Ginkgo biloba, applications for the clinician in practice.

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Abstract:

Growing interest in the field of Complementary and Alternative medicine (CAM) places new obligations on the clinician in practice. To address these new patient needs, it is important to develop cross referral relationships with graduates of accredited CAM schools, and to self educate using reputable resources. To assist in this process, a comprehensive review of Ginkgo biloba, the most well-studied botanical medicine, is provided. The history, chemical constituents, pharmacology & toxicity, dosage & potential interactions are presented. Double blind research, showing Ginkgo biloba's efficacy in conditions including cerebrovascular insufficiency, memory impairment, Alzheimer's disease, multi-infarct dementia, resistant depression, peripheral arterial insufficiency, venous insufficiency, and asthma, is summarized. Studies suggesting efficacy of Ginkgo biloba in tinnitus, schizophrenia, psychotic organic brain syndrome, vertigo of undetermined origin, and PMS are also reviewed. Lastly, resources are listed to assist the clinician in locating, and developing cross referral relationships with, properly educated CAM providers.

Introduction:

Booming interest in the field of Complementary and Alternative Medicine (CAM), with increased patient visits to CAM providers requires practicing conventional clinicians to develop some understanding of these therapies, which today nearly half their patients are using.[1]

Furthermore, without mandatory licensing for CAM providers [many states still allowing unrestricted use of the title *Naturopathic Doctor* (ND) as example,] it is important that clinicians identify and refer their patients only to well-educated CAM professionals competent in the basic and clinical sciences. Advice-giving laypersons and mail-order CAM diploma holders, who are prevalent, have little if any formal clinical CAM experience, have not taken boards in CAM, and because lacking formal education in botanical medicine, therapeutic nutrition, and the interactions of these therapies with pharmaceuticals, may provide recommendations harmful to your patients.

This situation affords the conventional clinician a few options: 1) Enroll in one of two accredited Naturopathic Medical Schools for a minimum 4-5 year full-time post graduate program of study for a degree in Naturopathic Medicine.[2,3] 2) Enroll in one of over 50 accredited schools of acupuncture and minimum 3-year course for a degree in Acupuncture or Chinese herbal medicine. 3) Self educate with reputable resources, becoming familiar with CAM therapies which might benefit your patient population, or 4) Find and develop a cross-referral relationship with a credentialed ND or LAc (Licensed Acupuncturist). The latter two, more realistic for clinicians in practice, are what this article will attempt to begin to facilitate by first, reviewing the double-blind study supported clinical applications of *Ginkgo biloba* (one of the most popular phytomedicines today); and second, provide referral resources for well-trained CAM providers.

History:

Ginkgo biloba (Ginkgo/ Maidenhair tree), the world's oldest living species of tree dates back over 200 million years. It is the sole survivor of the Ginkgoaceae era, and despite being nearly extinguished during the ice age, it survived in China where record of its first medicinal use was documented nearly 5000 years ago. Chen Noung (2767-2687 BC,) in the pharmacopoeia: *Chen Noung Pen T'sao,* recommended Ginkgo for respiratory ailments and memory loss in the elderly, which interestingly enough, is what Ginkgo is often recommended for today.[4,5,6] Today, nearly 500 scientific papers now documenting Ginkgo's effects make it the most well-researched botanical medicine available. With 10 million prescriptions written worldwide for *Ginkgo biloba* extract (GBE) in 1989 alone, and a 140% growth in the use of Ginkgo from 1997 to 1998, it is likely a plant medicine your patients are using or considering.[5,7]

Chemical Composition:

Ginkgo biloba, like most plant medicines contains many active constituents, believed to have synergistic effects. Flavonoids including quercetin, kaempferol, and isorhamnetins; trilactonic diterpenes: Ginkgolide A, Ginkgolide B, Ginkgolide C; a trilactonic sesquiterpene: bilobalide; and proanthocyanidins are thought to afford Ginkgo it's medicinal effects.[5,8] Other constituents such as glucose, rhamnose, hydroxykinurenic, kynurenic, protocatechic, vanillic, and shikimic acids, D-glucaric acid, ginkgolic acid, and related alkyphenols have also been isolated.[9]

Pharmacology:

