Signal

Ginkgo biloba L. and cardiac arrhythmias

Prof. Joanne Barnes New Zealand, Dr. Florence van Hunsel the Netherlands

Summary

This analysis considered 162 reports identified using the Standardised MedDRA Queries - SMQ (broad) for cardiac arrhythmias (dataset: 11 September 2019) and the substance *Ginkgo biloba* (Gb) in VigiBase, the WHO global database of individual case safety reports. For all reports where Gb was the sole suspect drug (n=92), there were 46 cases with dechallenge information, and of those, 39 had a positive dechallenge. Among the 25 reports with a high completeness score (>=0.75), Gb was the sole suspect drug for 20 reports; dechallenge information was given for 14 of these cases, all of which provided some documentation of positive dechallenge. For most of this subset of 14 reports, the specified time to onset of the reactions was within days. Pre-existing arrhythmias may cause a wide range of symptoms, including tinnitus (which was the indication for use of ginkgo in 18 of the 162 reports), so confounding by indication cannot be excluded. A mechanism by which *Ginkgo biloba* could induce cardiac arrhythmias is not clear; however, the number, nature and diversity (geographical origin, range of products implicated) of the reports and published cases indicate a signal between *Ginkgo biloba* and cardiac arrhythmias.

Signal

WHO Collaborating Centre for International Drug Monitoring
Box 1051, S-751 40, Uppsala, Sweden
Tel: +46 18 65 60 60 www.who-umc.org

Uppsala Monitoring Centre

Restricted

Introduction

Ginkgo (*Ginkgo biloba* L.; Ginkgoaceae) is a dioecious plant that has been used in medicine for around 5,000 years.[1] Traditional Chinese medicine (TCM) uses the seeds (kernel/nuts) and leaves of ginkgo trees for therapeutic purposes.[2] The chemical constituents of the leaves and seeds of *G. biloba* (Gb) are quite different, although both parts contain ginkgolic acids.[2] Today, standardised concentrated extracts and other formulations of Gb leaves are marketed worldwide, and used in cognitive deficiency, intermittent claudication (generally resulting from peripheral arterial occlusive disease), and vertigo and tinnitus of vascular origin.[2]

Internationally, there are substantial differences in the ways in which herbal medicines and other 'natural health' products/'complementary medicines' and 'dietary/food supplements' are regulated, or whether they are regulated at all. Gb-containing products are available under different regulatory regimes; in many countries they are marketed as a 'dietary/food supplement', 'natural health product', and, in some countries, as a herbal medicinal product. Under Health Canada's Natural Health Product Regulations, the monograph for Gb leaf allows product licence applications for Gb-containing products for the following uses/purposes: *"helps to enhance cognitive function in adults"; "helps to enhance memory in adults"; "helps to support peripheral circulation"; "helps to enhance cognitive function and memory in adults"*.[3]

In the European Union (EU), Gb-containing traditional herbal medicinal products granted a Traditional Herbal Registration (THR) may be indicated for *"the relief of heaviness of legs and the sensation of cold hands and feet associated with minor circulatory disorders"*.[4] In the UK, several Gb leaf products have been granted Traditional Herbal Registrations (THR) for relieving *"symptoms of Raynaud's syndrome and tinnitus, based on traditional use only"*.[5] There are some Gb-containing products that have 'regular' marketing authorisations. This is possible in the EU under the regulatory provisions for 'well-established use', which allow Gb-containing herbal medicinal products authorised under this system to be indicated for *"the improvement of (age-associated) cognitive impairment and of quality of life in mild dementia"*.[4] Oral doses typically comprise 120–240 mg dry extract in two or three divided doses.[2]

British Pharmacopoeial (BP) standard refined and quantified *Ginkgo biloba* L. leaf dry extract contains: flavonoids, expressed as flavone glycosides (Mr 756.7), 22-27% (dried extract); sesquiterpene lactones: bilobalide 2.6-3.2% (dried extract), ginkgolides A, B and C 2.8-3.4% (dried extract); ginkgolic acids: maximum 5 ppm (dried extract).[6] As with other herbal medicinal products, there is variation in the qualitative and quantitative composition of ginkgo leaf crude plant material and commercial ginkgo leaf products;[7] further, products containing different Gb leaf extracts have different *in-vitro* dissolution rates, resulting in differences in bioavailability in humans.[8] There may be substantial differences between the pharmaceutical quality of authorised herbal medicinal products containing *Ginkgo biloba* L. leaf extracts, and that of Gb-containing products sold as 'dietary supplements', and they may lack pre-market assessment of quality, effectiveness (typically based on evidence of 'traditional use') or efficacy, and safety.[9]

Cardiac arrhythmias are disorders of heart rhythm; they can consist of abnormalities in rate, regularity, or site of origin (e.g. supraventricular or ventricular) of the cardiac impulse, or conduction disturbances resulting in abnormal sequences of activation.[10] Cardiac arrhythmias can cause a diverse range of symptoms, including cardiac symptoms, such as tachycardia, bradycardia, or palpitations, as well as other symptoms, such as dyspnoea, weakness, dizziness, light-headedness, and syncope; they can also lead to cardiac arrest and sudden death. Some cardiac arrhythmias are asymptomatic. Cardiac arrhythmias can be supraventricular or ventricular, and slow (bradyarrhythmia) or fast (tachyarrhythmia). Supraventricular arrhythmias include atrial fibrillation, atrial flutter, and paroxysmal supraventricular tachycardia; ventricular arrhythmias include ventricular tachycardia, ventricular fibrillation and long QT syndrome. Ventricular tachycardia may appear similar to supraventricular tachycardia on an ECG trace yet is treated very differently.[10] Causes and risk factors for cardiac arrhythmias include electrolyte disturbances, congenital channelopathies, hypertension, myocardial infarction, thyroid disease, diabetes, cardiomyopathy, other heart damage and previous heart surgery. Certain types of arrhythmias can also be drug- (e.g. in digoxin toxicity) or substance-induced (use of caffeine, nicotine, excess alcohol, or 'recreational' drugs, such

as amphetamines). Most antiarrhythmic agents can have proarrhythmic effects, and some medicines or non-prescription products can have cardiac adverse effects.[11]

This assessment involved a data extract from VigiBase, the WHO global database of individual case safety reports, for *Ginkgo biloba* (substance) and Cardiac arrhythmias (MedDRA SMQ broad). The search included only single-ingredient *Ginkgo biloba* products; of note is that the Cardiac arrhythmias (MedDRA SMQ broad) standardised query includes the preferred term (PT) syncope and loss of consciousness, but not dizziness. The observed number of reports for the SMQ was roughly as expected. Case narratives, if present, were not translated except where the authors had some knowledge of the language in which the narrative was written (French, German).

