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

Heidi P. Fransen¹*, Sylvia M.G.J. Pelgrom¹#, Barbara Stewart-Knox², Dries de Kaste¹ and Hans Verhagen¹,²

¹National Institute for Public Health and the Environment (RIVM), Bilthoven, the Netherlands; ²Northern Ireland Centre for Food and Health (NICHE), University of Ulster, Coleraine, Northern Ireland

#Present affiliation: NOTOX BV

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/C3029) 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
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 bilobalide (Table 1). The concentration of ginkgolic acid

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

Ginkgolic acid Below 5 ppm

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).

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
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 x 1 capsule          | 10.1                                              | Yes                                                                             | 38.4                                        | Yes                                                                           | Yes                                                                              | Yes                       |
| 7967        | Ginkgo biloba extract (24%) | 1 x 1-2 capsules      | 2.8                                               | No                                                                              | 12.9                                        | Yes, only at maximum dose                                                      | No                                                                              | Yes                       |
| 7968        | Ginkgo biloba extract (24% Ginkgo flavoglycosides + 6% terpene lactones) 60 mg/capsule | 1 x 2 capsules        | 4.5                                               | Yes                                                                             | 16.1                                        | Yes                                                                           | Yes                                                                              | Yes                       |
| 7969        | Ginkgo biloba             | 3 x 2 capsules        | 0.9                                               | No                                                                              | 0.3                                         | No                                                                            | No                                                                              | Yes                       |
| 7970        | Ginkgo biloba folia 80 mg/tablet | 1 x 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 x 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 x 1 capsule        | 5.9                                               | Yes                                                                             | 12.4                                        | Yes                                                                           | Yes                                                                              | No                        |
| 7973        | Ginkgo biloba 96 mg/capsule | 3 x 1 capsule         | 0.3                                               | No                                                                              | 2.3                                         | No                                                                            | No                                                                              | Yes                       |
| 7974        | Ginkgo biloba, 50% 100 mg/tablet | 3 x 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 x 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 x 10-20 droplets    | 0.5                                               | Yes                                                                             | NA                                          | NA                                                                            | Unknown                                                                         | Yes                       |
| 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/capsules | 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 24 × 25 droplets                                                              | 1 × 1 tablet           | 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% ginkgo flavon 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                                                                            | 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                                                                            | Yes                          |
| 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)     | 3 x 1 capsule          | 1.1                                              | No                                                                              | 2.1                             | No                                                                                          | No                                                     | Yes                         |
| 7989       | Ginkgo biloba (24% extract: 24% flavoglycosides and 6% terpenes) 60 mg/capsule | 3 x 1 capsule          | 4.8                                              | Yes                                                                             | 15.1                            | Yes                                                                                          | Yes                                         | Yes                         |
| 7990       | Ginkgo biloba (24%)      | 1 x 1 capsule          | 4.0                                              | No                                                                              | 50.1                            | Yes                                                                                          | No                                                      | Yes                         |
| 7991       | Ginkgo biloba extract    | 1 x 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 x 1-2 capsules       | 2.7                                              | No                                                                              | 7.6                             | No                                                                                          | No                                                      | Yes                         |
| 7993       | Ginkgo biloba extract    | 1 x 1-2 tablets        | &                                                | No                                                                              | 4.0                             | No                                                                                          | No                                                      | Yes                         |
| 7994       | Ginkgo biloba extract    | 1 x 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 x 1 tablet           | 2.2                                              | Yes                                                                             | 9.0                             | Yes                                                                                          | No                                                      | Yes                         |

