the scientific literature revealed results from studies of Ginkgo interaction with medicines (ticlopidine and diazepam) in humans. [42, 65] The rest 5 publications were reviews. [1, 41, 31, 51, 58] Kim et al. [42] evaluated the potential pharmacodynamic and pharmacokinetic interactions between ticlopidine and GBE in open-label, randomized, 2-period, 2-treatment, 2-sequence, single-dose crossover study, conducted in 24 healthy Korean male volunteers. All volunteers were randomly assigned to a sequence group for the 2 treatments, which consisted of ticlopidine 250 mg alone and ticlopidine 250 mg with GBE 80 mg, separated by a 1-week washout period between the treatments. Bleeding time was determined just before dosing and at 5, 12, and 48 hours after dosing. Platelet aggregation was evaluated before dosing and at 4, 8, 26, and 48 hours after dosing. Ticlopidine concentrations were determined by a validated method using HPLC and ultraviolet detection. The addition of a single dose of GBE did not prolong the bleeding time and was not associated with additional antiplatelet effects compared with the administration of ticlopidine alone. The coadministration of GBE with ticlopidine was not associated with any significant changes in the pharmacokinetic profile of ticlopidine compared with ticlopidine administered alone.

Zuo et al. [65] studied the pharmacokinetic parameters of diazepam and one of its metabolites, N-demethyldiazepam, compared after oral administration of diazepam (10 mg) in the absence or presence of oral GBE (120 mg bid, for 28 days) in 12 healthy volunteers. The results suggested that GBE, when taken in normally recommended doses over a 4-week time period, may not affect the pharmacokinetics of diazepam via CYP2C19 and the excretion of N-desmethyldiazepam in healthy volunteers. No herb-medicine interaction was observed between GBE and diazepam during the study.

In summary, 26 medicines were investigated in the selected screened publications (Table 1). One of the most researched medicines for interaction with GBE were non-steroidal antiinflamatory medicines (acetylsalicylic acid, celecoxib, flurbiprofen, ibuprofen and rofecoxib), antiplattelet and anticoagulant agents such as clopidogrel, ticlopidine and warfarine, antivirals (lopinavri, ritonavir), benzodiazepines (diazepam, midazolam) and antidepresants (bupropion, trazodone). There were also immunosupresants (cyclosporin), anticonvulsants (divalproex sodium), proton pumb inhibitors (omeprazole) etc. subject to research for interaction with GBE. The majority of publication in the studied period (2005-2010) were dedicated to warfarin (6 literature reviews and 2 randomized studies), acetylsalicilc acid (3 literature reviews, 2 double-blind trials and 1 review of medical records) as well as bupropion, talinonol and ticlopidine. The literature reviews and case reports indicated for inetacrtion between GBE and warfarin, but this was not confirmed from the trials performed in 2005-2010 which found that GBE at recommended doses do not significantly affect clotting status and GBE showed no effect on the kinetics or dynamics of warfarin. A possible explanation about this discrepancy between the trials data and case reports or medical records, could be overdosing and/or interpatient variabilites. A similar finding concerns aspirin-GBE interaction where even the blind-fashion trial findings are contradictory.

