Clinical Studies on Ginkgo (*Ginkgo biloba* L.)

Cerebral Insufficiency (Alzheimer's Disease, Multi-infarct Dementia, Cerebro-Organic Syndrome)

Author/Year	Subject	Design	Duration	Dosage	Preparation	Results/Conclusion
Van Dongen *et al.*, 2000	Dementia and age-associated memory impairment (AAMI)	R, DB, PC, MC, PG n=196 older patients with mild to moderate dementia or AAMI; intention to treat analysis	Total 24 weeks. Patients randomized to usual dose, high dose, or placebo for 3 months, then randomized again for next 3 months	80 mg, 2x/day or 120 mg, 2x/day or placebo	EGb-761	In 24 weeks, ginkgo group showed no improvement compared to placebo in outcome measures (neuropsychological testing, digit memory span, verbal learning, depressive mood, self-evaluated health and memory, and behavioral evaluation). No benefit was seen for higher dose or extended duration of ginkgo. Ginkgo did not benefit any subgroups. Authors concluded that ginkgo is not effective to treat mild to moderate dementia or AAMI.
Rigney *et al.*, 1999	Memory and psychomotor performance	R, DB, PC, CO (5-way) n=31 asymptomatic individuals (30-59 years old)	Each treatment was taken for 2 days and separated by a washout period of 5 days or more	50 mg, 3x/day; or 100 mg 3x/day; or 120 mg, 1x/day in a.m.; or 240 mg/day in a.m.; or placebo	Kaveri® LI 1370 (50 mg film-coated tablets)	Ginkgo produced a non-significant cognitive improvement in overall word recall (short-term working-memory task) (p=0.318) and significantly increased integrative capacity of the central nervous system (based on the critical flicker fusion threshold test) (p=0.043). There was no improvement in choice reaction time. Authors concluded that improvements in asymptomatic controls are most pronounced for working memory, and in individuals over 50 years of age.
Brautigam *et al.*, 1998	Cerebral insufficiency	R, DB, PC n=197 elderly patients with cognitive impairment	6 months	1.9 ml, 3x/day undiluted; or 1.9 ml, 3x/day (1:1 dilution) or placebo	Geriaforce® (liquid extract)	Low-dose ginkgo treatment significantly improved short-term visual memory more than high dose or placebo treatment (based on contrast statistical analysis of the Benton Test of Visual Retention-Revised task) (p=0.0076). There was no improvement in the following parameters: attention or concentration (based on Expended Mental Control Test); short-term memory or learning curve (based on Rey Test part 2). Overall, ginkgo had limited efficacy in this battery of subjective and objective tests. [Note: The ginkgo extract used in this trial is not phyto-equivalent with the 2 preparations upon which most of the studies on ginkgo have been conducted.]
Kanowski *et al.*, 1997	Dementia	R, DB, PC, MC, P n=156 elderly patients with Alzheimer's disease or multi-infarct dementia	6 months	120 mg 2x/day or placebo	EGb-761 (120 mg capsule)	Per protocol and intent-to-treat analyses significantly favored EGb-761 over placebo (p=0.012). Clinical Global Impressions scores, a measure of psychopathological assessment, increased 15% (p<0.05). Syndrom-Kurztest, for the assessment of attention and memory, improved 20% (p<0.05). Overall, EGb-761 was well-tolerated and effective in treatment of Alzheimer's disease and multi-infarct dementia.
Le Bars *et al.*, 1997	Dementia	R, DB, PC, MC, P n=202 elderly patients with mild to severe Alzheimer's disease or mulit-infarct dementia	13 months	40 mg, 3x/day or placebo	Ginkgold® (EGb-761 40 mg tablet)	Patients receiving ginkgo had no significant change in ADAS-Cog score (evaluates memory, language skill, and orientation), but by comparison there was significant worsening in placebo group (p=0.04). Patients taking ginkgo had mild improvement on GERRI test, (assesses daily living and social behavior) while placebo group had significant worsening (p=0.04). Both groups had slight worsening in CGIC, (assesses overall psychopathology). It was concluded that ginkgo is safe and capable of stabilizing or improving cognitive performance and social functioning of demented patients for 6 months to 1 year.
Hofferberth, 1994	Dementia	R, DB, PC n=40 elderly patients with Alzheimer's disease	3 months	80 mg per day (2x 40 mg) or placebo	EGb-761 film-coated tablets (Tebonin® forte)	Of individuals treated with ginkgo, 90.5% had significant improvement in memory and attention as assessed by Syndrom-Kurztest total value at end of study (p=0.00017). Improvements were seen in all 5 subsets of the SCAG (cognitive disturbances, emotional disturbances, lack of drive, social behavior, and somatic disturbances) (p<0.01). Authors concluded treatment improved memory, attention, psychopathology, psychomotor performance, functional dynamics, and neurophysiology after one month. Ginkgo was well-tolerated.