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. 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.
### 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 |
| 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% ginkgo-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.* | 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 | | Standardized *Ginkgo biloba* extracts: EGb761 (24% flavonoid glyco, 6% terpene lactones) GKS01 (24% flavo, 6% terpene) LI1370 (27% flavo, 7% terpene) *Ginkgo biloba* forte (24% flavo, 6% terpene) | 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 | Study design + duration | Study population (N, age group) | Information on background diet, matrix and compliance? |
|-------------------------------|------------|-----------------------------------|------------------------|-------------------------------|------------------------------------------------------|
| **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 |
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: weighted 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, tinnitus, 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 neuropsychological 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)) | 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) \( p = 0.02 \). | 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** | **Specification Ginkgo biloba + dose (PASSCLAIM criterion I + 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 ginkgo flavonglycoside, 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 LI1370: 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. |
| Intermediary of health effect | References | Specification *Ginkgo biloba* + dose (PASSCLAIM criterion I + 2E) | Study design + duration (PASSCLAIM criterion 2) | Study population (N, age group) (PASSCLAIM criteria 2A + 2B) | Information on background diet, matrix, and compliance? |
|-------------------------------|------------|---------------------------------------------------------------|-----------------------------------------------|---------------------------------------------------------------|-----------------------------------------------------|
| 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 GKS01: 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 | Randomized, placebo-controlled, double-blind, 42-month pilot study | Cognitively intact subjects, N = 118 | 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 hemostasis, 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 I + 2) | 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 | Ciezla 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 | Study design + duration | Study population (N, age group) | Information on background diet, matrix, and compliance? |
|-------------------------------|------------|---------------|--------------------------|--------------------------------|-----------------------------------------------------|
| **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 biloba-lide) | 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: sequel 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 |
| Intermediary of health effect | 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 | Restriction on vitamin E intake |
|                               |                                                             |                                               | 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. |
| 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 | Specification Ginkgo biloba + dose (PASSCLAIM criterion I +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 on psychological 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 |
| 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**<br> 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: 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 | 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. |
| References | Test methods (PASSCLAIM criteria 3 + 4) | Effect size (per dosing or time) (PASSCLAIM criteria 2H + 5) | Remarks |
|------------|----------------------------------------|---------------------------------------------------------------|---------|
| Burns et al. (41) | Study 2: test performed pre- and post-intervention (12 weeks) cognitive abilities testing | 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. |
| Canter | 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) | | |
| Elsabagh et al. (83) | 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: PASAT difference 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; FACP recognition of faces, CRSPST 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. |
| 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.                                           |
| 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 |
| 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. |
| 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:** study confirms that single dose of Ginkgo biloba exerts effects on cerebral bioelectrical activity in healthy, young volunteers.

**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.

**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.

**Conclusion authors:** largely ineffective in enhancing memory

**Comment:** no baseline measurements, in order to avoid practice effects; comparability of the two groups assumed.
| 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, 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 (articulatory 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 tasks (DSST); line analog rating scales for subjective sedation (LSEQ); 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. |
| 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 neurologist, 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. |
| 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 | 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. |
| 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. |
### Table 3b (Continued)

| 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 GBE761 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 GBE761 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. |
| 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. Comments: 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. Comments: no placebo used; no baseline measurements; sequel to study mentioned above; subjects selected their own treatment option. |
| 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 months Primary 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) | Intention 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 viscometer) 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 hepato-cyte 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.
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...
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.