Reports in VigiBase

This analysis was undertaken at the request of UMC subsequent to a 2016 joint Lareb/UMC (unpublished) analysis that concluded that the 123 VigiBase cases and literature reports available at that time suggested a signal relating to use of *Ginkgo biloba* and cardiac arrhythmias. In the current analysis (September 2019), 164 case reports were identified in the data extracted from VigiBase. Two reports appeared to be duplicates and, for these, the most recent report only was included in the analysis. Thus, this analysis comprised 162 reports containing adverse drug reaction (ADR) terms identified using the SMQ (broad) for cardiac arrhythmias for the (herbal) substance *Ginkgo biloba*. The reaction start date was recorded for around 80% of the 162 reports and, for around 40% of these, was during the last five years.

Patient characteristics for these 162 reports are summarised in Table 1. Two-thirds of the cases concerned females, and over 70% of patients involved were 45 years or over. The indication, or reason for use, of Gb was given for fewer than 40% of cases; the most common indications were tinnitus/*"ear noises"* (n=18), Alzheimer's disease, dementia, cognitive disorder, memory impairment (n=10), perfusion/ circulatory disorders (n=6), hearing disorders other than tinnitus, hearing loss (n=5), vertigo, vestibular disorders (n=4), unspecified prophylaxis (n=3). In one case, the indication for use of Gb was palpitations.

There were around 30 different proprietary Gb product names for the reported medication; these products were labelled as containing Gb leaf or leaf extracts. Around 17% of reports stated only the generic, common or binomial name for Gb, i.e. ginkgo, *Ginkgo biloba*, including incorrect spellings (e.g. *Gingko biloba*), without specifying a product, type of preparation or plant part. In one report (from the Republic of Korea), the medication was described as 'Ginkgonis semen', meaning the seed of Gb. In most instances, Gb was taken as an oral formulation, although there were two cases where Gb had been administered intramuscularly, and six cases where Gb was administered intravenously. The indications for use of parenteral Gb preparations were typically poorly described and included tinnitus, or unspecified heart, cerebrovascular, peripheral, or psychotic disorders, or prophylaxis (not further specified).

The reports came from 18 countries, with Germany and the Republic of Korea contributing the highest number; these two countries collectively contributed more than half (56%) of the reports. All other countries had contributed between 1 and 10 reports, with the exception of France (n=16). Geographically, most countries were in Europe (n=13) and contributed two-thirds of the reports; 25% of the reports came from Asia (n=one country: Republic of Korea), 8% were from North America (n=two countries), and the remainder (1.2%) were from South America and Africa (n=two countries).

Overall, 55 cases (34%) met the definition for serious ADR outcomes; of these, there were five deaths, and four cases were classed as life-threatening; the remainder (n=45; one not stated) were classed as serious because they resulted in/prolonged hospitalisation, were disabling/incapacitating, or otherwise medically significant. There were a further two deaths among cases not coded as serious ADRs; in both these cases, it was stated that the reaction may have contributed to the death.

Gb was the sole suspect drug in 92 (57%) cases. Dechallenge (mostly through drug withdrawal, rather than dose reduction) was documented for 46 of these cases; the dechallenge outcomes were: recovered (n=37; 80%); recovering (n=2); not recovered (n=1); unknown (6; 13%).

One case report can comprise multiple reported ADRs. For these 162 reports, the ADRs within the

Table 1. Characteristics of patients described in VigiBase reports identified using the SMQ (broad) for cardiac arrhythmias and substance *Ginkgo biloba* (dataset date: 11 September 2019) for all reports (n=162) and for the subset of reports with a completeness score of >= 0.75 (n=25)

Characteristic		All reports (n=162) n (%)	Reports with completeness score[a] >= 0.75 (n=25) n (%)
Sex	Female	107 (66%)	17 (68%)
	Male	52 (32.7%)	8 (32%)
	Not stated	3	-
Age	< 18 years	2*	-
	18 – 44 years	25	5
	45 – 64 years	41	6
	65 – 74 years	39	9
	> 75 years	37	5
	Not stated	18**	-

** one participant was stated to be '0 years', the other '12 months'*

*** one was stated to be an adult*

a) The completeness score is a multidimensional measure of the quantity of information provided on each individual case safety report (ICSR) with respect to certain pre-selected data entry fields on the report; each of these fields is given a score if it contains information, each field score is weighted, and then the scores are combined into one overall score for the whole ICSR. The maximum total score is 1.0

SMQ cardiac arrhythmias consisted of 26 MedDRA Preferred Terms (PTs). The five most frequently reported were: palpitations (n=67), tachycardia (n=24), loss of consciousness (n=14), syncope (n=13) and bradycardia (n=10). See Table 2 for all SMQ cardiac arrhythmias MedDRA PTs.

The ten most frequently co-reported ADRs by MedDRA PT were: dizziness (n=22), headache (n=14), nausea (n=13), hyperhidrosis (n=8), paraesthesia (n=8), dyspnoea (n=7), tinnitus (n=7), vomiting (n=7), anxiety (n=6), tremor (n=6). It is notable that tinnitus is one of the indications for use of Gb.

Other medicines most frequently co-reported, including where stated as an active ingredient of a multi-ingredient medicinal product, were acetylsalicylic acid (n=11), ascorbic acid (n=11), levothyroxine (n=9), and tocopherol (n=8).

