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Review

Potential interaction of *Ginkgo biloba* leaf with antiplatelet or anticoagulant drugs: What is the evidence?

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Some writers hold the view that the combination of *Ginkgo biloba* with anticoagulant or antiplatelet drugs represents a serious health risk. Such concerns are largely based on the assumption that Ginkgo has clinically relevant antiplatelet activity, as well as accounts of bleeding episodes associated with Ginkgo consumption. To investigate whether these bleeding episodes have a pharmacodynamic, idiosyncratic or coincidental basis, a review of controlled clinical studies and case reports was undertaken. Results from controlled studies consistently indicate that Ginkgo does not significantly impact haemostasis nor adversely affect the safety of coadministered aspirin or warfarin. Most of these studies were undertaken using EGb 761, a well-defined extract of *Ginkgo biloba*. In contrast, EGb 761 has not generally been implicated in the case reports. In general, the quality of these case reports is low. Nevertheless, the possibility of an idiosyncratic bleeding event due to Ginkgo use cannot be excluded on the basis of the available information. However, there is scant information from case reports or controlled trials to support the suggestion that Ginkgo potentiates the effects of anticoagulant or antiplatelet drugs. Such high-level safety concerns for this herb are deemed to be unsupported by the currently available evidence.

Keywords: Aspirin / EGb 761 / *Ginkgo biloba* / Herb – drug interaction / Warfarin

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1 Introduction

Ginkgo biloba is a deciduous tree that has survived unchanged for around 150 million years. This living fossil, as described by Charles Darwin, may have been saved from extinction by the Chinese who revered the tree and planted it around their temples [1, 2]. Only the seed of the Ginkgo tree was used in traditional Chinese medicine [3]. In the 1960s a group of German scientists working for the herbal firm Schwabe were investigating the effects of exotic herbs on circulation. They found that the leaf of Ginkgo was particularly active in promoting peripheral circulation. A special, highly concentrated and standardised extract was developed and codenamed EGb 761 [1, 2]. This extract was initially standardised for its total flavonoid content. But when it became known that the terpenoids in Ginkgo (bilobalide and the ginkgolides) were potent platelet-activating factor (PAF) antagonists, EGb 761 was also standardised against these quality markers. There is now a proliferation of Ginkgo products on the world market and it has become one of the best-selling herbs. However, many of these generic Ginkgo products do not reflect the same phytochemical profile of EGb 761.

As noted above, EGb 761 was initially developed as a treatment for peripheral circulatory problems such as intermittent claudication and a syndrome described as "cerebral insufficiency". Only later did the research focus shift to Alzheimer's disease [4]. It was this early focus on peripheral circulation, coupled with the potent PAF antagonism of the ginkgolides, that probably led to the perception that EGb 761 possessed clinically relevant antiplatelet activity. Hence in 1996, when a 33-year-old Korean woman was diagnosed with spontaneous bilateral subdural haematomas, her regular use of *Ginkgo biloba* was implicated as the cause [5]. The authors wrote: "We postulate that this patient's subdural haematomas may have occurred, at least in part, due to the presence of abnormal platelet aggregability due to the chronic ingestion of ginko biloba (sic), an inhibitor of PAF".

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Abbreviations: AA, arachidonic acid; **ADP,** adenosine diphosphate; **INR**, international normalised ratio; **NSAIDs,** non-steroidal inflammatory drugs; **PAF**, platelet-activating factor; **TXB_2**, thromboxane B_2

Despite this cautious approach in not wholly attributing causality to Ginkgo, attributions of bleeding episodes ascribed to Ginkgo intake have subsequently been reported at regular intervals. About 21 cases have been described to date. In seven of these cases an interaction between Ginkgo and either an antiplatelet or anticoagulant drug was further implicated. Despite this relative scarcity of reported cases, the potential interaction of Ginkgo with such agents has become an intense focus, perhaps almost a mantra, for writers and reviewers of the therapeutic properties of this herb. In some circles it appears to be an accepted truth that the combined use of Ginkgo with either anticoagulant or antiplatelet drugs is potentially dangerous and should be avoided. For example, various books reviewing herb use [6 – 8] hold this view, as do several websites (for example http://www.rxlist.com/cgi/alt/ginkgo_wcp.htm). Also, the authors of a recent survey of two outpatient practices for potential herb – drug interactions classified the combination of Ginkgo and warfarin as a "potentially severe interaction" [9].