Ginkgolides A, B, & C, and bilobalide have been shown to increase circulatory perfusion, antagonize platelet activating factor (PAF), have neuroprotective effects, and serve as cognitive activators. The flavone glycosides possess antioxidant and mild platelet aggregation inhibiting activities.[10,11,12] *Ginkgo biloba* extract (GBE), according to the German Commission E (a regulating agency similar to our FDA), has the following actions: inhibition of the development of cerebral edema, retinal edema, cellular lesions in the retina, and age-related reduction of muscarinergic cholinoceptors. GBE stimulates choline uptake in the hippocampus, improves hypoxic tolerance, and glucose utilization. It also has membrane stabilizing and blood viscosity lowering effects.[8]

Absorption of *Ginkgo biloba* in animal studies using radiolabeled extract showed a 60% absorptive efficiency following oral administration with peak serum levels at 1.5 hours supporting an upper GI absorption site. The flavonoids were found to accumulate in the aorta, eyes, skin, and lungs; the heart muscle retained twice the activity of a comparative volume of skeletal muscle, and adrenal glands were also a site of accumulation. Seventy two hours post administration, the hippocampus and striated bodies showed 5 times greater uptake than the blood,[5,12] while T1/2 for Ginkgolide A, B, and bilobalide were 4.50, 10.57, and 3.21 hours respectively, supporting the need for TID dosage.[15]

Clinical Applications:

Cerebrovascular Insufficiency:

Several studies have tested the efficacy of GBE for improving status in those with cerebrovascular insufficiency. In a double blind trial of 90 patients conducted by Vesper & Hansgen over a twelve-week course, Ginkgo was found to improve several clinical parameters of measure including:1) Patient attention in tasks requiring quick orientation and readaptation, 2)

Attentiveness over a long period of time, 3) Visual memory performance in parameters sensitive for cerebral insufficiency, 4) Changes in the patient's subjective performance, and 5) Changes in the patient's objective behavior as observed by others.[16] Results also showed GBE to be significantly superior to placebo in all parameters measured.

Taillandier et al. in a multicenter study with longitudinal design, performed under strict methodological conditions, found GBE effective against cerebral disorders associated with aging in166 patients. Results became statistically significant at 3 months, increased during the following months, and were congruent with the overall clinical assessment by the specialist in charge.[17]

Another study of 24-week duration by Grassel on 72 patients with cerebral insufficiency found statistically significant improvements in short term memory after 6 weeks, and learning rate (as measured by psychometric testing) after 24 weeks.[18]

Perhaps the most convincing study involved a "gold standard" meta-analysis of eleven double blind studies where efficacy of GBE was tested. After elimination of three studies because of inadequacy of data provided (necessary for meta analysis), the authors found seven of the eight remaining studies to support GBE's statistically significant superiority to placebo in patients with cerebrovascular insufficiency. Only one of the eight studies was inconclusive. GBE produced improvement in parameters including: single symptoms, total score of clinical symptoms, and global effectiveness.[19] Clearly, such evidence would seem to support the efficacy of GBE use in cerebrovascular insufficiency.

Memory Impairment:

Despite GBE being heavily marketed to promote mental clarity, and although evidence supports such use in persons with decreased cerebrovascular blood flow, memory improvement from GBE in healthy individuals is poorly documented. While in a crossover study of 18 elderly men and women (mean age 69.3 years), orally administered GBE was found to significantly improve the speed of information processing in dual-coding tests, a study of eight healthy females found differences between GBE and placebo in only one of three methods of evaluation.[20,21] Although the author of the later study found the improvement in the one test parameter as “highly significant”, more evidence is needed before recommending GBE for memory improvement in otherwise healthy individuals.