VigiBase reports with high completeness score

Among the 162 reports, 25 (15%) had a completeness score of >= 0.75. As for the full set of reports, two-thirds of the 'high completeness score' subset cases concerned females, and over 70% of patients were aged 45 years or over. For these reports, the indication for use of Gb was given in all but one case; among these cases, the most common indications for use of Gb were tinnitus (n=6), cognitive disorder, memory impairment (n=3), perfusion/circulatory disorders (n=3), hearing disorders other than tinnitus, hearing loss (n=3), unspecified prophylaxis (n=3). In one case, the indication for use of Gb was 'vitamin supplementation'. There were nine different proprietary Gb product names described as the reported medication; these products are labelled as containing Gb leaf or leaf extracts; three reports stated only the generic, common or binomial name for Gb, i.e. ginkgo, *Ginkgo biloba*, including incorrect spellings (e.g. *Gingko biloba*), without specifying a product, type of preparation or plant part.

In over 80% of these cases, Gb was taken as an oral formulation; there were two cases where Gb had been administered intramuscularly, and one case where it was administered parenterally (not further specified). The indications for use of parenteral Gb preparations were typically poorly described and included tinnitus (n=1), or peripheral vascular disorders, or prophylaxis (not further specified).

This subset of reports originated from 10 countries,

Table 2. Characteristics of case reports (n=162) in VigiBase by MedDRA PT-level*

Reaction (PT)	All reports (n=162)	Reports with completeness score of >= 0.75 and Gb as sole suspect and positive dechallenge (n=14)
Palpitations	67	6
Tachycardia	24	1
Loss of consciousness	14	-
Syncope	13	2
Bradycardia	10	1
Arrhythmia	9	1
Atrial fibrillation	8	1
Heart rate increased	7	-
Heart rate irregular	4	-
Electrocardiogram abnormal	3	-
Extrasystoles	3	-
Atrioventricular block first degree	1	-
Cardiac arrest	4	-
Heart rate decreased	3	-
Supraventricular tachycardia	2	-
Torsade de pointes	2	-
Ventricular fibrillation	2	-
Ventricular tachycardia	2	1
Adams-Stokes syndrome	1	-
Arrhythmia supraventricular	1	-
Cardiac fibrillation	1	1
Cardio-respiratory arrest	1	-
Electrocardiogram QT prolonged	1	-
Sinus bradycardia	1	-
Sudden death	1	-
Supraventricular extrasystoles	1	-

** Each case report may comprise one or more ADR PT*

with Germany and the Republic of Korea contributing the highest numbers of reports; collectively contributing more than half (56%). All other countries contributed one or two reports. Geographically, most countries (n=7) were in Europe and contributed 68% of the reports; 24% of the reports came from Asia (n=one country: Republic of Korea), and the remainder (8%) were from South America and Australia (n=two countries; one report each).

Overall, 10 cases (40%) met the definition for serious ADR outcomes; of these, there was one death, one case was classed as life-threatening, five cases resulted in/prolonged hospitalisation, and three were otherwise medically significant.

Gb was the sole suspect drug in 20 (80%) cases. Dechallenge (drug withdrawal, n=13; dose reduction, n=1) was documented for 14 (70%) of these cases; the dechallenge outcomes were: recovered (n=12; 86%); recovering (n=1); for a further report the information on dechallenge outcome was conflicting (n=1). These 14 cases are detailed in Table 3. All these cases referred to oral administration of Gb, although

one listed an IV/IM injectable formulation of Gb as the suspected medicine. Five of these reports were considered 'serious', and none were fatal; seven had occurred from 2016 to the date of the data extract (September 2019).

For these 14 reports, the ADRs within the SMQ cardiac arrhythmias consisted of eight MedDRA Preferred Terms (PTs); the most frequently reported being palpitations (n=6). Table 2 shows all SMQ cardiac arrhythmias MedDRA PTs for these 14 reports. The most frequently co-reported ADR by MedDRA PT was dizziness (n=6); headache (n=2), nausea (n=2), and blood pressure decreased (n=2) were the only other co-reported ADR PTs reported more than once. For ten of these 14 reports, no other medicines were co-reported. However, for one of them, the case narrative revealed that the patient was taking a 'dietary supplement' sourced from the USA that contained Gb leaf extract and vinpocetine 5mg.

Two other reports of the 20 in which Gb was the sole suspect drug concerned patients who had received parenteral formulations of Gb on one day for tinnitus and unspecified peripheral vascular disease. Patient 1, female, 65 years, took 87.5mg, parenteral route not stated; patient 2, female 61 years, took 5mL, intramuscularly. Both patients experienced reactions within one day of receiving the treatment (patient 1: skin discolouration, bradycardia, hypotension, nausea, shock; patient 2: tachycardia, dyspnoea, hypertonia); the reactions resulted in hospitalisation for patient 1 and thus were described as serious; both patients were reported to have recovered. Aspects of patient 1's reaction are consistent with symptoms of an anaphylactic reaction; anaphylaxis was not indicated by the reporter.

Literature and Labelling

As many products containing *Ginkgo biloba* are sold and marketed as 'dietary supplements', such products will not have an official Summary of Product Characteristics (SmPC) against which to check whether arrhythmias are labelled. However, Gb-containing products that have 'regular' marketing authorisations, such as those authorised in the EU under the provisions for 'well-established use', do have official product information. It is beyond the scope of this signal review to identify and assess the SmPC for every Gb-containing product on the global market. However, as an example, the SmPC for a Gb-containing product marketed in Ireland does not list undesirable effects relating to cardiac arrhythmias.[12] In the EU, SmPCs for herbal medicinal products are based on the respective EU herbal monographs (formerly known as the Community herbal monographs). The EU herbal monograph produced by the European Medicines Agency (EMA) Committee on Herbal Medicinal Products (HMPC) for *Ginkgo biloba* L. folium (ginkgo leaf) lists dizziness as a common undesirable effect under 'nervous system disorders',[4] but does not list any effects relating to cardiac arrhythmias. The monograph also refers to a clinical study indicating that the C_{max} of nifedipine may be increased by G. *biloba* leaf: increases in C_{max} of up to 100% occurred in several participants, who then experienced dizziness and worsening of hot flushes.[4]

