

GINKGO BILOBA: A MONOGRAPH

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Botanical Name:	<i>Ginkgo biloba</i> L.
Family:	Ginkgoaceae
Pharmaceutical Name:	Herba and Semen <i>Ginkgo biloba</i>
Synonyms:	Kung-sun shu Pai-kuo Fei-o-hsieh (flying moth leaf) Fu chi-chia (Buddha's fingernails) Ya-chiao pan (duck foot) Ling-jen Yen hsing Yin guo Pai-kuo jen or Bai gou or Yin hsing (seeds)

Botanical Description: A prehistoric tree that can be dated back at least 200 million years, the *Ginkgo* tree would be extinct if not for its cultivation by Far Eastern monks in temple gardens (1). Thus the *Ginkgo biloba* is a living fossil Gymnosperm that can live up to 1,000 years growing as high as 125 feet, with a trunk diameter of 3-4 feet (2,3). The trunk is erect with a gray bark that can be deeply cracked. The tree is a deciduous, dioecious conifer with distinctive male and female forms. Branches can be long or short, forming a dense crown when old in growth. Leaves on the long branches are single, while leaves on the short branches are clustered. Its leaves grow in a unique fan shaped feature that is indicative of the plant. They are two lobed or biparted at the apex, thus *biloba*; on a long petiolated stem, with forked parallel veins radiating from the petioled cuneate base, to the undulate or irregularly shallow parted leaf margin. The mature orange-yellow fruit is a drupe that is obovate or ellipsoid and rich in butyric acid and the seed is a nut that surrounds a woody stone. It is this seed that was greatly used in Traditional Chinese Herbal Medicine (TCHM).

Habitat: Rich sandy soil with no resistance to cold; once common in Europe and North America but was destroyed everywhere by the Ice Age, except China (5). Introduced to Europe in 1730, growing well in temperate

climates (2,4). In the late 17th century, Dr. Engelbert Kaempfer, a German botanist and physician was the first European to discover and catalog the tree. In 1771 Linnaeus named the tree *Ginkgo biloba* (5). It can be found as an introduced species in the United States, brought into the country in 1784 by William Hamilton near Philadelphia (5). The tree is found now throughout much of the United States as a cultivated ornamental tree. It is extremely resistant to all kinds of pollution, viruses and fungi, and was extensively planted in Asian, European and American cities for these features.

Collection: Traditionally, Asians have collected the seeds after the fruit has fallen off the female tree and onto the ground. Thick gloves are worn when collecting the fruit because of its rich butyric acid content that can cause blistering to the skin if touched. Often the fruit of the tree has a particularly foul and pungent odor, likened to 'dog vomit.' The leaves are collected in the summer, and it is the leaves of these younger, cultivated plants that are used in medicinal herbal preparations more commonly today.

Folklore: The ethnobotanical use of this plant dates back 5,000 years. It is called the ancient or "doyen" of trees because of its antiquity (2). Its medicinal use can be traced back to the first summarizations written by the Chinese, in the *Nei-ching*, a medical classic which consisted of 18 volumes and 162 chapters. The first revision of the *Nei-ching*, the *Shen Nung Pen Tsao* (book of materia medica), was *Ginkgo's* first

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RESEARCH REVIEW

introduction into a written pharmacopeia, a book describing more than three hundred medicines and their therapeutic actions (1). The seeds of the *Ginkgo* have also been found listed in other ancient Chinese writings, for example the *Household Materia Medica of China*, 1350 AD (2). The modern phytotherapeutic use of the leaves is different than most herbs, because there is little folklore about its usage. Modern usage started in the 1970s with a large body of scientific literature infiltrating the scientific community in a relatively short period of time. "A herb of longevity from a living fossil tree" (2), it is held by Taoists as an herb representing unity with duality in its ability to affect this duality energetically in healing.

Traditional Chinese Properties:

Neutral and astringent; pleasantly sweet yet bitter and biting to the taste. Seeds can be poisonous.

Meridians Entered: Lung and Kidney meridians; exerting astringency on pulmonary energy stopping coughs, asthma and wheeze. While stabilizing kidney qi function to expel phlegm, stops discharges and stabilizes the lower burners.

Text in which it first appears: First materia medica of China, *Shen Nung Pen Tsao*, 2000 years ago, authors unknown (1).

INTRODUCTION

Ginkgo biloba is an ancient Traditional Chinese Herbal Medicine (TCHM) that is classified within this system as a neutral herb that affects the lung and kidney meridians. The Chuang-fu (or Zang-fu) refers to the five viscera (chuang or solid organs) and bowels (fu or hollow organs) in the human body. The five solid viscera are the liver, heart (including the pericardium), spleen, lungs and kidneys. The six hollow organs are the gallbladder, stomach, large intestine, small intestine, the urinary bladder, and the san-chiao, or triple burner. The meridians that are affected by the *Ginkgo* are of the solid organs, lungs and kidneys. Functionally, the solid and hollow organs (viscera and bowels) are paired off with each other sharing a coordinating division of labor. These combinations of each solid and hollow organ stimulate yet control each other. Also, the vital organs are related to other tissues in the body, for example if your kidney qi is weak you may have weak, aching knees and be losing your hair. Though the ter-

minology of the five solid and six hollow organs resembles that of Western medicine, the TCHM practitioner's references do not particularly match those of Western thought. The TCHM practitioner's standpoint of function, location and description are quite different.

TCHM FUNCTIONS AND MEDICINAL USE

In China, the seeds of the *Ginkgo biloba* plant are the part predominantly used in TCHM therapeutics. Acting on the lung and kidney meridians, they were traditionally used for pulmonary tuberculosis, asthmatic disorders, and congestive coughs with thick phlegm. They also have a tonifying effect on the urinary system, stabilizing spermatogenesis and stopping leukorrhea by stabilizing the San Jiao or lower burners. The seeds (nuts) are made into a soup to help with lower burner fluid imbalance symptoms like diarrhea or dysbiosis. The seeds are also used classically as an antibiotic or antifungal. Seeds and seedcoats are used in doses of 1 to 3 grams in a decoction, or pan fried for eating.

WESTERN FUNCTIONS AND CLINICAL USE

Phytopharmacological studies into the active constituents in the leaves of the *Ginkgo* tree began in the late 1950s, with the phytopharmaceutical company Karlsruhe in Germany and Dr. Wilmar Schwabe leading the research (3). Their twenty plus years of research resulted in a concentrated standardized extract known as EGb761 (3). Standardized to 24% flavonglycoside with 10% quercetin, this product is often called GBx (2). *Ginkgo biloba* extracts (GBE) are marketed in the world market under several synonyms, Tanakan, Rokan and Tebonin, and exist in the European market in both parenteral and intravenous forms (3,5). "GBE is the most frequently prescribed phytomedicine in Europe today. Its impressive track record of more than 400 pharmacological and clinical studies and reports also makes it the best researched phytomedicine in the world" (3).

ACTIVE CONSTITUENTS

The most active ingredients are flavonglycosides or ginkgolide heterosides (heteroginkgosides or ginkgosides) and the terpene lactones. The ginkgo heterosides are flavonoid molecules that are unique to the ginkgo. It is these ginkgo-fla-

vone glycosides that are typically standardized to 24% for their phytopharmaceutical activity. The primary terpene lactones are three ginkgolides A,B,C, as well as bilobalide. These ginkgolides and bilobalide again are specific to the ginkgo.

The ginkgo flavonoid glycosides are molecules that contain an aglycone flavonoid portion bound to a glucoside sugar. The three major aglycones are quercetin, kaempferol, and isorhamnetin. The glucoside sugars are glucose and rhamnose, monoglucoside and diglucoside sugars respectively that are found in esterified and nonesterified forms (5). Other significant flavonoids include proanthocyanidins which are largely composed of dimers and oligomers of delphinidine and cyanidin (5). The terpene molecules are the diterpene ginkgolides A, B, and C and the sesquiterpene bilobalide, and are generally standardized to 6% in the marketed extract (3,5). The difference between the three ginkgolides is the presence of one, two, or three hydroxyl groups. The bilobalide is a trilactone with a tertiary butyl group (5). See Figures 1, 2, and 3.

- Ginkgolides are unique twenty carbon terpenes that occur naturally only in the roots and leaves of the *Ginkgo*. The molecules incorporate a tert-butyl group and six 5-membered rings and are specific and potent antagonists of platelet activating factor (PAF), a potent inflammatory autotoxin. Ginkgolides are now being developed as therapeutic agents and very promising results have been obtained in clinical trials on shock, organ preservation and thermal injury (6).
- Pharmacologically there are two groups of substances which are of some significance: the flavonoids, effective as oxygen free-radical scavengers, and the terpenes (i.e., the ginkgolides) with their highly specific action as platelet activating factor (PAF) inhibitors. Clinically important indications for *Ginkgo biloba* extracts are cerebral insufficiency and atherosclerotic disease of the peripheral arteries of intermediate severity. In several placebo controlled studies, symptoms of cerebral insufficiency have been significantly altered. Most of the trials

were using the extracts EGb761 and LI 1370 (7).

MECHANISM OF ACTION

The following list of actions is taken from the revised German Commission E Monograph for Ginkgo (GBE), June 21, 1994 (8).