The intention of this review is firstly to critically examine the likelihood that *Ginkgo biloba* (and specifically EGb 761 or extracts which match its phytochemical profile) has the propensity to influence normal haemostasis. After all, this is the apparent basis of any concern regarding its potential to interact with antiplatelet or anticoagulant drugs. Next, the controlled clinical investigations of potential interactions are reviewed and discussed. Following this, the published case reports of bleeding or interaction concurrent with Ginkgo use are briefly described (mainly in tabular form). Finally, these cases are assessed in the context of the above information and pertinent conclusions are made.

2 Ginkgo and haemostasis

Several of the case reports concerning Ginkgo and bleeding (see Section 4) refer to the study of Chung and coworkers [10] published in 1987 as supportive of a causative connection. In this investigation a ginkgolide mixture codenamed BN 52063 was administered to six normal volunteers in a double-blind, placebo-controlled crossover study. Single doses of 80 mg and 120 mg of BN 52063 significantly inhibited PAF-induced platelet aggregation *ex vivo* compared to placebo. However, it must be considered that BN 52063 is not the same as EGb 761. In fact, EGb 761 contains around only 4% ginkgolides. Hence the doses of ginkgolides administered were around an order of magnitude in excess of those that routinely result from ingestion of EGb 761.

This important dosage issue is also not considered by reviewers of a subsequent study, where it was found that around five times the normal daily dose of EGb 761 (15 mL of Tanakan which contained 600 mg of EGb 761) significantly inhibited PAF-induced platelet aggregation *ex vivo* [11]. An open-label single-dose design was used and results were compared with baseline 2, 4 and 8 h after ingestion of the Ginkgo. The authors also noted that bleeding time and coagulation were not affected.

EGb 761 has also been shown to inhibit platelet aggregation *in vitro* [10 – 12]. However, the relevance of such *in vitro* studies to the normal clinical use of the extract must be questioned, given the issues of oral bioavailability and the high concentrations used for the *in vitro* studies. This consideration was highlighted in a recent study by Koch [13], which found that the PAF-mediated aggregation of human platelets was inhibited by ginkgolides at concentrations generally more than 100 times higher than the peak plasma values measured after oral intake of EGb 761. Koch suggested that since PAF is a weak platelet activator which does not appear to be of importance for primary haemostasis, serious doubts exist that the PAF antagonistic effect of the ginkgolides could be responsible for abnormal bleeding in patients taking EGb 761.

Kudolo and coworkers [14] have recently investigated the impact of a Ginkgo extract on platelet function, but more from the perspective of the modification of platelet aggregation under pathological conditions. Enhanced aggregation, particularly in response to collagen, is a common occurrence in diabetes that increases the risk of developing cardiovascular disease. In an open label design, both healthy volunteers and patients with type 2 diabetes consumed 120 mg of a standardised Ginkgo extract for 3 months [14]. There was no effect of Ginkgo ingestion on platelet aggregation induced by epinephrine, adenosine diphosphate (ADP) or ristocetin. The urinary thromboxane B_2 (TXB_2) metabolite 11-dehydro-TXB_2 and prostacyclin metabolites were marginally but significantly reduced, but only in the non-diabetic group. Bleeding times were not investigated.

The above investigation lacked a placebo group, which was addressed in a subsequent study. Here, 12 non-diabetic volunteers undertook a randomised, double-blind, placebo-controlled crossover study [15]. Active treatment consisted of 120 mg of a standardised Ginkgo extract for 3 months. The effect of Ginkgo on arachidonic acid (AA)-induced platelet aggregation was not significant. However, AA-stimulated TXB_2 production by platelets was significantly decreased in the Ginkgo treatment cycles ($p < 0.005$). Although Kudolo and team have suggested, because of their findings for TXB_2, that Ginkgo has aspirin-like effects, this is not supported by the lack of activity of Ginkgo on AA-induced platelet aggregation.

It is also important to note that although Kudolo and coworkers [15, 16] claimed to be working with EGb 761, they were in fact using brands purchased from health food stores or pharmacies in the USA. The phytochemical characteristics of these products in relation to EGb 761 were not defined, although the extracts were described as standardised for flavonoids and terpenoids. This product difference

may be of relevance, since a number of commercial Ginkgo extracts with apparently similar levels of standardisation to EGb 761 are available to manufacturers. However, many of these extracts have significantly different phytochemical profiles to EGb 761, most notably because of fortification with added flavonoids or lack of removal of ginkgolic acids (which are potentially allergenic and considered to be undesirable) [17, 18].