Alzheimer's disease & Multi-infarct Dementia:

Several studies suggest that GBE may be helpful in treating Alzheimer's disease and multi-infarct dementia, with few if any side effects. In a North American double blind study of 202 patients randomly receiving GBE 120mg/ d or placebo for 52 weeks, GBE was superior and effective to an extent clinically recognized by caregivers. Objective parameters of measure included the Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog), Geriatric Evaluation by Relative's Rating Instrument (GERRI), and Clinical Global Impression of Change (CGIC). Results showed the GBE group to have a mean ADAS-Cog score 1.4 points better and a GERRI score 0.14 points better than the placebo group. Moreover, 27% of GBE patients vs. 14% of placebo patients achieved a 4-point improvement on the ADAS-Cog (translating to a GBE efficacy of nearly double or 100% more than placebo). Finally, 37% of the GBE group vs. 23% of the placebo group improved their GERRI score. No difference was seen in the CGIC, and no significant differences were observed in the occurrence of side effects between GBE and

placebo. The authors concluded GBE was safe, and appeared to help cognitive performance and social functioning of patients with dementia as evaluated through both objective and subjective methods.[22] Considering the induced improvement demonstrated by GBE, and with similar occurrence of side effects in comparison to placebo, this author would agree.

A 1996 multicenter double-blind, placebo controlled prospective study by Kanowski et al. evaluated 156 patients with presenile and senile primary degenerative dementia of the Alzheimer's type (DAT), and multi-infarct dementia (MID) who used either GBE 120mg bid or placebo for 24 weeks. A multidimensional evaluation approach using objective variables of Clinical Global Impressions (CGI) for psychopathological assessment, Syndrome-Kurztest (SKT) for assessment of attention and memory, and Nurnberger Alters-Beobachtungsskala (NAB) for assessment of activities of daily life were used. Efficacy was defined as response in at least two of the three variables. Within a conservatively defined response criterion, 28% of the GBE group responded vs. 10% in the placebo group. Similar effects were noted with GBE in both types of dementia with a slightly better response for those with DAT. Five patients reported minor side effects of skin reactions, gastrointestinal complaints, and headache. [23]

In a study by Hasse, Halama, and Horr, 4 weeks of intravenous infusions of GBE or placebo were used in 40 patients with moderate dementia, either Alzheimer's, vascular, or mixed type. Severity of disease had to correspond to stages 4 or 5 of Reisberg's Global Deterioration Scale for patients to be included in the study. Primary outcome measures included activities of daily living as assessed by the NAB, the CGI, and actual intelligence assessed by the Kurztest fur Allgemeine Intelligenz (KAI). Following therapy, patients receiving GBE scored significantly higher on each outcome measure than those receiving the placebo. GBE also ranked superior in self-rated activities of daily living, improvement of the most prominent symptom, and decrease in depression, demonstrating GBE efficacy on behavioral, psychopathologic, and psychometric planes.[24]

Resistant depression:

In a double blind study by Schubert & Halama 40 patients age 51-78 with a diagnosis of resistant depression (insufficient response to tri/tetracyclic antidepressants for at least 3 months,) received either GBE 80mg TID or placebo for eight weeks while continuing their antidepressant drugs. In the GBE group, the median Hamilton Depression Scale scores dropped from 14 to a remarkable 7 in four weeks, then to 4.5 by week eight. Only a one-point drop occurred in the placebo group. Overall cognitive function was improved, and no side effects were reported[25] showing potential therapeutic benefit of GBE in resistant depression.

Peripheral Arterial Insufficiency/ Improved Microcirculation:

Effects on microcirculation and peripheral arterial insufficiency are also areas where GBE has been well studied. In a double blind randomized trial of 79 patients with peripheral arteriopathy (Fontaine's stage IIB,) GBE was evaluated. After 6 months of 40mg oral dosage, GBE was shown to improve pain-free walking distance, maximum walking distance, and plethysmography recordings at a level statistically greater than placebo. The objective results also correlated with the physician's and patients' overall assessments of response to treatment.[26]

Two other controlled studies, utilizing intravenous administration of GBE, also demonstrated improved microcirculation after GBE administration. A smaller, single blind (n=10) study by Jung et al. found impressively improved microcirculation on healthy volunteers. In it, GBE

produced an exceptional 15.6% decrease in erythrocyte aggregation and a 57% increase in nail bed capillary perfusion at two hours and one hour post administration respectively. Both observations were statistically significant with p values less than 0.0001 & 0.0004. Significant changes in blood pressure, heart rate, erythrocyte rigidity, plasma viscosity, Hematocrit, thrombocyte and leukocyte counts, thrombocyte aggregation and number of circulating thrombocyte aggregates was not seen with GBE or placebo.[27] Koltringer et al. also had similar findings in 42 patients where GBE significantly increased doppler-measured microcirculation, and viscoelasticity of blood, both in a dose dependent manner.[28]

