ANTIOXIDANTS & REDOX SIGNALING
Volume 1, Number 4, 1999
Mary Ann Liebert, Inc.

Review

Ginkgo Biloba Leaf Extract: Review of Biological Actions and Clinical Applications

TOSHIKAZU YOSHIKAWA, YUJI NAITO, and MOTOHARU KONDO

ABSTRACT

The number of studies on Ginkgo biloba leaves is rapidly increasing. A variety of effects of Ginkgo biloba leaf extract (GBLE) have been identified. GBLE contains many different flavone glycosides and terpenoides. GBLE has an antioxidant action as a free radical scavenger, a relaxing effect on vascular walls, an antagonistic action on platelet-activating factor, an improving effect on blood flow or microcirculation, and a stimulating effect on neurotransmitters. Besides a direct scavenging action on active oxygen species, GBLE exerts an anti-inflammatory effect on inflammatory cells by suppressing the production of active oxygen and nitrogen species. GBLE inhibited the increase in the products of the oxidative decomposition low-density lipoprotein (LDL), reduced the cell death in various types of neuropathy, and prevented the oxidative damage to mitochondria, suggesting that GBLE exhibits beneficial effects on neuron degenerative diseases by preventing chronic oxidative damage. The study using a model of ischemia-reperfusion injury has also demonstrated the protective effect of GBLE on cardiac muscle and its antioxidative action *in vivo*. Favorable results have been obtained in double-blind, placebo-controlled, comparative trials of patients with memory disorders, obstructive arteriosclerosis, and dementia. We review the recent studies on GBLE with respect to its various pharmacological actions, such as a scavenging activity on free radicals and an inhibitory action on lipid peroxidation. GBLE shows a very strong scavenging action on free radicals, and is thus considered to be useful for the treatment of diseases related to the production of free radicals, such as ischemic heart disease, cerebral infarction, chronic inflammation, and aging. Antiox. Redox Signal. 1, 469–480.

INTRODUCTION

ALTHOUGH GINKGO BILOBA has been used in Chinese medicine for as long as 5,000 years, mainly for the treatment of asthma and bronchitis, only recently has Ginkgo biloba leaf extract (GBLE) been found useful in clinical trials. This extract is now commonly prescribed, particularly in Germany and France. It is made from the dried leaves of Ginkgo biloba. In a multistep procedure, the unwanted substances are eliminated while the active principles are concentrated. The resulting liquid extract is dried to give 1 part of extract obtained from 50 parts of raw drug (leaves). As shown in Fig. 1, the extract contains 33 different flavone glycosides, mainly the glycorhamoside ester of quercetin or kaempferol, and the terpenoides (ginkgolides A, B, C, and bilobalide), which account for 24% flavone glycosides and 6% terpenoides (Drieu, 1988).

The various pharmacological actions of GBLE may be caused by one or more of the active ingredients it contains. The following actions or effects of GBLE have been reported: an antioxidant action as a free radical scavenger, a relaxing action on vascular walls, an inhibitory action on platelet-activating factor

First Department of Medicine, Kyoto Prefectural University of Medicine, Kyoto 602-8566, Japan.