Further, the EMA's final assessment report on *Ginkgo biloba* L. folium (ginkgo leaf) includes information that is relevant to this signal. The report compiled information on Gb-containing products marketed in the EU, and products marketed in several countries were described as listing palpitation [sic], palpitations and/or arrhythmia(s) as risks.[13] Also, product information from one country included the statement that *"concomitant intake of ginkgo leaf and nifedipine has caused an increased heart frequency of 5-10% in well beings* [volunteers?]", but this may be due to the Gb-related increase in C_{max} of nifedipine discussed above; the EMA assessment also included statements from several countries regarding the need to use ginkgo with caution with vasodilators, antiarrhythmics, and medicines causing bradycardia.

There is little information in the scientific literature relating to an association between ginkgo and arrhythmias. The earliest reference identified for this assessment is from a book summarising research literature and sponsor data on a specific Gb extract, EGb-761 (Tebonin® forte, developed by Willmar Schwabe) that has been extensively researched in clinical and preclinical studies. This text summarises spontaneous reports received by the sponsor (Schwabe) for Tebonin® forte from 1982 to 1988,[14] which include *"palpitation"* [sic] among other reported adverse reactions (including dizziness). It is possible that these data are the source of the *"palpitation(s)"* listings on Gb-containing products that are referred to in the EMA final assessment report (reference 10) on *Ginkgo biloba* L. folium discussed above.

Several published case reports describe arrhythmia-type adverse reactions; at least one (reference 17) is included in the VigiBase reports described above. One report describes a 35-year-old woman who experienced frequent nocturnal palpitations lasting several minutes after taking a *Ginkgo biloba* leaf extract (240mg/day) as a general tonic.[15] The woman had no previous medical history, clear chest X-ray, and no physical abnormalities; electrocardiographic (ECG) examination showed a sinus rhythm of 80 beats/minute without conduction abnormalities or ST-T changes, and Doppler echocardiography did not reveal any cardiac structural or functional abnormalities. However, a 24-hour Holter ECG monitoring showed four nocturnal episodes of paroxysmal atrial fibrillation. The woman stopping taking Gb and her symptoms resolved within days; a repeated 24-hour ECG Holter did not show any arrhythmias over the following 12 months.[15]

Another report describes episodes of ventricular arrhythmia in a generally healthy 49-year-old man who had been taking Gb (40mg three times daily) for two weeks to improve his cognitive function. The man described experiencing palpitations and ECG showed sinus rhythm with frequent ventricular premature beats.[16] The palpitations stopped within two days of discontinuing Gb, but returned two days after the man resumed ginkgo treatment two weeks later. ECG again showed frequent ventricular ectopic beats similar to those of the first episode. These resolved within one day of stopping ginkgo. A further case describes an electrical storm in a 72-year-old man with ischaemic cardiomyopathy and who had an implantable cardioverter defibrillator (ICD).[17] The man had been taking a standardised Gb extract (120mg daily) for tinnitus for three weeks and experienced several episodes of dizziness. His ICD device revealed that he had experienced 1,440 episodes of sustained ventricular tachycardia over the previous four months, with a substantial proportion occurring in the previous ten days. The man stopped taking Gb and his condition improved markedly within days. Ventricular premature contractions have also been reported in a 37-year-old woman who had been taking Gb 180mg/day (no further product details given) for 5 months and who had undergone a surgical procedure.[18]

Systematic reviews (e.g. Birks et al, 2009[19]) of randomised clinical trials of Gb extracts typically report that there is no difference in the overall frequency of reported adverse reactions among participants receiving ginkgo preparations versus placebo. Interestingly, the Cochrane systematic review and meta-analysis of ginkgo preparations for cognitive impairment and dementia found that the adverse event dizziness was reported significantly *less* frequently for high doses (>200mg special extract daily) of *Ginkgo biloba* than for placebo, although this analysis was based on data from only two randomised clinical trials.[19]

Preclinical studies give conflicting results regarding the effects of *Ginkgo biloba* and its constituents on cardiac rhythm: both pro- and anti-arrhythmic effects have been reported in different animal models. For example, several experimental studies describe effects of *Ginkgo biloba* and/or its constituents on action potential duration and cationic currents in rodent ventricular myocytes.[20,21] Other studies have reported positive chronotropic and inotropic effects for Gb extract and certain constituents in rat-isolated atria, suggesting the potential to induce atrial arrhythmias.[22] Anti-arrhythmic effects have been described in studies in isolated guinea-pig ventricular myocytes, which showed that Gb extract and the constituent ginkgolide can prevent ischaemic arrhythmias and have an antiarrhythmic effect via inhibition of potassium and calcium ion currents.[23] Earlier studies reported a concentration-dependent antiarrhythmic effect for the Gb extract EGb-761 on reperfusion-induced arrhythmias in isolated rat hearts.[24]

Discussion and conclusion

A total of 162 reports of cardiac arrhythmias associated with *Ginkgo biloba* use was identified in VigiBase for this signal review. The reaction start date was during the last five years for at least one third of the reports. The few published case reports appeared between 2002 and 2013, and the signal has not otherwise been published, so the possibility of notoriety or publicity bias (a type of selection bias relating to the greater likelihood of a case being reported if the person had been exposed to a drug known, thought, or likely to cause the adverse event of interest[25]) is likely to be small.

The 162 reports came from 18 countries. Where reports are received from several countries, this can strengthen the likelihood of there being a causal association. Of note is that this extract from VigiBase

did not contain any reports from China; this is unusual given the use of *Ginkgo biloba* in traditional Chinese medicine for thousands of years.[1] The absence of reports from China could, in part, reflect different indications and patterns of use of Gb there, or different susceptibility to this particular type of ADR, but is likely to be due to differences in identifying and/or reporting ADRs in China for this category of products/preparations.[26]

It is important to note that this combination (*Ginkgo biloba* and cardiac arrhythmia) was initially identified as a *potential* signal during a joint signal detection sprint involving the UMC and the Netherlands Pharmacovigilance Centre Lareb, with a focus on finding safety concerns reported by patients.[27] The assessment described here was a manual review of cases, and focussed particularly on those with a higher (>= 0.75) completeness score.

