Original Article

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Assessment of health claims, content, and safety of herbal supplements containing *Ginkgo biloba*

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Abstract

Background: European Regulation 1924/2006 states that all health claims made on foods need to be substantiated scientifically.
Objective: To apply the PASSCLAIM criteria for the scientific substantiation of health claims on foods to herbal supplements containing *Ginkgo biloba*. Evaluation of three selected claimed health effects for *G. biloba* (improvement of blood circulation, improvement of symptoms of old age, and improvement of memory) was achieved through review of publicly available scientific data. A total of 35 human intervention studies were evaluated. Commercially available products claimed to contain mainly *G. biloba* ($N=29$) were randomly sampled in the Netherlands and analyzed for their content on ginkgo extract. Also, a toxicological risk assessment was performed.
Results: The three selected health claims investigated could not be substantiated. This was mainly because of a lack of data from studies in healthy volunteers. In most studies results performed with a 24% standardized *G. biloba* extract were described. However, our chemical analysis showed that 25 of the 29 sampled products did not contain the required minimum 24% standardized extract. Moreover, in most preparations the content of substances typical for *G. biloba* did not conform to what was declared on the label. Since toxicity data for *G. biloba* are very limited, a safety limit could not be established.
Conclusions: Evidence is lacking for three health claims of herbal products with *G. biloba*. Neither safety nor efficacy can be guaranteed at the recommended daily dose. The multidisciplinary approach described in this paper provides good insight into issues that are relevant for the evaluation of health claims for herbal food supplements.

Keywords: *Ginkgo biloba*; *health claims*; *substantiation*; *botanicals*; *content*; *safety*

Received: 16 April 2010; Revised: 27 August 2010; Accepted: 1 September 2010; Published: 30 September 2010

The European Regulation 1924/2006 on nutrition and health claims made on foods states that health claims made on foods, including *functional foods* and *dietary supplements*, have to be scientifically substantiated (1). Articles 5.1.a and 6 state that generally accepted scientific evidence is needed for this. An overview of the new European Regulation for health claims has recently been published (2–4). In short, reduction of disease risk claims and claims referring to children's development and health are accounted for in Articles 14 and 13.5, and require to be reviewed separately by the European Food Safety Authority (EFSA). A complete dossier containing details of all studies pertinent to the proposed claim is required for an application under Article 14 of the Health Claim Regulation and should be supplied to EFSA via one of the EC member states. EFSA will assess these health claims on a case-by-case basis, leading to an authorization by the European Commission (2, 4, 5). Health claims other than Article 14 and 13.5 claims, the so-called 'generic claims' are accounted for in Article 13.1. These claims are based on 'generally accepted scientific evidence.' For these 'generic claims,' no complete dossier per claim is required (6), and similar applications can be evaluated in batches. The European Commission aimed to adopt a Community list of permitted claims by 31 January 2010, but this

deadline was not achieved owing to the very high number of proposals for health claims submitted (2).

To help manufacturers with their preparation and submission of Article 14 health claims (reduction of disease risk claims and claims referring to children's development and health) and 13.5 health claims (based on new scientific developments), in July 2007, EFSA published a guidance document 'Scientific and technical guidance for the preparation and presentations of the application for authorization of a health claim' (2, 7). The document specifies what information manufacturers have to include in their application, in particular, with regard to the scientific data that is needed (7). Criteria for the scientific substantiation of health claims on foods were developed from 2001 to 2005 in the EU-sponsored PASSCLAIM project (8, 9) and these were taken into account in setting down the EFSA guidance. According to these criteria, a comprehensive review of human studies on the relationship of the food or nutrient to the claimed health effect is systematically and transparently undertaken before a decision can be made on the claim. Human studies are considered pertinent to the claim. Data of animal or *in vitro* studies can be used as supporting evidence. The totality of scientific data needs to be included and then the evidence needs to be weighed. Blinded placebo-controlled trials in healthy human samples carry most weight.

The project described in this paper applies the PASSCLAIM criteria for scientific substantiation of health claims on foods to herbal supplements containing *Ginkgo biloba*, which were used as a model. This paper is largely based on a RIVM report in Dutch from 2007 which was posted on the RIVM website only (http://www.rivm.nl/bibliotheek/rapporten/320106001.html). Upon many requests to have this report also available in the English scientific literature, we have written the current version. We have not changed the conclusions of the original report, but we have updated the literature and developments where applicable.

G. biloba originates from the *G. biloba* tree. For herbal supplements, usually a *G. Biloba* leaf extract is used, although the seeds can also be used in dietary supplements. However, in the scientific literature, only effects of the standardized leaf extract are supported (10). A standardized leaf extract (GB-STE; extract of dry *G. biloba* leaves with acetone and water) contains 22–27% of flavone glycosides and 5–7% of terpene lactones, with 2.8–3.4% of ginkgolide A, B, and C, and 2.6–3.2% of bilobalide (Table 1). The concentration of ginkgolic acid (GAS) needs to be below 5 ppm in a GB-STE (11). The two most considered GB-STEs in studies are EGb761 (12) and LI 1370. A WHO monograph indicates the use of *G. biloba* extract for symptomatic treatment of mild to moderate cerebrovascular insufficiency, improvement of pain-free walking distance in patients with peripheral arterial occlusive disease (PAOD), and treatment of inner ear problems like tinnitus (11). These are not health claims but medical claims, which are prohibited on foods and food products (1). In Germany, Commission E has approved the use of *G. biloba* for the same three indications (13).

Table 1. Substances typical for *Ginkgo biloba*

Substance	Specification of substance	Included in standardized leaf extract (e.g. EGb761 or LI1370)
Flavone glycosides	Quercetin Kaempferol Isorhamnetin	22–27% flavone glycosides
Terpene lactones	Ginkgolide A Gingkolide B Ginkgoblide C Bilobalide	5–7% terpene lactones (2.8–3.4% ginkgolide A, B, C, 2.6–3.2% bilobalide)
Ginkgolic acid		Below 5 ppm

A random check on the existence and quality of files for substantiation of claims on herbal supplements of the Dutch Food and Consumer Product Safety Authority in 2003 showed that the claim substantiation process was unsatisfactory for herbal supplements in general (14). The outcome of that study resulted in this evaluation study. The aims of the current study were threefold: (a) analysis of herbal supplements containing *G. biloba* ($N = 29$) randomly sampled in Dutch shops by the Dutch Food and Consumer Product Safety Authority (VWA); (b) scientific substantiation of three selected claimed health effects of *G. biloba* (including effective dose of substances typical for *G. biloba*, if available) through an overview of publicly available, scientific data; and (c) risk assessment of *G. biloba* and, if possible, derivation of a level for safe use.

Methods

Product analysis

In August and September 2005, 29 *G. biloba* food supplements were sampled in the Netherlands. An inventory was made of the indications for use as stated on the label. Claims for a positive influence on memory and/or concentration or improvement of blood circulation were most frequently mentioned. Only four products didn't have any claims on the label (see Table 2).

To determine the degree to which the content of the substances typical for *G. biloba* were analog to what was declared on the label, the main components of *G. biloba*, flavone glycosides (also known as flavonoids), and terpene lactones were analyzed. Flavone glycosides were analyzed by using high-pressure liquid chromatography (HPLC) according to the method of Mesbah et al. (15), but with an extra hydrolysis step added to the pretreatment step. Without this hydrolysis step, no flavonoids were detected in the samples. Terpene lactones were analyzed using

Citation: Food & Nutrition Research 2010, **54**: 5221 - DOI: 10.3402/fnr.v54i0.5221

Table 2. Analytical data and claims on products investigated

Product No.	Declaration on the label	Recommended daily dose	Analyzed amount of terpene lactones (mg/daily dose)	Meets criterion for terpene lactone levels in standardized extract? (6–17 mg)	Analyzed amount of flavonoids (mg/daily dose)	Meets criterion for flavonoid levels in standardized extract? (24–65 mg)	Meets criteria for terpene lactones and flavonoid levels in standardized extract (based on daily dose)	Claims present on the label
7966	*Ginkgo biloba* extract-24% 180 mg/capsule	1 × 1 capsule	10.1	Yes	38.4	Yes	Yes	Yes
7967	*Ginkgo biloba* extract (24%)	1 × 1–2 capsules	2.8	No	12.9	Yes, only at maximum dose	No	Yes
7968	*Ginkgo biloba* extract (24% Ginkgo flavoglysides + 6% terpene lactones) 60 mg/capsule	1 × 2 capsules	4.5	Yes	16.1	Yes	Yes	Yes
7969	*Ginkgo biloba*	3 × 2 capsules	0.9	No	0.3	No	No	Yes
7970	*Ginkgo biloba* folia 80 mg/tablet	1 × 1 capsule	1.3	No	3.5	No	No	Yes
7971	Extract from fresh leaves of *Ginkgo biloba* (7.5% flavoglycosides) 40.5 mg/coated tablet	3 × 1–2 tablets	1.4	Yes, only at maximum dose	4.0	No	No	Yes
7972	*Ginkgo biloba* extract. Standardized extract at least 24% ginkgosides + 6% terpene lactones 120 mg/2 capsules	2 × 1 capsule	5.9	Yes	12.4	Yes	Yes	No
7973	*Ginkgo biloba* 96 mg/capsule	3 × 1 capsule	0.3	No	2.3	No	No	Yes
7974	*Ginkgo biloba*, 50% 100 mg/tablet	3 × 1 tablet	0.3	No	0.9	No	No	Yes
7975	Standardized *Ginkgo biloba* extract (50:1), 24% ginkgo flavoglycosides of 3,000 mg fresh plant 60 mg/capsule	1 × 1–3 capsules	3.5	Yes, only at maximum dose	13.1	Yes, only at maximum dose	Yes, only at maximum dose	No
7976	*Ginkgo biloba*	3 × 10–20 droplets	0.5	Yes	NA	NA	Unknown	Yes

Table 2 (*Continued*)

Product No.	Declaration on the label	Recommended daily dose	Analyzed amount of terpene lactones (mg/daily dose)	Meets criterion for terpene lactone levels in standardized extract? (6–17 mg)	Analyzed amount of flavonoids (mg/daily dose)	Meets criterion for flavonoid levels in standardized extract? (24–65 mg)	Meets criteria for terpene lactones and flavonoid levels in standardized extract (based on daily dose)	Claims present on the label
7977	*Ginkgo biloba* extract. Standardized on 24% flavoglycosides and 6% terpene lactones of 10,000 mg dried leave 200 mg/capsule	1 × 1 capsule	3.3	No	45.4	Yes	No	Yes
7978	*Ginkgo biloba* leaf extract (50:1 extract with 24% ginkgo flavon glycosides) 60 mg/caps	1–3 × 1 capsule	6.2	Yes	20.1	Yes, only at maximum dose	Yes, only at maximum dose	Yes
7979	*Ginkgo biloba* 26 mg/tablet	3 × 1 tablet	3.0	Yes	7.0	No	No	Yes
7980	*Ginkgo biloba*	2–4 × 25 droplets	0.1	No	NA	NA	No	Yes
7981	*Ginkgo biloba* standard extract (24% ginkgo flavoglycosides, 6% terpene lactones) 80 mg/tablet	1 × 1 tablet	1.8	No	20.7	No	No	Yes
7982	100% *Ginkgo biloba* concentrate	3–4 × 20–30 droplets	0.3	Yes, only at maximum dose	NA	NA	Unknown	No
7983	*Ginkgo biloba* folia. (min 24% ginkgoflavon glycosides and 6% ginkgo terpene lactones) 120 mg/3 capsules	3 × 1 capsule	4.4	Yes	10.2	Yes	Yes	No
7984	*Ginkgo biloba* extract (leaf) 250 mg/capsule	3 × 1–2 capsules	2.0	Yes, only at maximum dose	8.0	Yes, only at maximum dose	Yes, only at maximum dose	Yes
7985	100 ml, bevat liquid extract of *Ginkgo biloba* (folia) 40%	30–40 droplets	0.1	No	NA	NA	No	Yes
7986	*Ginkgo biloba* (dries leaf) 250 mg/tablet	3 × 1 tablet	0.8	No	1.9	No	No	Yes
7987	*Ginkgo biloba* (dried leaf, standardised on 24% ginkgo flavon glycosides 14.4 mg and 6% terpenes 3.6 mg) 60 mg/tablet	1–2 × 1 tablet	5.3	Yes, only at maximum dose	16.0	Yes, only at maximum dose	Yes, only at maximum dose	Yes