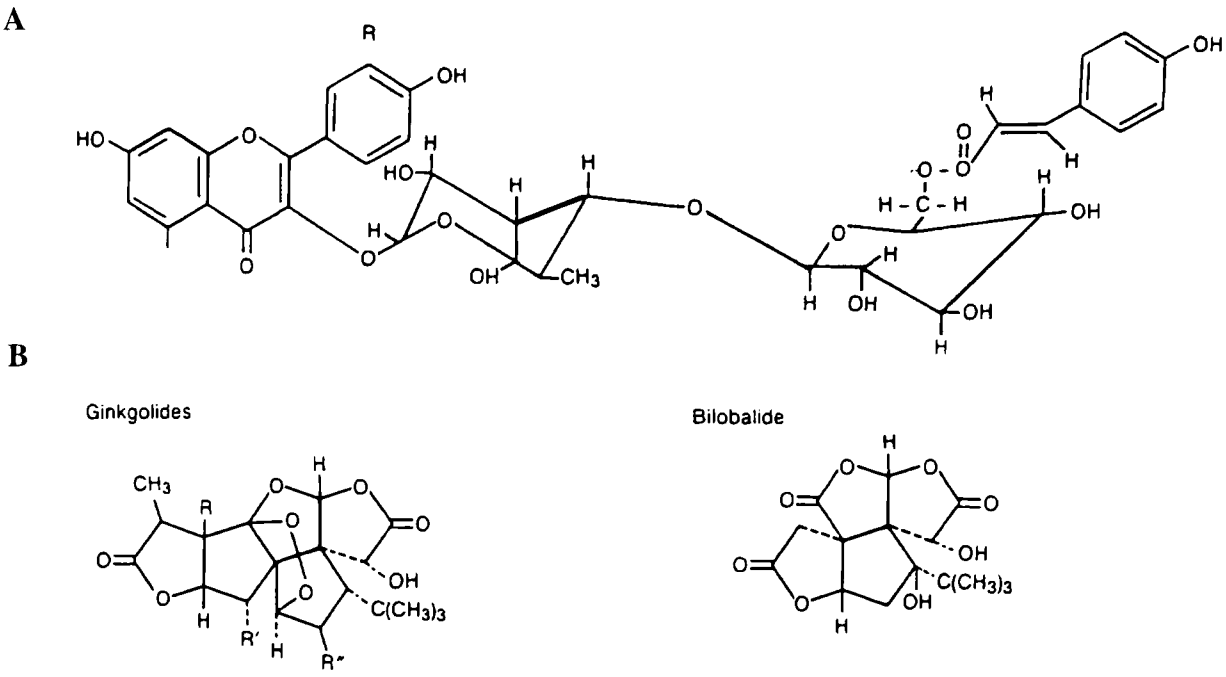

FIG. 1. Principal constituents of ginkgo biloba leaf extract (GBLE).

A. The glucorhamnoside esters of kaempferol (R = H) and quercetin (R = OH). **B.** The ginkgolide and bilobalide.

	R	*R'*	*R"*
Ginkgolide A	OH	H	H
Ginkgolide B	OH	OH	H
Ginkgolide C	OH	OH	OH

(PAF), an improving effect on blood flow or microcirculation, and a stimulating effect on neurotransmitters. In addition to these experimental findings, favorable clinical results have been obtained, including subjective improvement of symptoms of cerebrovascular disorders, mainly in European studies (Kleijnen and Knipschild, 1992). In 1992, the pharmacological actions, pharmacokinetics, and clinical use of GBLE were reviewed by Kleijnen and Knipschild in the Lancet. Since then, the number of scientific publications on Ginkgo biloba leaves has been increasing, with about 30 reports published each year. We now report recent advances in GBLE with respect to its pharmacological actions, such as its scavenging activity on free radicals, and its inhibitory action on lipid peroxidation, as well as the results of recent clinical investigations. We review selected experimental studies published during 1995–1999, and controlled clinical studies published during 1991–1999.

PHARMACOLOGICAL ACTIONS OF GBLE

Antioxidant ability of GBLE

Scavenging activity of GBLE on free radicals: Shi and Niki (1998) recently established a method of determining the activity of GBLE as a hydrogen donor by stoichiometric and kinetic studies (Table 1). They found 6.62×10^{19} active hydrogens in 1 gram of GBLE; the second-order rate constant for GBLE obtained at 25°C was 0.13 $(g/L)^{-1}s^{-1}$. We developed an electron paramagnetic resonance (EPR) spectrophotometric method to determine the scavenging activity of GBLE on three kinds of free radicals: the superoxide radical, the hydroxyl radical,