- Improvement of hypoxic tolerance, particularly the cerebral tissue.
- Inhibition in the development of traumatically or toxically produced cerebral edema and acceleration of decongestion.
- Reduction of retinal edema and of cellular lesions in the retina.
- Inhibition of age-related reduction of muscarinic choline receptors and alpha-2-adrenoreceptors as well as stimulation of choline absorption in the hippocampus.
- Increase in memory performance and learning capacity.
- Improvement in compensation of disturbed equilibrium.
- Improvement in circulatory perfusion, particularly in the region of microcirculation.
- Improvement in the rheological properties of the blood.
- Inactivation of toxic oxygen radicals.
- Antagonism of platelet-activating factor.
- Neuroprotective effect.

PHARMACOKINETICS

- The pharmacokinetics of Ginkgolide A, B and bilobalide, which were extracted from the dried leaves of the *Ginkgo biloba* tree were investigated in 12 healthy volunteers, 6 men and 6 women with a mean +/-SD age = 25 +/- 5 years, after single dose administration of the Ginkgo extract. The subjects were given, on three different occasions, Ginkgo extract as either an oral solution or intravenously, single doses ranging from 0.90 mg to 3.36 mg. Blood and urine samples were collected after each dosing for up to 36-48 hours to measure Ginkgolide A, B and bilobalide. When given orally while fasting, the bioavailability is high for all three constituents. Food intake does not change the bioavailability quantitatively, but increases the rate of absorption. For the 3 compounds, after oral dosing while fasting, differences

FIGURE 1
TERPENE LACTONES IN GINKGO BILOBA EXTRACT(3)

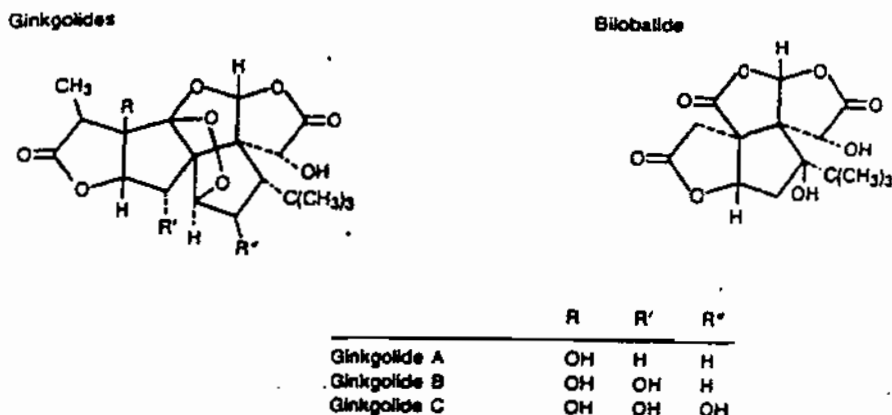
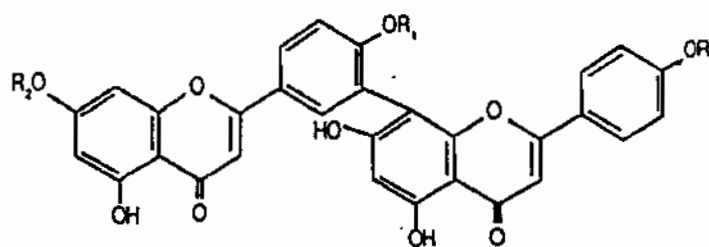
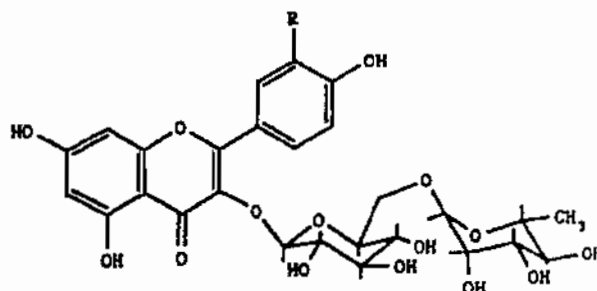


FIGURE 2
CHEMICAL CONSTITUENTS IN GINKGO (2)



Compound	R ₁	R ₂	R ₃
Amentoflavone	H	H	H
Bilobetin	CH ₃	H	H
IsoGinkgetin	CH ₃	H	CH ₃
Ginkgetin	CH ₃	CH ₃	H
Sciadopitysin	CH ₃	CH ₃	CH ₃

FIGURE 3
FLAVONE GLYCOSIDES IN GINKGO BILOBA EXTRACT (3)



R = H: kaempferol-3-O-rutinoside
 R = OH: quercetin-3-O-rutinoside (rutin)
 R = OCH₃: isorhamnetin-3-O-rutinoside

can be noted for the elimination half-lives which exhibit mean values equal to 4.5 hours for Ginkgolide A, 10.57 hours for Ginkgolide B and 3.21 hours for bilobalide (9). According to Drieu (one of the researchers in the above study), the total extract is more active than the single isolated constituents, which suggests a synergism among the various components that make up the plant (5).

- The pharmacokinetics of GBE studied in rats showed, by coupling with radiolabeled carbon 14, that absorption was at least 60%; these researchers strongly suspected that the upper gastrointestinal tract did most of that absorbing. During the first 3 hours radioactivity was found primarily in the plasma with the erythrocytes progressively uptaking the radiolabelled material for 48 hours until equilibrium was reached between the erythrocytes and the plasma (10).
- The flavonoids have an affinity for organs rich in connective tissue such as the aorta, eyes, skin and lungs with radioactivity concentrations in these tissues two to three times higher than that in plasma, with a little decrease in levels over time. The heart showed specific activity maintained twice as long as in the plasma. Radioactivity in the hippocampus and striated bodies in the brain at seventy two hours showed five times greater absorption than that of the plasma. The adrenal glands retained the highest level of radioactivity (5,10).
- One of the components in *Ginkgo biloba*, ginkgolide B, is a potent platelet activating factor antagonist. The terpene fractions, which contain the ginkgolides, may contribute to the neuroprotective properties of the *Ginkgo* leaf. The flavonoid fraction, containing free radical scavengers, is also an important aspect (11).
- Eighteen healthy volunteers received three different formulations of *Ginkgo biloba*: capsules in the A group, drops in the B group (Agnon Pharma) and tablets in the C group (Tebonin-Dr. W. Schwabe) in equal quantity, orally as a single dose and at an interval of at least five

days. The pharmacokinetic parameters of the most important flavonoid glycosides, quercetin, kaempferol and isorhamnetin, were established. The bioavailability was estimated using standard capsules as a standard formulation. Only the time to reach the peak concentration (Tmax) of quercetin, kaempferol and isorhamnetin administered in the form of capsules was significantly prolonged as compared with drops and tablets. It is concluded that the three formulations of *Ginkgo biloba* extract are bioequivalent (32).

- Two experiments were conducted to assess the EEG effects of three different dosages of a total *Ginkgo biloba* extract (EGb 761, Tebonin) and three different extractions of ginkgo (Tebonin and two fractions from it). The verum groups were tested against placebo using a double-blind cross-over design in 12 healthy males for each experiment. Verum was administered for 3 days preceding the recording sessions. Medication-related effects were obtained from most of the statistical measures, whereas dominant frequencies of the respective frequency band remained largely unchanged on the EEG (35).

CLINICAL EFFECTS

VASCULAR

CEREBROVASCULAR, CARDIOVASCULAR

- Eleven clinical trials were evaluated in a meta-analysis to prove the effectiveness of *Ginkgo biloba* extract LI 1370 (Kaveri forte). All the studies were placebo-controlled randomized double-blind studies, most using a dose of 150 mg QD. For all analyzed single symptoms significant differences were found with the *Ginkgo* extract showing cerebrovascular improvements in comparison to placebo (13).
- Sixty patients with cerebral insufficiency, the leading symptom being depression, were treated in a double-blind study for 6 weeks. The daily dose of 160 mg QD of *Ginkgo biloba* extract or placebo was given. At weeks 2, 4 and 6 changes in 12 typical symptoms

were compared with the last examination, and evaluated. The placebo group showed small but progressive improvements. The *Ginkgo* group showed overall significant improvements with best results in treatment weeks 4-6, with improvement in 11 out of 12 symptoms (14).

- A critical review of controlled trials in humans was done to establish the efficacy of *Ginkgo biloba* extracts in cerebral insufficiency. A comparison was made with trials of co-dergocrine, which is a registered drug for the same indications. All trials reported positive results. In most trials the dosage was 120 mg of *Ginkgo* extract QD, given for 4-6 weeks. For the best trials reviewed, there were no marked differences in the quality of the evidence of the efficacy of *Ginkgo* in cerebral insufficiency compared to co-dergocrine. These positive results of *Ginkgo* extract in treatment of cerebral insufficiency show clinical evidence similar to that of a registered product which is prescribed for the same disease process (18).
- A double-blind randomized placebo-controlled study was done on 72 outpatients with cerebral insufficiency, to test the effect of *Ginkgo biloba* extract EGb761 on basic parameters of mental performance. The test parameters were the psychometric computer-aided examination of short term memory and basic learning rate. Results showed statistically significant improvement in short term memory after 6 weeks with a statistical significance in learning rate after 24 weeks in the verum group, but not in the placebo group. It was concluded that treatment with EGb761 improves mental/mnemonic performance (19).
- A randomized study lasting 6 weeks with 80 geriatric patients with cerebrovascular disorders comparing the effectiveness and tolerance of dihydroergotoxine to that of *Ginkgo biloba* extract. On the basis of psychometric testing it was shown that treatment with either substance improved the condition of the patients. Intergroup comparisons showed no major statistical

significant differences between the two (21).