Table 2 (*Continued*)

Product No.	Declaration on the label	Recommended daily dose	Analyzed amount of terpene lactones (mg/daily dose)	Meets criterion for terpene lactone levels in standardized extract? (6–17 mg)	Analyzed amount of flavonoids (mg/daily dose)	Meets criterion for flavonoid levels in standardized extract? (24–65 mg)	Meets criteria for terpene lactones and flavonoid levels in standardized extract (based on daily dose)	Claims present on the label
7988	*Ginkgo biloba* (leaf) standardized on 0.5% flavonoides 250 mg/capsule	3 × 1 capsule	1.1	No	2.1	No	No	Yes
7989	*Ginkgo biloba* (24% extract: 24% flavoglycosides and 6% terpenes) 60 mg/capsule	3 × 1 capsule	4.8	Yes	15.1	Yes	Yes	Yes
7990	*Ginkgo biloba* (24% extract) 50 mg/capsule	1 × 1 capsule	4.0	No	50.1	Yes	No	Yes
7991	*Ginkgo biloba* extract (24% flavonoiden, 6% terpene lactones) 300 mg/2 capsules	1 × 2 capsule	5.0	Yes	42.9	Yes	Yes	Yes
7992	*Ginkgo biloba* (folia) dried extract (standardized on 24% flavon glycosides / 6% terpene lactones), max 5 ppm ginkgo acids 30 mg/tablet	1 × 1–2 capsules	2.7	No	7.6	No	No	Yes
7993	*Ginkgo biloba* extract 10 mg/tablet	1 × 1–2 tablets	&	No	4.0	No	No	Yes
7994	*Ginkgo biloba* extract (24% flavonoides, 6% terpene lactones) 300 mg/2 capsules	1 × 2 capsules	3.3	Yes	35.3	Yes	Yes	Yes
8410	Extract 24% (9.6 mg flavonoides, 2.4 mg terpene lactones) 40 mg/ tablet	3 × 1 tablet	2.2	Yes	9.0	Yes	Yes	No

Note: NA, not analyzed (method not suitable); &, not present.

HPLC with refractive index-detection (RI), also based on the method of Mesbah et al. (15), but with RI-detection instead of the UV-detection, because UV-detection leads to interfering peaks. Reference material included a standardized 24% extract and Tavonin® (16, 17). The Dutch guideline 'Besluit Geneesmiddelen Wet' (18) states that the amount of *the active substance* present in a pharmaceutical product has to be 90–110% of the declared amount. To prove the presence of a 24% standardized *G. biloba* extract in the products, the amount of bilobalide compared to the total amount of terpene lactones was calculated. A ratio of 39–59% was used as a reference, corresponding to the ratio used in the European Scientific Cooperative On Phytotherapy (ESCOP) monograph (19).

Health claim substantiation

Three commonly encountered claimed health effects for *G. biloba* were selected: improved blood circulation, effects on symptoms of old age, and improved memory. Examples of such claims used are: 'helps for cold hands and feet; improves memory; protects against symptoms of old age; natural memory booster.' Per health effect a literature search was conducted in publicly available, objective scientific data:

- reference and text books and monographs, e.g. ESCOP and WHO (11, 19);
- scientific articles, with the emphasis on human studies, searched via PubMed, Toxline, Cochrane Library, and references from articles, in Dutch and English. Search terms used were: ginkgo; *Ginkgo biloba*; LI 1370; EGb761; meta-analysis; review; randomized controlled trial; viscosity; microcirculation; blood flow; elderly; symptoms of old age; cognition; cognitive function; and memory.

An overview of the available literature per health effect can be found in Table 3, including not only studies in healthy volunteers ($n = 24$), but also some important patient studies ($n = 11$). The PASSCLAIM criteria were applied to assess if the health claims can be supported by the totality of the data and weighing of the evidence (8). The criteria are that the product needs to be characterized and administered in amounts consistent with its intended consumption. Studies should include representative human study groups, have appropriate controls, an adequate study duration, characterized background diets, and monitor compliance of the study group. The target variable should change in a statistically significant way and the change should be biologically meaningful for the target group. Dependent on the quality of the data, per health claim a conclusion was drawn as to the substantiation of the claim with reference to the strengths and weaknesses therein.

Toxicity

Information on toxicity of *G. biloba* was obtained by searching literature databases (Medline, PubMed, Toxline), international documentation (Commission E monograph, ESCOP monograph, Hager's Handbuch, European Medicines Agency – EMEA – information on animal drugs, CBG – College ter Beoordeling van Geneesmiddelen – [Dutch Medicines Evaluation Board] information on drugs, WHO, Herbalgram information, National Toxicology Program – NTP), and the internet. In the Commission E monograph, ESCOP monograph, and Hager's Handbuch, toxicity of the standardized extract EGb 761 is described. The toxicity evaluation in the current evaluation is based on those reports as well as recent NTP studies and recent literature, predominantly case reports, and reports on interaction with frequently/commonly used medication. In addition to *G. biloba* and the GB-STE, data on GAS were considered for evaluation. Because of their toxic properties, the presence of GAS is limited in standardized *G. biloba* preparations to maximum 5 ppm (11). However, in non-standardized *G. biloba* preparations, GAS can be present at higher levels.

Results and discussion

Product analysis

For 16 products, both the detailed content and the recommended dose were declared on the label (see Table 2). For 13 products, the declaration was unclear, e.g. the recommended dose was stated, but the amount of flavonoids and terpene lactones in this dose was not stated in the declaration. Only two of the 29 products met the pharmaceutical guideline (the amount present in the product is 90–110% of the declared amount) for terpene lactones. For flavonoids, seven out of the 29 products met the guideline. Only one product met the guideline for both components. Only four products met the criteria of a ratio of 39–59% (the amount of bilobalide compared to the total amount of terpene lactones). Based on the daily dose and the concentration of terpene lactones and flavonoids found in the products, a dose range of substances typical for *G. biloba* was calculated; 16 products did not meet the dose range for terpene lactones and flavonoids for a 24% standardized extract.

In summary, when the components of herbal supplements were evaluated according to the guideline for pharmaceuticals, that require the presence of 90–110% of the declared amount, one out of 29 *G. biloba* products meets the guideline.[1] The amount of terpene lactones and flavonoids found vary between 27–358% for terpene lactones and between 86–418% for flavonoids.

[1] The guideline for pharmaceuticals (18) was used because no alternative guidelines for herbal supplements were available.

Citation: Food & Nutrition Research 2010, **54**: 5221 - DOI: 10.3402/fnr.v54i0.5221

Table 3. Studies included

Table 3a. Meta-analyses and systematic reviews

Intermediary of health effect	References	Specification *Ginkgo biloba*+dose (PASSCLAIM criterion 1+2E)	Study design+duration (PASSCLAIM criterion 2)	Study population (*N*, age group) (PASSCLAIM criteria 2A+2B)	Information on background diet, matrix and compliance? (PASSCLAIM criteria 2D+2F+2G)
Blood circulation: patient studies					
Intermittent claudication	Nicolai et al. (23)	Standardized *Ginkgo biloba* extract, in most studies EGb761	Meta-analysis; 14 randomized, controlled trials	Patients (18 years and older) with intermittent claudication, stage II according to Fontaine, stages 1–3 according to Rutherford	For some studies information is included
Peripheral arterial occlusive disease (PAOD)	Horsch and Walther (21)	EGb761; daily dose: 120 mg (five studies) or 160 mg (four studies); study period: 1 ×6 weeks, 1 ×3 months, 6 ×6 months	Meta-analysis; 9 clinical trials, randomized, double-blind, placebo-controlled. Total 619 patients criteria: randomized, double-blind, placebo-controlled, clinical studies, oral application form of EGb761, assessment of pain-free walking distance.	Patients with the indication peripheral arterial occlusive disease (PAOD) in stage II according to Fontaine	No information
Intermittent claudication	Pittler and Ernst (22)	*Ginkgo biloba* extract, 3 ×EGb761, other studies GB extract not further specified daily dose: 5 × 120 mg; 3 × 160 mg Study period: 1 ×6 weeks, 1 × 12 weeks, 6 ×24 weeks	Meta-analysis, 8 studies. Inclusion criteria: randomized, double-blind, placebo controlled, no combination with other medications or remedies, assess walking distance, no language restrictions. Methodologic quality assessed by scoring system.	Patients with intermittent claudication (n =415), categorized according to the Fontaine criteria.	No information
Cerebral insufficiency	Hopfenmuller (82)	Mostly used of 150 mg/day *Ginkgo biloba* extract (LI1370)	*Meta-analysis* 8 placebo controlled, randomized double-blind studies (out of 11). Studies were comparable with regard to diagnoses, inclusion and exclusion criteria and methodology.	Elderly patients (21–63 to 55–80 year); with cerebral insufficiency; in- and exclusion criteria comparable.	No information

Table 3a (*Continued*)

Intermediary of health effect	References	Specification *Ginkgo biloba*+dose (PASSCLAIM criterion 1+2E)	Study design+duration (PASSCLAIM criterion 2)	Study population (*N*, age group) (PASSCLAIM criteria 2A+2B)	Information on background diet, matrix and compliance? (PASSCLAIM criteria 2D+2F+2G)
Cerebral insufficiency	Kleijnen and Knipschild (24)	EGb 761 (24% gingko-flavone glycosides, 6% terpenoids); LI 1370 (25% ginkgo-flavone glycosides, 6% terpenoids). *There may be differences in composition of preparations depending on manufacturing process used.* In most trials, 120–160 mg/day, divided in three doses, was used; 6 weeks to 12 months.	*Systematic review* eight randomized double-blind, placebo-controlled human studies (out of 40), investigating the utility of *Ginkgo Biloba* for 'cerebral insufficiency.'	Patients aged 50+ with mild to moderate symptoms of cerebral insufficiency (indication and duration of symptoms specified if known).	No information
Memory improvement: studies in healthy volunteers					
Cognitive function in healthy subjects	Canter and Ernst (87)	Standardized *Ginkgo biloba* extracts: EGb761 (24% flavonoid glyco, 6% terpene lactones) GK501 (24% flavo, 6% terpene) LI1370 (27% flavo, 7% terpene) *Ginkgo biloba* forte (24% flavo, 6% terpene) At different dose	Review: of placebo-controlled double-blind trials: 9 trials, mainly short term (1–30 days). (literature search to Nov 2001)	Healthy subjects with no diagnosed relevant medical condition, mean age <60 year, EXCLUDING subjects with age-related memory impairment or 'cerebral insufficiency.'	No information

