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Ginkgo biloba for cerebral insufficiency

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1 By means of a critical review we tried to establish whether there is evidence from controlled trials in humans on the efficacy of *Ginkgo biloba* extracts in cerebral insufficiency.

2 The methodological quality of 40 trials on Ginkgo and cerebral insufficiency was assessed using a list of predefined criteria of good methodology, and the outcome of the trials was interpreted in relation to their quality. A comparison of the quality was made with trials of co-dergocrine, which is registered for the same indication.

3 There were eight well performed trials out of a total of 40. Shortcomings were limited numbers of patients included, and incomplete description of randomization procedures, patient characteristics, effect measurement and data presentation. In no trial was double-blindness checked. Virtually all trials reported positive results, in most trials the dosage was 120 mg Ginkgo extract a day, given for at least 4–6 weeks. For the best trials, there were no marked differences in the quality of the evidence of the efficacy of Ginkgo in cerebral insufficiency compared with co-dergocrine. The results of the review may be complicated by a combination of publication bias and other biases, because there were no negative results reported in many trials of low methodological quality.

4 Positive results have been reported for *Ginkgo biloba* extracts in the treatment of cerebral insufficiency. The clinical evidence is similar to that of a registered product which is prescribed for the same indication. However, further studies should be conducted for a more detailed assessment of the efficacy.

Keywords *Ginkgo biloba* review controlled trials mental functioning

Introduction

Extracts from the leaves of the *Ginkgo biloba* tree (maidenhair tree) are used by patients with complaints of peripheral vascular disease such as intermittent claudication, and in the treatment of cerebral insufficiency. Twelve symptoms in elderly people would be typical for cerebral insufficiency and are claimed to be relieved by treatment with Ginkgo: difficulties of concentration and memory, being absent minded, being confused, lack of energy, tiredness, decrease of physical performance, depressive mood, anxiety, dizziness, tinnitus and headaches. These symptoms have been associated with decreased cerebral circulation; sometimes they are considered early symptoms of dementia either of the degenerative or the multiple infarctions type. Often no explanation for the symptoms is found.

Several mechanisms of action from Ginkgo extracts have been described (Braquet, 1988; DeFeudis, 1991; Drieu, 1986; Schilcher, 1988; Wagner *et al.*, 1989): (1) Effects on blood circulation such as vasoregulating activity of arteries, capillaries, veins (increased blood flow) and rheological effects (decreased viscosity, antagonistic to platelet activating factor receptors); (2) Metabolic changes, for example on neuron metabolism (increased tolerance for anoxia); (3) Beneficial influence on neurotransmitter disturbances; (4) Prevention of damage of membranes caused by free radicals. These effects may be caused by single active ingredients, or by the combined action of the many active agents found in Ginkgo extracts. The most important are considered flavonoid substances (Ginkgo-flavone glycosides, bioflavonoids) and terpenoids (ginkgolides and bilobalide).

There are four Ginkgo preparations which have been used in controlled trials: Tebonin®, Tanakan®, rökan® and Kaveri®. The first three are different names for the same extract called EGb 761, and they are standardized on the amount of Ginkgo-flavone glycosides (24%) and

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Table 1 Methodological assessment of studies on Ginkgo and cerebral insufficiency