- A double-blind placebo-controlled trial was conducted in 55 patients with acute ischemic stroke. The verum group consisted of 21 patients and the placebo group had 26. The verum group received 40 mg of Ginkgo extract at 6 hourly intervals, along with routine management. The placebo group was given tablets of the same size, shape and color at the same intervals. The patients with confirmed ischemic infarction via computerized tomography (CT) scan were reassessed at 2 and 4 weeks. Both groups showed significant improvements and the difference between the groups in degree of change was negligible. Estimation of relative changes of neurological deficit based on baseline values was also negligible. In conclusion the trial researchers concluded that an extract of Ginkgo of 40 mg within 6 hours of stroke is too low a dose to be clinically beneficial in patients with cerebral ischemic infarct. They deduce that while the usefulness of the plant extract has been clinically demonstrated in more than 40 trials of chronic cerebral ischemia these benefits were not evident in their study group because the study population had stroked within the past 48 hours (22).
- Chronic cerebral retinal insufficiency syndrome is a specific expression of a generalized vascular cerebral deficiency. The effect of *Ginkgo biloba* extract on patients suffering from sporadic late onset dementia of Alzheimers type is evidenced in two different ways: by the aging process and by the disease process via changing brain glucose energy metabolism, maintenance of calcium homeostasis, and membrane stability. It was concluded that some nootropic drugs such as dihydroergotoxine, *Ginkgo biloba*, nicergoline, nimodipine, piracetam and pyritinol-HCl all exert positive effects on clinical symptoms of dementia. There is clear evidence that *Ginkgo biloba* acts on membrane lability (43).

- In vestibular compensation, unilateral vestibular differentiation causes ocular motor and postural disorders. Three classes of drugs were selected for review because of the amount of experimental evidence relating to them and because they are for the most part safe for use in humans: melanotropic peptides, calcium antagonists and gangliosides/*Ginkgo biloba* extract EGb.761. It was concluded that the Ginkgo extract has a positive effect by accelerating compensation (51).
- Endothelial cells are the first target of any change occurring within the blood due to their localization at the interface between blood and tissue. Alterations of their functions can seriously impair organs. Ginkgo extract EGb 761 and one of its constituents, bilobalide, were shown to inhibit the hypoxia induced decrease in ATP content in endothelial cells *in vitro*. Bilobalide was found to increase glucose transport under normal but not hypoxic conditions. Interestingly both Ginkgo and bilobalide prevented the increase in total lactate production observed after 60 minutes of hypoxia, delaying the onset of glycolysis activation. Both compounds were shown to increase the respiratory control ratio of mitochondria isolated from liver of rats tested orally. Since ischemia is known to uncouple mitochondria, the protection of ATP content and the delay in glycolysis activation observed during hypoxia in the presence of EGb 761 and bilobalide were explained as a protection of mitochondrial respiratory activity, during the first 60 minutes of hypoxia. Both compounds retain the ability to form ATP, reducing the cell's need to induce glycolysis (58).
- Two placebo-controlled studies examined the effect of either 169 mg QD *Ginkgo biloba* extract (GBE) or piracetam 2.4 or 4.8 g/d on memory function. The results of both studies suggest that nootropic drug treatment and memory training each have an effect on different cognitive functions and are complementary. The function of EGb 761 on the reversibility of visual field disturbances was

tested using a randomized double-blind study design in two phases with two dose levels. The main parameter measured was the change in the luminous density difference threshold after therapy with EGb 761. In group B the dose was 160 mg QD and a significant increase in retinal sensitivity was seen within 4 weeks. In the lower dose group (at 80 mg QD) sensitivity was not seen until increasing the dose to 160 mg QD. The results showed that damage to the visual fields by chronic lack of blood flow is significantly reversible with *Ginkgo biloba* (31).

- In a survey, primary care physicians in Goettingen, Germany, were asked which drugs would be chosen to treat cognitive disorders, e.g., cerebral insufficiency. Most frequently chosen were piracetam, *Ginkgo biloba*, and nimodipine. Family physicians considered *Ginkgo biloba* more often than nimodipine or co-dergocrine (40).
- Impaired glucose utilization in 49 discrete structures of rat brain received treatment with *Ginkgo biloba* extract EGb 761. Oral administration of EGb 761 at 50 or 150 mg/kg/day to adult male rats for 15 days did not modify body weight, mean arterial blood pressure, the concentrations of glucose or hemoglobin in blood, blood gases or arterial pH. The treatments produced only slight to moderate changes in glucose utilization in the various brain structures. Glucose utilization was significantly decreased in the frontoparietal somatosensory cortex, nucleus accumbens, cerebellar cortex and pons only at the dose of 50 mg/kg of EGb 761. These effects appear useful in explaining mechanisms underlying the clinical use of Ginkgo extract in treating problems associated with cerebral glucose utilization (64).

Maturopathic Implications

Ginkgo biloba has the ability to affect a wide range of vascular systems: arterial, microcirculatory and venous, as well as the ability to increase total perfusion rates. This ability is directly related to Ginkgo's effect on the endothelial lining of the vessel wall. "Its vasodilating action

is stimulating the release of endothelium-derived relaxing factor (EDRF) and prostacyclin. In addition, GBE inhibits enzymes in a way that leads to smooth muscle cell relaxation in the wall of the vessel" (5). Due to Ginkgo's free radical scavenging ability, it is able to clear toxic cellular metabolites that accumulate during hypoxia while balancing glucose metabolism, thus enhancing cellular stability and restoring circulation in cases of vasomotor paralysis, as well as acting as a relaxant in vasomotor spasticity. Ginkgo's ability to improve mitochondrial respiration indirectly affects the ionic potential across the membranes and stabilizes the blood brain barrier, which is significantly affected by aging (2). "Three primary actions for GBE have been shown: Hemodynamic-GBE exerts an anti-ischemic action and relieves arteriolar spasm; Hemorrhologic-GBE counteracts platelet and erythrocyte hyperaggregability; Metabolic-GBE allows better glucose and oxygen uptake under ischemic conditions thereby stimulating aerobic glycolysis and promoting lactate clearance. The ability of GBE to improve circulation has made it a common treatment for both cerebrovascular insufficiency and intermittent claudication. GBE has also been shown to increase microcirculation" (3).

ALZHEIMER'S AND DEMENTIA

- A study was conducted to investigate the effects of *Ginkgo biloba* extract (Ginkobene) on cognitive information processing via long latency auditory event related potentials. A double-blind placebo-controlled study of 48 patients (29 women and 19 men), ages ranging between 51-79 years with a diagnosis of age-associated memory impairment was conducted. Fifty-seven days of treatment consisted of giving 40 mg TID QD Ginkgo extract or placebo. The *Ginkgo biloba* group after acute, chronic and superimposed drug administration showed a shortened P300 latency. It was hypothesized that the decrease in the P300 latency in the treatment group may reflect a shorter stimulus evaluation time for information processing (17).
- A study of 31 patients over the age of 50 with mild to moderate degree of memory impairment was conducted over 6 months in a double-blind placebo-con-

trolled parallel group design to study the effects of a standardized *Ginkgo biloba* extract. The extract contained 24% flavonoid glycosides and 6% terpenes, and the test was on cognitive function. Dosage was 40 mg PO TID of verum or placebo. Psychometric testing was done at treatment weeks 12 and 24. Statistical analysis of the data as compared to baseline showed that the Ginkgo extract had a beneficial effect on cognitive function in the verum group of patients (20).

- The efficacy of Ginkgo extract EGb 761 in outpatients with presenile and senile primary degenerative dementia of the Alzheimer type and multi-infarct dementia was investigated in a randomized, double-blind placebo-controlled, multi center study. Two hundred and sixteen patients were included in the randomized 24 week treatment period. They received either a dose of 240 mg PO QD of verum or placebo. Clinical efficacy was assessed by means of a responder analysis with therapy response being defined as response in at least two of the three primary variables. The data was collected from the 156 patients who completed the study. The frequency of therapy responders in the two treatment groups differed significantly in favor of the EGb 761 group. Thus, the clinical efficacy of the *Ginkgo biloba* special extract EGb 761 in dementia of the Alzheimer type and multi-infarct dementia was confirmed, while also being well tolerated (33).
- Eighteen elderly men and women with a mean age of 69 years, with slight age-related memory impairment, were included in a crossover study design. Each subject group received either placebo or Ginkgo extract EGb 761 in a dose of either 320 mg or 600 mg QD. After each dose of Ginkgo extract there was a significant shift toward a shorter response time, indicating improvement in the speed of information processing (34).
- Forty patients with a mean age of 68 years suffering from moderate dementia (Alzheimer, vascular or mixed type) were included in a study to test the

efficacy of *Ginkgo biloba* extract EGb 761. Infusions of either EGb 761 or placebo were administered 4 days per week for 4 weeks. No relevant group difference was discovered at baseline. After therapy, patients of the verum group scored significantly better on each outcome measure than the placebo group. Superiority of EGb 761 therapy was also found with respect to a self-rating scale for instrumental activities of daily living, and decreased depression. Thus, the clinical efficacy of EGb 761 could be shown on three planes of assessment: the behavioral, the psychopathologic and the psychometric. It was confirmed in patients with moderate dementia, that short-term intravenous infusion therapy with *Ginkgo biloba* results in an improvement of psychopathology and cognitive performance, which is reflected in an increased ability to cope with the demands of daily living (39).