Table 3a (*Continued*)

Intermediary of health effect	References	Specification *Ginkgo biloba*+dose (PASSCLAIM criterion 1+2E)	Study design+duration (PASSCLAIM criterion 2)	Study population (*N*, age group) (PASSCLAIM criteria 2A+2B)	Information on background diet, matrix and compliance? (PASSCLAIM criteria 2D+2F+2G)
Memory improvement: patient studies					
Cognitive decline/dementia	Birks et al. (28) (updated in 2007 and 2009 (30, 32)	All but one study * used a Ginkgo preparation based on the standard extract (=24 mg flavone glycosides, 6 mg ginkgolides/100 mg); daily dose: 80–600 mg/day (usually < 200).	*Meta-analysis* 33 included studies: unconfounded, randomized, double-blind controlled; duration 3–52 weeks (majority 12 weeks) update 2009: 36 included trials	People with acquired cognitive impairment, including dementia, of any degree of severity. Excl: other serious illnesses, other mental illnesses, illness that can cause the memory problems; many excluded people with a history of abuse of alcohol, drugs, or medication. Most, but not all studies excluded patients on vasoactive drugs, antipsychotics, neuroleptics, cholinergic, antidepressants.	No information
Alzheimer disease	Oken et al. (98)	EGb761 and Tanakan daily dose: 120–240 mg Study duration: 12–24–26 weeks	Meta-analysis of 4 studies inclusion criteria: sufficiently characterized patients with diagnosis of Alzheimer disease; clearly stated study exclusion criteria for depression, other neurologic disease, central nervous system-active medications; use of standardized ginkgo extract; randomized placebo-controlled, double-blind study design; at least one objective assessment of cognitive function as outcome measure; sufficient statistical information	Patients with a diagnosis of Alzheimer disease, by criteria; *N*=424 (212 ginkgo group, 212 placebo group)	Use of central nervous system-active medications excluded

Citation: Food & Nutrition Research 2010, **54**: 5221 - DOI: 10.3402/fnr.v54i0.5221

Table 3a (*Continued*)

References	Test methods (PASSCLAIM criteria 3+*4)*	Effect size (per dosing or time) (PASSCLAIM criteria 2H+5)	Remarks
Nicolai et al. (23)	Absolute claudication distance (ACD) at end of study (available in 11 trials (N = 477)).	Increase of 64.5 metres (−1.8–130.7, non-significant) of GB treatment vs. placebo at the end of the study periods.	*Conclusion authors*: the clinical relevance of a non significant improvement of 64.5 metres in ACD is questionable. It was concluded that *Ginkgo biloba* has no significant effect on walking distance in people with intermittent claudication.
Horsch and Walther (21)	Ratio of the walking distance between EGb761 and placebo	Duration studies: 6 months, as required by guidelines (8); 3 months and 6 weeks (1): Pooled estimator of the ratio = 1.23 (1.16–1.31) improvement in pain-free walking distance 34 and 33 m; this equals an increase of at least 30% compared to man values at baseline, results are clinically relevant according to study guidelines.	*Conclusion authors*: this review confirms the efficacy of EGb761. It demonstrates statistical significance of the difference with respect to placebo and clinical relevance for the treatment of PAOD patients. *Comment*: high variability between study designs, study conditions and centers within each study.
Pittler and Ernst (22)	Pain-free walking distance: defined using devices that forced the patients to walk at a set speed.	Duration of studies: 6–24 weeks 7/8 trials: weighted mean differences that favored GB compared to placebo, 4/8 trials significant differences. Statistical pooling: significant difference in the increase in pain-free walking distance GB compared to placebo: weighed mean difference 34 meters (95% CI 26–43)	*Conclusion authors:* results suggest that *Ginkgo biloba* extract is superior to placebo in the symptomatic treatment of intermittent claudication. Overall effects seem modest, of uncertain clinical relevance, no final judgment on the efficacy of this treatment. *Comment:* only one trial reported the randomization procedure that was used.
Hopfenmuller (82)	Symptom improvement ginkgo compared to placebo. Symptoms among others: headache, tinitus, concentration, dizziness, fear, bad memory, forgetfulness	For all analyzed single symptoms: sign differences, superior of ginkgo. Total of clinical symptoms: seven studies confirmed effectiveness of ginkgo, one study inconclusive.	*Conclusion authors*: Therapeutical effectiveness of *Ginkgo biloba* regarding the clinical symptoms complex confirmed.
Kleijnen and Knipschild (24)	Different per study, a.o. symptoms, overall assessment doctor/patient, cognitive test battery, behavioral rating scale.	All but one trial (of eights investigated) showed positive effects of *Ginkgo biloba* compared with placebo on the symptoms; significant improvements after 12 weeks/ 3 months. Dose: 112–160 mg/day.	*Conclusion authors:* therapy is warranted for patients with mild to moderate cerebral insufficiency, but further studies are needed, with larger numbers of patients; treatment must be for 4–6 weeks before positive effects can be expected. Differences are large enough to be clinically relevant. *Comment*: only 8 out of 40 studies were well performed.

Table 3a (*Continued*)

References	Test methods (PASSCLAIM criteria 3+*4)*	Effect size (per dosing or time) (PASSCLAIM criteria 2H+5)	Remarks
Canter and Ernst (87)	Objective and/or subjective outcome measures of cognitive function (*excl* studies which measure only neurophysiological parameters such as EEG). Different outcome measures, e.g. Sternberg, Critical Flicker Fusion, Choice Reaction Time, LARS, Image recognition, Image free-recall, CDR test battery, speed of attention, immediate word recall, Stroop test.	In the single-dose and medium-term studies stat sign positive effects are largely confined to one or at most two tests from a larger battery of tests. All of these trials failed to report subjective effects of the extract. A positive subjective effect was reported only in the longest trial.	*Conclusion authors:* there is no sufficient evidence to advocate Ginkgo for cognitive enhancement in healthy populations, the effects reported in these trials are few and inconsistent. Need for long-term trials with healthy subjects. The use of *Ginkgo biloba* as a 'smart' drug cannot be recommended on the basis of the evidence available to date.
Birks et al. (28) (updated in 2007 and 2009 (30, 32)	● GCI scale by physician ● Cognition, change from baseline ● ADL ● Mood and emotional function Doses below and above 200 mg/day and the different treatment times of <12 weeks, 12 weeks, 24 weeks, 52 weeks, are analyzed separately	*CGI scale (dichotomized)* Benefits associated with *Ginkgo biloba* at dose <200 mg/day, duration <12 weeks: OR 15.32 (5.90–39.80) $p = <0.0001$; and dose >200 mg/day, duration 24 weeks: OR 2.16 (1.11–4.20) $p = 0.02$. *Cognition* Benefit for ginkgo compared with placebo at 12 weeks (<200 mg and >200 mg), 24 weeks (all doses), 52 weeks (<200 mg/day). *ADL* Benefit for ginkgo compared with placebo at <12 weeks (dose <200), 24 weeks (dose <200), 52 weeks (dose <200) *Mood and emotional function* Benefit for ginkgo at <12 weeks, dose <200 mg/day 12 weeks, dose <200 mg/day 24 weeks, dose < 200 mg/day	*Conclusion authors:* overall there is promising evidence of improvement in cognition and function with ginkgo. However, three more modern trials show inconsistent results. There is need for more trials to confirm the efficacy *new preparation, Geriaforce, was used, ethanolic extract of ginkgo leaves (1:4), contains 0.20 mg/ml flavone glycosides, 0.34 mg/ml ginkgolides. Update 2009: three more trials included. Conclusion authors: 'Many of the early trials used unsatisfactory methods, were small, and publication bias cannot be excluded. The evidence that *Ginkgo biloba* has predictable and clinically significant benefit for people with dementia or cognitive impairment is inconsistent and unreliable.'
Oken et al. (98)	Objective measures of cognitive function in Alzheimer disease. SKT (syndrome-Kurztest), choice reaction time, ADAS-cog, 10-item battery (incl Benton Visual Retention Test, digit symbol, word list recall, and reaction time), mini-mental state examination (MMSE), kendrick digit copying and object learning tasks, digit recall, classification task.	Overall significant effect size of 0.40, $p < 0.0001$. This modest effect size translated into a 3% difference in the ADAS-cog.	*Conclusion authors*: small but significant effect of 3–6-month treatment with 120–240 mg of *Ginkgo biloba* extract. The clinical significance of this effect size is less clear. Further research in the area will need to determine if there are functional improvements and to determine the best dosage. *Comment*: only four studies met inclusion criteria, out of 57. Almost all studies reported positive effects, majority for 'cerebral insufficiency,' if this diagnosis was not further specified, article was not included.

Table 3b. Original studies

Intermediary of health effect	References	Specification *Ginkgo biloba* + dose (PASSCLAIM criterion 1+2E)	Study design+duration (PASSCLAIM criterion 2)	Study population (N, age group) (PASSCLAIM criteria 2A+2B)	Information on background diet, matrix, and compliance? (PASSCLAIM criteria 2D+2F+2G)
Blood circulation: studies in healthy volunteers					
Skin blood flow	Boelsma et al. (27)	3 ×80 mg/day EGb761 (Tavonin), 3 weeks	Randomized, double-blind, placebo-controlled, crossover study, 3 weeks with a 2 week wash out period	27 Caucasian non-smoking subjects (10 male, 17 female), aged 55–74 years. Excl criteria: metabolic or endocrine disease, history of medical or surgical events (e.g. CVD, skin diseases, hypertension), anticoagulant therapy and/or chronic use of vasoactive agents	Use of dietary supplements not allowed, no alcohol on evening before test day and on test day, no coffee on test day; compliance was checked (98%)
Cognitive performance and blood viscosity	Santos et al. (25)	Dried *Ginkgo biloba* extract, 80 mg/day: 24% flavonoide, 6.1% terpenoide, 2.7% bilobalide, 1.7% ginkgolide A, 0.9% ginkgolide B, and 0.8% ginkgolide C	Double-blind, random (except for matching on education years), placebo-controlled, independent group design, 8 months	48 male volunteers, non-demented, aged 60–70 years, with cognitive abilities within normal range, with complaints of mild loss of memory. Excl: psychiatric or neurological disorders, history of drug addiction or heavy alcohol drinking, on medication or drugs that might interfere with neurological testing.	Patient compliance was controlled by a number of control procedures, restriction of drugs and medication that might interfere with testing.
Forearm hemodynamics	Mehlsen et al. (81)	*Ginkgo biloba* extract (Gibidyl Forte), containing 9.6 mg ginkgoflavonglycoside, 2.4 mg terpenlactones per tablet, three times a day for 6 weeks	Randomized, double-blinded placebo-controlled, cross-over design	16 healthy subjects, median age 32 years (21–47). Excl criteria: history of neurological, cardiovascular, pulmonary, gastrointestinal, hepatic, renal disease, hypertensive	No information
Memory improvement: studies in healthy volunteers					
Cognitive abilities in healthy adults	Burns et al. (41) [Included in review Canter]	Ginkgoforte 120 mg/day (3 ×40 mg): containing per tablet 40 mg ginkgo extract, standardized to contain 10.7 mg flavon glycosides (24%) and 2.7 mg ginkgolides (6%), 12 weeks	12-week double-blind, fixed-dose, placebo-controlled, parallel groups design	Study 1: healthy older adults (55–79 years, males and females) $n=93$. Study 2: healthy young adults (18–43 years) $n=104$ (all males) Excl criteria: cardiovascular medication, known cardiovascular condition, anticoagulant, dietary supplements with blood-thinning effect (e.g. fish oil), medication that affects mental performance or mood, injury that might impair performance on test, e.g. stroke.	Background diet: no blood-thinning supplements. Regarding compliance: contacted at a weekly basis to monitor for side effects and to encourage compliance, unused capsules returned to laboratory, compliance (>75% of capsules used) was 100% in study 1, 4 non-compliant in Study 2.