References
1. Regulation (EC) No 1924/2006 of the European Parliament and of the Council of 20 December 2006 on nutrition and health claims made on foods. Official J Eur Union 2007; 50: 3-18. Available from: http://eur-lex.europa.eu/LexUriServ/site/en/oj/2007/L_012/L_0122/20071118en00300118.pdf [cited 30 November 2009].
2. Verhagen H, Vos E, Frandel S, Heinonen M, van Loveren H. Status of nutrition and health claims in Europe. Arch Biochem Biophys 2010; 501: 6-15.
3. Asp NG, Bryngelsson S. Health claims in Europe: new legislation and PASSCLAIM for substantiation. J Nutr 2008; 138: 1210S-SS.
4. Verhagen H. The current status of nutrition and health claims in Europe. J Clin Biochem Nutr 2008; 43: 1–5.
5. European Food Safety Authority. Nutrition and health claims – Article 14. Available from: http://www.efsa.europa.eu/en/ndaclaims/ndaclaims14.htm [cited 30 November 2009].
6. European Food Safety Authority. Nutrition and health claims – Article 13. Available from: http://www.efsa.europa.eu/en/ndaclaims/ndaclaims13.htm [cited 30 November 2009].
7. European Food Safety Authority. Scientific and technical guidance for the preparation and presentation of the application for authorisation of a health claim. Opinion of the scientific panel on dietetic products, nutrition and allergies. EFSA J 2007; 530: 1-44.
8. Aggett PJ, Antoine JM, Asp NG, Bellisle F, Contor L, Cummings JH, et al. PASSCLAIM: consensus on criteria. Eur J Nutr 2005; 44: i5–30.
9. ILSI. Information on the PASSCLAIM project. Available from: http://europe.ilsio.org/activities/ecprojects/PASSCLAIM/ [cited 30 November 2009].
10. Blumenthal M, Busse WREa. The Complete German Commission E Monographs – therapeutic guide to herbal medicines. Austin: American Botanical Council; 1998.
11. WHO. WHO monographs on selected medicinal plants: folium Ginkgo. Vol. 1. Geneva: WHO; 1999, pp. 154-67.
12. Mahadevan S, Park Y. Multifaceted therapeutic benefits of Ginkgo biloba L.: chemistry, efficacy, safety, and uses. J Food Sci 2008; 73: R14-9.
13. Ponto LL, Schultz SK. Ginkgo biloba extract: review of CNS effects. Ann Clin Psychiatry 2003; 15: 109–19.
14. Martena MJ. Dossiercontrole kruidenpreparaten. Inspecties en inzicht in de aanwezigheid en kwaliteit van dossiers ter onderbouwing van gezondheidsclaims bij kruidenpreparaten. VWA/Ks/W regio Zuid; 2004, (Dutch)
15. Meahesh MK, Khalifa SI, El-Gindy A, Tawfik KA. HPLC determination of certain flavonoids and terpene lactones in selected Ginkgo biloba L. phytopharmaceuticals. Farmaco 2005; 60: 583–90.
16. CBG (College ter Beoordeling van Geneesmiddelen), Tavonin. IB; Samenvatting van de kenmerken van het product (Dutch). Available from: http://www.cbg-meh.nl/CGB/nl/humane-geneesmiddelen/geneesmiddeleninformatiebank/default.htm [cited 30 November 2009].
17. CBG (College ter Beoordeling van Geneesmiddelen). Geneesmiddeleninformatiebank (Dutch). Available from: http://www.cbg-meh.nl/CGB/nl/humane-geneesmiddelen/geneesmiddeleninformatiebank/default.htm [cited 30 November 2009].
18. Besluit Geneesmiddelenwet. Available from: http://wetten.overheid.nl/bwwr0021672; 2007 [cited 30 November 2009].
19. ESCOP. The scientific foundation for herbal medicinal products. 2nd ed. Exeter: ESCOP Monographs; 2003.
20. WHO. Diet, nutrition and the prevention of chronic diseases. Report of the joint WHO/FAO expert consultation WHO
Technical Report Series, No. 916 (TRS 916). Geneva: WHO; 2003.
21. Horsch S, Walther C. Ginkgo biloba special extract EGb 761 in the treatment of peripheral arterial occlusive disease (PAOD) – a review based on randomized, controlled studies. Int J Clin Pharmacol Ther 2004; 42: 63–72.
22. Pittler MH, Ernst E. Ginkgo biloba extract for the treatment of intermittent claudication: a meta-analysis of randomized trials. Am J Med 2000; 108: 276–81.
23. Nicolai SP, Kruidenier LM, Bendermacher BL, Prins MH, Teijink JA. Ginkgo biloba for intermittent claudication. Cochrane Database Syst Rev 2009; 2: CD006888.
24. Ivens TA, Goldstein N, Witterda C, Walther C. The nootropic effects of Allium sativum and Ginkgo biloba. Phytopharmacology 2007; 14: 447–51.
25. Boelsma E, Lamers RJ, Hendriks HF, van Nesselrooij JH, Roza L. Evidence of the regulatory effect of Ginkgo biloba extract on skin blood flow and study of its effects on urinary metabolites in healthy humans. Planta Med 2004; 70: 1052–7.
26. DeKosky ST, Williamson JD, Fitzpatrick AL, Krommal RA, Ives DG, Saxton JA, et al. Ginkgo biloba for prevention of dementia: a randomized controlled trial. JAMA 2008; 300: 2253–62.
27. Cicero AF, Cao F, Song Y, et al. Ginkgo biloba extract for the treatment of peripheral arterial occlusive disease (PAOD). Cochrane Database Syst Rev 2009; 2: CD003120.
28. Bursi F, De Rijk MR, de Vries E, van Gils J. Ginkgo biloba leaf extracts using the popliteal lymph node assay in the mouse. Int J Immunopharmacol 2002; 24: 229–36.
29. Baron-Ruppert G, Luepke NP. Evidence for toxic effects of alkanol extracts from Ginkgo biloba L. in vivo. Toxicology 2002; 177: 167–77.
30. Krieglstein J, Ahlemeyer B, Selke D, Schaper C, Klumpf S. Ginkgo biloba induces neuronal death and activates protein phosphatase type-2C. Eur J Pharmacol 2001; 430: 1–7.
31. Benjamin J, Muir T, Briggs K, Pentland B. A case of cerebral haemorrhage associated with Ginkgo biloba extract. Postgrad Med J 2001; 77: 112–7.
32. Ahlemeyer B, Selke D, Schaper C, Klumpf S, Krieglstein J. Ginkgo biloba leaf extracts in healthy people. Hum Psychopharmacol 2002; 17: 267–77.
33. Solomon PR, Adams F, Silver A, Zimmer J, DeVeaux R. Ginkgo for memory enhancement: a randomized controlled trial. JAMA 2002; 288: 835–40.
34. Campbell S, Facqhr J, Mazzetti P, Rossi P, Piepoli M, et al. Safety and efficacy of Ginkgo biloba-containing dietary supplement on cognitive function, quality of life, and platelet function in healthy, cognitively intact older adults. J Am Diet Assoc 2007; 107: 422–32.
35. Snitz BE, O’Meara ES, Carlson MC, Arnold AM, Ives DG, Rapp SR, et al. Ginkgo biloba for preventing cognitive decline in older adults: a randomized trial. JAMA 2009; 302: 2663–70.
systematic review of the literature: a case report and systematic review of the literature. J Gen Intern Med 2005; 20: 657-61.