First author	*Year*	*Preparation*	*Result*	*CH*	*NU*	*RA*	*IN*	*DB*	*EF*	*DA*	*Total*
Maximum				10	30	20	5	20	10	5	100
Schmidt	1991	Kaveri	sign.	10	20	20	5	20	10	5	90
Brüchert	1991	Kaveri	sign.	10	30	10	5	10	10	5	80
Meyer	1986a	Tanakan	sign.	10	20	10	5	20	10	5	80
Taillander	1986	Tanakan	sign.	10	25	10	5	20	10	0	80
Haguenauer	1986	Tanakan	sign.	10	10	20	5	20	10	3	78
Vorberg	1989	Kaveri	sign.	10	15	10	5	20	10	5	75
Eckmann	1990	Kaveri	sign.	10	10	10	5	20	7	5	67
Wesnes	1987	Tanakan	sign.	7	10	10	5	20	10	5	67
Arrigo	1986	Tebonin	sign.	9	15	10	5	10	10	3	62
Augustin	1976	Tanakan	sign.	6	25	10	5	10	5	0	61
Halama	1991	Kaveri	sign.	10	0	10	5	20	10	5	60
Meyer	1986b	Tanakan	sign.	10	25	10	0	0	10	5	60
Halama	1988	Tebonin	sign.	8	0	10	5	20	10	3	56
Chesseboeuf	1979	Tanakan	pos.	10	10	20	5	0	5	5	55
Maier-Hauff	1991	Kaveri	sign.	10	0	10	5	20	8	0	53
Weitbrecht	1986	Tebonin	sign.	10	0	5	5	20	10	3	53
Schwerdtfeger	1981	Rökan	sign.	8	0	5	5	20	10	5	53
Moreau	1975	Tanakan	sign.	3	10	10	5	20	3	0	51
Dieli	1981	Tanakan	sign.	7	0	5	5	20	8	5	50
Eckmann	1982	Tebonin	sign.	5	10	10	5	10	5	5	50
Dubreuil	1986	Tanakan	pos.	9	0	20	5	5	10	0	49
Hofferberth	1991a	Kaveri	sign.	5	10	10	5	10	8	0	48
Hofferberth	1991b	Rökan	sign.	6	0	5	5	20	5	5	46
Rai	1991	Tanakan	pos.	8	0	10	5	20	3	0	46
Franco	1991	Tanakan	pos.	5	10	10	5	0	10	5	45
Hofferberth	1989	Rökan	sign.	5	0	5	5	20	5	5	45
Israël	1987	Tanakan	pos.	6	0	5	5	20	8	0	44
Haan	1982	Tebonin	pos.	6	10	10	5	0	8	5	44
Claussen	1984	Rökan	sign.	6	0	5	5	20	5	3	44
Gerhardt	1990	?	pos.	6	10	10	5	0	10	0	41
Hartmann	1991	Kaveri	neg.	6	10	0	5	10	8	0	39
Gessner	1985	Rökan	pos.	4	0	5	5	10	8	5	37
Agnoli	1980	Tebonin	sign.	6	0	5	5	10	10	0	36
Hamann	1985	Tebonin	pos.	8	0	5	5	10	5	3	36
Teigeler	1984	Tebonin	pos.	3	0	5	5	10	3	5	31
Pidoux	1983	Tanakan	sign.	3	0	5	5	10	5	0	28
Chartres	1987	Tanakan	pos.	8	0	5	0	10	5	0	28
Natali	1979	Tanakan	pos.	7	0	0	5	0	10	5	27
Bono	1975	Tanakan	sign.	4	0	0	5	10	5	0	24
Israël	1977	Tanakan	pos.	3	0	0	5	0	5	5	18

Total: total number of points scored
sign.: index group fared better (author stated that result was significant)
pos.: positive trend (or significant effect for only some of the effect measurements)
neg.: no difference between Ginkgo and placebo groups

(CH) Patient characteristics; (NU) Number of patients per group; (RA) Randomization; (IN) Intervention well described; (DB) Double blind; (EF) Effect measurement well described; (DA) Data presentation.

terpenoids (6%). The fourth is standardised on the same ingredients in comparable dosages (25% Ginkgoflavone glycosides, and recently also 6% terpenoids). The dosage is 3 tablets of 40 mg Ginkgo extract a day, given for at least 4–6 weeks.

In Germany, *Ginkgo biloba* is one of the most frequently prescribed drugs: more than 5 million prescriptions in 1988, at a cost for the health insurance of 370 million DM (Anonymous, 1989; Schwabe & Paffrath, 1989). In 1989, this cost was for Tebonin alone 219 million DM, and for rökan 62 million DM. This is by far the highest amount, followed by Adalat (nifedipine) with 195 million DM (Schwabe & Paffrath, 1990). In France there is also a large Ginkgo market, whereas in other countries such as the Netherlands, the U.K. and the U.S.A. most people and physicians have never heard of Ginkgo.