Table 3b (*Continued*)

Intermediary of health effect	References	Specification *Ginkgo biloba* + dose (PASSCLAIM criterion 1+2E)	Study design+duration (PASSCLAIM criterion 2)	Study population (N, age group) (PASSCLAIM criteria 2A+2B)	Information on background diet, matrix, and compliance? (PASSCLAIM criteria 2D+2F+2G)
Cognitive effects/ memory in healthy people	Elsabagh et al. (83) [Included in review Canter]	120 mg ginkgo (Ginkgo one-a-day tablets), extract LI 1370: 25% flavonoids, 6% total terpene lactones	Placebo-controlled double-blind design; exp 1: 1 day (acute treatment), $n=52$ exp 2: 6 weeks (chronic treatment), $n=40$	University students, 18–26 years, $n=92$ excl criteria: use of psychoactive or anticoagulant medication, alcohol or drug dependence, pregnancy or lactation, use of ginkgo, ginseng or soya isoflavone supplements within a month.	Psychoactive or anticoagulant medication, supplements excluded.
Long-term memory	Persson et al. (84)	Not specified, selection from a database, based on self-reported regular use of *Ginkgo biloba* over a period of up to 2 years.	Prospective cohort study, community-dwelling volunteers; control group 1 (not using suppl.), control group 2 (suppl. users)	Healthy adult volunteers $n=40$ out of a database of 3,500 adults (35–85 years); reported currently using, and had been using *Ginkgo biloba* regularly during a longer period of time. $n=19$ used GB >2 years, mean intake of remaining was 5.3 months. Excl: sensory handicaps, organic disease (e.g. dementia), mental retardation	No information
Bioelectrical effects of ginkgo	Kennedy et al. (85)	Single dose of GK501, 360 mg/day	Double-blind placebo-controlled, balanced crossover exp, 7 day wash-out	Healthy young volunteers (<40 years), mean age 26.6 years, 10 female, 5 male volunteers; in good health; excl criteria: illicit drug use, use of herbal or prescribed medication, smoking >5 cigarettes a day	Abstained from caffeine-containing products throughout each study day, abstained from alcohol from 12 h prior to testing day; compliance monitored (intern study)
Cognition and mood	Hartley et al. (86)	Ginkgo 120 mg/day, Ginkgo one-a-day tablets (LI1370)	Double-blind placebo-controlled study, 7 days.	Healthy, postmenopausal women, 53–65 years $n=31$ excl criteria: use or HRT in previous 12 months, smoking >20 cigarettes/day, current illness, use of psychoactive medication.	Vitamin and mineral use: 10 in ginkgo group, nine in placebo group; fish oil supplements eight in each group.

Table 3b (*Continued*)

Intermediary of health effect	References	Specification *Ginkgo biloba* + dose (PASSCLAIM criterion 1+2E)	Study design+duration (PASSCLAIM criterion 2)	Study population (N, age group) (PASSCLAIM criteria 2A+2B)	Information on background diet, matrix, and compliance? (PASSCLAIM criteria 2D+2F+2G)
Chronic administration	Stough et al. (88) [Included in review Canter]	*Ginkgo biloba* (Blackmore's *Ginkgo biloba* Forte, EGb761, 2000 mg containing 120 mg of active ingredient); 24% flavone glycosides, 6% bilobalide.	Randomized double-blind placebo-controlled trial, 30 days	61 young healthy volunteers. Excl criteria: past history of head injury requiring hospitalization, intellectual developmental disability, past or current neurological or psychiatric illness, inability to speak or understand English, past or current history of substance abuse, current pregnancy, currently taking other putative cognitive enhancers, current use of any other medication.	Currently taking other putative cognitive enhancers =exclusion; compliance monitored.
Memory	Moulton et al. (89)	LI1370, 120 mg/day	Double-blind, placebo-controlled design; 5 days	Healthy male college students: mean age 20.5 years $n=30$	No information
Quality of memory	Kennedy et al. (39) [Included in review Canter]	Acute dose ginkgo 120, 240, 360 mg/day GK501: 24% flavone glycosides, 6% terpene lactones.	Placebo-controlled multi-dose, double-blind balanced crossover design, 1 day.	Undergraduate volunteers ($n=20$), 18 female, 2 male, in good health excl criteria: medication use, heavy smoking (>10/day)	Abstained from caffeine-containing products and alcohol throughout each study day; compliance monitored (intern study)
Short-term cognitive effects	Rigney et al. (90) [Included in review Canter]	Four acute doses of ginkgo: 120–150–240–300 mg ginkgo (LI1370), each treatment was taken for a period of 2 days, separated by a 5 day washout period.	Randomized, double-blind, placebo-controlled 5-way cross-over design; at study centre	Asymptomatic volunteers, $n=31$, 30–59 years, good physical and mental health, no concomitant medication	Advised to abstain from alcohol (compliance checked) and caffeinated products; subjects stayed at study centre during the day.
Prevention of cognitive decline	Snitz et al. (38)	EGb761, 120 mg twice daily	5-year randomized double-blind placebo-controlled trial	Normal elderly or those with mild cognitive impairment; $n=3072$ Exclusion: dementia at baseline; neurological or neurodegenerative disease, higher risk of dementia (e.g. Parkinson), treatment with cognitive enhancers, AD medication, anticoagulants; bleeding disorders, thrombocytopenia.	All selection criteria were reported in an earlier study: (91)

Table 3b (*Continued*)

Intermediary of health effect	References	Specification *Ginkgo biloba* + dose (PASSCLAIM criterion 1+2E)	Study design+duration (PASSCLAIM criterion 2)	Study population (N, age group) (PASSCLAIM criteria 2A+2B)	Information on background diet, matrix, and compliance? (PASSCLAIM criteria 2D+2F+2G)
Prevention of cognitive decline	Dodge et al. (37)	Standardized GB extract, 3 ×80 mg daily: at least 6% terpene lactones and 24% flavone glycosides Study period: 42 months	Randomized, placebo-controlled, double-blind, 42-month pilot study	Cognitively intact subjects, $N=118$ Inclusion criteria: age 85 or older, informant available, no subjective memory complaint, normal memory function defined by an education-adjusted score on the WMS-R, MMSE >23, 6, clinical dementia Rating =0, free from depressive symptoms (CES-D-10 <4).	All participants also received a standard multivitamin containing 40 IU vitamin E; the dose of over-the-counter supplements must not be changed during the course of the trial, the presence and dose will be recorded; compliance: pill count
Cognitive function in healthy, cognitively intact older adults	Carlson et al. (36)	Ginkgo based supplements containing *Ginkgo biloba* (23.2% flavonoid glycosides, 6.7% terpeneolactones, 160 mg/day (a composition within the ranges used in EGb761) + 68 mg gotu kola, 180 mg DHA, bioflavonoid concentrate, vitamin A and beta-carotene	Randomized, double-blind placebo-controlled parallel design trial, duration 4 months	Subjects aged 65–87 years ($n=90$) without dementia or depression, not taking psychoactive medications or medications or supplements that alter hemostatis, no history of bleeding disorders. Other exclusion criteria: tobacco use, consumption of more than two alcoholic drinks a day, more than three servings of fish a week, unstable heart disease, use of aspirin, NSAIDs, warfarin.	All participants were given a standard multivitamin/mineral supplement in addition to the study product to minimize confounding factors related to high supplement use. Participants needed to maintain habitual diet
Mild cognitive impairment; ongoing trail, baseline data	DeKosky et al. (91)	EGb761, 120 mg twice daily	5-year randomized double-blind placebo-controlled trial	Normal elderly or those with mild cognitive impairment; $n=3,072$ Exclusion: dementia at baseline; neurological or neurodegenerative disease, higher risk of dementia (e.g. Parkinson), treatment with cognitive enhancers, AD medication, anticoagulants; bleeding disorders, thrombocytopenia.	Restriction on vitamin E intake

Table 3b (*Continued*)

Intermediary of health effect	References	Specification *Ginkgo biloba* + dose (PASSCLAIM criterion 1+2E)	Study design+duration (PASSCLAIM criterion 2)	Study population (N, age group) (PASSCLAIM criteria 2A+2B)	Information on background diet, matrix, and compliance? (PASSCLAIM criteria 2D+2F+2G)
Cognitive abilities in healthy adults	Burns et al. (41) [Included in review Canter]	Ginkgoforte 120 mg/day (3 ×40 mg): containing per tablet 40 mg ginkgo extract, standardized to contain 10.7 mg flavonglycosides (24%) and 2.7 mg ginkgolides (6%), 12 weeks	12-week double-blind, fixed-dose, placebo-controlled, parallel groups design.	Study 1: healthy older adults (55–79 years, males and females) $n=93$. Study 2: healthy young adults (18–43 years) $n=104$ (all males). Excl criteria: cardiovascular medication, known cardiovascular condition, anticoagulant, dietary supplements with blood-thinning effect (e.g. fish oil), medication that affects mental performance or mood, injury that might impair performance on test, e.g. stroke.	Background diet: no blood-thinning supplements. Regarding compliance: contacted at a weekly basis to monitor for side effects and to encourage compliance, unused capsules returned to laboratory, compliance (>75% of capsules used) was 100% in study 1, 4 non-compliant in Study 2.
Mental functioning, healthy volunteers	Cieza et al. (92)	EGb761 240 mg, 2 ×120	4-week, randomized, double-blind, placebo-controlled, parallel-group, monocentric study	66 healthy volunteers, 50–65 years, without age-associated cognitive impairment excl: concomitant medication, with exception of menopausal hormone-replacement therapy	Intake of concomitant medications known to affect cognitive function not permitted; compliance monitored.
Cognitive effects in healthy older adults	Mix and Crews (34)	*Ginkgo biloba* extract EGb761, 180 mg/day or placebo.	Placebo-controlled, double-blind, randomized trial, 6 weeks	$n=262$, men and women, no memory impairment, >60y, MMSE ≥26 Excl: history of dementia or significant neurocognitive impairment, active or clinically sign cardiovascular, neurological, pulmonary, endocrine, renal, hepatic, gastrointestinal, hematological or oncological diseases, uncontrolled hypertension, learning disabilities, psychiatric or substance abuse disorder, history of bleeding disorder, hemorrhagic stroke, treatment with anticoagulant or psychotropic medications. Ginkgo use before study terminated 28 days for start.	Treatment with anticoagulant or psychotropic medications exclusion criteria; compliance assessed via pill counts.