Other studies, including a meta analysis of 5 placebo controlled clinical trials, support orally administered GBE as improving walking distance, decreasing ischemia, and reducing pain in patients with peripheral artery disease. Convincing results of increased walking distance (0.75 times the standard deviation higher than placebo,) and a 38% decrease in ischemia (vs. a 5% increase in the placebo group,) were observed.[29,30] Also, decreased pain levels, which began six months after treatment, and continued to improve throughout the 16-month study,[31] are clinical outcomes your patients would appreciate.

Lastly, a unique preliminary study by Lebuisson, Leroy, and Rigal investigated GBE's effects in macular degeneration. In their double-blind (n=10) study group, significant improvements were noted in long distance visual acuity after treatment.[32] Although having a small sample size, this study and other studies demonstrating GBE's efficacy in improving microcirculation suggest a possible role for GBE in dry-type macular degeneration or ischemia-related retinopathy where no effective conventional treatments are available.

Venous insufficiency:

The suspected endothelial stabilizing effects of GBE, via its flavonoid content, have long been thought to promote venous wall integrity. In an attempt to verify this, Janssens et al. studied GBE in patients diagnosed with chronic venous insufficiency who had double the level of circulating endothelial cells (CECs) compared to healthy controls. Increased CECs are associated with decreased vessel integrity. They found that a 4-week treatment with GBE led to a statistically significant decrease of CECs compared to controls. They concluded that the reduction in CECs is one mechanism where GBE is helpful in patients with chronic venous insufficiency.[33]

Asthma:

GBE's antagonistic effect on platelet activating factor (PAF,) documented in multiple studies, is one of the postulated mechanisms for GBE's efficacy in reducing reactivity in patients with asthma and allergy.[34,35,36,37] A study by Li, Zhang, and Yang, at Qingdao Hospital of Integrated Traditional and Western Medicine, found that administration of an alcohol extract of Ginkgo leaves significantly reduced the airway hyper-reactivity and clinical symptoms of patients with asthma. Pulmonary function was also found to be significantly improved.[38] With few or no side effects compared to conventional asthma preventive treatments, and considering the results of this study, GBE deserves consideration in the long-term plans for your patients with asthma or allergy.

Other conditions:

Studies suggest GBE's potential efficacy in other conditions including tinnitus, schizophrenia, psychotic organic brain syndrome, vertigo of undetermined origin, and premenstrual syndrome (PMS).

For tinnitus, although one study (n=20,) based on patient preference (no objective measure) did not support GBE efficacy, two larger multicenter studies (n=103, n=259) found GBE to improve parameters including chronicity, site, and periodicity of disease.[39,40,41] In one of the larger studies, where evaluations were carried out by ten E.N.T. specialists over the course of 13 months, it was determined that GBE improved tinnitus in all patients irrespective of initial description or prognostic factors.

In a multicenter 16-week study by Luo, Shen, and Meng, efficacy of GBE was evaluated with a double-blind approach in 545 patients with chronic schizophrenia. All patients continued their maintenance neuroleptics throughout the study. The treatment group, which received 120mg GBE TID showed greater reductions in the brief psychiatric rating scale (BSRS,) and the Scale for the Assessment of Negative Symptoms, compared to controls. The GBE group also exhibited improvements in BSRS factors including retardation and thought disturbance. Traditional global rating method showed a marked 44.98% improvement with the GBE group vs. 20.98% in the control.[42] All improvements were noted starting six weeks after treatment.

Hofferberth investigated the efficacy of 40mg TID dosage GBE in patients with psychotic organic brain syndrome in an 8-week German study. This well designed study, which used both subjective and objective parameters of evaluation, found a highly significant difference between the treatment and control group in several areas of measure including saccadic eye movement tests, psychometric tests, the Wiener Determination Test, and Number Connection Test.[43]

Compelling results were also noted in a multicenter study of 70 patients with vertiginous syndrome of short duration, where efficacy was based on intensity, frequency, and duration of symptoms. After a three-month treatment period, 47% of the GBE group was symptom free vs. 18% of the placebo group.[44] Although vertigo (of short duration) can resolve spontaneously, the results of this study seem to indicate GBE may have some application in patients with vertigo.