In contrast to Kudolo and team, five other controlled clinical trials from five different research groups have not established any significant impact of *Ginkgo biloba* on haemostasis parameters. In a relatively early study, Jung and coworkers [19] investigated the impact of a Ginkgo extract (Kaveri, Lichtwer) on blood fluidity and cutaneous microcirculation using a randomised, placebo-controlled single-blind design involving ten healthy volunteers [19]. Platelet aggregation *ex vivo* was not impacted by the Ginkgo treatment and neither was the number of circulatory platelet aggregates. However, a significant decrease in erythrocyte aggregation was observed. The active treatment consisted of a single dose of 112.5 mg of a Ginkgo extract containing 27% flavonoids, 4.1% ginkgolides and 2.2% bilobalide.

A US team of investigators studied EGb 761 at 160 mg/day for 6 months using a randomised, double-blind, placebo-controlled design involving 51 elderly volunteers (mean age 87.2 ± 2.1 years). The study was undertaken as part of the Dementia Prevention Study [20]. While there was a significant reduction in collagen/epinephrine- and collagen/ADP-induced platelet aggregation for both groups over the 6-month period, there was no significant difference observed between the placebo and Ginkgo groups.

A team of Turkish scientists also investigated the effect of EGb 761 on haemostasis in 40 elderly patients aged 65 – 79 years [21]. In an open-label study, patients consumed 240 mg of EGb 761 for 7 days. Compared to baseline, prothrombin time, activated partial thromboplastin time, international normalised ratio (INR), and epinephrine- and ADP-induced platelet aggregation were unchanged by the Ginkgo treatment.

A prospective, randomised, double-blind, placebo-controlled study was initiated in 32 young healthy male volunteers [22]. Compared to placebo, EGb 761 at 120, 240 and 480 mg/day for 14 days had no impact on haemostasis, coagulation, fibrinolysis and platelet function. Specifically, bleeding time and platelet aggregation induced by ADP, collagen and thrombin receptor agonist peptide were not significantly altered.

In perhaps the most comprehensive study to date, scientists at Schwabe investigated the effect of 240 mg/day of EGb 761 in 50 healthy male volunteers using a randomised, double-blind, placebo-controlled crossover design [23]. Active treatment was for 7 days and 29 coagulation and bleeding parameters were assessed. None of these showed any evidence of an inhibition of blood coagulation or platelet aggregation from EGb 761 intake.

Reviews and meta-analyses of clinical trials have shown that EGb 761 has a remarkably low incidence of side effects [24 – 27], and there were no differences between Ginkgo and placebo in the adverse event profile [25, 28, 29]. Only 0.5% of 9772 patients reported adverse events over 44 clinical trials. Adverse events reported have included mild gastrointestinal complaints, headache, dizziness, allergic skin reactions and palpitations [25]. Notably, no events linked to abnormal bleeding have been observed in these trials.

However, the argument has been proposed that such studies, including the controlled investigations into bleeding parameters noted above, lack sufficient power or duration of Ginkgo use to detect even moderate increases in bleeding risk [30]. In this context a recent examination of case reports for Ginkgo and bleeding is highly relevant [31]. An excerpt of the Mediplus database in Germany providing information for 320 644 patients observed between 1 July 1999 and 30 June 2002 was used to evaluate reported bleeding events. Over 810 077 patient years of observation, 22 586 bleeding events were reported, giving an average of 2.79 events *per* 100 years of observation. The prevalence for the entire population can be assumed to be lower, since only individuals consulting a physician were included in the database. The prevalence of bleeding during intake of any medication was estimated at 3.51 events *per* 100 years, while it was 1.63 when no medication was taken. When the risk of bleeding from a variety of drugs used in dementia was assessed, the cholinesterase inhibitors had the highest relative risk (1.44), while EGb 761 or any Ginkgo preparation (as approved in Germany) were around 1. In other words, the frequency of reported bleeding events in patients taking Ginkgo was the same as that in patients not taking Ginkgo. No increase in the prevalence of bleeding during EGb 761 intake compared to periods without EGb 761 was seen for coadministration of aspirin, phenprocoumon or for any other anticoagulant or antiplatelet medication.