KEY: ADAS-Cog – Alzheimer's Disease Assessment Scale-cognitive subscale, **C** – controlled, **CC** – case-control, **CGIC** – Clinical Global Assessment of Change, **CH** – cohort, **CI** – confidence interval, **Cm** – comparison, **CO** – crossover, **CS** – cross-sectional, **DB** – double-blind, **E** – epidemiological, **GERRI** – Geriatric Evaluation by Relative's Rating Instrument, **GLC** – concentrated ginkgo leaf product, **LC** – longitudinal cohort, **MA** – meta-analysis, **MC** – multi-center, **MMSE** – Mini Mental Status Exam, **n** – number of patients, **O** – open, **OB** – observational, **OL** – open label, **OR** – odds ratio, **P** – prospective, **PB** – patient-blind, **PC** – placebo-controlled, **PG** – parallel group, **PS** – pilot study, **QPEG** –quantitative pharmaco-electroencephalogram, **R** – randomized, **RC** – reference-controlled, **RCS** – retrospective cross-sectional, **RS** - retrospective, **S** – surveillance, **SB** – single-blind, **SC** - single-center, **SCAG** – Sandoz Clinical Assessment Scale, **SKT** – Syndrom-Kurztest, **U** – uncontrolled, **UP** – unpublished, **VC** – vehicle-controlled, **WAIS** – Wechsler Adult Intelligence Scale.

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Cerebral Insufficiency (Alzheimer's Disease, Multi-infarct Dementia, Cerebro-Organic Syndrome) (cont.)