- In psychiatry two of the most used natural compounds are reserpine and *Ginkgo biloba* extract (EGb). Findings indicated significant quantitative central nervous system effects. Furthermore the CNS effects were similar to other psychoactive compounds classified as cognitive activators. Recent studies in which EGb 761 demonstrated therapeutic effects in the treatment of dementia have earned EGb the approval of the German BGA (Bundesgesundheitsamt) for such use (45).
- Pharmacological therapy with nootropics, e.g., *Ginkgo biloba*, is recommended as early as possible in the treatment of dementia. Nootropics have no side effects.
- Extracts of *Ginkgo biloba* leaves produce reversible inhibition of rat brain monoamine (MAO). Both MAO-A and B types were inhibited to a similar extent. The MAO inhibitory compounds were present in dried or fresh *Ginkgo biloba* leaves as well as in commercially prepared capsules. MAO inhibition by Ginkgo may be a mechanism underlying reported anti-stress and anti-anxiolytic activities of this natural product (63).

Naturopathic Implications

Brain cells are extremely susceptible to lipid peroxidation due to their high percentage of unsaturated fatty acids. The effect of ginkgo extract as a free radical scavenger and membrane stabilizer is most evident in the central nervous system (5). Preferentially the brain needs oxygen and glucose to function optimally. With decreased cerebral reperfusion due to the natural aging process, a chain of reactions is set in place which disrupts cell membranes and thus membrane potentials, ultimately leading to cellular death. The primary neuro-protective actions of Ginkgo have been attributed to the terpene lactones, which focus on the ability of the ginkgolides to block the action of platelet aggregation factor (PAF). "High levels of PAF are associated with damage to nerve cells, diminished cerebral blood flow, various inflammatory conditions, and transplant rejections" (3). *Ginkgo biloba* has the remarkable ability to prevent metabolic and neuronal disturbances due to cerebral ischemia and hypoxia by enhancing the oxygen use and cellular uptake of glucose, restoring metabolic aerobic glycolysis. Whatever the biochemistry, Ginkgo was shown to act as a nootropic agent by increasing cognitive function and increasing alpha wave activity. Specifically, Ginkgo improves membrane functions, diminishes cerebral edema, improves mitochondrial respiration, inhibits the action of proteolytic enzymes while stabilizing lysosomal membranes (5). "All these metabolic effects are in addition to GBE's ability to reestablish tissue perfusion...normalize the circulation in the areas most affected by microembolization (small deposits of blood clots) in the hippocampus and striatum...GBE promotes an increased rate of nerve transmission, improved synthesis and turnover of cerebral neurotransmitters, and promotion of acetylcholine receptors in the hippocampus" (5).

PERIPHERAL CIRCULATION

- Recent randomized, placebo-controlled double-blind study with parallel group comparison was done to test the efficacy of *Ginkgo biloba* extract (EGb761) on 42 men (ages 47-82) with angiographically proven peripheral arterial occlusive disease of the lower extremities with intermittent claudication lasting

minimally 6 hours. The therapeutic groups were treated with either the EGb761 at 40 mg TID PO or placebo for a duration of twenty four weeks following a two week placebo run in phase. The absolute changes in pain free walking distance in treatment weeks 8, 16 and 24 was statistically significant in the Ginkgo's group as compared to placebo. The Doppler index remained unchanged in both therapeutic groups (12).

- A systematic review was done to evaluate the effectiveness of *Ginkgo biloba* in the treatment of intermittent claudication. Ten controlled heterogeneous trials were evaluated. All the studies implied that *Ginkgo biloba* is an effective therapy for intermittent claudication (16).
- Eighteen patients with stable intermittent claudication were put in a randomized double-blind cross-over study comparing the effects of *Ginkgo biloba* extract GB-8 at a dose of 12 mg QD with placebo. All patients were treated for three months and the effects of arterial insufficiency were quantified by measurements of systemic and peripheral systolic blood pressure and pain-free maximal walking distances. Short term memory was objectively assessed. In conclusion, the study showed that treatment with the GB-8 improves some cognitive functions in geriatric patients with moderate arterial insufficiency, but did not change signs and symptoms of vascular disease in a randomized placebo controlled single-blind cross-over study of 10 healthy patients (23).
- In a randomized open clinical trial involving 42 patients with pathological visco-elasticity values, the effect of a single intravenous injection of 50, 100, 150 or 200 mg of *Ginkgo biloba* extract EGb 761 on the microcirculation of the skin was assessed by Doppler cytometry and visco-elasticity of whole blood. Results showed a dose-dependent significant increase in the microcirculation, but in visco-elasticity the dose dependency was less marked. The study confirmed the positive effect of EGb 761 on the microcirculation and whole

blood visco-elasticity in patients with pathological visco-elasticity values in a dose-dependent manner (27).

- Methods of meta-analysis are applied to controlled clinical trials with *Ginkgo biloba* extract EGb 761 in patients with peripheral arterial disease. Included were 5 placebo controlled clinical trials with similar design and inclusion criteria. It was shown that the treatment effect was the same in all trials with a global effect size estimated as 0.75. This means that the mean increase in walking distance achieved by EGb 761 is 0.75 times the standard deviation higher than that achieved by placebo. This value is highly significant revealing a marked therapeutic effect of Ginkgo for the treatment of peripheral arterial disease (29).
- The effect of EGb 761 *Ginkgo biloba* extract was studied, measuring transcutaneous partial pressure of oxygen during exercise. This measure provides a good noninvasive estimation of local arterial perfusion and constitutes a real index of local and regional capillary perfusion. Twenty patients between the ages of 44-73 suffering from intermittent claudication, or atherosclerotic arterial occlusive disease in stage II diagnosed for more than 1 year were included and randomized into two treatment groups. The first group was given 320 mg QD of the *Ginkgo biloba* extract for 4 weeks and the second group was given placebo. The study confirmed significantly the rapid antiischemic action of EGb 761 and its value in the management of peripheral arterial occlusive disease presenting with intermittent claudication (60).

Naturopathic Implications

Due to the high flavonoid content of *Ginkgo biloba*, one of the first areas of modern phytotherapeutic study was the vascular system. "In several studies Gbx has been shown to protect the body from arterial blockage, while increasing levels of glucose and ATP at the cellular level to maintain energy level of individual cells that might be affected." (2) Studies show that due to the ability of Ginkgo to stabilize vascular endothelial cells while increasing beneficial prostaglandins,

cellular damage caused by free radical destruction, specifically the diabetic retina, can be inhibited. Coinciding with Ginkgo's ability to affect vessel wall integrity and vascular perfusion, it also inhibits histamine release by influencing the muscular receptor sites. Ginkgo also stimulates the release of catecholamine neurotransmitters (epinephrine and norepinephrine), and increases dopamine synthesis. Thus Ginkgo affects the vascular system, the cardiovascular system, the neuroendocrine system and the nervous system. "Gbx has been found to 'reactivate' norepinephrine and the beta-receptors, producing among other things, dilation of airways in the lungs, dilation of peripheral blood vessels (muscular circulation)" (2). This increase in vascular perfusion is contiguous to the microcirculation across the blood brain barrier, giving *Ginkgo biloba* a total effect on the intertwined vascular systems of the body. For example, Ginkgo's effect on intermittent claudication not only increases peripheral circulation, but increases the function of walking with an associated decrease in pain (pain-free walking). "Numerous studies have shown success using 120 mg of GBE daily in stage II intermittent claudication. GBE is also recommended for vertigo, tinnitus in the Commission E monograph and limited evidence suggests potential use of GBE for Raynaud's Disease" (3).

PLATELET AGGREGATION AND ERYTHROCYTE FUNCTION

• The influence of *Ginkgo biloba* (Kaveri) has been studied *in vivo* on blood fluidity and cutaneous microcirculation. Microcirculation was measured before and every 30 min for 4 hours after administration of *Ginkgo biloba* and fluidity was determined before and after 1, 2 and 4 hours. Significant changes in blood pressure or heart rate were not found in either verum or placebo group. Hematocrit, plasma viscosity, erythrocyte rigidity, thrombocyte and leukocyte count as well as thrombocyte aggregation and the number of circulating thrombocyte aggregates were also not influenced by either group. A remarkable influence on decreasing erythrocyte aggregation was observed after 2 hours in the verum group. The

blood flow in nail bed capillaries also increased significantly at 1 hour post administration of the Ginkgo extract (24).