3 Ginkgo in conjunction with aspirin and warfarin

In the Dementia Prevention Study investigation noted earlier, 15 participants were also taking aspirin [20]. EGb 761 was not deemed to have any interaction with aspirin. This study has only been published to date in abstract form.

In a double-blind, double-dummy design, 50 healthy male volunteers were randomly allocated in equal numbers to receive either aspirin (500 mg/day), followed by aspirin (500 mg/day) plus EGb 761 (240 mg/day), or the reverse [32]. Bleeding time, coagulation parameters and platelet function in response to various agonists were determined. As might be expected, aspirin given alone clearly prolonged bleeding time from 4.1 to 6.2 min. However, there was no additional impact from adding Ginkgo. For aspirin plus EGb 761, bleeding time increased from 4.2 to 6.3 min. Sim-

ilarly the addition of Ginkgo to aspirin had no significant impact on platelet aggregation induced by collagen, ADP, AA, epinephrine and PAF. The authors suggested that the coadministration of Ginkgo with aspirin does not constitute a safety risk.

A double-blind, crossover study consisting of three treatment periods of 4 wk (with a 2-wk washout period) investigated the impact of coenzyme Q_{10} or a Ginkgo extract (not EGb 761, 100 mg/day) on patients already stabilised on long-term warfarin [33]. Twenty-four patients treated with warfarin for recurrent venous thromboembolism, mechanical heart valves or chronic atrial fibrillation were enrolled in the study. Throughout the observation periods the INR remained stable and major bleedings and thromboembolic events were not observed.

An open label, three-way crossover randomised study in 12 healthy male volunteers investigated the effect of EGb 761 (240 mg/day) or ginger (3.6 g/day) on both the pharmacokinetics and pharmacodynamics of warfarin [34]. Participants received a single 25-mg dose of warfarin alone or after a 7-day pre-treatment with EGb 761 or ginger. Dosing with the herbs was continued for 7 days after the single warfarin dose. INR and platelet aggregation were not affected by EGb 761 or ginger alone, and neither herbal treatment had any impact on the pharmacokinetics of warfarin. Furthermore, there was no difference in INR or platelet aggregation in the warfarin plus EGb 761 or warfarin plus ginger treatments compared to warfarin alone.

It can be validly argued again that these studies, being small and of short duration, lack sufficient power to predict low frequency, more idiosyncratic responses. However, the counter-argument is that there is scant evidence to imply that EGb 761 is more likely to cause such rar. In fact, Ginkgo has only been singled out for such investigations because of the dire warnings about a high risk of interaction with anticoagulant and antiplatelet medications. At the very least it can be categorically stated that such concerns regarding a high risk of interaction are not supported by these controlled clinical studies. In addition, as noted earlier, a large database study found that there was no increased frequency of bleeding when EGb 761 was combined with such drugs [31].

4 Case reports linking Ginkgo to bleeding episodes

All published case reports that could be located linking Ginkgo use to a subsequent bleeding episode are summarised in Table 1. This table is based on the publication of Bent and coworkers [30], but represents an update and modification of their work. Reported events are listed in chronological order.

From the table it is clearly evident that the quality of the case report evidence is very low. In particular, the importance of documenting exactly what the patient was taking and confirming this by a visual inspection of the actual product appears to have been rarely considered, if at all. Relying on an anecdotal account from the patient of what they were taking (or as in some reports, the patient's spouse or relative) is clearly inadequate. Given the great potential for variability in herbal products, the ideal approach is to carefully document the label details including the product name and characteristics, level of standardisation, presence of other potentially active ingredients, batch number and type of extract used. On this last point, an analysis of the product to confirm its phytochemical profile would have provided very useful information.

Further to this, there is only one documented case report in Table 1 where it was confirmed that EGb 761 was involved, and here the patient was also taking aspirin. In fact, given the demographics of the case reports, it is likely that the Ginkgo products involved in these reports exhibited significantly different phytochemical profiles, both from each other and EGb 761. This might include different amounts and relative levels of the various ginkgolides, fortification with added flavonoids or lack of removal of the ginkgolic acids. Any of these factors might account for a less favourable safety profile for Ginkgo in terms of bleeding risk.