Table 1. Medicines involved in Ginkgo-medicine interactions' research

INN	Type of study	Results
Androstendione	In vivo study in rats [14]	GBE strongly increased liver CYP450 content and altered the ex-vivo biotransformation of androstendione, as well as metabolism of endogenous steroids. However, in human subjects no effect on the urinary steroid profile was observed after intake of EGb 761 for 28 days (240 mg daily). The effects of GBE on medicine metabolising enzymes are specific for rats and may not be extrapolated to man.
Acetylsalicylic acid	In a blinded fashion, one of the agents was administered to 10 adult volunteers for 2 weeks. At the end of the 2-week period, in vivo platelet function was quantified using the PFA-100 assay [8] Review of controlled trials [10] Double-blind, placebo-controlled, parallel design trial of 4-week duration [25] Review of medical records of 200 patients [28] Literature review [34] Literature review [65]	In vivo platelet function was not affected by the administration of any herbal agent and was markedly inhibited with the administration of aspirin [8] GBE does not significantly impact haemostasis nor adversely affect the safety of coadministered aspirin [10] In older adults with peripheral artery disease or cardiovascular disease risk, a relatively high dose of Ginkgo biloba combined with 325 mg/day daily aspirin did not have a clinically or statistically detectable impact on indices of coagulation examined over 4 weeks, compared with the effect of aspirin alone [25] Eleven of the potential class 2 interactions involved over-the-counter products (aspirin and ginkgo biloba).[28] Clinical cases indicate interactions of ginkgo with aspirin [34] Ginkgo biloba caused bleeding when combined with warfarin or aspirin [65]
Bupropion	In vitro study of catalytic activity of CYP2B6 as assessed by the bupropion hydroxylation assay with recombinant enzyme and hepatic microsomes [45] Fourteen healthy male volunteers received orally administered bupropion (150 mg) alone and during treatment with GBE 240 mg day for 14 days [46]	GBE and its flavonol aglycones are naturally occurring inhibitors of in vitro CYP2B6 catalytic activity and bupropion hydroxylation [45] GBE administration for 14 days does not significantly alter the basic pharmacokinetic parameters of bupropion in healthy volunteers [46]
Celecoxib	Literature review [51]	In vitro or animal study or theoretical based on pharmacology evidences for interaction between GBE and celecoxib [51]
Cilostazol and Clopidogrel	Literature review [3] A randomized, open-label, crossover study of 10 healthy male volunteers [6]	Ginkgo has the potential to cause significant interactions with anticoagulant and antiplatelet medicines, and also with medicines metabolized by the cytochrome P450 enzyme system, especially by CYP3A4 [3] Coadministration of GBE either with cilostazol or clopidogrel did not enhance antiplatelet activity compared with individual agents. Ginkgo biloba potentiated the bleeding time prolongation effect of cilostazol. There was no significant correlation between prolongation of bleeding time and inhibition of platelet aggregation
Cyclosporin	Investigation of the influences of ginkgo and onion on the absorption and disposition of cyclosporin in rats in a cross-over design [63]	GBE markedly decreased the oral bioavailability of cyclosporin
Divalproex sodium	A case of a 55-year-old male who suffered a fatal breakthrough seizure, with no evidence of non-compliance with his anticonvulsant medications [45]	The autopsy report revealed subtherapeutic serum levels for both anticonvulsants Depakote and Dilantin. Concomitant with his prescribed medications, the decedent was also self-medicating with a cornucopia of herbal supplements and nutraceuticals, prominent among which was Ginkgo biloba
Diazepam	Comparison between the pharmacokinetic parameters of diazepam and one of its metabolites, N-demethyldiazepam, after oral administration of diazepam (10 mg) in the absence or presence of oral GBE (120 mg bid, for 28 days) [64]	No medicine-medicine interaction was observed between GBE and diazepam.
Fexofenadine	Open-label study, evaluating the effect of 2 weeks of standardized GBE administration on the steady-state exposure of lopinavir and ritonavir in 14 healthy volunteers administered lopinavir/ritonavir to steady-state. In addition, single oral doses of probe medicines midazolam and fexofenadine were administered prior to and after 4 weeks of GBE (following washout of lopinavir/ritonavir) to assess the influence of GBE on CYP3A and P-gp activity, respectively [53]	Lopinavir, ritonavir and fexofenadine exposures were not significantly affected by GBE administration
Flurbiprofen	Randomized, double-blind, 2-way crossover study. The effect of Ginkgo biloba on the activity of CYP2C9, the isoform responsible for S-warfarin clearance, was assessed in 11 healthy volunteers who received single 100-mg doses of flurbiprofen, a probe substrate for CYP2C9. Subjects also received either a GBE (3 doses of 120 mg) or matching placebo [29]	Mean kinetic variables for flurbiprofen with either placebo or G biloba were elimination half-life, 3.9 versus 3.5 hours; total AUC, 57 versus 55 microg/mL h; and oral clearance, 32.9 versus 31.6 mL/min. None of these differences was significant
Ibuprofen	Literature review [34]	Clinical cases indicate interactions of ginkgo with ibuprofen
Lopinavir	See fexofenadine study [53]	Lopinavir exposures were not significantly affected by GBE administration
Midazolam	See fexofenadine study [53] CYP2C9 probe (tolbutamide, 125 mg) and CYP3A4 probe (midazolam, 8 mg) were orally administered to 10 male healthy volunteers before and after GBE intake (360 mg/d) for 28 days, and they received 75 g glucose after the dosing of tolbutamide [61]	GBE decreased midazolam AUC(0-infinity) and C(max) by 34% ($p = 0.03$) and 31% ($p = 0.03$), respectively, relative to baseline [53] AUC0-infinity for midazolam was significantly (25%) increased by GBE intake and oral clearance was significantly (26%) decreased [61]