Table 3b (*Continued*)

Intermediary of health effect	References	Specification *Ginkgo biloba* + dose (PASSCLAIM criterion 1+2E)	Study design+duration (PASSCLAIM criterion 2)	Study population (N, age group) (PASSCLAIM criteria 2A+2B)	Information on background diet, matrix, and compliance? (PASSCLAIM criteria 2D+2F+2G)
Acute nootropic effects	Nathan et al. (93)	*Ginkgo biloba* 120 mg, 3 ×40 mg (Ginkgoforte, 10.7 mg ginkgo flavonglycosides, 2.7 mg ginkgolides and bilobalide)	Repeated measures, double-blind, placebo-controlled design, 7 day washout period.	Healthy older subjects, $n=11$ 50–70 years Excl: history of dementia, psychiatric disorders or neurological diseases; history of bleeding disorders, gastrointestinal disorders; use of anticoagulants, antidepressants, anti-psychotics, anxiolytics, ACE inhibitors, anti-Parkinson medication or cognitive enhancing drugs or herbs; smoking.	Instructed not to consume caffeine containing food or drinks on testing days, eat two pieces of toast before testing.
Learning and memory in healthy elderly	Solomon et al. (35)	*Ginkgo biloba* extract 40 mg, three times a day. (Ginkgoba, EGb761)	6-week randomized, double-blind, placebo-controlled trial, parallel-group study	Healthy elderly volunteers, 60–82 years old, $n=219$ (111 ginkgo, 108 placebo), mini-mental state examination scale (MMSE) >26. Excl criteria: history of psychiatric or neurologic disorder, life-threatening illness in last 5 years, psychoactive medication use last 60 days.	No information on background diet; compliance evaluated by telephone twice, exclusion of 6 doses were missed in a 2-week period or didn't take 3 consecutive doses; envelopes returned.
Activities of Daily living and mood	Cockle et al. (94)	Standardized special extract, LI1370, 120 mg/day, 4 months	4-month trial, no randomization, not blind, no placebo	Free living older volunteers, $n=5028$, mean age 68.9 years (on GB extract $n=1,000$) Excl: anticoagulants, antidepressants	No information, compliance not monitored
Activities of Daily living and mood	Trick et al. (95)	LI1370: sequal of study Cockle et al. 94: 120 mg/day, 6 month follow-up	6 month trial (follow-up postal survey), no randomization, not blind, no placebo: subjects selected their own treatment option; four groups: ginkgo 10 months, ginkgo 4 months, ginkgo 6 months, no ginkgo	Free living, older volunteers, $n=1,570$ [of 5,028 in Cockle et al. (94)]	No information; compliance not monitored

Table 3b (*Continued*)

Intermediary of health effect	References	Specification *Ginkgo biloba* + dose (PASSCLAIM criterion 1+2E)	Study design+duration (PASSCLAIM criterion 2)	Study population (N, age group) (PASSCLAIM criteria 2A+2B)	Information on background diet, matrix, and compliance? (PASSCLAIM criteria 2D+2F+2G)
Memory improvement: patient studies					
Dementia	DeKosky et al. (31)	EGb761, 120 mg twice daily	5-year randomized double-blind placebo-controlled trial	Normal elderly or those with mild cognitive impairment; $n=3,072$ Excl: dementia at baseline; neurological or neurodegenerative disease, higher risk of dementia (e.g. Parkinson), treatment with cognitive enhancers, AD medication, anticoagulants; bleeding disorders, thrombocytopenia.	Restriction on vitamin E intake
Dementia and age-associated memory impairment	van Dongen et al. (96)	*Ginkgo biloba* special extract EGb761: 160 mg/day (usual dose)or 240 mg/day (high dose)	24-week, randomized, double-blind, placebo-controlled, parallel-group, multicenter trial; after 12-weeks second randomization.	Elderly patients (>50 years) with dementia (Alzheimer disease or vascular dementia) or age-associated memory impairment (AAMI), impaired cognitive functioning, objectively or subjectively, in absence of dementia – criteria available – $n=214$; mean age: 82.5 years Excl: severe depression, IQ <80, serious co-morbidity, sources of interference, impermissible co-interventions (e.g. antipsychotic drugs, cholinergic therapy)	Use of antipsychotic drugs, anti-Parkinson medication, neuroleptics, antidepressants, cholinergic therapy, and vasoactive drugs in excl criteria; compliance monitored by pill counting

Table 3b (*Continued*)

Intermediary of health effect	References	Specification *Ginkgo biloba* + dose (PASSCLAIM criterion 1+2E)	Study design+duration (PASSCLAIM criterion 2)	Study population (N, age group) (PASSCLAIM criteria 2A+2B)	Information on background diet, matrix, and compliance? (PASSCLAIM criteria 2D+2F+2G)
Dementia (Alzheimer's, vascular, or mixed) or age-associated memory impairment	van Dongen et al. (97) [Included in review Birks]	160 or 240 mg *Ginkgo biloba* extract per day (EGb761)	24-week randomized double-blind placebo-controlled study $n=214$. Efficacy, dose-dependence and durability evaluated at 12 and 24 weeks. After 12 weeks, ginkgo users randomized to either continue ginkgo or go to placebo.	Older persons, >50 years, with dementia (either Alzheimer's dementia or vascular dementia, mild to moderate degree) or age-related memory impairment (AAMI), $n=214$, mean age 83.9 years Excl criteria: severe depression, inadequate level of pre-morbid intelligence (IQ >80), serious co-morbidity (in particular pathological conditions considered either non-treatable underlying causes of dementia and cognitive disorders or sources of interference with trial, like tumors), co-interventions, drugs with debilitating influence orn psychical or cognitive functioning and drugs with a claimed nootropic action	Drugs with claimed nootropic action (e.g. antipsychotic drugs, anti-Parkinson medication, neuroleptics, cholinergic therapy, antidepressants, and vasoactive drugs) not permitted; compliance measured.
Alzheimer and multi-infarct dementia	Le Bars et al. (29) [Included in meta-analysis Birks and in meta-analysis Oken]	EGb761 120 mg/d (3 ×40 mg): with a 14-day single-blind placebo run-in period. Study duration: 52 weeks	52-week randomized double-blind placebo-controlled parallel-group multicenter trial	Mildly to severely demented outpatients with Alzheimer disease or multi-infarct dementia, diagnosed according criteria, without other significant medical conditions, aged 45+ (mean age 69), $n=202$	No information; compliance monitored by pill counts

Table 3b (*Continued*)

References	Test methods (PASSCLAIM criteria 3+4)	Effect size (per dosing or time) (PASSCLAIM criteria 2H+5)	Remarks
Blood circulation: studies in healthy volunteers: insufficient evidence			
Boelsma et al. (27)	Skin blood flow: assessed on forefoot with laser Doppler flow meter after 3 weeks. Metabolic fingerprinting: changes in urinary metabolites measured.	Blood flow after 3 weeks: placebo EGb761 baseline 10.4±6.7; 7.1±4.4 $p<0.01$ peak 29.1±18.9; 20.9±16.8 $p<0.01$ subjects with highest resting blood flow demonstrated a decrease after treatment, subjects with average blood flow no change, subjects with lowest resting blood flow slight increase after treatment.	*Conclusion authors:* mean decrease of skin blood flow with ginkgo use. The data suggest that EGb761 exerts dilatory or constrictive effects on blood vessels probably according to the physiological/pathological condition. Effects of GB on skin blood flow in healthy humans may be either inhibitory or enhancing which may be related to individual metabolism; healthy subjects under normal conditions are functioning close to optimum conditions, so less or not influenced by improvement.
Santos et al. (25)	SPECT Blood viscosity determined with a rotational viscosimeter neuropsychological assessment (before and at 8 months)	SPECT: significant differences between the groups in medial-temporal area, area one basal ganglia, area two basal ganglia; sign increase of cerebral perfusion in left hemisphere areas. Blood viscosity baseline 8 months placebo 4.1±0.8; 4.8±0.7 $p<0.0001$ ginkgo 4.6±0.6 3.6±0.6 $p<0.0001$ sign difference between the groups, $p<0.0001$	*Conclusion authors*: significant reduction in blood viscosity and increased cerebral perfusion in several areas. Appears to be effective in the treatment of cognitive deficits in older people.
Mehlsen et al. (81)	Measurements of systemic blood pressure and forearm hemodynamics: at time of inclusion, 3, 6, 9, 12 weeks. Forearm blood flow measured by venous occlusion technique; forearm venous capacity: single measurement after venous occlusion	Forearm blood flow: GB treatment vs. placebo 3 weeks: 3.2 ml vs. 2.2 ml $p<0.05$ 6 weeks: 3.3 ml vs. 2.8 ml $p<0.05$ forearm venous capacity: GB treatment vs. placebo 3 weeks: 1.2 ml vs. 0.8 ml $p<0.05$ 6 weeks: 1 ml vs. 0.8 ml n.s.	*Conclusion authors:* GB extract is able to dilate forearm blood vessels causing increments in regional blood flow without changing blood pressure levels in healthy subjects. Our study has confirmed the claimed vasodilating effect of GB extract on peripheral vessels preferentially on the arterial/arteriolar level. *Comment*: No difference made between subjects with high, average, low resting blood flow, Boelsma et al. (27) have shown that this could influence the effect.

Table 3b (*Continued*)

References	Test methods (PASSCLAIM criteria 3+4)	Effect size (per dosing or time) (PASSCLAIM criteria 2H+5)	Remarks
Memory improvement: studies in healthy volunteers: insufficient evidence			
Burns et al. (41) [Included in review Canter]	Study 2: test performed pre- and post-intervention (12 weeks) *cognitive abilities testing* Concept-formation Raven's Progressive Matrices Information Digit Span Picture Recognition Visual matching Digit Symbol Memory for Names Visual-Auditory learning PASAT Stroop Color Word test chronometric testing 'odd-man-out' reaction time task (OMO) inspection time subjective well-being Profile of Mood States (POMS)	Study 2: withdrawal of 21 participants. Digit symbol, small effect size $d=0.17$, $p<0.10$, enhanced performance in ginkgo group. No stat sign effects of ginkgo enhancement.	*Conclusion authors*: positive results limited to a single cognitive measure, for the older participants only. Study 2 only males, because ethics committee didn't approve inclusion of females at child-bearing age in absence of any evidence of effects during pregnancy. No studies that are directly comparable in healthy young adults, others focused on acute effects of higher doses, or short term interventions. Sample sizes were adequate for detecting medium-sized differential improvement of about half a standard deviation.
Elsabagh et al. (83) [Included in review Canter]	Exp 1: subjects tested after 4 h Exp 2: subjects tested at baseline and 6 weeks National Adult Reading Test-Revised (NART-R), Hospital Anxiety and Depression Scale (HAD), Intra Dimensional/ Extra Dimensional set shifting task (IDED), Stockings of Cambridge (SoC), Spatial working memory (SWM), pattern recognition memory (PRM), spatial recognition memory (SRM), word recall, picture recall, paced auditory serial addition task (PASAT)	Exp 1: significantly improved performance on tests of sustained attention (PASAT) and PRM, no effects on SRM, SWM, IDED, SoC. Exp 2: no sign effects on mood or any of the cognitive test Comment: PASATdifference at baseline between groups in Exp 2 is similar to the effect found in exp 1!!	*Conclusion authors*: in line with literature, acute administration improved performance in tests of attention and memory; however, after 6 weeks no effects in young, healthy participants, suggesting that tolerance develops.
Persson et al. (84)	Eight memory tasks: SPTB free recall of sentences encoded by enactment; VTB free recall of sentences encoded by verbal rehearsal; FLUA verbal fluency, FLUPB verbal fluency; SRB word comprehension; FACRN recognition of faces, CRSPT cued recall of sentences encoded by enactment; CRVT cued recall of words encoded by verbal rehearsal	No significant differences between ginkgo group and control group 1 or control group 2. Significant effect in the cued recall test of sentences for control group 2 compared to ginkgo group, in favor of control group! No explanation for this result.	*Conclusion authors*: regular use of *Ginkgo biloba* during a long period of time does not enhance memory performance in healthy participants with intact cognitive functions. No well-controlled studies found supporting the claims for long-term effects on memory. *Comment*: unknown dose and frequency of use ginkgo. Authors assume that recommendations are followed.