and the diphenyl-*p*-picrylhydral (DPPH) radical. GBLE (HIGINKO 40) was provided by Takehaya Co., Ltd. (Tokyo). Superoxide radicals and hydroxyl radicals were altered to more stable radicals by treatment with a radical trapping agent 5,5'-dimethyl-1-pyrroline-*N*-oxide (DMPO) before measurement by EPR, because they have a short life in aqueous solution. Superoxide radicals are produced by the hypoxanthine-xanthine system, whereas hydroxyl radicals are produced by the iron sulfate-hydrogen peroxide (Fenton reaction) system. EPR spectrometry in the presence of DMPO revealed DMPO-OOH radicals derived from superoxide radicals and DMPO-OH radicals derived from hydroxyl radicals. GBLE was then added to the respective reaction systems, which were measured by EPR. The degree of scavenging activity of GBLE on free radicals was estimated from the rate of decrease in signal intensity as measured by EPR. Similarly, DPPH radicals were mixed with GBLE, and the resulting mixture was measured by EPR spectrometry. The extent of scavenging activity was estimated from the ratio of signal intensities as measured by EPR. Results confirmed that each signal intensity of DMPO-OOH, DMPO-OH, and DPPH (Fig. 2) decreased, in accordance with the concentration of GBLE. Thus, GBLE scavenged each of these radicals as related to concentration of GBLE, although its scavenging effect was greater against the superoxide and DPPH radicals (Fig. 3). Similar results of EPR have been reported by Noda *et al.* (1997) and Miyajima *et al.* (1994) using another GBLE. Lee *et al.* (1998) also demonstrated that GBLE (EGb 501) inhibits the serotonin-stimulated mitogenesis of bovine pulmonary artery smooth muscle cells via scavenging superoxide and blocking its mitogenic effect. From data comparing the reactivity of components of GBLE against the superoxide radical in dimethyl in dimethyl sulfoxide as an aprotic solvent, it is suggested that the scavenging effect of ginkgolides B, C, J, and bilobalide on superoxide contributes to the antioxidative properties of GBLE (Scholtyssek *et al.*, 1997).

The scavenging action of GBLE on the peroxyl radicals produced by the chain reaction of lipid peroxidation has also been investigated. GBLE scavenged peroxyl radicals produced from such azo compounds as 2,2-azo *bis*(2-amidino propane) hydrogen dichloride (AAPH) and 2,2-azo *bis*(2,4-dimethyl valero nitrile) (AMVN), and thereby inhibits the oxidation of low-density lipoproteins (LDL) by these azo compounds (Maitra *et al.*, 1995). The flavonoids, which are among the ingredients of

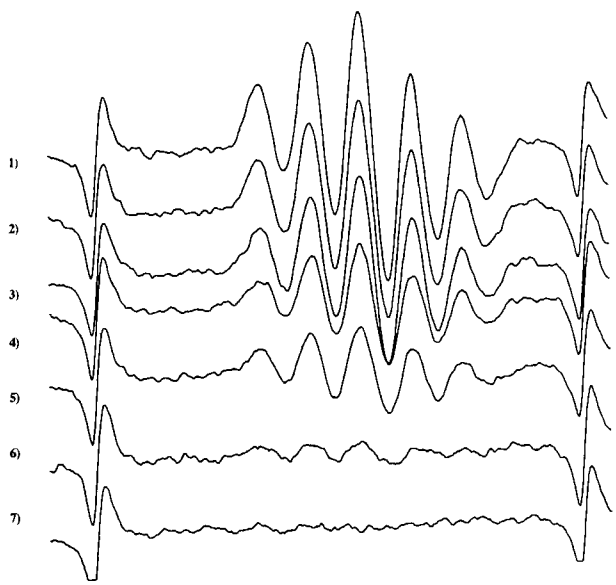

FIG. 2. Effect of GBLE on DPPH EPR signal. 1) DPPH only; **2)** GBLE 0.1 ng/ml; **3)** GBLE 1.0 ng/ml; **4)** GBLE 10 ng/ml; **5)** GBLE 100 ng/ml; **6)** GBLE 1,000 ng/ml; **7)** GBLE 10,000 ng/ml.