In this article, the evidence from controlled trials in humans of the clinical efficacy of *Ginkgo biloba* will be presented. The methodological quality of those trials will be emphasized. Because Ginkgo is not registered in many countries, we also compared the quality of the evidence with that of a widely registered product for similar indications: ergoloid mesylates, also called co-dergocrine (Hydergine®) for cerebral insufficiency.

Methods

Trials in humans assessing the effects of Ginkgo on clinical symptoms on cerebral insufficiency were

eligible if parallel index and control groups were included. Crossover trials were also eligible. Trials in healthy volunteers were excluded.

Experiments were found by means of various strategies: (1) computer searches: MEDLINE online 1966–91 (Keyword: *Ginkgo biloba*) and EMBASE online 1974–91 (Keywords: Ginkgo, *Ginkgo biloba*); (2) checking references extensively, in articles on clinical research and in textbooks (DeFeudis, 1991; Fünfgeld, 1988); (3) personal communication with researchers; (4) correspondence with and visiting major manufactuers of *Ginkgo biloba* medications. Trials published in any language were eligible, without restrictions. Interestingly, one trial we knew of was not identified in our computer search (Halama, 1988). When we checked, it turned out that this publication can be found using the free text term *Gingko*. We identified several other articles on Ginkgo in which the word was spelled as Gingko! It could well be that in other subjects this problem of computer searches will also occur.

We asked the manufacturer of Hydergine® to send us the best clinical trials of their product. We compared the best studies of *Ginkgo biloba* with five studies of Hydergine®.

To explore the possibility that an increasing number of methodological shortcomings is reflected in the results of the trials, criteria for a methodological assessment of the experiments were established. A motivation and discussion of these criteria and scores has been published earlier (Kleijnen *et al.*, 1991a).

Starting from a maximum score of 100 points, we divided these among seven methodological criteria.

1) *Patient characteristics adequately described: 10 points* Description of the patients (gender, age, hospitalized or outpatient) and the symptoms, including their duration and severity.

2) *Number of patients analyzed: 30 points* 100 or more patients per group = 30 points, 75–99 patients per group = 25 points, 50–74 patients = 20 points, 40–50 patients = 15 points, 25–40 patients = 10 points. A crossover trial with 70 participants (35 given active treatment and 35 placebo in each period) would score 10 points (Kleijnen *et al.*, 1991b).

3) *Randomization: 20 points* Twenty points if the method of randomization was described and correct, 10 points if the method was not described or if some form of pseudo-randomization was applied. If there were fewer than 25 participants per group, half the score was given unless there was prestratification (matching) on relevant items and a table showing comparable baseline characteristics.

4) *Intervention well described: 5 points* Administration of Ginkgo preparations: doses and duration of treatment.

5) *Double-blinding: 20 points* Twenty points if the placebo was described as indistinguishable, 10 points if double-blinding was only mentioned.

6) *Effect measurement relevant and well described: 10 points* Measurement of the effect must be sensible and reproducible. Five points each for relevance and adequate description.

7) *Presentation of the results in such a manner that the analysis can be checked by the reader: 5 points* Depending on the effect measurement, at least the mean(s) and standard deviation, standard error, or confidence interval in each group must be mentioned, or the number of patients with a certain outcome (for example, if rates or proportions were used).

Sometimes only part of the score was given if the description was unclear, or if only some of several interventions, measurements of outcome, or data presentations met the criteria. In the second criterion we chose to use the number of patients analyzed instead of the number randomized because in many publications dropouts were not accounted for. For the effect measurement, because we wanted to know whether Ginkgo treatment reduces the patient's complaints, we considered clinical effects (severity of symptoms) more important than pathophysiological effects, such as an electroencephalogram. As for the statistical criterion, we did not demand confidence intervals for the comparisons between groups because then virtually no trials would score the criterion.

All articles were scored at least twice, and differences mostly caused by reading errors were resolved by discussions. The largest difference was 15 points. Assessment of articles using these criteria provides a score that gives an indication of the methodological quality of each trial.