Lastly, a multicenter double blind controlled study by Tomborini & Taurelle evaluated GBE's effects in reducing congestive symptoms of PMS. Their study produced data on 143 women between ages 18 and 45 who had experienced at least seven days of congestive symptoms per menstrual cycle over at least two cycles. Participants received GBE from the 16th day of one cycle to the 5th day of the next. Results showed GBE effective in reducing the congestive symptoms of PMS at a level significantly greater than placebo. Breast symptoms showed greatest improvement, although other congestive as well as neuropsychological symptoms also showed improvment.[45]

Dosage & Toxicity:

Virtually all of the supporting evidence behind the use of *Ginkgo biloba*, has been on use of concentrated and standardized extracts of the herb to ensure reproducibility in the clinical setting. Standardization of herbal medicines is a multistep process, and in the case of Ginkgo fifty pounds of leaves produce about one pound of extract. Standardized extracts containing 24% ginkgo flavone glycosides & 6% terpene lactones, at an oral dose of 40 to 80mg three times daily is what has been shown to be effective.[6,8,9] However, the extract should be administered for at least 6-8 weeks (preferably 3-4 months) before evaluating its efficacy.[13]

Dosage of parenteral use of Ginkgo ranges from 50 to 100mg daily, although intravenous preparations are not readily available in this country.[8] No toxic effects have been found in studies utilizing recommended dosages of Ginkgo extracts; parameters including blood pressure, serum, triglycerides, cholesterol, hepatic transaminases, bilirubin, hepatic microsomal drug oxidation enzymes, and glucose were all unaffected.[9,14] The LD_{50} of *Ginkgo biloba* extract is 15.3g/kg, with no mutagenicity detected.[13]

Adverse effects, Contraindications, & Potential Interactions:

Ginkgo biloba extract is well tolerated with rare occurrence of side effects. Of 9,772 patients in 44 double blind studies, 21 persons had GI discomfort, 7 had headache, and six had dizziness. *Ginkgo biloba* is contraindicated in patients known to be hypersensitive to it, although health risks and major side effects following proper administration have not been recorded. Allergic skin reactions have been observed rarely in response to ingestion or contact with the fruit pulp leading to erythema, edema, pruritis, and GI irritation[5,8,9] and therefore use of the fruit should be avoided. Possible hypersensitive reactions may include spasms & cramps, atonia & adynamia.[5,8] The use of Ginkgo preparations during pregnancy and lactation has not been studied, and therefore its use during these times is not recommended. Since Ginkgolide B has potent PAF inhibitory effects, Ginkgo extracts should be used with caution or not at all when other antithrombotic therapies including warfarin, heparin, aspirin, even standardized extracts of garlic or ginger are employed.

Conclusion:

With the growing patient demand for alternative, complementary, natural, or integrated approaches in treating disease, it is increasingly important for clinicians to develop referral relationships with well-trained CAM providers. Likewise it is important for conventional clinicians to become familiar with CAM therapies their patients may be considering or using. *Ginkgo biloba* extract (GBE), one of the most commonly used and best-researched phytomedicines, has documented efficacy for many conditions. Use of GBE in cerebrovascular insufficiency, memory impairment in the elderly, Alzheimer's disease, multi-infarct dementia, resistant depression, peripheral artery insufficiency, venous insufficiency, and asthma is well supported by multiple studies. GBE for tinnitus, schizophrenia, psychotic organic brain syndrome, vertigo of undetermined origin, and PMS, although less supported, still deserves serious consideration because of GBE's high tolerability, and the limited or complete lack of efficacy with conventional treatments for these conditions

References:

1. Eisenberg DM, et al. Trends in alternative medicine use in the United States, 1990-1997: results of a follow-up national survey. *JAMA* 1998;280:1569-1575.
2. Pournadeali K, Yarnall SR. Nonphysician clinicians in the health care workforce. *JAMA* 1999;281(6):510-511.
3. Council on Naturopathic Medical Education. (Oral communication) September 1998.
4. Rouse J. Ginkgo biloba: Mind, Mood, and Memory. *Clinical Nutrition Insights.* Advanced Nutrition Publications Inc. 1998;6(7): 1-2.