Author/Year	Subject	Design	Duration	Dosage	Preparation	Results/Conclusion
Vesper and Hansgen, 1994	Cerebral insufficiency	R, DB, PC, MC n=86 elderly patients with cerebral insufficiency	3 months	50 mg, 3x/day or placebo	Kaveri® LI 1370 (50 mg film-coated tablets)	Target parameters and results were established with help of computer diagnostics and demonstrated improved reaction time, concentration ($p<0.05$), and mental flexibility ($p<0.05$), and improved memory ($p<0.05$), improved concentration power ($p<0.05$) after several weeks of ginkgo treatment.
Grässel, 1992	Cerebral insufficiency	R, DB, PC, MC n=53 elderly patients with cerebral insufficiency	24 weeks	80 mg, 2x/day or placebo	Rökan® EGb-761 (80 mg film-coated tablets)	Computer aided measurements revealed improved short-term memory and learning rate after treatment for 6 weeks or 24 weeks, respectively.
Brüchert *et al*., 1991	Cerebral insufficiency	R, DB, PC n=209 patients with typical symptoms of cerebral insufficiency	3 months	50 mg, 3x/day or placebo	Kaveri® LI 1370 (50 mg film-coated tablets)	After 12 weeks, statistically significant improvements were demonstrated on 8 out of 11 typical symptoms. In ginkgo group, period for figure connection test was improved by 25% vs. only 14% in placebo group ($p<0.01$) Both physicians and patients judged highly significant differences between ginkgo and placebo.
Halama, 1991	Dementia of degenerative or vascular origin	R, DB, PC n=42 patients with presenile, senile, and arteriosclerotic dementia	3 months	50 mg, 3x/day or placebo	Kaveri® LI 1370 (50 mg film-coated tablets)	After 12 weeks, significant differences between ginkgo and placebo group for 7 out of 11 typical symptoms. Ginkgo group was significantly faster in carrying out figure configuration test after 6 and 12 weeks. Authors concluded that ginkgo treatment resulted in improvement in cerebral functional capacity in patients with degenerative and vascular dementia.
Rai *et al*., 1991	Memory impairment	R, DB, PC, P n=27 elderly patients with mild to moderate memory impairment	6 months	40 mg, 3x/day or placebo	Tanakan® EGb-761 (40 mg tablets)	Ginkgo improved performance on digit-copying subtest of Kendrick battery at both 12 ($p=0.022$) and 24 ($p=0.017$) weeks, and improved speed of response on computerized classification task ($p=0.02591$), and mean reaction time ($p=0.0502$). Although the digit recall task at 24 weeks showed much lower scores ($p=0.032$), further analysis indicated that ginkgo has beneficial effects on mental efficiency.
Schmidt *et al*., 1991	Cerebral insufficiency	R, DB, PC n=99 patients with cerebral insufficiency	3 months	150 mg/day or placebo	Kaveri® LI 1370 (50 mg film-coated tablets)	After only 4 weeks, 8 of 12 typical symptoms of cerebral insufficiency improved significantly ($p<0.05$ to $p<0.01$) compared to placebo. Ginkgo was very well-tolerated.
Eckmann, 1990	Cerebral insufficiency	R, DB, PC n=58 patients with cerebral insufficiency with leading symptom of depressive mood.	6 weeks	160 mg/day or placebo	LI 1370 liquid form	Marked differences in improvement of 11 of 12 symptoms in ginkgo group compared to placebo group. Largest number of improvements observed between 2nd and 4th week of treatment.
Hofferberth, 1989	Cerebro-organic syndrome	R, DB, PC n=36 elderly patients with cerebro-organic syndrome	2 months	40 mg, 3x/day or placebo	Rökan® EGb-761 (40 mg film-coated tablets)	Psychometric tests showed improved visual response speed with reduced saccade (eye movement) duration and latency (Saccade test) ($p<0.0001$), and improved reaction time (Vienna determination test and trail making test) ($p<0.0001$). Researchers concluded ginkgo is well-tolerated and of clinical efficacy.
Vorberg *et al*., 1989	Cerebral insufficiency	R, DB, PC n=96 patients with typical symptoms of cerebral insufficiency	3 months	15 ml, 3x/day (112 mg/day) or placebo	LI 1370 liquid form (Kaveri®)	Severity of symptoms improved in ginkgo group by 50% compared to only 25% with placebo. Statistically significant differences between ginkgo and placebo could be demonstrated for these symptoms: loss of memory, lack of concentration, anxiety, dizziness, and headache ($p<0.05$ to $p<0.001$).

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Cerebral Insufficiency (Alzheimer's Disease, Multi-infarct Dementia, Cerebro-Organic Syndrome) (cont.)