Results

In Germany, 20 studies have been performed for cerebral insufficiency; 15 studies have been performed in France, three studies come from Italy and two from the U.K. Fifteen of these 40 studies were published in journals indexed in the Index Medicus. Using 65 points as cut-off point, eight trials are of acceptable quality. The six best trials are briefly described below. For the other trials, the methodological assessment shows shortcomings: small numbers of patients, inadequate description of randomization procedures, patient characteristics, effect measurement and data presentation. All but one trial show positive effects compared with placebo on symptoms as described in the introduction part. The only trial with negative results was in patients with dementia of vascular origin (Hartmann & Frick, 1991).

Schmidt *et al.* (1991) treated 99 out-patients (average age 59 years, average duration of symptoms 26 months) with the diagnosis 'cerebral insufficiency' for 12 weeks, with Ginkgo containing a daily dose of 150 mg Ginkgo extract. Fifty patients received Ginkgo and 49 placebo. There were no patients excluded from the analysis after randomisation. In addition to overall assessments of the treatment's effects by the patients and the doctors (on a 4-point ordinal scale), each of 12 symptoms (as mentioned in the introduction) was scored on an ordinal scale of 4 categories of severity. For these symptoms, the difference in improvement between the verum and placebo group was used for the effect measurement. After 12 weeks, significant differences were found for eight of the 12 symptoms. The overall assessment of the patients' complaints after 12 weeks showed that in the Ginkgo group 70% felt improved compared with 14% of the placebo group. Judgement by the doctors after 12

weeks showed that in 72% of the patients treated with Ginkgo an improvement had taken place, compared with 8% of the patients on placebo treatment.

Brüchert *et al.* (1991), in a multi-centre trial of the German Association of General Practitioners, assessed the efficacy of 150 mg Ginkgo extract for 12 weeks in 303 outpatients with cerebral insufficiency. The average age was 69 and the average duration of the complaints was 46 months. Eleven symptoms (as mentioned in the introduction except being confused) were present in at least 45% of these patients. Ninety-five percent of the patients experienced difficulties of memory. There were 94 patients excluded from the analysis after randomisation. Reasons for exclusion were effect measurement at the wrong time in 40 cases (Ginkgo/placebo: 21/19), inclusion criteria not met (11/12), concomitant treatments which were not allowed (10/15), and in discontinuation of treatment (4/11). One hundred and ten patients received Ginkgo and 99 placebo. In addition to overall assessments of the treatment's effects by the patients (on a 4-point ordinal scale) and the doctors (on a 3-point ordinal scale), each of the 11 symptoms was scored on an ordinal scale of 4 categories of severity. For these symptoms, the difference in improvement between the Ginkgo and placebo group were used for the effect measurement. After 12 weeks, significant differences were found for eight of the 12 symptoms. The overall assessment of the patients' complaints after 12 weeks showed that in the Ginkgo group 83% felt improved compared with 53% of the placebo group. According to the doctors, 71% of the patients treated with Ginkgo, compared with 32% of the patients on placebo treatment, had improved within 12 weeks.

Meyer (1986a) treated patients (average age 50 years) with tinnitus and associated symptoms, such as dizziness and hearing impairment. The average duration of the complaints was 4–5 months; Ginkgo (4 ml containing 160 mg Ginkgo extract a day) or placebo was given for 3 months; and patients were followed up for 13 months. The overall effects were assessed on a 6-point ordinal scale and the symptoms a 4-point ordinal scale. Improvement or cure was found after an average of 70 days in patients receiving Ginkgo compared with 119 days in patients treated with placebo.

Taillander *et al.* (1986) treated 210 elderly patients (average age 82 years) with symptoms such as dizziness, tinnitus, headaches, lack of energy, and difficulties of concentration and memory with 160 mg Ginkgo extract or placebo daily, and the effect measurement took place after 3, 6, 9 and 12 months. There were 44 patients excluded from the analysis after randomisation, 21 in the Ginkgo group and 23 on placebo. Reasons for exclusion were discontinuation of treatment (Ginkgo/placebo: 11/8), death (8/13), side effects (1/2) and one stroke (patient on Ginkgo). For the effect measurement, they used a scale for the clinical assessment of geriatric patients, consisting of 17 items scored on a 7-point ordinal scale (l'échelle d'appréciation clinique en gériatrie, E.A.C.G.). Differences were assessed between groups both as a comparison of patients at the end of the study, and as contrast or change from randomisation between the groups. The latter results were as follows for 3, 6, 9 and 12 months respectively (Ginkgo/placebo): 10/4%, 15/4%, 15/8% and 17/8%.