Table 3b (*Continued*)

References	Test methods (PASSCLAIM criteria 3+4)	Effect size (per dosing or time) (PASSCLAIM criteria 2H+5)	Remarks
Kennedy et al. (85)	Participants assessed 4 h after consuming treatment: EEG recording	Significant decreases in theta and beta wavebands, predominantly in frontal scalp areas; ginkgo not associated with modulation of evoked potentials.	*Conclusion authors:* study confirms that single dose of *Ginkgo biloba* exert effects on cerebral bioelectrical activity in healthy, young volunteers.
Hartley et al. (86)	Cognitive testing at baseline and day 7. *Episodic memory* Weschler Memory Scale-Revised: immediate and delayed paragraph recall Delayed Matching-to-Sample test Long-term episodic memory *Frontal lobe function* Two tests selected from CANTAB *Sustained attention* PASAT *Mood ratings* VAS scales	Episodic memory: ginkgo group sign better in some, but not all parameters Frontal lobe function: ginkgo group sign better, but not in test of planning. PASAT: ginkgo group sign better No differences in mood ratings	*Conclusion authors*: 1 week of ginkgo treatment improved performance in three of the cognitive tasks. The benefits of ginkgo on memory and frontal lobe function are modest. Few ginkgo effect, at marginal levels of significance.
Stough et al. (88) [Included in review Canter]	Well-validated neuropsychological tests at baseline and 30 days: Digit Symbol Substitution Test Speed of Comprehension Test Symbol Digit Modalities Test Digit Span Trail Making Test Rey Auditory Verbal Learning Test Inspection Time Cognometer Battery of Tests (simple RT and working memory)	Significant changes of EGb761 compared to placebo for: Digit Span Backwards ($p < 0.05$) Working Memory Speed ($p < 0.05$) Rey Auditory Verbal Learning Test, delay list ($p < 0.01$) These sign changes indicate significant EGb761 related improvements specifically in memory processes.	*Conclusion authors*: EGb761 treatment improves memory processes, particularly working memory and memory consolidation. This improvement was clearly evident to participants throughout the trial, they subjectively noticed it. Further research is urgently required to substantiate these finding in healthy participants.
Moulton et al. (89)	Sternberg memory scanning test vocabulary and digit span subtests WAIS-R Wechsler Adult Intelligence Scale-Revised reading span test prose recall test	No significant differences on any tests between ginkgo en placebo, except for Sternberg Memory Scanning Test.	*Conclusion authors:* largely ineffective in enhancing memory *Comment:* no baseline measurements, in order to avoid practice effects; comparability of the two groups assumed

Table 3b (*Continued*)

References	Test methods (PASSCLAIM criteria 3+4)	Effect size (per dosing or time) (PASSCLAIM criteria 2H+5)	Remarks
Kennedy et al. (39) [Included in review Canter]	CDR computerised assessment battery prior to dosing and at 1, 2.5, 4 and 6 h after: word presentation, immediate word recall, picture presentation, simple reaction time, digit vigilance task, choice reaction time, spatial working memory, numeric working memory, word recall, delayed word recognition, delayed picture recognition, speed of attention, accuracy of attention, quality of memory, speed of memory.	Dose-dependent improvement of the speed of attention-factor at 2.5 and 6 h: sign improvement for 240 and 360 mg. Quality of memory: convincing pattern, performance sign enhanced for dose 120 mg at 1 and 4 h; 240 mg: same trend toward sign. Also, a number of time- and dose-specific changes (both positive and negative) in performance of the other factors.	*Conclusion authors:* acute administration of *Ginkgo biloba* (240 and 360 mg) is capable of producing a sustained improvement in attention in healthy young volunteers. *Comment*: improvement was not replicated in similar study in the same population Kennedy (40)
Rigney et al. (90) [Included in review Canter]	Test battery conducted pre-dose and hourly. Range of cognitive outcome measures: immediate word recall (central loop component of working memory); Sternberg's Short Term Memory Scanning Task (articulary loop component of working memory); stroop color task; word recall test (immediate and delayed); critical flicker fusion (CFF); choice reaction time (CRT); digit symbol substitution taks (DSST); line analog rating scales for subjective sedation (LARS); leeds sleep evaluation questionnaire (LSEQ); wrist actigraphy subjective measures of sedation and sleep	Sternberg: reaction times GBE 120 mg and 300 mg sign. faster than placebo on both days; most evident for 120 mg: mean decrease in reaction time of 69 ms on day 1, 73.8 ms on day 2; more pronounced in older age group 50–59 years: day 1 decrease of 165.6 ms, day 2 decrease of 172.2 ms. 120 mg produces most evident effects	*Conclusion authors*: effects on aspects of cognition in normal healthy volunteers are more pronounced for memory, particularly working memory, than for arousal or selective attention; 120 mg produces the most evidence effect. *Comment by* Solomon et al. (35): only improvement found with 1 dose of ginkgo (120) in oldest group 50–59, and only in one of the multiple tests of memory administered *Comment*: subjects were trained on the experimental measures to a performance plateau to mitigate against learning effects before proceeding to the study. Total of 31 volunteers, unknown number in age group 50–59 years. *Comment by ESCOP*: the results suggested that cognition-enhanced effects of the extract are more likely to be apparent in individuals aged 50–59 years, compared to 30–50 years
Snitz et al. (38)	Assessments repeated every 6 months Primary outcome: incidence of all-cause dementia. Secondary outcomes: rate of cognitive and functional decline, incidence of cardiovascular and cerebrovascular events, mortality	Median follow-up 6.1 years. No differences between GB and placebo group in domain memory, attention, visuospatial abilities, language, executive functions, 3MSE, ADAS-Cog.	*Conclusion authors*: GB did not result in less cognitive decline in older adults compared to placebo.
Dodge et al. (37)	Outcome measures: mild cognitive decline (CDR =0 to CDR =0.5), rated by a neurologists, decline in memory function (10-word Word List Delayed Recall test); adverse events.	No differences between GB and placebo group in cognitive decline or memory function decline. After controlling for medication adherence level, lower risk of cognitive decline and lower decline in memory function.	*Comment:* Ginkgo did not effect cognitive function, because the study was under powered. Information as to the vehicle and content of the placebo is not provided. The participants were provided vitamin E tablets; this may have confounded any potential effect of *Ginkgo biloba*. There was an apparently high rate of (non-hemorrhagic) stroke among the treatment group.

Citation: Food & Nutrition Research 2010, **54**: 5221 - DOI: 10.3402/fnr.v54i0.5221

Table 3b (*Continued*)

References	Test methods (PASSCLAIM criteria 3+4)	Effect size (per dosing or time) (PASSCLAIM criteria 2H+5)	Remarks
Carlson et al. (36)	Six standardized cognitive function tests: SF-36 quality of life questionnaire, platelet function analyzer, monitoring of adverse events.	87% completed study. Cognitive function above average at baseline. 1 of 6 cognitive tests significant better after 4 months ($p=0.03$) in placebo group. No significant differences in quality of life, platelet function or adverse events	*Conclusion authors*: the data do not support the use of *Ginkgo biloba* supplements to improve cognitive function or quality of life in healthy adults.
DeKosky et al. (91)	Assessments repeated every 6 months Primary outcome: incidence of all-cause dementia. Secondary outcomes: rate of cognitive and functional decline, incidence of cardiovascular and cerebrovascular events, mortality	Ongoing trial	
Burns et al. (41) [Included in review Canter]	Study 1: tests performed pre- and post-intervention (12 weeks) *cognitive abilities testing* Woodcock-Johnson Psych-Educational Battery-Revised Spot-the-Word Self-Ordered Pointing chronometric testing 'odd-man-out' reaction time task (OMO) inspection time *subjective well-being* Profile of Mood States (POMS)	Study 1: withdrawal of 13 participants. Longer-term memory, assessed by associational learning tasks showed improvement with ginkgo: Long-term storage and retrieval (Glr), part of Woodcock, $d=0.52$, $p=0.04$ No stat sign difference on any other measure.	*Conclusion authors*: our result suggests that intermediate-term storage and retrieval among elderly persons can be differentially improved by taking ginkgo. Positive results limited to a single cognitive measure, for the older participants only. Sample sizes were adequate for detecting medium-sized differential improvement of about half a standard deviation.
Cieza et al. (92)	Primary and secondary outcome measures at baseline and day 28. Primary outcomes: subject's judgment of own mental health, general health, Quality of Life on VAS scales Secondary outcomes: *stimulus representation (perception)* Increment Threshold for Visual Stimuli (ITVS) *information processing* Digit connection test-G (DCT-G) Worl list test (WL) *emotional evaluation* profile of mood states (POMS) subjective intensity scale-mood (SIS-M) self-rating depression scale (SDS) *action, reaction, volition and decision* Finger tapping test-personal tempo (PT) Finger tapping test-speed (MT) Auditory choice reaction time (ART) *activation/attention* color word test (CWT) incidental learning test (ILT) subjective intensity scale-tiredness (SIS-T) *temporal mechanism* auditory order threshold test (AOT) temporal reproduction test (TR) sensorimotor synchronization test (SMS)	Primary outcomes: self-estimated mental health and quality of life significant better in ginkgo group Secondary outcomes: stimulus representation: no differences information processing: no differences emotional evaluation: no differences action/reaction: in favor of ginkgo in some aspects of ART, MT activation/attention: no differences temporal mechanism: in favor of ginkgo in some TR test	*Conclusion authors*: no effect on memory, perception, activation/attention and temporal organization, possibly due to short time period, low reliability of performed tests and the study group (enhancement in some mental functions can be clearly shown in cognitively impaired patients, but less in healthy volunteers). Positive effect on general mental health and quality of life of elderly people after a treatment of 4 weeks.