Author/Year	Subject	Design	Duration	Dosage	Preparation	Results/Conclusion
Halama *et al.*, 1988	Cerebro-vascular insufficiency	R, DB, PC n=40 elderly patients with mild to medium cere-brovascular insufficiency	3 months	40 mg, 3x/day or placebo	Tebonin® forte EGb-761 (40 mg film-coated tablets)	After 12 weeks of ginkgo treatment, there was signifi-cant improvement in SCAG scale (p=0.00005), dizziness, (p<0.001), tinnitus (p=0.035), and lessened indifference to surroundings.
Wesnes *et al.*, 1987	Idiopathic cognitive impairment	R, DB, PC n=54 elderly patients with idiopathic cognitive impairment	3 months	40 mg, 3x/day or placebo	Tanakan® EGb-761 (40 mg film-coated tablets)	Treatment improved cognitive function and mental efficiency based on a battery of computerized and pen-cil-and-paper tasks (number matching, p=0.0183; word recognition, p=0.026), and increased interest in everyday life. Researchers concluded that ginkgo may be poten-tially helpful in treating early stages of primary degener-ative dementia.
Taillandier *et al.,* 1986	Cerebral insufficiency	R, DB, PC, MC n=166 elderly patients with cerebral insufficiency	12 months	2 ml, 3x/day (160 mg /day), or placebo	Tanakan® EGb-761 liquid form (40 mg/ml)	Scores on geriatric clinical evaluation scale test (meas-uring intellectual functions, mood, social insertion, and neurosensory disorders) were improved after 3 months of ginkgo treatment (p<0.05) and reached 17% improve-ment for placebo (p=0.01). Authors concluded that ginkgo is effective in ameliorating cerebral disorders due to aging.
Arrigo, 1986	Cerebro-vascular insufficiency	R, DB, PC, CO n=80 elderly patients with chronic cere-brovascular insufficiency	45 days drug; 15 days wash-out; vs. 45 days control; 15 days wash-out	40 mg, 3x/day or placebo	Tebonin® forte EGb-761	Ginkgo improved memory (p<0.0001), logical thinking, and vigilance, based on WAIS (p<0.01), a Word Recognition task and a Memory Table (p<0.0001). In addition, ginkgo lessened headache, dizziness, tinnitus, visual impairment, and asthenia, based on self-assessment by patients.

Peripheral Vascular Disease (Intermittent Claudication)

Author/Year	Subject	Design	Duration	Dosage	Preparation	Results/Conclusion
Schweizer and Hautmann, 1999	Peripheral Arterial Occlusive Disease; Fontaine's Stage IIb	R, DB, MC, P n=74	6 months	120 mg/day (n=38); 240 mg/day (n=36)	Rökan®	Pain-free walking distance improved with both 120 mg and 240 mg treatments, with a mean increase of 60.6 meters, and 107 meters, respectively (p=0.0253). The superiority of the higher dose was statistically significant and demonstrated a substantial therapeutic benefit.
Peters *et al.*, 1998	Intermittent claudication	R, DB, PC, MC n=111	6 months	40 mg, 3x/day or placebo	Tebonin® forte EGb-761 40 mg film-coated tablets	Ginkgo group experienced a significant decrease of pain associated with walking and increased walking distance, at 8 (p=0.017), 16 (p=0.007), and 24 (p=0.016) weeks.
Bauer, 1984	Peripheral arterial insufficiency, Fontaine's Stage IIb	R, DB, PC, PG n=79	6 months	40 mg, 3x/day or placebo	Rökan® EGb-761 40 mg film-coated tablets	Ginkgo group experienced decreased pain associated with walking, improved walking distance, and increased limb perfusion. Ginkgo was concluded to be a beneficial clinical treatment.

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Respiratory Conditions (Asthma and Acute Mountain [Altitude] Sickness)