59. Vale S, Suhrarnekt haemorrhage associated with Ginkgo biloba. Lancet 1998; 352: 36.

60. Schneider C, Bord C, Misse P, Arnaud B, Schmitt-Bernard CF. Spontaneous hyphema caused by Ginkgo biloba extract. J Fr Ophthalmo 2002; 25: 731–2.

61. Yagmur E, Piatkowski A, Groger A, Pallua N, Gressner AM, Kiefer P. Bleeding complication under Ginkgo biloba medica- tion. Am J Hematol 2005; 79: 343–4.

62. Evans V. Herbs and the brain: friend or foe? The effects of ginkgo and garlic on warfarin use. J Neurosci Nurs 2000; 32: 229–32.

63. De Smet PA. Herbal remedies. N Engl J Med 2002; 347: 2046–56.

64. Abebe W. Herbal medication: potential for adverse interactions with analgesic drugs. J Clin Pharm Ther 2002; 27: 391–401.

65. Meisel C, Johne A, Roots I. Fatal intracerebral mass bleeding associated with Ginkgo biloba and ibuprofen. Atherosclerosis 2003; 167: 367.

66. Rowin J, Lewis SL. Spontaneous bilateral subdural hematomas associated with chronic Ginkgo biloba ingestion. Neurology 1996; 46: 1775–6.

67. Fessenden JM, Wittenborn W, Clarke L. Ginkgo biloba and garlic on warfarin use. J Neurosci Nurs 2000; 32: 229–32.

68. Hauser D, Gayowski T, Singh N. Bleeding complications precipitated by unrecognized Ginkgo biloba use after liver transplantation. Transpl Int 2005; 18: 377–9.

69. Izzo AA, Ernst E. Interactions between herbal medicines and prescribed drugs: a systematic review. Drugs 2001; 61: 2163–75.

70. Houser D, Gayowski T, Singh N. Bleeding complications precipitated by unrecognized Ginkgo biloba use after liver transplantation. Transpl Int 2005; 18: 377–9.

71. Rosenblatt M, Mindel J. Spontaneous hyphema associated with ingestion of Ginkgo biloba extract. N Engl J Med 1997; 336: 1108.

72. Beck AM, DeWitt BA, Lukes AL. Potential interactions between alternative therapies and warfarin. Am J Health Syst Pharm 2000; 57: 1221–7 (quiz 1228–30).

73. Yoshioke M, Ohnishi N, Koihi T, Obata Y, Nakagawa M, Matsumoto T, et al. Studies on interactions of functional foods or dietary supplements and medicines. IV. Effects of Ginkgo biloba leaf extract on the pharmacokinetics and pharmacodynamics of nifedipine in healthy volunteers. Biol Pharm Bull 2004; 27: 2006–9.

74. Bone KM. Potential interaction of Ginkgo biloba leaf with antplatelet or anticoagulant drugs: what is the evidence? Mol Nutr Food Res 2008; 52: 764–71.

75. WHO. Natural health products and drug interactions. WHO Drug Inf 2004; 18: 120–1. Available from: http://www.who.int/ druginformation [cited 30 November 2006].

76. EFSA. Nutrition and Health Claims. Available from: http://www.efsa.europa.eu/EFSA/esfala_locale-1178620753812_1178621456747.htm; 2004 [cited 30 November 2009].

77. Rowlands JC, Hoadley JE. FDA perspectives on health claims presentations for qualified health claims. Crit Rev Food Sci Nutr 2008; 48: 248–56.

78. Hooker NH, Teratanavarit R. Dissecting qualified health claims: evidence from experimental studies. Crit Rev Food Sci Nutr 2008; 48: 160–76.