Disproportionality analysis conducted using VigiLyze indicates that there are *fewer* reports than expected, based on the overall reporting for *Ginkgo biloba* and the overall reporting for cardiac arrhythmias. Subgroup analyses in VigiLyze do not reveal disproportionalities for any individual countries or age groups or other variables (for individuals aged 18-44 years, there are 26 reports versus 15 expected, but this is not statistically significant and could reflect random variability). However, disproportionality analysis for *Ginkgo biloba* and 'palpitations', the most commonly reported PT (Preferred Term) for ginkgo in the cardiac arrhythmias SMQ, revealed 67 reports on palpitations compared to 38 expected and thus gives a (marginally) positive IC_{025} (information component; IC_{025} is the lower end of the 95% credibility interval for the IC) value (0.4; analysis conducted 17 January 2020).

It is not known what impact the under-reporting of any ADRs associated with *Ginkgo biloba* from China (and, possibly, some other countries) has had on the disproportionality analyses. However, unless a substantial proportion of these 'missing' ADRs for *Ginkgo biloba* relate to cardiac arrhythmias, accounting for a large number of 'missing' ADRs associated with *Ginkgo biloba* would likely result in this combination having even fewer reports than expected. Nevertheless, disproportionality analysis based solely on aggregated numbers of reports can overlook possible signals.[28]

The 162 reports related to around 30 different proprietary Gb products, and 17% of the reports did not identify a specific manufacturer's product, describing ginkgo in generic terms only. At least some of the proprietary product names may relate to the same extract of *Ginkgo biloba* marketed under different names in different countries. Nevertheless, the range of products implicated strengthens the likelihood that this is, indeed, a signal. Similarly, dose and dosage information was often incomplete, or unclear; where provided, doses and dosages were typically within, or lower than, the recommended range for Gb leaf extracts.

Several of the proprietary products have a well-established use or other marketing authorisations and, therefore, are required to comply with pharmaceutical quality standards. As a substantial proportion of the reports relate to these 'authorised' Gb products, this *may* strengthen the likelihood that, if there is a causal relationship, the reaction is related to the phytochemical constituents of *Ginkgo biloba*, rather than to constituents that are present because of adulteration in the supply chain. However, poor quality, including adulteration, of Gb-containing products marketed as 'food/dietary supplements' sold on European and other markets is well documented,[9,29,30] and the possibility that this problem is relevant to some of the cases discussed here cannot be excluded.

It is also notable, and of concern, that one case narrative revealed that the patient was taking a 'dietary supplement' sourced from the USA that contained Gb leaf extract and vinpocetine 5 mg; this information was only evident from the case narrative and vinpocetine was not listed on the case report as a drug of exposure. Vinpocetine is a synthetic derivative of apovincamine, a vinca alkaloid obtained from the leaves of the lesser periwinkle *Vinca minor* L. Products containing vinpocetine, with or without ginkgo, are promoted as dietary supplements for, e.g. *"supporting healthy brain function"*, but there is a lack of robust clinical evidence to support these claims.[31]

For all reports where Gb was the sole suspect drug (n=92), there were 46 cases with dechallenge information and, of those, 39 had a positive dechallenge. Among the 25 reports with a high completeness score (>=0.75), Gb was the sole suspect drug for 20 reports; dechallenge information was documented for 14 of these cases and, all

information considered, there was evidence that dechallenge was positive. For most of this subset of reports, the specified time to onset of the reactions was within days. Two of the reports (both from non-health-professionals) provided some rechallenge information. For one, the case narrative states that the patient reported a positive rechallenge four times. The other report indicates rechallenge within a month of stopping Gb and after the reaction (palpitations) had resolved; the outcome is not entirely clear on the report, but appears to indicate that the reactions were resolved/resolving. Three other reports state that rechallenge was performed, but the outcome is stated as unknown.

Although positive dechallenge (and, more so, positive rechallenge) can indicate a causal relationship, in some cases, concomitantly used drugs are indicative of a pre-existing cardiac disorder, and for some cases, information on medical history is lacking. Pre-existing arrhythmias may cause a wide range of symptoms, including tinnitus (which was the reason for use of ginkgo in 18 of the 162 reports), so confounding by indication cannot be excluded. For example, with reference to the total number of reports, other medicines most frequently co-reported included acetylsalicylic acid, which could be being taken for prophylaxis of cardiac events in patients at risk, and levothyroxine, indicating thyroid disease, which can be a risk factor for cardia arrhythmias. Also, one of the 14 reports (Table 4, case 4) stated that the patient concerned was taking acenocoumarol for atrial fibrillation (start date not given), began taking Gb leaf extract for tinnitus, and experienced tachycardia, nausea and vomiting within 6-7 days.

Literature on the association between *Ginkgo biloba* and cardiac arrhythmias in humans comprises a small number of case reports, at least one of which is included in the VigiBase reports. There is limited and, in part, conflicting information from preclinical studies, in that different studies have described pro- and, more usually, anti-arrhythmic effects for Gb extracts.[20-24] In general terms, however, some medicines with anti-arrhythmic effects can have pro-arrhythmic complications;[11] whether this applies to *Ginkgo biloba* requires investigation. Like other herbal medicines, ginkgo extracts are complex chemical mixtures. Two important groups of compounds found in ginkgo leaf extracts are the ginkgo flavonoid glycosides and the terpene lactones, but other chemical constituents may contribute to the pharmacological (and toxicological) effects of ginkgo preparations.