- A study was done of Gincosan which is a preparation containing 60 mg of *Ginkgo biloba* standardized to 24% ginkgo flavone glycosides and 100 mg of Ginseng standardized to 4% ginsenosides. In an acute trial of 10 volunteers with a mean age of 26 years, hemorrhheological and circulatory effect as well as blood pressure behavior was monitored after the administration of gincosan. Systolic blood pressure decreased significantly both for the large dose group (120 mg *Ginkgo biloba* and 200 mg ginseng) and low dose group (60 mg of *Ginkgo biloba* and 100 mg of Ginseng). Diastolic blood pressure and heart rate decreased only in the high dosage group. The pathologically increased spontaneous platelet aggregation is reduced by both dosages. Erythrocyte velocity in nail fold capillaries increased significantly only in the high dosage group. Also found was a trend toward a decrease in the systolic blood pressure (25).
- *Ginkgo biloba* special extracts exert positive effects on hemorrheology and platelet aggregation and free radical scavengers, and possess PAF antagonistic properties. They also protect against hypoxia and ischemia, hamper experimentally induced cerebral edema, have favorable properties on neurotransmitters and enhance cerebral blood flow. Clinically, EGb 761 has proven favorable effects on intellectual functioning, equilibrium disturbances and peripheral artery occlusions thus being an extract with a clear indication for these diseases (28).
- Twenty outpatients with a long history of elevated fibrinogen levels and plasma viscosity, and a variety of underlying diseases were given treatment with *Ginkgo biloba* extract EGb 761, at a dose of 250 mg QD for 12 weeks. The clinical diagnoses included coronary heart disease, hypertension, hypercholesterolemia and diabetes mellitus. A significant improvement in the fibrinogen levels and hemorrhheological properties was seen.

The medication can thus positively influence these cardiovascular risk factors over the long term (30).

- The antioxidant potential of *Ginkgo biloba* extract (EGb761) on healthy human erythrocyte membranes was investigated. The antioxidant effect of EGb 761 is dose dependent and increases with incubation time (49).

Naturopathic Implications

The terpene lactone constituents of *Ginkgo biloba* are the primary contributors to Ginkgo's ability to act as a neuroprotectant. The ginkgolides' ability to block platelet aggregation is demonstrated through their ability to block the action of platelet aggregation factor (PAF). "High levels of PAF are associated with damage to nerve cells, diminished cerebral blood flow, various inflammatory conditions, and transplant rejection" (3). As shown in the natural process of aging, free radicals like PAF increase with age and may contribute to cardiovascular disease and cognitive remission. Ginkgo has the effect of not only decreasing the viscosity of the blood but also increasing the microcirculation. As an antioxidant it protects the vascularity and decreases PAF. Because of its free radical scavenging ability combined with its protective effect in ischemic, hypoxic events Ginkgo is an important therapy in cerebrovascular events, and other brain traumas. "GBE and isolated ginkgolides have profound effects on platelet function, including inhibition of platelet aggregation, adhesion, and degranulation. These effects appear to be a result of direct membranar and antioxidant effects, increased synthesis of prostacyclin, inhibition of the enzyme phosphodiesterase, and antagonism of platelet activating factor... GBE ginkgolides compete with PAF-acether (PAF inhibitors) for binding sites. They also inhibit the various events induced by PAF-acether, including calcium influx and phospholipase activation. These actions may be responsible for many of the clinical effects of GBE" (5). This explains the membrane stabilization properties that ensue from Ginkgo's antioxidant effects. Membrane stabilization may also be one direct effect of Ginkgo's inhibition of the enzyme phosphodiesterase and antagonism of PAF with the increased synthesis of series 2 prostacyclins.

DIABETES

- The complex relationship between progression of distal symmetric polyneuropathy (DSP) induced by diabetes mellitus and hemorrheological changes was investigated in patients. The study had 42 patients suffering from diabetes mellitus for 15 years +/-10 months. Platelet reactivity was statistically improved, but erythrocyte aggregation was increased with or without treatment (53).
- The alterations usually associated with diabetic retinopathy correspond to the blood retinal barrier disruption due to the participation of oxygenated free radicals in the pathogenesis of diabetic retinopathy. *Ginkgo biloba* extract, 100mg/kg day for two months, (EGb 761) was used in the treatment group of rats. After 2 months a significant (60%) decrease in retinopathy was observed (55).

Naturopathic Implications

One of the long term effects of diabetes mellitus is peripheral arterial insufficiency. A reduction of blood flow to an area creates a hypoxic ischemic event which increases the production of toxic metabolites and cellular free radicals causing tissue damage and destruction. This destruction is due to the free radical accumulation reacting on the cellular membrane. "GBE's free radical scavenging effect, combined with its vascular effects and its ability to increase metabolic processes during decreased blood supply, suggest that it may have clinical efficacy in cases of obliterate arterial disease and other causes of arterial insufficiency" (5). Also interestingly enough, studies have shown that Ginkgo enhances glucose utilization by enhancing the oxygen use and cellular uptake of glucose, restoring metabolic aerobic glycolysis in hypoxic events. Ginkgo is able to increase peripheral vascular blood flow, stabilize endothelium cells in the vessel walls, decrease damage to nerve cells while enhancing stability to the neuron, and decrease the toxic effects of ischemia to tissues. All of these properties makes this phytotherapeutic extremely important in the management of diabetes.

PREMENSTRUAL SYNDROME

- A study testing the efficacy of standardized *Ginkgo biloba*

extract (EGb 761) in treating congestive symptoms of premenstrual syndrome (PMS) was done in a controlled multicentric double-blind study versus placebo. The population was a group of 165 women, ages ranging between 18 and 45, with concomitant symptoms of suffering for 3 consecutive cycles during at least 7 days per cycle. The characteristics of patients and PMS were the same in both groups. During the two following cycles each patient received either EGb 761 or placebo from the 16th day of the cycle till the 5th day of the next cycle. The verum was effective against the congestive symptoms of PMS, particularly painful, tender breast symptoms. Neuropsychological symptoms were also improved in the treatment group. In conclusion the EGb 761 is an alternative therapeutic to be used in treating PMS (26).

IMPOTENCE

- A study investigated the effect of subfractions of extracts from Ginkgo on human and rabbit cavernosal tissue and thus the possible treatment of impotence. Among the fractions of the *Ginkgo biloba* extract (GBE), nonginkgolide nonflavonoid fraction (NGF) has the most potent relaxing effect on vascular smooth muscle, in a dose-dependent manner. One fraction of the NGF showed pharmacological actions on corpus cavernosum smooth muscle via the signal transduction pathway, while another is mediated by intracellular cAMP and perhaps partially by antagonizing the adrenergic nervous system. A hyperpolarizing effect via potassium channel opening might also be related to this relaxing effect. In conclusion the subfractions of NGF, especially 304U-1, have a relaxing effect on corpus cavernosum tissue and possibly could be used as a drug for intracavernosal injection therapy (36).
- A clinical trial was done to look at GBE's effect in impotency caused by arterial insufficiency. Sixty men with arterial erectile dysfunction who had not reacted to papaverine injections were treated with up to 50 mg. They were given a dose of GBE of 60

mg QD PO for 12-18 months. Penial arterial blood flow was evaluated by duplex sonography every 4 weeks. First signs of improved blood flow were seen after 6-8 weeks; after 6 months of treatment 50% of the men had regained potency, and in 20% of the remaining men papaverine injections were then successful; the other 25% showed improved arterial blood flow but the injections were not successful; 5% remained unchanged (5).

Naturopathic Implications

In a traditional wholistic approach, both conditions of PMS and impotency are due to pelvic congestion, therefore the implications and biochemical interactions work for either condition. Improvement of arterial reperfusion is a direct effect of Ginkgo on the endothelial cells, enhancing arterial and venous flow. Thus there is an increase in blood flow to the pelvic organs with a synergistic increase in venous return. In the case of PMS, this increase in flow alone can improve clinical symptoms by simply removing toxic metabolites while increasing antioxidant effects and decreasing clot formation due to inhibition of PAF. For impotency the above mentioned effects also apply, showing that over time the accumulative effects of Ginkgo can actually reverse impotency in some men. Using the same principles of reducing pelvic stagnation, the naturopathic physician can successfully treat hemorrhoids with Ginkgo. "Up to 86% of patients reported stopped bleeding and pain, but less effectiveness was noted on fissures" (2).