79. Mehlsen J, Draback H, Winberg N, Winther K. Effects of a Ginkgo biloba extract on forearm haemodynamics in healthy volunteers. Clin Physiol Funct Imaging 2002; 22: 375–8.

80. Hopfenmuller W. Evidence for a therapeutic effect of Ginkgo biloba special extract. Meta-analysis of 11 clinical studies in patients with cerebrovascular insufficiency in old age. Arzneimittelforschung 1994; 44: 1005–13 (German).

81. Elsahagh S, Hartley DE, Ali O, Williamson EM, File SE. Differential cognitive effects of Ginkgo biloba after acute and chronic treatment in healthy young volunteers. Psychopharmacology (Berl) 2005; 179: 437–46.

82. Persson J, Bringlov E, Nilsson LG, Nyberg L. The memory-enhancing effects of Ginseng and Ginkgo biloba in healthy volunteers. Psychopharmacology (Berl) 2004; 172: 430–4.

83. Kennedy DO, Scholey AB, Brewley L, Marsh VR, Moore B, Ashton H. Electroencephalograph effects of single doses of Ginkgo biloba and Panax ginseng in young volunteers. Pharmacol Biochem Behav 2003; 75: 701–9.

84. Hartley DE, Heinze L, Elsahagh S, File SE. Effects on cognition and mood in postmenopausal women of 1-week treatment with Ginkgo biloba. Pharmacol Biochem Behav 2003; 75: 711–20.

85. Canter PH, Ernst E. Ginkgo biloba: a smart drug? A systematic review of controlled trials of the cognitive effects of Ginkgo biloba extracts in healthy people. Psychopharmacol Bull 2002; 36: 108–23.

86. Stough C, Clarke J, Lloyd J, Nathan PJ. Neuropsychological changes after 30-day Ginkgo biloba administration in healthy participants. Int J Neuropsychopharmacol 2001; 4: 131–4.

87. Moulton PL, Boyko LN, Fitzpatrick JL, Petros TV. The effect of Ginkgo biloba on memory in healthy male volunteers. Physiol Behav 2001; 73: 659–65.

88. Rigney U, Kimber S, Hindmarsh I. The effects of acute doses of standardized Ginkgo biloba extract on memory and psychomotor performance in volunteers. Phytother Res 99; 13: 408–15.

89. DeKosky ST, Fitzpatrick A, Ives DG, Saxton J, Williamson J, Lopez OL, et al. The Ginkgo Evaluation of Memory (GEM) study: design and baseline data of a randomized trial of Ginkgo biloba extract in prevention of dementia. Contemp Clin Trials 2006; 27: 238–53.

90. Cieza A, Maier P, Poppel E. Effects of Ginkgo biloba on mental functioning in healthy volunteers. Arch Med Res 2003; 34: 373–81.

91. Nathan PJ, Ricketts E, Wesnes K, Mrazek L, Greville W, Stough C. The acute nootropic effects of Ginkgo biloba in healthy older human subjects: a preliminary investigation. Hum Psychopharmacol 2002; 17: 45–9.

92. Cockle SM, Kimber S, Hindmarsh I. The effects of Ginkgo biloba extract (LI 1370) supplementation on activities of daily living in free living older volunteers: a questionnaire survey. Hum Psychopharmacol 2000; 15: 227–35.

93. Trick L, Boyle J, Hindmarsh I. The effects of Ginkgo biloba extract (LI 1370) supplementation and discontinuation on activities of daily living and mood in free living older volunteers. Phytother Res 2004; 18: 531–7.

94. van Dongen M, van Rossum E, Kessels A, Siehorst H, Knipschild P. Ginkgo for elderly people with dementia and age-associated memory impairment: a randomized clinical trial. J Clin Epidemiol 2003; 56: 367–76.

Citation: Food & Nutrition Research 2010, 54: 5221 - DOI: 10.3402/fnr.v54i05221
97. van Dongen MC, van Rossum E, Kessels AG, Sielhorst HJ, Knipschild PG. The efficacy of ginkgo for elderly people with dementia and age-associated memory impairment: new results of a randomized clinical trial. J Am Geriatr Soc 2000; 48: 1183–94.

98. Oken BS, Storzbach DM, Kaye JA. The efficacy of Ginkgo biloba on cognitive function in Alzheimer disease. Arch Neurol 1998; 55: 1409–15.

*Heidi P. Fransen
National Institute for Public Health and the Environment (RIVM)
Bilthoven, the Netherlands
Email: heidi.fransen@rivm.nl