References	Test methods (PASSCLAIM criteria 3+4)	Effect size (per dosing or time) (PASSCLAIM criteria 2H+5)	Remarks
Mix and Crews (34)	objective, standardized neuropsychological measures at start and end: Selective Reminding Test (SRT) Wechsler Adult Intelligence Scale-III Block Design and Digit Symbol Coding Wechsler Memory Scales (WMS) subjective Follow-up Self-Report Questionnaire	More improvement on SRT tasks (2 out of 9) compared to placebo sign. greater improvement on WMS compared to placebo (but also sign. difference on baseline!!) sign. more subjects rated themselves as improved.	*Conclusion authors:* objective and subjective results provide evidence of the potential efficacy of EGb761 in enhancing certain neuropsychological/memory processes of cognitively intact older adults, 180 mg daily for 6 weeks. Large-scaled clinical trials are needed to examine the efficacy of EGb761 on the neuropsychological processes of younger, cognitively intact groups. *Comment:* No predefined primary and secondary endpoints, because of relative absence of previous clinical trials.
Nathan et al. (93)	Testing pre- and 90 min post-drug administration (peak plasma levels): CDR computer test numeric working memory spatial working memory picture recognition simple reaction time choice reaction time AVLT (Rey auditory verbal learning task)	No acute effects of *Ginkgo biloba* on cognitive functioning.	*Conclusion authors:* no acute nootropic effects of *Ginkgo biloba* in healthy older humans. *Comment by authors*: no significant effects of 120 mg *G. biloba* in healthy older subjects, but other studies find memory enhancing effects at higher doses (600 mg) or with more chronic administration.
Solomon et al. (35)	Test of learning and memory: California Verbal Learning Test (CVLT), Logical Memory subscale of the Wechsler Memory Scale-Revised (WMS-R); Visual Reproduction subscale. Test of attention and concentration: Digit Symbol subscale of the Wechsler Adult Intelligence Scale-Revised (WAIS-R), the Stroop test, the Digit Span (WMS-R); Mental Control (WMS-R). Test of expressive language: Controlled Category Fluency test; Boston Naming Test + Memory Questionnaire for participant + global evaluation for spouse (Caregiver Global Impression of Change rating scale). All tests (with exception of global evaluation) administered at beginning and end.	Analysis of the modified intent-to treat population: 88% completed study. No significant differences between treatment groups on any outcome measure. Also no difference in the evaluation. In total, 14 different measures of cognition were evaluated in the study. Seven of the measures were better in the placebo group, seven in the ginkgo group. None of the differences were statistically significant.	*Conclusion authors:* ginkgo did not enhance performance on standard neuropsychological tests of learning, memory, naming and verbal fluency, or attention and concentration. No measurable benefit in cognitive function in elderly adults with intact cognitive function, when taken following the manufacturer's instructions. *Comments by letters* (JAMA, 2003): product is not tested, exact quantity of the active ingredients remains unknown; randomization performed by lead investigator, tests conducted by pill providers, baseline differences for several of the tests are not discussed. *Comment in ESCOP*: use of non-matching placebos (different dosage forms) criticized.
Cockle et al. (94)	B-ADL Scale (at baseline + 4 months); self-rating ADL scale; Line Analog Ratings Scales of mood and sleep (months 1–4)	Sign differences between ginkgo and control group on all scales at each time point (1–4 months)	*Conclusion authors*: GBE has beneficial effects on areas of functioning that have implications for quality of life in an older population. *Comment:* subjects not randomized, no placebo, subjective questionnaires, compliance not measured.
Trick et al. (95)	At the end of the 6 months follow-up period: Line Analog rating scale (LARS), self rating ADL scale	Sign. differences in mean overall LARS and SR-ADL score between the three treatment groups. Magnitude of improvement on all scales was related to overall duration of GBE supplementation.	*Conclusion authors:* Sign. differences between the groups suggests that the extract had a demonstrable effect in improving mood and the self-assessed performance of the tasks of everyday living. *Comment*: no placebo used; no baseline measurements; sequel to study mentioned above; subjects selected their own treatment option.

Table 3b (*Continued*)

References	Test methods (PASSCLAIM criteria 3+4)	Effect size (per dosing or time) (PASSCLAIM criteria 2H+5)	Remarks
Memory improvement: patient studies			
DeKosky et al. (31)	Assessments repeated every 6 monthsPrimary outcome: incidence of all-cause dementia. Secondary outcomes: rate of cognitive and functional decline, incidence of cardiovascular and cerebrovascular events, mortality	Hazard ratio (GB compared to placebo group): all-cause dementia: 1.12 (0.94–1.33, $p=0.21$) Alzheimer disease: 1.16 (0.97–1.39, $p=0.11$)	*Conclusion authors:* No effect of GB in reducing incidence of dementia or Alzheimer disease in elderly individuals
van Dongen et al. (96)	Outcomes measured after 4, 8, 12, 18, 24 weeks. Memory and attention Syndrome Kurz Test (SKT, psychometric functioning); *Clinical Global Impression* of change (CGI-2, by nurse), *activities of daily life* Nuremberg Gerontopsychological Rating Scale for Activities of Daily Living (NAI-NAA, behavioral functioning)	Intervention period: 24 weeks, $n=123$; 79 ginkgo, 44 placebo Ginkgo (both doses) vs placebo, mean change of scores: SKT: + 0.4 (−0.9 −1.7) CGI-2: +0.1 (−0.3–0.4) NAI-NAA: −0.4 (−1.9–1.2) positive small difference in favor of Ginkgo, but not statistically significant nor clinically meaningful for dementia subgroup nor AAMI subgroup.	*Conclusion authors:* the trial results do not support the view that ginkgo is beneficial for patients with dementia or age-associated memory impairment. *Comment by authors:* AAMI and beginning dementia patients used, because it is assumed that relative mild stages of cognitive decline provide for the clearest manifestations of any effect. The negative results of this trial cannot fully neutralize the positive results of previous studies.
van Dongen et al. (97) [Included in review Birks]	Assessment of objective measures of cognitive performance, after 12 and 24 weeks: *neuropsychological testing* trail-making speed digit memory span verbal learning *clinical assessment* presence and severity of geriatric symptoms (SCAG), depressive mood (GDS), self-perceived health and memory status *behavioral assessment* self-reported level of instrumental daily life activities	Intention-to-treat analysis: no beneficial effects on neuropsychological, psychopathological, or behavioral outcomes for ginkgo group compared to placebo at $t=24$ weeks. At $t=12$ weeks: 2 ginkgo groups (high-and low-dose) combined performed better at self-reported activities of daily life, but worse at self-perceived health status, compared to placebo.	*Conclusion authors*: ginkgo is not effective as a treatment for older people with mild to moderate dementia or age-associated memory impairment. *Comment:* External validity of the study questioned, all kinds of memory loss were included, heterogeneous population.
Le Bars et al. (29) [Included in meta-analysis Birks and in meta-analysis Oken]	*Primary outcome measures at baseline, 12, 26, and 52 weeks. Cognitive impairment by* Alzheimer's Disease Assessment Scale–Cognitive subscale (ADAS–Cog) *daily living and social behavior by* Geriatric Evaluation by Relative's Rating Instrument (GERRI) *general psychopathology by* Clinical Global Impression of Change (CGIC)	Intent to treat analysis, EGb761 compared to placebo: *ADAS-Cog* 1.4 points better, $p=0.04$ improvement of at least 4-point: 27% EGb group compared to 14% placebo-group, $p=0.005$ *GERRI score* 0.14 points better, $p=0.004$ improvement 37% EGb group compared to 23% placebo-group, $p=0.003$ *CGIC* no significant difference	*Conclusion authors:* EGb761 is capable of stabilizing and improving the cognitive performance and the social functioning of demented patients for 6 months to 1-year. *Comment:* only 137 patients completed the trial: 78 EGb group, 59 placebo-group. *comment by* van Dongen et al. (96): Modest improvement of the cognitive performance and the social functioning of the demented patients involved. No objective measures of cognitive performance, cognitive impairment measured.

The presence of a 24% standardized extract was detected in four products.

Health claim substantiation

The (combined) PASSCLAIM criteria were checked per health effect, for the selected studies (see Table 3). The final step of the assessment, PASSCLAIM criterion 6, weighing of the evidence, is neither worked out in detail in PASSCLAIM (8), nor in the EFSA guidance document (7). In practice, this is done now by EFSA on a case-by-case basis (2). In our assessment we have used the WHO criteria (20), which categorizes data into convincing evidence (consistent results from adequately powered, randomized placebo-controlled trials of the claimed substance in human subjects representative of the normal/target population, under normal conditions of use and assessing endpoints relevant to the claim), probable evidence (consistent results from small randomized placebo-controlled trials of the claimed substance or active ingredients contained therein in sufficient numbers of human subjects representative of the normal/target population, under normal conditions of use and assessing endpoints relevant to the claim and/or human epidemiological studies), possible (or supporting) evidence (consistent results from animal or in vitro studies of the claimed substance or active ingredients contained therein and assessing endpoints relevant to the claim) and insufficient evidence (inconsistent results and/or studies which do not consider the substance which is the subject of the claim and/or the target population and/or endpoints relevant to the claim). Below, a summary of the available evidence per health effect will be given. A detailed description and comments on individual meta-analyses, systematic reviews, and individual studies are given in Table 3.

Health effect 1: improved blood circulation

Treatment of the disease claudication intermittens is one of the best-known uses of *G. biloba*. There is a registered medicine on the market containing *G. biloba*, Tavonin®, which is used for patients that don't respond (enough) to walking exercise (16). In *patients* with claudicatio intermittens, a positive effect at a dose of 120 mg/day was seen in two meta-analyses (21, 22). However, a recent systematic review that included 739 patients from 14 trials (with different dosage and duration of treatment) didn't find a significant effect on walking distance in people with claudication intermittens (23). Such clinical studies, however, may not be considered pertinent to a claim for the general population.

'Cerebrovascular insufficiency' is an expression often used in literature concerning *G. biloba*. It is an inaccurate expression that is often used to describe a collection of symptoms associated with dementia (11) or the effects of reduced cerebral blood flow in the elderly (24). For the purpose of this evaluation, therefore, cerebrovascular insufficiency has been considered a disease. A systematic review by Kleijnen and Knipschild including patients with mild to moderate cerebrovascular insufficiency showed that treatment with 112–160 mg/day *G. biloba* for 4–6 weeks was effective for cerebrovascular insufficiency (24).

An overview of available studies in healthy subjects can be found in Table 3. Few human studies are available that have investigated specifically the microcirculation and improved blood circulation in healthy subjects consuming *G. biloba*. Santos et al. (25) did find a lower blood viscosity (determined with a rotational viscosimeter) in 48 older men that used 80 mg/day *G. biloba* extract for a period of 8 months. Another study by the same group also described a decreased blood viscosity (measured using 'Wells-Brookfield Cone/Plate Viscometer' DV-I) in 25 adult men taking 80 mg GB-STE a day (26). A randomized double blind placebo-controlled trial with 240 mg/day EGb761 for 3 weeks in 27 older subjects found a vasoregulation role of *G. biloba* (27). Unfortunately, the studies described above included different blood flow parameters, therefore, comparison of the studies is complicated.

We concluded there was insufficient evidence that GB-STE use results in improved blood circulation in healthy subjects.

Health effect 2: improvement of symptoms of old age

To enable scientific evaluation, a claim must include in the wording some reference to the target population and the health effect. Current practice within EFSA holds that such a claim is too vague for evaluation. 'Symptoms' and 'old age' need to be defined and the wording of the claim altered to reflect relevant measurable endpoints. If the claim was submitted through Article 13.1, it would not be evaluated. If submitted through Article 13.5, the dossier could be returned to the applicants who in some cases would be afforded the opportunity to re-word the claim to enable evaluation subsequent to re-submission.

Health effect 3: improved memory

Studies on Alzheimer and dementia show inconsistent results for the effect of *G. biloba* (28–31). In the latest updated version of a systematic review, looking at cognitive impairment and dementia, it was concluded that the evidence for a clinically significant benefit of *G. biloba* is unreliable (32).

A systematic review on the effects of *G. biloba* on the memory of healthy subjects concluded that *G. biloba* didn't improve memory (33). The results of several trials using *G. biloba* have been contradictory.