In only one case [30] was an abnormal bleeding time confirmed by blinded measurement (bleeding time assessment is a relatively subjective technique). An objective assessment of platelet function was undertaken in only one of the cases, where decreased platelet aggregation to collagen and normal aggregation to ADP, epinephrine and ristocetin was observed [35].

Another remarkable feature is that for the 15 cases where duration of use was stated, in 11 of these the Ginkgo product had been taken for at least 5 months. Bent and coworkers [30] have suggested that this could imply a cumulative effect on bleeding propensity with prolonged use. However, it could equally be argued that since Ginkgo was being used for a prolonged period prior to the bleeding episode, other more immediate factors acting alone were the causative agents.

The co-ingestion of drugs which can elevate the risk of bleeding was reported in seven of the 21 cases: one case for warfarin, three cases for aspirin and three cases for other non-steroidal anti-inflammatory drugs (NSAIDs). These instances of bleeding episodes might therefore represent an adverse interaction between Ginkgo and the prescribed medication. In the case involving warfarin described by Matthews [36], the patient's INR was substantially elevated, which would account for the bleeding episode. Matthews consequently attributed an anticoagulant activity to Ginkgo, something which is not supported by any research. Also, any pharmacokinetic effect of Ginkgo on warfarin has now been discounted by a controlled clinical trial. Hence, while the patient's warfarin was certainly destabilised, the evi-

Table 1. Adverse bleeding events reports for *Ginkgo biloba*

Reference	Age/ gender	Daily dose [mg]/ identity of product	Duration	Possible mitigating factors/potential interaction	Bleeding event	Dechallenge	Rechallenge	Bleeding time
Rowin and Lewis [5]	33, F	120, NR	2 years	Paracetamol, egotamine/ caffeine	Bilateral subdural haematomas	Yes, 15 mo	No	Increased (unblinded)
Gilbert [38]	72, F	150, NR	6 – 7 months	NR	Subdural haematoma	NR	No	No
Rosenblatt and Mindel [39]	70, M	80, Ginkoba (EGb 761)	1 wk	Aspirin 325 mg/day	Spontaneous hyphema	Yes, 3 mo	No	No
Vale [40]	61, M	120 to 160, NR	6+ months	None stated	Subarachnoid haemorrhage	Yes, 4 mo	No	Mildly increased (unblinded)
Matthews [36]	78, F	NR	2 months	Hypertension, warfarin	Left parietal haemorrhage	No	No	No
Fessenden *et al.* [41]	34, M	NR	NR	Laparoscopic cholecystectomy	Blood in fluid drained from abdomen postoperatively	NR	No	No
Hoffman [42]	69, M	253.4, NR	"Years"	Lisinopril, glyburide, rofecoxib. Hypertension, head injury	Subdural haematomas	Yes, 1 wk	No	Abnormal (unblinded)
Benjamin *et al.* [43]	56, M	120, NR	18 months	None stated	Cerebral haemorrhage	NR	No	No
Miller and Freeman [44]	78, M	150, Not known	6 months	Fall	Subdural haematoma	NR	No	No
Schneider *et al.* [45]	65, M	600, Ginkgor Fort	8 wk	None stated	Spontaneous hyphema	Yes, 18 mo	No	No
Garcia *et al.* [46]	75, M	80, NR	1 month	NR	Cerebellar haematoma	NR	No	No
Hauser *et al.* [47]	59, M	NR	NR	Liver transplant, cirrhosis, low platelets, 81 mg aspirin/day	Perihepatic haematoma, vitreous haemorrhage	Yes, NR	No	No
Fong and Kennear [48]	65, F	120, NR	2 years	None stated	Retrobulbar haemorrhage	NR	No	No
Meisel *et al.* [49]	71, M	80, Gingium	2.5 years	Ibuprofen 600 mg/day 4 wk	Intracerebral mass bleeding (death)	NA	NA	No
Bent *et al.* [30]	73, M	75, NR	6 – 7 months	Vitamin E	Ecchymosis, epistaxis	Yes, 4 y	Yes	Increased (blinded)
MacVie and Harney [50]	78, F	NR	5 months	None stated	Vitreous haemorrhage	Yes, 8 mo	No	No
Yagmur *et al.* [35]	75, F	80, Gingium	2 years	Surgery	Postoperative bleeding	Yes, 10 d	No	No, but platelet function slightly abnormal
Jayasekera *et al.* [51]	65, M	NR	NR	Surgery, diclofenac, other herbs	Postoperative bleeding	NR	No	No
Bebbington *et al.* [52]	77, F	120, NR	NR	Surgery, aspirin	Postoperative bleeding	Yes but bleeding only stopped 6 weeks later	No	No
Destro *et al.* [53]	53, F	160, NR	NR	Surgery, otherwise NR	Postoperative bleeding	NR	No	No
Destro *et al.* [53]	51, F	160, NR	NR	Surgery, otherwise NR	Postoperative bleeding	NR	No	No