Author/Year	Subject	Design	Duration	Dosage	Preparation	Results/Conclusion
Gertsch *et al*., 2002	Acute mountain sickness (AMS)	R, DB, PC n=26 sea level residents	1 day prior to ascent	60 mg or placebo, 3x/day	*Ginkgo biloba* extract (brand not stated)	Participants traveled by air from sea level to 4,205 meters over 3 hrs with 1 hr at 2,835 m. Ginkgo group showed significantly lower median Lake Louise Self-report scores (LLSR) than placebo (4, range 1–8 vs. 5, range 2–9, p=0.03). Ginkgo lowered the incidence of AMS but this effect was not deemed statistically significant compared with placebo (58.3% vs. 92.9%, p=0.07). Authors conclude pretreatment with ginkgo one day prior to rapid ascent may reduce severity of AMS.
Leadbetter *et al*., 2001	Acute mountain sickness (AMS)	DB, PC n=40	5 days prior to ascent	120 mg or placebo, 2x/day	*Ginkgo biloba* extract (brand not stated)	Ginkgo reduced the incidence and severity of AMS when taken 5 days prior to an ascent of 4,300 meters. The ginkgo group demonstrated a decrease in incidence of AMS of 33% compared with 68% in the placebo group (p<0.02).
Li *et al*., 1997	Asthma	PC n=61	2 months	45 g crude herb, 10 ml, 3x/day (15 g/10 ml) (equates to 1,400 mg of standard extract) or placebo	Concentrated ginkgo leaf liquid product (produced by Quindao Fengyi Biotechnology Limited). Contains 14.5 mg/ml flavone glycosides and 2.8 mg/ml terpene lactones	Improved airway reactivity test at 4 and 8 weeks (p<0.05). Improved pulmonary function test at 8 weeks (p<0.05) including forced expiratory volume and peak expiratory flow rate.
Roncin *et al*., 1996	Control of acute mountain (altitude) sickness (AMS) and vascular reactivity to cold exposure	R, DB, PC n=44	30 days	80 mg, 2x/day or placebo	Tanakan® EGb-761 80 mg tablets	Ginkgo was effective in preventing AMS. No individuals receiving prophylactic experienced AMS, compared to 41% taking placebo (p=0.0014). Respiratory symptoms of altitude sickness occurred in 13.6% of the ginkgo group (p=0.000012), compared to 81.8% of the placebo group. Of ginkgo subjects, 18% reported moderate or severe impairment of diuresis at high altitude compared with 77% of placebo subjects. Ginkgo also reduced vasomotor disorders of the extremities, as demonstrated by plethysmography (p<10–8) and questionnaire (p<10–9). Authors concluded ginkgo treatment was effective.

Tinnitus and Acute Cochlear Deafness

Author/Year	Subject	Design	Duration	Dosage	Preparation	Results/Conclusion
Drew and Davies, 2001	Tinnitus	DB, PC n=956	12 weeks	50 mg, 3x/day or placebo	LI 1370 or placebo	The researchers concluded that 50 mg ginkgo extract LI 1370 given 3 times daily for 12 weeks is no more effective than placebo. This conclusion was based upon participant's assessment of tinnitus before, during, and after treatment.
Meyer, 1986	Tinnitus	R, DB, PC, MC n=103 patients with recent tinnitus (appearing within the previous 12 months)	13 months	2 ml, 2x/day or placebo	Rökan® EGb-761 liquid form	Ginkgo treatment significantly improved symptoms of tinnitus compared to placebo (p=0.05). The time before disappearance or distinct improvement in 50% of tinnitus cases was 70 days in ginkgo group, compared to 119 days for placebo. Authors concluded that treatment with ginkgo improves the evolution of tinnitus.

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Tinnitus and Acute Cochlear Deafness (cont.)

Author/Year	Subject	Design	Duration	Dosage	Preparation	Results/Conclusion
Dubreuil, 1986	Acute cochlear deafness	R, DB, C n=20 individuals with acute cochlear deafness (partial or complete) within the preceding week	30 days	4 ml liquid ginkgo extract 2x/day or 2 tablets nicergoline 3x/day	Rökan® EGb-761 or nicergoline	Ginkgo was superior over nicergoline, an alpha-blocker commonly prescribed for the same indication. By day 10, ginkgo group had an average gain of 30 decibels/frequency, compared to a 21-decibel gain with nicergoline treatment. By day 30, ginkgo patients had gained on average 34 decibels/frequency, compared to 23 decibels for nicergoline patients. After one month of treatment, ginkgo group registered a total gain exceeding the nicergoline group by 67 decibels, (6-15 decibels, depending on frequency). The small sample size demands cautious conclusions; however, ginkgo demonstrated much greater efficacy than nicergoline. Therapeutic results were obtained as early as day 10; however, several weeks of treatment are suggested to consolidate the result.