ANTI-OXIDANT EFFECTS

- *In vitro* and *in vivo* studies were done on the antagonistic effects of free radical scavenging and platelet activating factor showing a concentration dependent superoxide dismutase activity of the Ginkgo extract (15).
- Specific therapies are needed to address the trigger role of free radicals in the delayed functional and metabolic myocardial recovery following cardiopulmonary bypass (CPB) in humans. The clinical study was designed to evaluate 15 patients undergoing aortic valve replacement, whether the extent of CPB and reperfusion induced lipid peroxidation, ascorbate depletion, tissue necrosis, and/or

cardiac dysfunction. All these parameters were reduced by orally administered *Ginkgo biloba* extract EGb 761 (Tanakan) 320 mg QD in a verum group of 8, compared to a placebo group of 7, for 5 days before surgical intervention. Plasma samples were obtained from the peripheral circulation and the coronary sinus at crucial stages of the operation (i.e., before incision, during ischemia, and within the first 30 minutes post unclamping) and up to 8 days postoperatively. Upon aortic unclamping EGb 761 inhibited the transcardiac release of thiobarbituric acid, and attenuated the early (5-10 minutes) decrease of I dimethylsulfoxide/ascorbyl free radical levels. The Ginkgo extract also significantly reduced the more delayed leakage of myoglobin and had an almost significant effect on ventricular myosin leakage. These results demonstrate the usefulness of *Ginkgo biloba* extract to limit oxidative stress in cardiovascular surgery and suggest the passive role of highly bioavailable terpene constituents of the drug (37).

- Antioxidant mechanisms have been postulated to be the origins of the pharmacological effects of *Ginkgo biloba* extract EGb 761 for treating peripheral vascular diseases and cerebrovascular insufficiency in the elderly. *In vitro* evidence reports that EGb 761 scavenges various reactive oxygens like nitric oxide, superoxide, hydroxyl and oxiferryl radicals. However the ability of EGb 761 to scavenge peroxy radicals (reactive spp. mainly involved in the propagation step in lipid peroxidation) was not previously investigated. The investigators measured the protective effects of the Ginkgo extract in the oxidation of peroxy radicals in solution and those generated from liposomes or in human low density lipoproteins. Also measured was the effect of the extract on the oxidation of human LDL exposed to the accumulation of cholesterol linoleate ester hydroperoxides and a depletion of alpha-tocopherol and beta-carotene. The extract protected against oxidative stress in all systems even being an efficient scavenger of peroxy radicals. The study results extend the *Ginkgo biloba* extracts' antioxi-

dant range to include peroxy scavenging (41).

- The antioxidant effects of *Ginkgo biloba* extract (EGb 761) on copper mediated human low density lipoprotein (LDL) oxidative modification were evaluated. The inhibition was EGb 761 concentration dependent, and the extract was found to have a powerful antioxidant effect on copper mediated LDL oxidative damage (47).
- An *in vitro* model used healthy human erythrocyte suspensions to compare the antioxidant effects of standardized *Ginkgo biloba* extract (EGb 761) with those of water soluble antioxidants like ascorbic acid, glutathione and uric acid, as well as lipid soluble alpha tocopherol and retinol acetate. The results suggest that all of the antioxidants, except ascorbic acid, have antioxidant potential in this system in a concentration dependent manner. EGb 761 was found to be more effective than water soluble antioxidants and as effective as lipid soluble antioxidants. The antioxidant effects of the Ginkgo extract were equal to the antioxidant effects of alpha tocopherol and retinol acetate (48).
- *In vitro* effects on lipid peroxidation in human liver microsomes was investigated. *Ginkgo biloba* extract (GBE) was dosed at 15, 50, 150 micrograms/ml. GBE inhibited the cyclosporin A lipid peroxidation in a dose dependent manner. This effect of the Ginkgo extract was diminished but not abolished by adding an iron molecule (FeCl₃) to the medium of incubation. The results suggest that Ginkgo might be able to prevent radical mediated damage to human membranes caused by cyclosporin A (50).
- Examinations were carried out to evaluate the correlation between ultraviolet light load and oxidative stress as well as the way oxidative stress is influenced by nutritive free radical scavengers. After 14 day supplementation with *Ginkgo biloba* extract, the extent of oxidative stress could be inhibited during a second exposure to ultraviolet light. The clastogenous effect of sunshine and ultraviolet light must be regarded as a factor for initiating and promoting carcinogenesis in the total organism which might

be inhibited by Ginkgo supplementation (52).

- In this study, human brain total superoxide dismutase activity was assayed. *Ginkgo biloba* extract EGb 761 was highly active in inhibiting superoxide dependent nitro blue tetrazolium reduction as well as SOD activity (56).
- Ischemic induced lipid peroxidation in tissue damage in spinal cord injury was studied. Ginkgo was shown to be protective in rats where controls became paraplegic. Results suggest that Ginkgo has protective effect against ischemic spinal cord injury by the antioxidant effect (62).

Naturopathic Implications

Ginkgo biloba extract is one of the few plants extensively studied in a western medical science model. Antioxidant mechanisms have been postulated to be the origins of the pharmacological effects of *Ginkgo biloba*. *In vitro* evidence reports that it scavenges various reactive oxygens like nitric oxide, superoxide, hydroxyl and oxoferryl radicals. However the ability of *Ginkgo biloba* to scavenge peroxy radicals (reactive spp. mainly involved in the propagation step in lipid peroxidation) was measured, the protective effects of the Ginkgo extract against the oxidation of peroxy radicals in solution or in human low density lipoproteins was proved. Also measured was the effect of the extract on the oxidation of human LDL exposed to the accumulation of cholesterol linoleate ester hydroperoxides and a depletion of alpha-tocopherol and beta-carotene. The extract protected against oxidative stress in all systems, even being an efficient scavenger of peroxy radicals (41). Ginkgo provides phytotherapeutic benefits that not only act as local and systemic antioxidants, but also increases circulation and delivery of antioxidants to the peripheral vascular systems, the neuroendocrine systems and across the blood brain barrier.

ANTIMICROBIAL EFFECTS

- The sesquiterpene bilobalide, extracted from *Ginkgo biloba* leaves, was tested *in vitro* and *in vivo* for the ability to inhibit *Pneumocystis carinii* growth. Bilobalide was inhibitory to trophozoites cultured on human embryonic lung fibroblasts, inducing microscopically detectable morphological changes in the cytoplasm of the parasite. In immunologically suppressed rats

infected with *P. carinii* trophozoites, the daily intraperitoneal administration of bilobalide (10mg/kg of body weight for 8 days) lowered the number of organisms by approximately 99%. There was no apparent toxicity. These studies suggest that the sesquiterpene bilobalide might be useful for therapy of and prophylaxis against *P. carinii* infections in humans (38).

- One study looked at the effect of *Ginkgo biloba* on liver collagen fibrosis from chronic persistent and active hepatitis B, confirmed by liver biopsy and examined with light and electron microscope before and after treatment. By the end of three months the results showed that serum pro-collagen-III-peptide, laminin, superoxide dismutase and malonyldialdehyde were significantly decreased after treatment. Liver fibrosis of patients was partly reabsorbed, allowing for partial remission. It was suggested that Ginkgo was effective in arresting the development of liver fibrosis in chronic hepatitis (42).
- This study examined the inhibitory effects of natural plant extracts against the collagenolytic activity of *Porphyromonas gingivalis*. The aqueous and 50% ethanolic extracts of *Ginkgo biloba* were used. The activity of the crude plant extract was higher than that of tetracycline-HCl, and Ginkgo also inhibited the cytotoxicity of *P. gingivalis* against human fibroblasts (57).

Naturopathic Implications

It is very exciting to find a phytotherapeutic that can act on a protozoan infection that can in some populations be lethal. *P. carinii* is a deadly secondary opportunistic infection that plagues the HIV/AIDS community. Ginkgo's ability to deliver itself to the microcirculation while acting as a membrane stabilizer and antioxidant, in addition to having anti-microbial effects, is unique. In the above mentioned studies, positive anti-protozoan, anti-viral, and anti-bacterial effects were found.

CLASTOGENIC FACTORS

- Clastogenic factors are found in plasma of persons irradiated accidentally or therapeutically. This study shows that there is a correlation between clastogenic activity and radiation dose and that these biomarkers of oxidative stress can be influenced

successfully by appropriate antioxidant treatment. Thirty workers who had been exposed to the Chernobyl explosion were treated with antioxidants from *Ginkgo biloba* leaves. The extract EGb 761 containing flavonoids and terpenoids was given at a dose of 40 mg TID for 2 months. The clastogenic activity of the plasma was reduced to control levels on the first day after the end of the treatment period. One year follow up showed that the benefit of treatment lasted approximately 7 months. The observation was that the antioxidants do not have to be given continuously. Clastogenic factors are thought to be risk factors for the development of late effects of irradiation (44).

- Laboratory work showed that clastogenic factors are not only increased by exposure to radiation, but also in those persons exposed to oxidative stress, and that clastogenic factor induced chromosome damage can be prevented by superoxide dismutase. In the present study *Ginkgo biloba* extract EGb 761 therapy provided regression or complete disappearance of clastogenic factors in the plasma after 2 months of treatment with EGb 761 at a dose of 40 mg TID (46).

Naturopathic Implications

These studies have given the naturopathic community new indications for the use of *Ginkgo biloba*. The extract shows a positive effect on precancerous factors initiated from radiation exposure. The free radical scavenging activity of Ginkgo plays an important role in its ability to affect cellular mutation as a result of radiation exposure. Ginkgo has the ability to also deliver itself, *via* increased perfusion, to the microcirculation and across the blood brain barrier to neurotransmitters. By having this wide systemic effect the Ginkgo can hypothetically be a true prophylaxis against cancer.