The key limitation of this analysis relates to the possibility of confounding by indication and the contribution(s) of possible underlying co-morbidities to the adverse reactions experienced. Another limitation is that the search in VigiBase using the substance *Ginkgo biloba* identified reports relating to single-ingredient Gb preparations only; therefore, reports of cardiac arrhythmias occurring in patients who took multi-ingredient products containing ginkgo have not been identified and assessed. Also, it is possible that patients could have described non-cardiac symptoms, such as dizziness, the PT for which is not included in the MedDRA SMQ (broad) for cardiac arrhythmias. Analysis of VigiBase reports for the PT dizziness and substance *Ginkgo biloba* could be part of further investigation in association with this signal.

In conclusion, although a mechanism by which *Ginkgo biloba* could induce cardiac arrhythmias is not fully elucidated, the number and nature of the cases in VigiBase and the additional published case reports suggest a signal between *Ginkgo biloba* and cardiac arrhythmias.

References

1. Isah T. Rethinking *Ginkgo biloba* L.: Medicinal uses and conservation. Pharmacogn Rev 2015;9(18):140–148. doi: 10.4103/0973-7847.162137
2. Barnes J, Anderson LA, Phillipson JD. Herbal Medicines. 3rd ed. London: Pharmaceutical Press, 2007.
3. Health Canada. Natural Health Product. GINKGO - *GINKGO BILOBA* (31 July, 2018). http://webprod.hc-sc.gc.ca/nhpid-bdipsn/atReq.do?atid=ginkgo.biloba&lang=eng
4. European Medicines Agency. 28 January 2015. EMA/HMPC/321097/2012 Committee on Herbal Medicinal Products (HMPC). European Union herbal monograph on *Ginkgo biloba* L., folium. Available at: https://www.ema.europa.eu/en/documents/herbal-monograph/final-european-union-herbal-monograph-ginkgo-biloba-l-folium_en.pdf [last accessed December 5, 2019]

5. Medicines and Healthcare products Regulatory Agency. Guidance. Herbal medicines granted a traditional herbal registration. Updated 13 September 2019. Available at: https://www.gov.uk/government/publications/herbal-medicines-granted-a-traditional-herbal-registration-thr/herbal-medicines-granted-a-traditional-herbal-registration [last accessed 5 December 2019]
6. British Pharmacopoeia. Vol. IV. London: Medicines and Healthcare products Regulatory Agency; 2019.
7. Kressmann S. Pharmaceutical quality of different *Ginkgo biloba* brands. J Pharm Pharmacol 2002;54:661-669.
8. Kressmann S, Biber A, Wonneman M, Schug B, Blume HH, Muller WE. Influence of pharmaceutical quality on the bioavailability of active components from *Ginkgo biloba* preparations. J Pharm Pharmacol 2002;45(11):1507-1514.
9. Czigle S, Tóth J, Jedlinszki N, Háznagy-Radnai E, Csupor D, Tekeľová D. *Ginkgo biloba* Food supplements on the European market - adulteration patterns revealed by quality control of selected samples. Planta Med 2018;84(6-07):475-482. doi: 10.1055/a-0581-5203
10. Brayfield A (ed). Martindale: The Complete Drug Reference (39th edition). London: Pharmaceutical Press (Publications division of the Royal Pharmaceutical Society of Great Britain), 2017.
11. Doig JC. Drug-induced cardiac arrhythmias. Incidence, prevention and management. Drug Safety 1997;17(4):265-275.
12. Health Products Regulatory Authority. Summary of Product Characteristics. Ginkgoforce Memory & Circulation Ginkgo tablets (Bioforce) Available at: https://www.hpra.ie/img/uploaded/swedocuments/LicenseSPC_TR0725-016-001_28102015143058.pdf [last accessed December 18, 2019]
13. European Medicines Agency. 28 January 2014. EMA/HMPC/321095/2012 Committee on Herbal Medicinal Products (HMPC). Assessment report on *Ginkgo biloba* L., folium. Available at: https://www.ema.europa.eu/en/documents/herbal-report/final-assessment-report-ginkgo-biloba-l-folium_en.pdf [last accessed 5 December 2019]
14. De Feudis FV. *Ginkgo biloba* extract EGb761. From chemistry to the clinic. Wiesbaden: Ullstein Medical, 1998
15. Russo V, Rago A, Russo GM, Calabro R, Nigro G. *Ginkgo biloba*: an ancient tree with new arrhythmic side effects. J Postgrad Med 2011; 57(3):221
16. Cianfrocca C, Pelliccia F, Auriti A, Santini M. *Ginkgo biloba*-induced frequent ventricular arrhythmia. Ital Heart J 2002; 3(11):689-691
17. Pfister O, Sticherling C, Schaer B, Osswald S. Electrical storm caused by complementary medication with *Ginkgo biloba* extract. Am J Med 2008; 121(11):e3-e4
18. Dube SK, Mahajan C, Prabhakar H, Singh GP. *Ginkgo biloba* may cause asymptomatic ventricular premature contractions! Indian J Anaesth 2013; 57(6):633-634
19. Birks J, Grimley Evans J. *Ginkgo biloba* for cognitive impairment and dementia. Cochrane Database of Systematic Reviews 2009, Issue 1. Art. No.: CD003120. DOI: 10.1002/14651858.CD003120.pub3.
20. Satoh H. Comparative Electropharmacological Actions of Some Constituents from Ginkgo biloba Extract in Guinea-pig Ventricular Cardiomyocytes. Evid Based Complement Alternat Med 2004; 1(3):277-284
21. Satoh H, Nishida S. Electropharmacological actions of *Ginkgo biloba* extract on vascular smooth and heart muscles. Clin Chim Acta 2004; 342(1-2):13-22
22. Kubota Y, Umegaki K, Tanaka N et al. Safety of dietary supplements: chronotropic and inotropic effects on isolated rat atria. Biol Pharm Bull 2002; 25(2):197-200
23. Zhao X, Yao H, Yin HL et al. *Ginkgo biloba* extract and ginkgolide antiarrhythmic potential by targeting hERG and ICa-L channel. J Pharmacol Sci 2013; 123(4):318-327
24. Tosaki A, Droy-Lefaix MT, Pali T, Das DK. Effects of SOD, catalase, and a novel antiarrhythmic drug, EGB 761, on reperfusion-induced arrhythmias in isolated rat hearts. Free Radical Biology & Medicine 1993;14(4):361-70
25. Pariente A, Gregoire F, Fourrier-Reglat A,