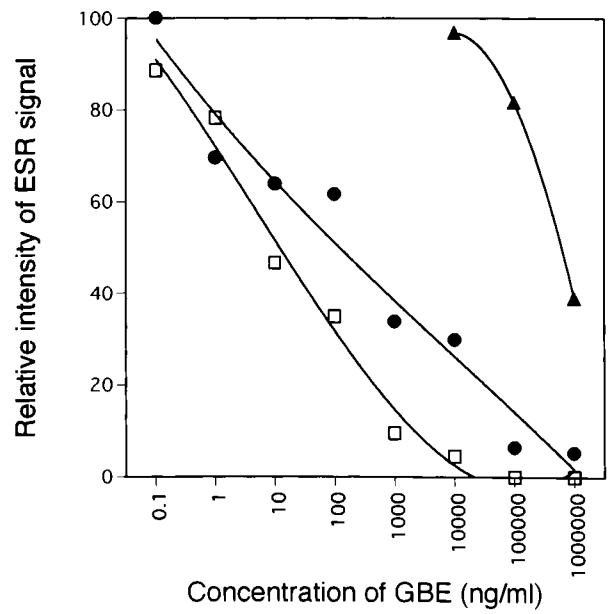

FIG. 3. Scavenging activity of GBLE on superoxide, hydroxyl, and DPPH radicals. (●) Superoxide radical; (▲) hydroxyl radical; (□) DPPH radical.

TABLE 1. ANTIOXIDANT PROPERTIES OF GBLE

Method[a]	*Action of GBLE*	*Reference*
Iron-dependent lipid peroxidation	Inhibited	Dumont *et al.*, 1995
LDL oxidation	Inhibited	Yan *et al.*, 1995
Peroxyl radical	Scavenged	Maitra *et al.*, 1995
Oxidative injury to retina	Inhibited	Droy-Lefaixt *et al.*, 1995
H_2O_2-induced lipid peroxidation	Inhibited	Kose *et al.*, 1995
Ischemia-reperfusion injury	Inhibited	Shen and Zhou, 1995
H_2O_2-neuron injury	Inhibited	Oyama *et al.*, 1996
$OH^{\cdot}$-induced apoptosis	Inhibited	Ni *et al.*, 1996
Macrphage oxidative burst	Inhibited	Rong *et al.*, 1996
tBHP-induced endothelial cell injury	Inhibited	Rong *et al.*, 1996
Hydroxyl radical	Scavenged	Noda *et al.*, 1997
Superoxide radical	Scavenged	Noda *et al.*, 1997
Macrophage NO production	Inhibited	Kobuchi *et al.*, 1997
H_2O_2-induced lipid eproxidation	Inhibited	Kose *et al.*, 1997
Superoxide in dimethylsulfoxide	Scavenged	Scholtyssek *et al.*, 1997
Intracellular superoxide	Scavenged	Lee *et al.*, 1998
Galvinoxyl radical	Scavenged	Shi and Niki, 1998
Mitochondrial aging by oxidative stress	Inhibited	Sastre *et al.*, 1998
$H_2O_2/OH^{\cdot}$ luminol system	Scavenged	Lugasi *et al.*, 1999
X/XO-induced retinopathy	Inhibited	Baudouin *et al.*, 1999

[a]LDL, Low-density lipoprotein; H_2O_2, hydrogen peroxide; $OH^{\bullet}$, hydroxyl radical; tBHT, *tert*-butyl hydroperoxide; NO, nitric oxide; X/XO, xanthine/xanthine oxidase.

GBLE, are considered to play a main role in the scavenging action on this active oxygen group. According to Noguchi *et al.* (1997), GBLE exerts its action as a radical-capturing antioxidant. Methyl linoleate was oxidized using AMVN in *t*-butanol to examine the suppressive action of GBLE on the production of methyl linoleate hydroperoxide. GBLE was found to inhibit the oxidation of methyl linoleate independent of concentration. To examine the antioxidant effect of GBLE on soybean phosphatidyl choline (PC) liposome membrane, a single-compartment liposome of the PC was oxidized using water-soluble AAPH and lipid-soluble AMVN as chain initiators. GBLE was found to suppress the production of PC hydroperoxide in the oxidation of PC liposome membrane initiated by AAPH as well as by AMVN in a concentration-dependent manner. The antioxidant present in GBLE captured radicals, even in the lipid layer of the liposome membrane. This is an important pharmacological action of GBLE that ultimately may have clinical application.