5. Murray MT. Ginkgo biloba. In: *Healing Power of Herbs*. 2nd ed. Rocklin, CA: Prima Publishing; 1995: 143-161.

6. Brown D. Ginkgo biloba. Phyto Fact Sheet. *Natural Product Research Consultants*.

7. Brevoort, P. The Booming U.S. Botanical Market. *Herbalgram*. 1998;44:33-46.

8. Fleming T, et al. *PDR® for Herbal Medicines*. Montvale, NJ: Medical Economics Inc.1998:871-873.

9. Anonymous. *Ginkgo biloba Extract (*EGb *761) in perspective*. Auckland 10, New Zealand: ADIS Press Ltd;1990:1-20.

10. Braquet P, ed. *Ginkgolides: Chemistry, Biology, Pharmacology and Clincal Perspectives, Vols 1 & 2*. Barcelona: JR Prous Science Publishers; 1992.

11. Krieglstein J. Neuroprotective properties of Ginkgo biloba constituents. *Zeits Phytother*. 1994;15:92-96.

12. Drieu K. Preparation and definition of Ginkgo biloba extract. In: Funfgeld EW, ed. *Rokan (Ginkgo biloba): Recent Results in Pharmacology and Clinic*. Berlin: Springer-Verlag. 1988: 32-36.

13. Anonymous. Monograph: Ginkgo. *Alternative Medicine Review*. 1998;3(1):54-57.

14. Duche JC, et al. Effect of Ginkgo biloba extract on microsomal enzyme induction. *Int J Clin Pharmacol Res*. 1989;9(3):165-168.

15. Fourtillan JB, et al. Pharmacokinetics of Bilobalide, Ginkgolide A and Binkgolide B in healthy volunteers following oral and intravenous administrations of Ginkgo biloba extract (EGb 761). *Therapie*. 1995;50:137-144.

16. Vesper j, Hansgen K.. Efficacy of Ginkgo biloba in 90 outpatients with cerebral insufficiency caused by old age. Results of a placebo controlled double-blind trial. *Phytomedicine*. 1994;1:9-16.

17. Taillandier J, Ammar A, Rabourdin JP et al. Treatment of cerebral aging disorders with Ginkgo biloba extract. A longtitudinal multicenter double-blind drug vs. placebo study. *Presse Med*. 1986;15:1583-1587.

18. Grasse E, Effect of Ginkgo-biloba extract on mental performance. Double-blind study using computerized measurement conditions in patients with cerebral insufficiency. *Fortschr Med*. 1992;110(5):73-76.

19. Hofenmuller 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(9):1005-1013.

20. Allain et al. Effect of two doses of ginkgo biloba extract (EGb 761) on the dual-coding test in elderly subjects. *Clin Ther*. 1993;15:549-558.

21. Hindmarch I. Activity of Ginkgo biloba extract on short-term memory. *Presse Med* 1986;15:1592-1594.

22. Le Bars PL, Katz MM, Berman N, et al. A placebo-controlled, double-blind, randomized trial of an extract of Ginkgo biloba for dementia. North American EGb Study Group. *JAMA*. 1997;278:1327-1332.

23. Kanowski S, Herrmann WM, Stephan K, et al. Proof of efficacy of the Ginkgo biloba special extract EGb 761 in outpatients suffering from mild to moderate primary degenerative

dementia of the Alzheimer type or multi-infarct dementia. *Pharmacopsychiatr*. 1996;29:47-56.