Haramburu F, Moore N. Impact of safety alerts on measures of disproportionality in spontaneous reporting databases: the notoriety bias. Drug Safety 2007;30(10):891–8

26. Van Hunsel F, van de Koppel S, Skalli S, Kuemmerle A, Teng L, Wang J-B, Barnes J. Analysis of hepatobiliary disorder reports associated with the use of herbal medicines in the global suspected ADR database VigiBase. Front Pharmacol 2019 https://doi.org/10.3389/fphar.2019.01326
27. Watson S, Chandler RE, Taavola H, Härmark L, Grundmark B, Zekarias A, Star K, van Hunsel F. Safety concerns reported by patients identified in a collaborative signal detection workshop using VigiBase: results and reflections from Lareb and Uppsala Monitoring Centre. Drug Safety 2018;41(2):203-212. doi: 10.1007/s40264-017-0594-2
28. Caster O, Juhlin K, Watson S, Norén N. Improved statistical signal detection in pharmacovigilance by combining multiple strength-of-evidence aspects in vigiRank. Retrospective evaluation against emerging safety signals. Drug Safety 2014;37:617–628
29. Avula B, Sagi S, Gafner S, Upton R, Wang YH, Wang M, Khan IA. Identification of *Ginkgo biloba* supplements adulteration using high performance thin layer chromatography and ultra-high performance liquid chromatography-diode array detector-quadrupole time of flight-mass spectrometry. Anal Bioanal Chem 2015;407(25):7733-46
30. Gafner S. Adulteration of *Ginkgo biloba* leaf extract. Botanical Adulterants Bulletin 2018;Jan:1-8 [available at: http://cms.herbalgram.org/BAP/BAB/GinkgoBulletin.html?ts=1516303084&signature=92fcc61fc4a8021c668efdf913c214e1; last accessed January 20, 2020]
31. Szatmári S, Whitehouse P. Vinpocetine for cognitive impairment and dementia. Cochrane Database of Systematic Reviews 2003, Issue 1. Art. No.: CD003119. DOI: 10.1002/14651858.CD003119.

Table 3. Characteristics of VigiBase reports identified using the SMQ (broad) for cardiac arrhythmias and substance *Ginkgo biloba* (dataset date: 11 September 2019) with a completeness score of >= 0.75, Ginkgo biloba as sole suspect drug, and a positive dechallenge (n=14)

Case	Sex, age	Serious	Year of Gb use and ADR	Gb product** and daily dose	Reason for use of Gb	Concomitant medicines	Treatment duration	Reactions (MedDRA preferred term)	Time to onset (from start of medication)	Outcome
1	m, 74	Yes	2015	Gb P1 120mg	Memory impairment	amlodipine simvastatin	8 days	Syncope Dizziness Nausea	8 days	Recovered
2	f, 75	Yes	2015-16	Gb P2 60mg and vinpocetine 5mg	Vitamin supplementation		NK	Atrial fibrillation Off label use	11 months	Recovered Unknown
3	f, 67	Yes	2018-18	Gb P3a 120mg daily	Light headedness		NK	Dizziness Circulatory collapse Syncope	unclear, but < 4 weeks	Recovered Recovered Recovered
4	f, 85	Yes	2014	Gb P4 3mL	Tinnitus	acenocoumarol	7 days	Tachycardia Vomiting Nausea	6 days for N&V; 7 days for tachycardia	Recovered Recovered Recovered
5	m, 72	Yes	2006-07	Gb P5 (n/s) 120mg	Tinnitus	acetylsalicylic acid bisoprolol ramipril simvastatin torasemide molsidomine	21 days stated in ICSR but does not match start/end dates	Ventricular tachycardia Dizziness Epigastric discomfort	NK	Recovered Recovered Recovered
6	m, 37	No	2017	Gb P3b 240mg	Prophylaxis	Hypericum perforatum (St John's wort) dry extract	3 days	Arrhythmia	NK	Recovering
7	m, 76	No	2018-19	Gb P6 120mg	Cognitive disorder		2 months	Chills Heart rate decreased Blood pressure decreased	NK	Recovered Recovered Recovered

8	f, 45	No	2015	Gb P7a two ampoules (17.5mg/5mL IV/IM)	Sensorineural hearing loss, unspecified		one day	Palpitations Dizziness Anxiety	within one day	Recovered Recovered Recovered
9	f, 80	No	2019	Gb P8 unclear	Tinnitus		one day	Dizziness Blood pressure decreased Palpitations	within one day	Recovered Recovered Recovered
10	f, 41	No	2010	Gb P9 160mg	Raynaud's syndrome		NK	Palpitations Headache	within one day	Recovered Recovered
11	m, 62	No	2014	Gb P9 120mg	Claudication intermittent		8 days	Bradycardia	8 days	Recovered
12	f, 62	No	2017	Gb P7b 80mg	Sudden idiopathic hearing loss		4 days	Palpitations	one day	Recovered
13	m, 36	No	2018	Gb P3a 240mg	Tinnitus		11 days	Palpitations	8 days	Recovered
14	f, 65	n/s	2002	Gb P3a 120mg	Heat stroke and sunstroke		49 days	Somnolence Insomnia Palpitations Cardiac fibrillation Headache Tremor	21 days	Not recovered* Not recovered* Not recovered* Not recovered* Not recovered* Not recovered*

> Case 7: ICSR states rechallenge was done, but no rechallenge outcome is stated.

> Case 8: ICSR states oral administration for Gb, but the Gb product listed is an injectable formulation in ampoules; ICSR states rechallenge was done, but no rechallenge outcome is given.

> Case 9: Dose is stated as half a tablet, but formulation is film tablets, which are not intended for breaking.