NR, not reported; NA, not applicable

dence indicates that Ginkgo was a most unlikely cause. In the three cases involving co-ingestion of aspirin it is impossible to make any assessment of an adverse herb – drug interaction, since bleeding times were not assessed. In only one case involving the other NSAIDs was bleeding time measured and it was abnormal. However, the NSAID involved in this case was Vioxx (rofecoxib), which is generally not regarded as having clinically significant antiplatelet activity.

To establish causality from case reports is difficult, even when well-documented accounts are available. The key factors which need to be considered are the timing of the event, the presence or absence of other factors, the result of withdrawing the treatment (dechallenge), the result of reintroducing the treatment (rechallenge) and other data supporting the association, such as previous cases and biological plausibility [37]. Rechallenge was not attempted in all bar one of the case reports in Table 1, presumably because of safety concerns. In most of the reported cases other clinical risk factors for bleeding were present. However, in five cases none were stated. Whether this means that the authors of these cases diligently exhausted all possible mitigating factors is uncertain. In only one of these five cases was the brand of the Ginkgo product stated.

At best, case reports serve as a warning for a potential problem. Specifically, the case reports in Table 1 suggest that Ginkgo may cause an increased bleeding tendency in a minority of users. This is most likely to be an idiosyncratic reaction and could be relatively rare (if at all). One conclusion is certain from the case reports: there is scant evidence to suggest that combining Ginkgo with anticoagulant or antiplatelet agents increases the risk of bleeding over and above the use of these agents alone. Naturally, anticoagulants are dangerous drugs and caution should be exercised when any treatment, or even dietary change, is combined with their use.

5 Conclusions

There is no evidence from controlled studies that normal doses of EGb 761 or closely similar extracts have any impact on haemostasis. Earlier studies using high doses or isolated ginkgolides have been inappropriately extrapolated to the normal use of EGb 761. In particular, the fact that the ginkgolides are PAF antagonists has falsely created the impression that EGb 761 is a clinically active antiplatelet agent. Later research does not support such an impression.

In terms of a potential herb – drug interaction, four small controlled studies found no additional impact on haemostasis when EGb 761 was combined with either aspirin or warfarin.

These results from controlled studies appear to be at odds with the 21 case reports published between 1996 and 2005, which describe adverse bleeding events in connection with the consumption of Ginkgo. The Ginkgo products were generally poorly described. EGb 761 was implicated in only one of these cases and it is possible that other components excluded from EGb 761 (namely, the ginkgolic acids) may increase the bleeding risk. However, given the low quality of the case reports, it is also possible that the use of Ginkgo was incidental to the bleeding episode. This latter position is supported by a database study involving a large number of patient observations where it was found that ingestion of Ginkgo did not increase the likelihood of experiencing a bleeding event. Nevertheless, these case reports may still represent an idiosyncratic reaction to Ginkgo, but more careful data collection is required to establish this.

In terms of the potential for Ginkgo to interact adversely with anticoagulant and antiplatelet drugs, there is little evidence from case reports to support this possibility. Results from controlled clinical trials together with those from the surveillance (database) study mentioned above suggest that concerns regarding such interactions are substantially overstated, especially if EGb 761 or phytochemically similar extracts are involved.

Conflict of interest statement: The author is a shareholder and technical consultant for MediHerb, which markets and sells Ginkgo products. However, this review was neither commissioned nor funded by MediHerb and has been written in the author's capacity as a university academic.

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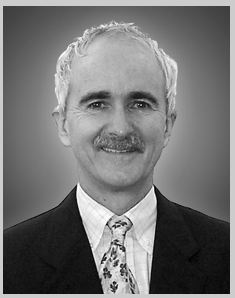

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