TOXICOLOGY

- 4-O-methylpyridoxine (MPN) was isolated from the seed of *Ginkgo biloba* and is responsible for the gin-nan food poisoning with cardinal symptoms of tonic/clonic convulsions and loss of consciousness. Infants are particularly vulnerable (61).

There has been shown, in most of the studies listed above, good tolerance to the leaf and leaf prepa-

rations of the *Ginkgo biloba*. Some adverse effects have been anecdotally reported when taken with aspirin or coumarins, in that the Ginkgo extract potentiated the blood thinning effects. "There are no known interactions with commonly prescribed drugs although concomitant use with anticoagulant medication should be closely monitored. The current Commission E monograph lists no contraindications to the use of GBE during pregnancy and lactation" (3). In all the human studies listed in the above monograph, all showed a good to excellent tolerance for the dosing ranges in the verum groups. In contrast to the tolerance of Ginkgo leaf extracts, the fruit has been shown to be very toxic. The fruit has a high concentration of butyric acid and can produce severe allergic reactions. "Contact with the fruit pulp causes erythema and edema, with the rapid formation of vesicles accompanied by severe itching, similar to an allergic reaction to the sumacs (poison ivy and poison oak), which suggests a cross-reactivity between *G. biloba* fruit and the sumac group" (5).

DOSAGE

The above research shows a positive effect in verum groups dosed between 40 mg per day to 240 mg several times a day. In all the studies that examined long term outcomes, the best success with Ginkgo was dose dependent over an extended period of time up to 6 months, with a lasting effect of 6 or more months after cessation of treatment. It was found that a standardized extract containing at least 24% ginkgo flavone glycosides and 6% terpene lactones has the best therapeutic effects.

BIOGRAPHY

Dr. Jody E. Noé practices Natural Family Medicine with emphasis on women's health care and pediatrics. She also specializes in cancer and other long term chronic disease. Dr. Noé received her Doctorate in Naturopathic Medicine from Bastyr University in Seattle, Washington.

She also has a graduate degree in botany and extensive experience researching the ethnobotany of Cherokee medicine. Dr. Noé had a family practice in Redmond, Washington, and served on the faculty of Bastyr University, before joining the Brattleboro Naturopathic Clinic. She has been published in the *Journal of Naturopathic Medicine*, where she is a peer reviewer, as well as in many lay publications. She is a founding member of the Botanical Medicine Academy.

REFERENCES

1. Institute of Traditional Chinese Medicine Hunan Province in China. 1970. A Barefoot Doctor's Manual. Translated 1977 by Cloudburst Press of America.

- Inc.; Madrona Publishers, Seattle: pp 228.
2. Willard, Terry, PhD. 1991. Wild Rose Scientific Herbal. Wild Rose College of Natural Healing, Ltd.; Calgary: pp 143-148.
 3. Brown, Donald, MD. 1997. *Ginkgo biloba* extract for age-related cognitive decline and early stage dementia—a clinical overview. Quarterly Review of Natural Medicine; NRPC, Inc., Seattle: pp 91-96.
 4. Ody, Penelope, MNIMH. 1993. The Complete Medicinal Herbal. Dorling Kindersley; London: pp 64-65.
 5. Murray, Michael T., ND. 1991. The Healing Power of Herbs. Prima Publishing; Rocklin: pp 118-132.
 6. Braquet, P. and D. Hosford. 1991. Ethnopharmacology and development of natural PAF antagonists as therapeutic agents. *J Ethnopharmacology*. April; 32:1-3, pp 135-9.
 7. Z'Brun, A. 1995. Ginkgo—myth and reality. *Schweiz Rundsch Med Prax*. Jan. 3; 84:1, pp 1-6.
 8. Monograph, *Ginkgo biloba* dry leaves (dry extract). 1994. *Bundesanzeiger*. June 21.
 9. Fourtillan, JB., AM Brisson, J Olrault, I Ingrand, JP Decourt, K Drieu, P Jouenne, and A Biber. 1995. Pharmacokinetic properties of Bilobalide and Ginkgolides A and B in healthy subjects after intravenous and oral administration of *Ginkgo biloba* extract (EGb761). *Therapie*. Mar-April; 50:2, pp 137-44.
 10. Moreau, JP., CR Eck, J McCabe and S Skinner. 1988. Absorption, distribution, and excretion of tagged *Ginkgo biloba* leaf extract in the rat. *Rokan-Recent Results in Pharmacology and Clinic*. Springer-Verlag; New York: pp 37-45.
 11. Smith, FF, K MacLennan and CL Darlington. 1996. The neuroprotective properties of the *Ginkgo biloba* leaf: a review of the possible relationship to platelet-activating factor (PAF). *J Ethnopharmacol*. Mar; 50:3, pp 131-9.
 12. Blume, J., M Kleser and U Hilscher. 1996. Placebo controlled double blind study of the effectiveness of *Ginkgo biloba* special extract EGb761 in trained patients with intermittent claudication. *Vasa*. 25:3; pp 265-74.
 13. Hopfenmüller, W. 1994. 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*. Sep; 44:9; pp 1005-13.
 14. Eckman, F. 1990. Cerebral insufficiency treatment with *Ginkgo biloba* extract. Time of onset of effect in a double blind study with 60 patients. *Fortschr Med*. Oct. 10:108-29; pp 557-60.
 15. Dłwok, M., B Kuklinski and B Ernst. 1992. Superoxide dismutase activity of *Ginkgo biloba* extract. *Z Gesamte Inn Med*. Jul; 47:7; pp 308-11.
 16. Ernst, E. 1996. *Ginkgo biloba* in treatment of intermittent claudication. A systematic research based on controlled studies in literature. *Fortschr Med*. Mar. 20:114:8; pp 85-7.
 17. Semlitsch, HV, P Anderer, B Saletu, GA Binder and KA Decker. 1995. Cognitive psychophysiology in nootropic drug research: effects of *Ginkgo biloba* on event related potentials (P300) in age associated memory impairment. *Pharmacopsychiatry*. Jul; 28:4; pp 134-42.
 18. Kleijnen, J. and P Knipschild. 1992. *Ginkgo biloba* for cerebral insufficiency. *Br J Clin Pharmacol*. Oct; 34:4; pp 352-8.
 19. Grüssel, E. 1992. Effect of *Ginkgo biloba* extract on mental performance. Double blind study using computerized measurement conditions in patients with cerebral insufficiency. *Fortschr Med*. Feb. 20:110:3; pp 73-6.
 20. Rai, GS., C Shovtin and KA Wesnes. 1991. A double blind, placebo controlled study of *Ginkgo biloba* extract (tanakan) in elderly outpatients with mild to moderate memory impairment. *Curr Med Res Opin*. 12:6; pp 350-5.
 21. Gerhardt, G., K Rogalla and J Jaeger. 1990. Drug therapy of disorders of cerebral performance. Randomized comparative study of dihydroergotoxine and *Ginkgo biloba* extract. *Fortschr Med*. Jun. 30:108-19; pp 384-8.
 22. Garg, RK., D Nag and A Agrawal. 1995. A double blind placebo controlled trial of *Ginkgo biloba* extract in acute cerebral ischaemia. *J Assoc Physicians India*. Nov. 43:11; pp 760-3.
 23. Drabaek, H., JR Petersen, N Wänberg, KF Hansen and J Mehlsen. 1996. The effect of *Ginkgo biloba* extract in patients with intermittent claudication. *Ugeskr Laeger*. Jul. 1: 158:27; pp 3928-31.
 24. Jung, F., C Mrowlet, H Klesewetter and E Wenzel. 1990. Effect of *Ginkgo biloba* on fluidity of blood and peripheral microcirculation in volunteers. *Arzneimittelforschung*. May; 40:5; pp 589-93.
 25. Klesewetter, H., F Jung, C Mrowlet and E Wenzel. 1992. Hemorheological and circulatory effects of Gincosan. *Int J Clin Pharmacol Ther Toxicol*, Mar; 30:3; pp 97-102.
 26. Tamborlini, A. and R Taurelie. 1993. Value of standardized *Ginkgo biloba* extract (EGb761) in the management of congestive symptoms of premenstrual syndrome. *Rev Fr Gynecol Obstet*. Jul-Sep; 88:7-9; pp 447-57.
 27. Kilringer, P., W Langsteger, Q Klima, F Reisecker and O Eber. 1993. Hemorheological effects of *Ginkgo biloba* extract EGb761. Dose dependent effect of EGb 761 on microcirculation and viscoelasticity of blood. *Fortschr Med*. Apr. 10: 111:10; pp 170-2.
 28. Hiltzenberger, G. 1992. The effect of *Ginkgo biloba* special extract (EGb 761, Tebfortan). *Wien Med Wochenschr*. 142:17; pp 371-9.
 29. Schneider, B. 1992. *Ginkgo biloba* extract in peripheral arterial diseases. Meta-analysis of controlled clinical studies. *Arzneimittel forschung*. Apr; 42:4; pp 428-36.
 30. Witte, S., I Anadere and E Waltza. 1992. Improvement of hemorheology with *Ginkgo biloba* extract. Decreasing a cardiovascular risk factor. *Fortschr Med*. May 10:110:13; pp 247-50.
 31. Raabe, A., M Raabe and P Ihm. 1991. Therapeutic follow up using automatic perimetry in chronic cerebroretinal ischemia in elderly patients. Prospective double blind study with graduated dose *Ginkgo biloba* treatment (EGb 761). *Klin Monatsbl Augenheilkd*. Dec; 199:6; pp 432-8.
 32. Wójcicki, J., B Gawronska-Szklarz, W Bleganowski, M Patajan, HK Smulski, L Samocholec and J Azkzewski. 1995. Comparative pharmacokinetics and bioavailability of flavonoid glycosides of *Ginkgo biloba* after a single oral administration of three formulations to healthy volunteers. *Mater Med Pol*. Oct-Dec; 27:4; pp 141-6.
 33. Kanowski, S., WM Herrmann, K Stephan, W Wierlich and R Hirt. 1996. 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. *Pharmacopsychiatry*. Mar ; 29:2; pp 47-56.
 34. Allain, H., P Raoul, A Lieury, F leCoz, JM Gandon and P d'Arbigny. 1993. Effect of two doses of *Ginkgo biloba* extract (EGb 761) on dual-coding test in elderly subjects. *Clin Ther*. May-Jun ; 15:3; pp 549-58.
 35. Känkel, H. 1993. EEG profile of three different extractions of *Ginkgo biloba*. *Neuropsychobiology*. 27:1; pp 40-5.
 36. Paick, JS and JH Lee. 1996. An experimental study of the effect of *Ginkgo biloba* extract on the human and rabbit corpus cavernosum tissue. *J Urol*. Nov ; 156:5; pp 1876-80.
 37. Pietri, S., JR Scgulin, P d'Arbigny, K Drieu and M Culcasi. 1997. *Ginkgo biloba* extract (EGb 761) pretreatment limits free radical-Induced oxidative stress in patients undergoing coronary bypass surgery. *Cardiovasc. Drugs Ther*. Apr ; 11:2; pp 121-31.
 38. Atzori, C., A Bruno, Q Chichino, E Bombardelli, M Scaglia and M Ghione. 1993. Activity of bilobalide, a sesquiterpene from *Ginkgo biloba*, on *Pneumocystis carinii*. *Antimicrob Agents Chemother*. Jul ; 37:7; pp 1492-6.
 39. Haase, J., P Halama and R Hirt. 1996. Effectiveness of brief infusions with *Ginkgo biloba* special extract EGb 761 in dementia of the vascular and Alzheimer type. *Z Gerontol Geriatr*. Jul-Aug ; 29:4; pp 302-9.
 40. Stoppe, G., H Sandholzer, J Staedt, S Winter, J Klefer and E RÄther. 1996. Prescribing practice with cognition enhancers in outpatient care: are there differences regarding type of dementia? Results of a representative survey in lower Saxony, Germany. *Pharmacopsychiatry*. Jul ; 29:4; pp 150-5.
 41. Maltra, I., L Marcocci, MT Droy-Lefaix and L Packer. 1995. Peroxyl radical scavenging activity of *Ginkgo biloba* extract EGb 761. *Biochem. Pharmacol*. May 26:49:11; pp 1649-55.
 42. Li, W., QT Dai and ZE Liu. 1995. Preliminary study on early fibrosis of chronic hepatitis B treated with *Ginkgo biloba* Composita. *Chung Duo Chung Sdi So Tsa Chih*. Oct; 15:10; pp 593-5.
 43. Hoyer, S. 1995. Possibilities and limits of therapy of cognition disorders in the elderly. *Z Gerontol Geriatr*. Nov-Dec 28:6; pp 457-62.
 44. Emerit, I., N Oganeslan, T Sarkislan, R Arutyunyan, A Pogossian, K Asrlan, A Levy and I Cernjavski. 1995. Clastogenic factors in the plasma of Chernobyl accident recovery workers: anticlastogenic effect of *Ginkgo biloba* extract. *Radiat. Res*. Nov; 144:2; pp 198-205.
 45. Ittl, T. and D Martorano. 1995. Natural substances in psychiatry (*Ginkgo biloba* in dementia). *Psychopharmacol. Bull*. 31:1; pp 147-58.
 46. Emerit, I., R Arutyunyan, N Oraneslan, A Levy, I Cernjavsky, T Sarkislan, A Pogossian and K Asrlan. 1995. Radiation induced clastogenic factors: anticlastogenic effect of *Ginkgo biloba* extract. *Free Radic Biol Med*. Jun 18:6; pp 985-91.
 47. Yan, LJ., MT Droy-Lefaix and L Packer. 1995. *Ginkgo biloba* extract (EGb 761) protects human low density lipoproteins against oxidative modifications mediated by copper. *Biochem Biophys Res Commun*. Jul 17, 212:2; pp 360-6.