It is now possible to detect free radicals *in vivo* by use of EPR spectrometry. Szabo *et al.* (1997) used EPR to detect directly the production of free radicals in the retina, using frozen retinal tissue after ischemia-reperfusion. They also reported on the inhibitory action of GBLE on free radicals. According to their study, free radicals, which showed the highest signal intensity after ischemia for 90 min and reperfusion for 3 min, were inhibited by GBLE in a concentration-dependent manner (25, 50, and 100 mg/kg). Their research is important because it shows the possibility of a scavenging action of GBLE on free radicals, or of a suppressive action on the production of free radicals *in vivo*. Free radicals reportedly participate in ischemia-reperfusion injury in the retina as well as in the gastrointestinal tract, heart, kidneys, and brain. Thus, GBLE would be expected to exert a wide variety of tissue-protective actions.

Inhibitory action of GBLE on lipid peroxidation: The inhibitory action of GBLE on lipid peroxidation was examined *in vitro* and *ex vivo* using an autoxidation model of the brain. *In vitro*, GBLE was added to rat brain homogenate, and the mixture was incubated at 37°C for 0, 30, 60, and 180 min. The resulting product of the thiobarbituric acid reaction was measured as an index of lipid peroxidation; the values obtained were compared with those obtained in the group that did not have GBLE added. Rats

were administered GBLE orally and 1 hr later, the brain homogenates were prepared, being incubated at 37°C for 0, 30, 60, and 180 min. The resulting thiobarbituric acid reaction products were measured; the values obtained were compared with those obtained in the group not given GBLE. GBLE was found to inhibit the autoxidation of brain *in vitro* in a concentration-dependent manner (Fig. 4) (Miyajima *et al.*, 1994). In a study of liver microsomes, GBLE also inhibited lipid peroxidation in a concentration-dependent manner (Seif *et al.*, 1995). The rate of autoxidation in brain homogenates after the administration of GBLE was also suppressed compared with the group without administration of GBLE (Miyajima *et al.*, 1994) (Fig. 4).

In experiments in which GBLE was administered to rats, this substance significantly suppressed an increase in lipid peroxidation in brain tissue exposed to ischemia-reperfusion (Seif *et al.*, 1995), and also, significantly inhibited the lipid peroxidation induced by iron-ascorbic acid and ischemia-reperfusion of the central retinal artery (Droy *et al.*, 1995), indicating that it protects against post-ischemic injury. An *in vitro* study demonstrated that GBLE significantly inhibited the lipid peroxidation induced by hydrogen peroxide (H_2O_2) in the erythrocytes of healthy volunteers as well as from patients with Behcet's disease; the antioxidant potency of GBLE appeared to be comparable with those of α-tocopherol and retinol acetate (Kose and Dogan, 1995; Kose *et al.*, 1997).

Suppressive action on the production of active oxygen: Besides a direct scavenging action on active oxygen, GBLE exerts an anti-inflammatory effect on inflammatory cells by suppressing the production of active oxygen and nitric oxide (NO). GBLE suppresses the production of active oxygen from macrophages in response to stimulation by zymosan (Rong *et al.*, 1996), as well as the production of NO from RAW264.7 cultured cells, in response to stimulation by lipopolysaccharide/interferon. Such suppression was both time- and concentration-dependent. GBLE inhibits the expression of iNOS mRNA at high concentrations, but had no effect on binding of transcription factor NF-κB with DNA nor did it possess a direct scavenging action on NO. On the basis of these findings, GBLE's main mechanism of action in the suppression of NO production appears to involve a direct inhibitory action on iNOS enzyme (Kobuchi *et al.*, 1997).