> Case 10: Patient report; the summary of the case narrative states that the dose was reduced and that the patient reported a positive rechallenge on four occasions.

> Case 11: Case narrative states that the patient's medical history indicates type-2 diabetes mellitus and femoral arterial occlusion.

** The ICSR dechallenge information states that the dechallenge outcome was resolved/resolving.*

*** Each number relates to a different proprietary product name, or a generic name where no specific product was given in the report.*

SIGNAL

WHO defines a signal as:

"Reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously". An additional note states: "Usually more than one report is required to generate a signal, depending on the seriousness of the event and the quality of the information".*

A signal is therefore a hypothesis together with supporting data and arguments. A signal is not only uncertain but also preliminary in nature: the situation may change substantially over time one way or another as more information is gathered. A signal may also provide further documentation of a known association of a drug with an ADR, for example: information on the range of severity of the reaction; the outcome; postulating a mechanism; indicating an "at risk" group; a dose range which might be more suspect; or suggesting a pharmaceutical group effect or a lack of such an effect by a particular drug.

Signals communicated by UMC are derived from VigiBase, the WHO global database of individual case safety reports. This database contains summaries of individual case safety reports of suspected adverse drug reactions, submitted by national pharmacovigilance centres (NCs) that are members of the WHO Programme for International Drug Monitoring. More information regarding the status of this data, its limitations and proper use, is provided in the Caveat on the last page of this document.

VigiBase is periodically screened to identify drug-ADR combinations that are unknown or incompletely documented. Combinations of such interest that they should be further reviewed clinically are sent to members of the Signal Review Panel for in-depth assessment. The Signal Review Panel consists of experienced international scientists and clinicians, usually affiliated with a governmental or an academic institution. The expert investigates the clinical evidence for the reaction being related to the suspected drug.

The topics discussed in the signals represent varying levels of suspicion. Signals contains hypotheses, primarily intended as information for the national regulatory authorities. They may consider the need for possible action, such as further evaluation of source data, or conducting a study for testing a hypothesis.

The distribution of signals is currently restricted to NCs, regulatory authority staff and their advisers, participating in the WHO Programme. Signals are sent to the pharmaceutical companies when they can be identified as uniquely responsible for the drug concerned. UMC does not take responsibility for contacting all market authorisation holders. As a step towards increased transparency, since 2012 UMC signals are subsequently published in the WHO Pharmaceuticals Newsletter.

National regulatory authorities and NCs are responsible for deciding on action in their countries, including communicating the information to health professionals, and the responsible market authorisation holders, within their jurisdiction.

In order to further debate, we encourage all readers of signals to comment on individual topics.

* Edwards I.R, Biriell C. Harmonisation in pharmacovigilance. Drug Safety 1994;10:93-102.

Responses from industry

Signals on products under patent are submitted to patent holders for comments. Responses from industry are unedited. The calculations, analysis and conclusions are theirs, and should be given serious but critical consideration in the same way as any scientific document. The WHO and UMC are not responsible for their findings, but may occasionally comment on them.

WHO Collaborating Centre for International Drug Monitoring
Box 1051, S-751 40, Uppsala, Sweden
Tel: +46 18 65 60 60 www.who-umc.org

Uppsala Monitoring Centre

Caveat Document

Statement of reservations, limitations and conditions relating to data released from VigiBase, the WHO global database of individual case safety reports (ICSRs). Understanding and accepting the content of this document are formal conditions for the use of VigiBase data.

Uppsala Monitoring Centre (UMC) in its role as the World Health Organization (WHO) Collaborating Centre for International Drug Monitoring receives reports of suspected adverse reactions to medicinal products from National Centres in countries participating in the WHO Programme for International Drug Monitoring. The information is stored in VigiBase, the WHO global database of individual case safety reports (ICSRs). It is important to understand the limitations and qualifications that apply to this information and its use.

Tentative and variable nature of the data

Uncertainty: The reports submitted to UMC generally describe no more than suspicions which have arisen from observation of an unexpected or unwanted event. In most instances it cannot be proven that a specific medicinal product is the cause of an event, rather than, for example, underlying illness or other concomitant medication.

Variability of source: Reports submitted to national centres come from both regulated and voluntary sources. Practice varies: some national centres accept reports only from medical practitioners; others from a broader range of reporters, including patients, some include reports from pharmaceutical companies.

Contingent influences: The volume of reports for a particular medicinal product may be influenced by the extent of use of the product, publicity, the nature of the adverse effects and other factors.

No prevalence data: No information is provided on the number of patients exposed to the product, and only a small part of the reactions occurring are reported.

Time to VigiBase: Some national centres make an assessment of the likelihood that a medicinal product caused the suspected reaction, while others do not. Time from receipt of an ICSR by a national centre until submission to UMC varies from country to country. Information obtained from UMC may therefore differ from that obtained directly from national centres.

For these reasons, interpretations of adverse effect data, and particularly those based on comparisons between medicinal products, may be misleading. The data comes from a variety of sources and the likelihood of a causal relationship varies across reports. Any use of VigiBase data must take these significant variables into account.

Prohibited use of VigiBase Data includes, but is not limited to:

- patient identification or patient targeting
- identification, profiling or targeting of general practitioners or practice

Any publication, in whole or in part, of information obtained from VigiBase must include a statement:

(i) recording 'VigiBase, the WHO global database of individual case safety reports (ICSRs)' as the source of the information

(ii) explaining that the information comes from a variety of sources, and the probability that the suspected adverse effect is drug-related is not the same in all cases

(iii) affirming that the information does not represent the opinion of the UMC or the World Health Organization.

Omission of this statement may exclude the responsible person or organization from receiving further information from VigiBase.

UMC may, in its sole discretion, provide further instructions to the user, responsible person and/or organization in addition to those specified in this statement and the user, responsible person and/or organization undertakes to comply with all such instructions.

WHO Collaborating Centre for International Drug Monitoring
Box 1051, S-751 40, Uppsala, Sweden
Tel: +46 18 65 60 60 www.who-umc.org