48. Kise, K. and P Dogan. 1995. Lipoperoxidation induced by hydrogen peroxide in human erythrocyte membranes. Comparison of the antioxidant effect of *Ginkgo biloba* extract (EGb 761) with those of water soluble and lipid soluble antioxidants. *J Int Med Res.* Jan-Feb; 23:1; pp 9-18.
49. Kise, K. and P Dogan. 1995. Lipoperoxidation induced by hydrogen peroxide in human erythrocyte membranes. Protective Effect of *Ginkgo biloba* extract (EGb761). *J Int. Med. Res.* Jan-Feb; 23:1; pp1-8.
50. Barth, SA., O Inselmann, R Engemann and HT Heldemann. 1991. Influences of *Ginkgo biloba* on cyclosporin A induced lipid peroxidation in human liver microsomes in comparison to vitamin E, glutathione and N-acetylcysteine. *Biochem Pharmacol.* May 15; 41:10; pp 1521-6.
51. Smith, PF. and CL Darlington. 1994. Can vestibular compensation be enhanced by drug treatment? A review of recent evidence. *J Vestib Res.* May-Jun; 4:3; pp 169-79.
52. Pletschmann, A., B. Kukilinski and A Otterstein. 1992. Protection from uv light induced oxidative stress by nutritional radical scavengers. *Z Gesamte Inn Med.* Nov; 47:11; pp 518-22.
53. Husstedt, IW., KH Grottemeyer, S Evers, F Staschewski and R Wetelewski. 1997. Progression of distal symmetric polyneuropathy during diabetes mellitus: clinical, neurophysiological, haemorrhological changes and self rating scales of patients. *Eur Neurol.* 37:2; pp 90-4.
54. Relsecker, F. 1996. Therapy approaches in cerebral cognitive deficits neuropsychiatric aspects. *Wien Med Wochenschr.* 146:21-22; pp 546-8.
55. Doly, M., MT Droy-Lefalx and P Braquet. 1992. Oxidative stress in diabetic retina. *EXS.* 62; pp 299-307.
56. Qsell, W., N Rechert, MB Youdim and P Riederer. 1995. Interaction of neuroprotective substances with human brain superoxide dismutase. An *in vitro* study. *J Neural Transm Suppl.* 45; pp 271-9.
57. Osawa, K., T Matsumoto, H Yasuda, T Kato, Y Naito and K Okuda. 1991. The inhibitory effect of plant extracts on the collagenolytic activity of cytototoxicity of human gingival fibroblasts by *Porphyromonas gingivialis* crude enzyme. *Bull Tokyo Dent Coll.* Feb; 32:1; pp 1-7.
58. Janssens, D., C Michiels, E Delaive, F Eltaers, K Drieu and J Remacle. 1995. Protection of hypoxia induced ATP decrease in endothelial cells by *Ginkgo biloba* extract and bilobalide. *Biochem Pharmacol.* Sep; 28, 50:7; pp 991-9.
59. Deberdt, W. 1994. Interaction between psychological and pharmacological treatment in cognitive impairment. *Life Sci.* 55:25-26; pp 2057-66.
60. Mouren, X., P Calilard and F Schwartz. 1994. Study of antithrombotic action of EGb 761 in the treatment of peripheral arterial occlusive disease by TcPo2 determination. *Angiology.* Jun; 45:6; pp 413-7.
61. Yagi, M., K Wada, M Sakata, M Kokubo and M Haga. 1993. Studies on the constituents of edible and medicinal plants. Determination of 4-O-methylpyridoxine in serum of the patient with gin-man food poisoning. *Yakugaku Zasshi.* Aug; 113:8; pp 596-9.
62. Akdemir, RK., H Kurtsoy, A Pasaoglu, H Kavuncu, I Pasaoglu and A Karak. 1995. Lipid peroxidation in experimental spinal cord injury. Comparison of treatment with *Ginkgo biloba*, TRH and methylprednisone. *Res Exp Med (Berl).* 195; pp 117-23.
63. White, HL., PW Scates and BR Cooper. 1996. Extracts of *Ginkgo biloba* leaves inhibit monoamine oxidase. *Life Sci.* 58:16; pp 1315-21.
64. Duverger, D., FV DeFeudis and K Drieu. 1995. Effects of repeated treatments with an extract of *Ginkgo biloba* (EGb 761) on cerebral glucose utilization in the rat and autoradiographic study. *Gen Pharmacol.* 26:6; pp 1375-83.
65. Brinker, Francis, ND. 1989. Botanical Research Summaries. Eclectic Dispensatory of Botanical Therapeutics; Portland; pp 5-16.