24. Hasse J, Halama P, Horr R. Effectiveness of brief infusions with Ginkgo biloba Special Extract EGb 761 in dementia of the vascular and Alzheimer type. *Z Gerontol Geriatr*. 2996;29(4):302-309.
25. Schubert H, Halama P. Depressive episode primarily unresponsive to therapy in elderly patients: Efficacy of Ginkgo biloba extract (EGb 761) in combination with antidepressants. *Geriatr Forsch*. 1993;3:45-53.
26. Bauer U. 6-Month double-blind randomised clinical trial of Ginkgo biloba extract versus placebo in two parallel groups in patients suffering from peripheral arterial insufficiency. *Arzneimittelforschung.* 1995;34:716-720.
27. Jung F, Mrowietz C, Kiesewetter H, Wenzel E. Effect of Ginkgo biloba on fluidity of blood and peripheral microcirculation in volunteers. *Arzeimittelforschung*. 1990;40:589-593.
28. Koltringer P, et al. Hemorheologic effects of ginkgo biloba extract EGb 761. Dose-dependent effect of EGb 761 on microcirculation and viscoelasticity of blood. *Fortshcr Med*. 1993;111(10):170-172.
29. Schneider B. Ginkgo biloba extract in peripheral arterial diseases. Meta-analysis of controlled clinical studies. *Arzneimittelforschung.* 1992;42:428-436.
30. Mouren X, Caillard P, Schwartz F. Study of antiischemic action of EGb 761 in the treatment of peripheral arterial occlusive disease by TcPo2 determination. Angiology. 1994;45(6):413-417.
31. Bauer U. Ginkgo biloba extract in the treatment of arteriopathy of the lower extremities. A 65 week trial. *Presse Med*. 1986;15:1546-1549.
32. Lebuisson DA, Leroy L, Rigal G. Treatment of senile macular degeneration with Ginkgo biloba extract. A preliminary double-blind drug vs. placebo study. *Presse Med*. 1986;15:1556-1558.
33. Janssens D et al. Increase in circulating endothelial cells in patients with primary chronic venous insufficiency: protective effect of Ginkor Fort in a randomized double-blind, placebo-controlled clinical trial. *J Cardiovasc Pharmacol*. 1999;33(1):7-11.
34. Markey AC et al. Platelet activating factor-induced clinical and histopathologic respoonses in atopic skin and their modification by the platelet activating factor antagonist BN52063. *J Am Acad Dermatol*. 1990;23(2):263-268.
35. Guinot p et al. Tanakan inhibits platelet-activating-factor-induced platelet aggregation in healthy male volunteers. *Haemostasis*. 1989;19(4):19-23.
36. Chung KF et al. Effect of a ginkgolide mixture (BN52063) in antagonising skin and platelet responses to platelet activating factor in man. *Lancet*. 1987;I:48-51.
37. Guinot P et al. Inhibition of PAF-acether induced wheal and flare reaction in man by a specific PAF antagonist. *Prostaglandins*. 1986;32(1):160-163.
38. Li M, Zhang H, Yang B. Efects of ginkgo leave concentrated oral liquor in treating asthma. *Chung Kuo Chung His I Chieh Ho Tsa Chih*. 1997;17(4):216-218.
39. Holgers KM, Axelsson A, Pringle I. Ginkgo biloba extract for the treatment of tinnitus. *Audiology*. 1994;33(2):85-92.

40. Meyer B. Multicenter randomized double-blind drug vs. placebo study of the treatment of tinnitus with Ginkgo biloba extract. *Presse Med*. 1986;15(31):1562-1564.
41. Meyer B. A multicenter study of tinnitus. Epidemiology and therapy. *Ann Otolaryngol Chir Cervicofac*. 1986;103(3):185-188.
42. Luo HC, Shen YC, Meng FQ. Therapeutic effect of shuxuening combining with neuroleptics for the treatment of chronic schizizophrenia—a double blind study. *Chung Kuo Chung His I Chieh Ho Tsa Chih*. 1997;17(3):139-142.
43. Hofferberth B. The efect of Ginkgo biloba on neurophysiological and psychometric measurement results in patients with psychotic organic brain syndrome. A double-blind study against placebo. *Arzneimittelforschung*. 1989;39(8):918-922.
44. Haguenauer JP et al. Treatment of equilibrium disorders with Ginkgo biloba extract. A multicenter double-blind drug vs. placebo study. *Presse Med*. 1986;15(31):1569-1572.
45. Tamborini A, Taurelle R. Value of standardized Ginkgo biloba (EGb 761) in the management of congestive symptoms of premenstrual syndrome. *Rev Fr Gynecol Obstet.* 1993;88(7-9):447-457.