Omeprazole	Literature review [34]	GBE decreases the plasma concentrations of omeprazole, ritonavir and tolbutamide
Risperidone	Literature review [34]	Clinical cases indicate interactions of ginkgo with risperidone
Ritonavi r	Literature review [34] See fexofenadine study [53]	Ginkgo (Ginkgo biloba) decreases the plasma concentrations of omeprazole, ritonavir and tolbutamide [34] Lopinavir, ritonavir and fexofenadine exposures were not significantly affected by GBE administration [53]
Rofecoxib	Literature review [34]	Clinical cases indicate interactions of ginkgo with rofecoxib
Simvastatin	Pre-clinical controlled trial (rats) [47]	High dose of gingko extract can induce the activity of CYP3A, and promote the metabolism of simvastatin, so the medical interaction should be focused when gingko extract is coadministered with simvastatin and other substracts of CYP3A
Sodium pertechnetate	In vivo study in rats on influence of an GBE on the bioavailability of the radiobiocomplex sodium pertechnetate (Na99mTcO4) [51]	GBE altered the Na99mTcO4 bioavailability in the kidneys, liver and duodenum.
Talinolol	Twelve healthy male volunteers took a single 100-mg oral dose of talinolol either alone or after pretreatment with 300 mg SchE twice daily or with 120 mg GBE three times daily for 14 days. On day 14, a single 100-mg oral dose of talinolol was administered [22] Ten unrelated healthy male volunteers were selected to participate in a 3-stage sequential study. Plasma concentrations of talinolol from 0 to 24 hours were measured by high-performance liquid chromatography after talinolol 100 mg was administrated alone, with a single oral dose of GBE (120 mg), and after 14 days of repeated GBE ingestion (360 mg/day) [23]	GBE increased the area under the curve (AUC)(0-24) of talinolol by by 21%. The C(max) of talinolol increased by 33%. The t(1/2) of talinolol increased by 11% [22] A single oral dose of GBE did not affect the pharmacokinetics of talinolol. Repeated ingestion of GBE increased the talinolol maximum plasma concentration (Cmax) by 36%, the area under the concentration-time curve (AUC)0-24 by 26% and AUC0-∞ by 22%, respectively [23]
Theophylline	In vivo controlled study in rats [60]	Increase in the total clearance of theophylline of about 30% (GBE 10 mg/kg, $P<0.05$) and 70% (GBE 100 mg/kg, $P<0.01$) compared with the control group after intravenous administration of theophylline (10 mg/kg). After oral administration of theophylline (10 mg/kg), the AUC(0-24h) of theophylline was reduced by 40% following pretreatment with GBE (100 mg/kg, $P<0.01$)
Ticlodipine	Literature review [3] Open-label, randomized, 2-period, 2-treatment, 2-sequence, single-dose crossover study. The treatments consisted of ticlopidine 250 mg alone and ticlopidine 250 mg with GBE 80 mg, separated by a 1-week washout period between the treatments [42]	Ginkgo has the potential to cause significant interactions with anticoagulant and antiplatelet medicines, and also with medicines metabolized by the cytochrome P450 enzyme system, especially by CYP3A4.[3] The coadministration of Ginkgo biloba extract with ticlopidine was not associated with any significant changes in the pharmacokinetic profile of ticlopidine compared with ticlopidine administered alone
Tolbitamide	Literature review [34] See midazolam [61]	Ginkgo (Ginkgo biloba) decreases the plasma concentrations of omeprazole, ritonavir and tolbutamide [34] The area under concentration versus time curve (AUC0-infinity) for tolbutamide after GBE intake was slightly but significantly (16%) lower than that before GBE intake. Concomitantly, GBE tended to attenuate AUC0-2 of blood glucose-lowering effect of tolbutamide [61]
Trazodone	Literature review [34]	Clinical cases indicate interactions of ginkgo with trazodone
Warfarin	Literature review [3] Literature review [5] Review of controlled trials [10] Randomized, double-blind, 2-way crossover study [29] Literature review [34] Three-way crossover randomized study in 12 healthy male subjects [38] Literature review [51] Literature review [65]	Ginkgo has the potential to cause significant interactions with anticoagulant and antiplatelet medicines, and also with medicines metabolized by the cytochrome P450 enzyme system, especially by CYP3A4 [3] Ginkgo reinforce warfarin action [5] GBE does not significantly impact haemostasis nor adversely affect the safety of coadministered warfarin [10] The results confirm previous controlled clinical studies showing no effect of ginkgo on the kinetics or dynamics of warfarin [29] Clinical cases indicate interactions of ginkgo with warfarin [34] Ginkgo and ginger at recommended doses do not significantly affect clotting status, the pharmacokinetics or pharmacodynamics of warfarin in healthy subjects [38] In vitro or animal study or theoretical based on pharmacology evidences for interaction between GBE and warfarin.[51] Ginkgo biloba caused bleeding when combined with warfarin or aspirin [65]

Discussion

Although potential herb-medicines interactions are highly prevalent, serious and clinically significant interactions are rare among hospitalised patients, according to the systematized publications. For the studied period (2005-2010) 26 medicines were examined for possible interactions with GBE and for most of them the information about possible interactions was previously published. The majority of the reviwed articles were literature reviews, case reports and medical records analyses. For some of the studied medicines such as warfarin and aspirin there were contradiction between the reported cases/reviews and controlled trials performed in 2005-2010.

Knowledge of herb-medicines interactions is limited and controlled trials in humans are lacking. More studies of herb-medicines interactions in humans are needed to be executed and the results made available to the specialists prescribing herbal food supplements as the knowledge of herb-medicines interactions is an important tool for rational use of medicinal products.

Most Ginkgo-containing products are dietary supplements in the majority of European counries and require speciall attention for possible interactions with medicines. As there is no such regulatory requirement, medical professionals should be more attentive to use of herbal products by their patients when prescribe medicinal products.

Special patients' education is needed in order to reduce the possible harm resulted from herbal-medicine interactions.

Conclusions

Drug interactions with products containing GBE are widely discussed in the literature but no regulatory measures have been taken. The introduction of food supplements safety requirements is necessary to improve the control over alternative products usage. More controlled trials are needed to confim the reuslts from case studies, medical records and literature reviews.

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