Most studies of *G. biloba* and aging have considered cognitive endpoints in subjects with mild impairment (13) or Alzheimer and dementia patients (28–31) with inconsistent results for a beneficial effect of *G. biloba*. In the latest updated version of a systematic review, looking at cognitive impairment and dementia, it was concluded that the evidence for a clinically significant benefit of *G. biloba* is unreliable (32). Studies employing clinical samples, however, cannot be considered pertinent to a claim for the general population. Evidence for benefit in healthy subjects is mixed.

A large trial including 262 healthy subjects aged 60 years and over, observed improved performance on validated memory tests with GB-STE (180 mg/day, 6 weeks) (34). In other trials, *G. biloba* did not enhance performance on tests of memory or other measures of cognitive function (35, 36). A double blind, longitudinal, intervention study by Dodge et al. (37) found some evidence for improved memory function in healthy elderly aged 85+years ($N=$ 118) treated with *G. biloba* (240 mg/day) compared to placebo after controlling for compliance. The observed effect, however, was weak and disappeared when other variables were controlled. That the subjects were also administered a multi-vitamin, may have confounded any effect for ginkgo. The authors do not appear to have declared the content of the placebo making it difficult to evaluate the report. The most recent trial, the GEM study, looking at cognitive decline in healthy older adults, did not find a difference in cognitive functioning between the *G. biloba* and the placebo group (38).

In a small ($N=20$) placebo-controlled study with GB-STE 240 or 360 mg/day, a positive effect was observed in young healthy volunteers in improvement in quality of memory and attention (39). However, this result could not be replicated in a similar study in the same study population (40). A double blind controlled study showed no effect of GB-STE 120 mg/day on the memory of healthy young males ($N=104$) (41).

In conclusion, there is insufficient evidence to substantiate the claim that *G. biloba* can improve memory in healthy subjects.

Toxicity

In the open literature there are no (animal) data on acute toxicity, carcinogenicity, reproduction toxicity, teratogenicity, neurotoxicity or immunotoxicity, but information on these toxicological endpoints are available in the Commission E monograph, ESCOP monograph, the EMEA report, and a recent NTP study (10, 19, 42). Reportedly, *G. biloba* is well absorbed upon oral intake in animals and human. However, this should be interpreted with care as *G. biloba* is an herbal preparation consisting of many components, which may show interactions. Indeed, most reports on kinetics focus on known ingredients of *G. biloba* such as ginkgolides A and B and bilobalide.

For GB-STE, low acute toxicity has been reported for rodents with LD50 values ranging from 1,100 (intravenous, rats and mice) to 7,725 mg/kg body weight (bw) (oral, mice). A 13-week gavage study in mice and rats with GB-STE (EGb761 dose levels 0, 65.5 [rats only], 125, 250, 500, 1,000 (rats and mice), and 2,000 (mice only) mg/kg bw per day) showed an increase in liver weight at all dose levels tested, and a dose-related increase in hepatocyte hypertrophy in male and female mice at and above 250 mg/kg bw and in male rats at all dose levels. In oral studies with rats and dogs during 6 months, a dose- and time-related mild temporary vasodilatation in cranial blood vessels was observed in dogs dosed at and above 100 mg GB-STE/kg bw from 35 days on (19).

Although GB-STE was reported not mutagenic in (among other tests) a Ames test by Commission E 1994 and ESCOP 2003, recently NTP (43) reported a positive Ames test. An *in vivo* micronucleus assay was negative for male mice, whereas for female mice the results were equivocal. ESCOP (19) reported no carcinogenic effects in a 2-year study in rats at dose levels of 4, 20, and 100 mg/kg bw. Oral administration of GB-STE to rats (up to 1.6 g/kg bw day) and rabbits (up to 0.9 g/kg bw day) did not show embryotoxic, teratogenic or reproduction toxicity effects (19).

GB-STE also contains GAS, to which immunotoxic, cytotoxic, mutagenic, and carcinogenic properties are ascribed (44–48). As a consequence, a maximum level for the presence of GAS in the GB-STE was set at 5 mg/kg (11). However, as not all *G. biloba* preparations included in the present study contain GB-STE, maximum levels of 5 mg/kg are not guaranteed, which may pose a health risk (49). Indeed, Chiu et al. (50) report higher levels (16–733 times) than 5 ppm in 13 of 14 *G. biloba* preparations.

Human studies

Reportedly, *G. biloba* is generally well tolerated by human (19, 51), albeit that some mild side effects have been reported [gastrointestinal complaints, headache, allergic skin reactions, nausea, dizziness, restlessness, heart palpitation, and weakness (16, 22, 51, 52)]. In addition to these mild effects, in several case studies side effects have been reported related to blood platelets, hemorrhage, and blood coagulation, which is in agreement with the PAF-inhibiting properties of *G. biloba* (53–61). In these case reports, reference is made to 'a ginkgo extract' or 'a ginkgo containing preparation,' without further specifications of the *G. biloba* preparation used. The duration and dose of intake of *G. biloba* prior to the reported PAF-related side effects ranges from 2 weeks to 2 years, respectively, 80–160 mg/day, well within the 'recommended' dose range.

Citation: Food & Nutrition Research 2010, **54**: 5221 - DOI: 10.3402/fnr.v54i0.5221

As for case studies on effects on bleeding, available data on interactions with drugs are also mainly associated with drugs involved in the treatment of blood coagulation and bleeding (53, 62–64). The ESCOP monograph (19) reports that there is no clear evidence for GB-STE on blood coagulation (alone or in combination with medicines). However, various case reports of interactions with drugs have been reported (16, 53, 54, 65–71). Interactions of herbal preparations with drugs are particularly relevant for drugs with a narrow therapeutic margin, it can result in more or stronger side effects or effect on the bioavailability of the drug (72, 73).

Although a direct causal relationship between *G. biloba* intake and observed effects in case studies is lacking (74), the absence of other risk factors, the PAF-inhibiting activity of *G. biloba*, and the disappearance of effects upon cessation of intake suggest such causality (59–61). The WHO has indicated to be careful with the use of *G. biloba* in combination with drugs that affect blood coagulation or platelet aggregation and to stop *G. biloba* use before a diagnostic treatment or an operation (49, 75).

Summarizing, the potential safety issues associated with *G. biloba* are severalfold. First, in most literature reports on *G. biloba*, the preparation used is not specified. There is no information on the levels of terpenoids, flavonoids, and GAS. Animal toxicity studies typically were performed with GB-STE, whereas in case studies no specification on the *G. biloba* preparation is given. Second, because of the immunotoxic, cytotoxic, carcinogenic, and genotoxic potential of GAS, the maximum level of GAS in GB-STE is limited to 5 ppm. However, if a preparation of *G. biloba* does not contain the GB-STE, a higher level of GAS cannot be excluded. Finally, *G. biloba* has PAF-antagonist activity, which may result in effects on platelet aggregation and blood coagulation. Indeed, there are various case studies reporting hemorrhages with intake of *G. biloba* preparations alone or in combination with drugs affecting platelet aggregation and blood coagulation. Moreover, the dose levels of case reports are within the range of 'recommended' dose levels. Nevertheless, exact dose levels are unknown. As a result of abovementioned available data, it is not possible to establish a safe level for intake of *G. biloba*.

Applicability of the PASSCLAIM criteria

There was insufficient evidence to substantiate the three selected health claims for *G. biloba*, when applying the PASSCLAIM criteria. However, there were some difficulties when applying the PASSCLAIM criteria. First, a clear definition of what sort of study sample constitutes a healthy target population is lacking. This relates to the representativeness of the study population for the target population. Asp and Bryngelsson (3) concluded that PASSCLAIM is useful for applicants for health claims and for the agencies that evaluate the evidence. Since herbal food supplements are intended for healthy persons, health claims for herbal food supplements have to be proven in studies performed with healthy persons who are representative of the target population. However, distinction between healthy, complaint and illness is not always clear (definition of 'a healthy person' is not clear). For this analysis we excluded patient studies, which left only a small number of available studies per health effect. The first opinions from EFSA seem to support this view (76).

Secondly, it is unclear to which degree a herbal supplement of an applicant should be identical to the product used in the human studies. Should they be exactly the same, or should they contain the same standardized extract? This study showed that most studies are performed reportedly using standardized *G. biloba* extract, but also that nearly every product found in the Dutch shops was not in conformity with the label declaration. When a claim can be substantiated using those studies, the product that sets the claim should resemble the standardized extract.

Thirdly, the PASSCLAIM criteria 4 and 5 require consideration of specific markers, or endpoints, depending on the type of claim made. Evaluation by an expert committee is recommended.

Finally, the procedure for weighing the evidence was not described in detail in the PASSCLAIM project. We used the WHO criteria to weigh the evidence. In contrast to the USA, where qualified health claims are allowed (77), the EU Regulation 1924/2006 was not designed for supporting qualified health claims. However, qualification of the evidence according to the WHO criteria has proved useful for scientific purposes. The value of such criteria in consumer communication has not yet been established. Indeed, in the USA experience, consumers do not make the anticipated distinction between substantiated and not substantiated (=qualified) health claims (2, 77–80). Hence the need for interdisciplinary groups of expert scientists to monitor and evaluate such claims.

Limitations of the study

There were some limitations of the present study. Firstly, there was no case with product-specific information, delivered by a manufacturer, to evaluate. Therefore, a search of publicly available literature was performed. It is possible that information is missing, e.g. information from negative or null trials or unpublished proprietary or confidential studies. In future, EFSA evaluations will endeavor to include all available information, including confidential data, for the substantiation of Article 14 and 13.5 claims. Secondly, regarding the *G. biloba* products that were included in this study, the sampling of these products was random from Dutch shops.

That the search was not exhaustive leaves the possibility that there were products available for purchase which were not analyzed and which contained at least the

minimum amount of *G. biloba* extract. The finding that the standardized 24% of *G. biloba* extract is often not incorporated into the food supplements, nevertheless, raises doubts as to the efficacy of such products. This analysis has also implied that it is not possible to establish a safe level for intake of *G. biloba.* Review of the science provided insufficient evidence with which to substantiate the three claims for *G. biloba.* In conclusion, the claim *G. biloba* and improvement in the symptoms of old age could not be evaluated. A cause and effect relationship between *G. biloba* and improved circulation or memory has not been established.

Conclusions and recommendations

The main conclusions in this study were:

- Three selected health claims for *G. biloba* could not be substantiated.
- Neither safety nor efficacy can be guaranteed at the recommended daily dose.
- The content of *G. biloba* containing products often did not conform to what was declared on the label.
- A multidisciplinary approach is needed to get insight in the relevant issues for health claim evaluation.

Moreover, the PASSCLAIM criteria need to be developed in more detail when used for general application on health claim substantiation for herbal supplements and there is also a need for clarification of the study conditions that are required for claim substantiation, especially with respect to patient studies. A multidisciplinary approach is recommended to assess health claims: analyses of substances typical for *G. biloba* in the products and toxicological risk assessment are needed for a full assessment. This provides a good insight into the several aspects that are significant for the evaluation of health claims for herbal substances.

Acknowledgements

We would like to thank Marja Pronk, Ellen de Rooij, and Bert Jan Baars (RIVM) for their valuable input. We also thank Martijn Martena (VWA) for his input during the first phases of the project.

Conflict of interest and funding

The authors have not received any funding or benefits from industry to conduct this study.

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