Haguenauer *et al.* (1986) assessed the effects of 160 mg Ginkgo extract or placebo daily for 3 months in 70 patients (average age 50) with a vertiginous syndrome and associated symptoms (tinnitus, headaches, nausea and hearing loss) of recent onset and undetermined origin. There were three drop-outs (Ginkgo/placebo: 1/2). Symptoms were assessed using a visual analogue scale (0–100 mm) and an overall evaluation by the doctor on a 5-point ordinal scale. After 3 months, symptoms had disappeared in 47% of patients treated with Ginkgo compared with 18% of those on placebo. The changes of the main symptom from randomisation as measured on the visual analogue scale after three months were 75% and 18% for the Ginkgo and placebo group respectively.

Vorberg *et al.* (1989) gave daily 112 mg Ginkgo extract, containing 30 mg Ginkgo-flavone glycosides to 100 patients with an average age of 70 years. Patients had at least four of the following symptoms: difficulties of concentration and memory, anxiety, dizziness, tinnitus and headaches. Four patients dropped out, 3 because of dissatisfaction with the treatment (Ginkgo/placebo: 1/2) and 1 placebo patient because of pneumonia and decompensatio cordis. The symptoms were scored on a 4-point ordinal scale. After 12 weeks' treatment improvements from baseline were for difficulties of concentration 54/19%, memory 52/17%, anxiety 48/17%, dizziness 61/23%, headaches 65/24% and tinnitus 37/12%.

No serious side effects were reported in any trial and, if present, side effects were not different from those in patients treated with placebo. This finding confirms the conclusion of DeFeudis (1991), who summarized the literature on side effects of Ginkgo, that there is generally a very low risk associated with EGb 761-containing products.

Published trials of co-dergocrine which we obtained from the pharmaceutical firm had equal scores on our methodological assessment. Table 2 shows the assessment of five trials of co-dergocrine which according to their firm were well performed.

A comparison shows that the quality of the trials on the efficacy of this registered product is not much different compared with the best evidence of Ginkgo available at the moment. A direct comparison of daily 120 mg Ginkgo and 4.5 mg dihydroergotoxine was made by Gerhardt *et al.* (1990), in patients (55–85 years) with symptoms such as dizziness, difficulties of memory and concentration, headaches and depressive mood. After 6 weeks both groups showed improvements, comparisons between groups showed no differences.

Discussion

There are 40 controlled trials on the efficacy of Ginkgo in patients with cerebral insufficiency. The authors of nearly all trials report at least a partially positive outcome. In most trials, the dosage used is 120–160 mg a day; whether other dosages have different effects remains to be determined. From most trials it appears

Table 2 Methodological assessment of studies on Hydergine® and mental functioning

Author	*Year*	*Preparation*	*Result*	*CH*	*NU*	*RA*	*IN*	*DB*	*EF*	*DA*	*Total*
Maximum				10	30	20	5	20	10	5	100
Lazzari	1983	Hydergine	sign.	9	30	10	5	20	10	0	84
Yoshikawa	1983	Hydergine	sign.	8	30	10	5	20	5	5	83
Bargheon	1973	Hydergine	sign.	5	20	20	5	20	10	0	80
McConnachie	1973	Hydergine	sign.	9	10	20	5	20	10	5	79
Hollingsworth	1980	Hydergine	sign.	9	10	20	5	20	10	0	74

Total: total number of points scored
sign.: index group fared better (author stated that result was significant)
pos.: positive trend (or significant effect for only some of the effect measurements)
neg.: no difference between Ginkgo and placebo groups

(CH) Patient characteristics; (NU) Number of patients per group; (RA) Randomization; (IN) Intervention well described; (DB) Double blind; (EF) Effect measurement well described; (DA) Data presentation.

that the treatment should be given for at least 4 to 6 weeks before positive effects can be expected. The effects in the trial of Taillander *et al.* (1986) are smaller (although still clinically relevant) than in the other trials. This may be due to the fact that the average age of the patients in that trial was very high (82).