Other

Author/Year	Subject	Design	Duration	Dosage	Preparation	Results/Conclusion
Engelsen *et al*., 2002	Drug interaction (long-term warfarin use in patients with recurrent venous thromboembolism, mechanical heart valves) or chronic atrial fibrillation)	R, DB, PC, CO n=21	4 weeks each phase with 2 week washout between each phase	100 mg ginkgo daily, 100 mg coenzyme Q10 daily or placebo	Bio-Biloba® (Ginkgo); Bio-Quinone® (CoQ10); placebo	The stability was confirmed by linear regression of INR values and geometric mean doses of warfarin did not change during treatment. The study concluded that CoQ10 and ginkgo do not interact with warfarin.
Hauns *et al*., 2001	Advanced colorectal cancer	Phase II n=32	Every 3 weeks, for 4 treatments (12 weeks)	350 mg ginkgo as a 30-minute i.v. infusion (days 1–6) followed by 500 mg/m2/d 5-FU as a 30-minute i.v. infusion (days 2–6)	EGb-761 and 5-Fluorouracil (5-FU)	The results suggested a good benefit-risk ratio of combining 5-FU and EGb 761 therapy as the second line treatment. Patients showed an overall response rate of 6.3%, with the disease progressing in 22 patients. Of these, the disease progressed in 17 patients after one course of treatment, 2 patients after 3 treatments, and 3 patients after 4 treatments. The study saw no change in 8 patients and a partial response in 2 patients.
Cohen and Bartlik, 1998	Sexual dysfunction secondary to SSRI use	O n=63	1 month	Average dose: 207 mg/day 40-60-120 mg, 2x/day (dosage range: 40–60 mg, 4x/day to 120 mg 2x/day)	Ginkgo extract (brand not stated) 40 or 60 mg capsules	Ginkgo was 84% effective in treating antidepressant-induced sexual dysfunction predominantly caused by selective serotonin reuptake inhibitors. Women were more responsive than men, with relative success rates of 91% versus 76%. Ginkgo had positive effects on desire, excitement, orgasm, and resolution phases of the sexual response cycle.
Itil *et al*., 1996	Effect on electrophysiological characteristics of the central nervous system	R, DB, PC, CO n=12	Acute treatment followed by a minimum 3-day washout	40 mg/day or 120 mg/day or 240 mg/day or placebo	Ginkgold® EGb-761	The higher doses had more pharmacological effects than the 40 mg dose, and the 120 or 240 mg dose may be clinically more beneficial (changes in alpha activity, p=0.002; change in coefficient of CEEG response, p=0.008). Ginkgo extract has electrophysiological effects in the central nervous system similar to other well-known cognitive activators.

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Other (cont.)

Author/Year	Subject	Design	Duration	Dosage	Preparation	Results/Conclusion
Halama, 1990	Depression	R, DB, PC n=20 elderly patients with moderately severe depression	2 months	80 mg, 3x/day or placebo. Patients continued taking existing antidepressive medication (75–100 mg/day Stangyl®, n=12; 75–100 mg/day Ludiomil®, n=5; 50–75 mg/day Pertrofan®, n=3).	Tebonin® forte EGb-761 (40 mg tablets)	Severity of depression lessened in 3 patients, was unchanged in 4, and became worse in 3 patients. Placebo-treated groups showed no lessened depression, while depression remained unchanged in 5 and worsened in 5 patients. Authors conclude that results are inconclusive.
Schaffler and Reeh, 1985	Hypoxia	R, DB, PC, CO n=8	5 weeks drug; 2-week washout, 1 week placebo	4 ml (80 drops), 2 ml 2x/day or placebo	Tebonin® forte EGb 761 liquid form	The oculomotor system was used to test effectiveness of ginkgo. Hypoxia-induced increase of corneoretinal resting potential and the augmented respiratory drive were reduced. Compared with placebo, saccadic eye movements and choice reaction times were significantly reduced under cumulative hypoxic stress. These findings were interpreted as indicative of a protective action against hypoxia, relevant to the treatment of cardiovascular insufficiency.

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