Considering the low quality of many trials, we find it hard to believe that there are no small trials with negative results. Probably such trials exist, but have not been published. On the other hand, large well-performed trials, which have taken much costs and effort, will be published regardless of the outcome. Because of this, we will base our conclusions only on these well-performed trials (scoring at least 65% of the maximum). Scarce data on the quality of clinical trials in uncontroversial areas indicate that the average methodological score in the 1980s is about 50% of the maximum score (Emerson *et al.*, 1990).

A problem with our methodological assessment is that limited description of the methods and the results in the publication may lead to a lower score. We believe, however, that a detailed description of this information is as important as using good methodology in practice. It would surely be very complicated if every single reader must go after the necessary information. Also, we scored the trials from the viewpoint of the practitioner who treats patients. From this point of view, information about what happens to the patient's symptoms is more important than for instance a change of the EEG, or the influence on blood rheology.

It could be argued that other critiera should be used for the methodological assessment and that this kind of assessment is rather subjective. However, we have selected well established criteria. Moreover, we see the total score only as an indication whether a trial is well performed or not. The scores on the individual items may give the reader an impression why we arrived at such a conclusion. We would like to emphasize that scoring five points more or less is not very important to us. Furthermore, it is always possible that a well performed trial has one fatal mistake, for instance a break of double-blindness, which would render the results worthless. The probability for making such a mistake may increase when the number of methodological shortcomings increases, i.e. when the score decreases. Unfortunately, we were not blinded in assessing the methodological score of every publication. We were already too familiar with the publications before we started to score them. This means that some degree of reviewer bias cannot be excluded. Any reader, however, can check our points assignment and apply different weights to different criteria.

Meta-analysis is becoming fashionable. In our opinion too much stress is put on statistical pooling of study results. Criteria for deciding whether therapies, patients from different parts of the disease spectrum and end points are similar enough to be pooled are not yet available. The rationale of reviews using a methodological assessment of the trial quality is that it makes no sense to combine data from good research with data from bad research. We did not pool the results of the better studies because the material is too heterogenous.

Double-blinding, even if the placebo is described as indistinguishable, has to be checked by asking the patients in which group they believe that they were during the trial. Blindness must be checked early in the trial, before the treatment is expected to have an effect, because positive effects would break the code. It is easy to state that a trial was double-blind, but patients and doctors have many ways to break the code. The Ginkgo and placebo preparations which were used in some of the trials were shown to us. They were absolutely identical in appearance, and they ought to be swallowed. However, when bitten on, the tablets can easily be distinguished, because of the bitter taste on the Ginkgo tablets, and because the contents look different. This might explain differences in favour of Ginkgo treatment. Double-blinding was not checked in any trial. However, in half of all trials the placebo was described as indistinguishable (at least for several characteristics). It appears that regarding double-blindness it is frequently not right to believe the authors' statements in the methodology section.

We compared the quality of the Ginkgo trials with well performed trials of co-dergocrine, which itself is not uncriticized. Looking at the evidence of only well performed trials, it can be concluded that the best trials of each product have the same quality.

For cerebral insufficiency, it must be mentioned that this is a strange compilation of different symptoms. There may very well be some common factors in the

aetiology, but one can easily argue that there is no connection whatsoever. We have described the characteristics of the patients in the best trials, and leave this problem to the reader.

From the mechanisms of action as described in the introduction, there seems to be some biological plausibility for potential beneficial effects of Ginkgo. Further support comes from controlled trials with healthy volunteers. Positive effects of Ginkgo were found using psychological tests for reaction and memory (Schaffler & Reeh, 1985; Subhan & Hindmarch, 1984).

Another way to assess the evidence is to ask yourself whether you would take Ginkgo when you would have similar symptoms. Our answer would be affirmative: considering that there appear to be no clear side effects, we both might try it. However, we think that for these indications additional evidence is warranted. Vertical reading of Table 1 immediately shows the major drawbacks of existing research. In future experiments double-blindness should be checked, and there should be larger numbers of patients, better description of randomization procedures, patient characteristics, effect measurement and data presentation.

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