Other antioxidant actions: Active oxygen is thought to play a role in cardiac diseases, par-

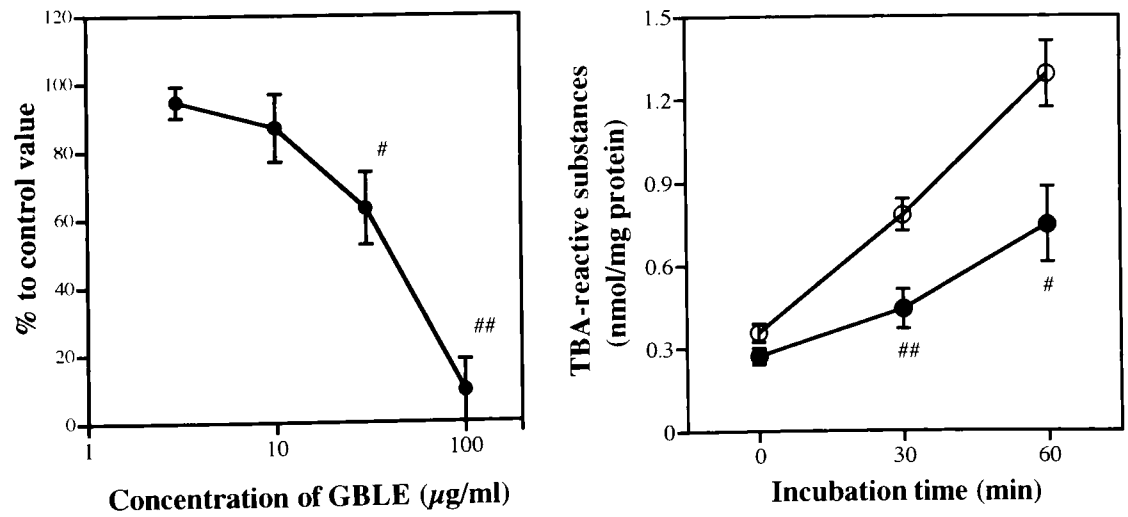

FIG. 4. Effect of GBLE on lipid peroxidation of rat brain homogenates *in vitro* and *ex vivo*. *In vitro* study: A mixture of 5% rat brain homogenates and GBLE suspension was incubated at 37°C for 60 min under the air. After the incubation, thiobarbituric acid (TBA)-reactive substances were measured by Ohkawa's method. #$p < 0.05$ and ##$p < 0.01$ vs the value of the control. *Ex vivo* study: GBLE (10 mg/kg) was orally administered 1 h before sacrifice. A 10% rat brain homogenate in 0.01 PBS was incubated at 37°C for 0, 30, and 60 min under air. After incubation, TBA-reactive substances were measured. (○) Control; (●) GBLE (10 mg/kg). #$p < 0.05$ and ##$p < 0.01$ vs the value of the control.

ticularly in ischemic heart diseases and in heart transplantation, which has been studied in experiments performed by many researchers. Tosaki *et al.* (1993) compared the efficacy of GBLE (EGB 761) with superoxide dismutase (SOD) plus catalase on reperfusion-induced arrhythmias in isolated rat hearts, and found that GBLE was a superior cardioprotective agent. Harmakai *et al.* (1994) investigated the effects of GBLE using a model of the isolated rat heart prepared by ischemia for 40 min and reperfusion for 20 min. GBLE improved cardiac function and inhibited the leakage of LDH, as well as the decrease in myocardial ascorbic acid. Those authors concluded that such improvement and inhibition were caused by the antioxidant effects of GBLE. Shen and Zhou (1995) examined the efficacy of GBLE in a rabbit ischemia-reperfusion injury. They found that GBLE suppressed an increase in lipid peroxide after reperfusion at the level of serum and cardiac muscle, and that it even inhibited the injury to the myocardial cells. Pietri *et al.* (1997a) used EPR to measure the free radicals produced after ischemia-reperfusion to examine the protective effect of the GBLE ginkgolides A and B and bilobalide on cardiac muscle. They concluded that the effect of GBLE and of its terpenoid constituents is caused by the *in vivo* oral administration or *ex vivo* addition to the perfusate, and that the protective action of GBLE originates from the terpene fraction that contains ginkgolide A. They report that the protective action on cardiac muscle is not the result of a direct scavenging action on free radicals, but a suppressive action on the production of free radicals (Pietri *et al.*, 1997a).

Active oxygen is thought to play a role in the etiology and pathogenesis of arteriosclerosis. It has been found that the initial arteriosclerotic lesion is formed through the following steps: the oxidation of LDL by active oxygen, the incorporation of the oxidized LDL into macrophages, and the deposition of the resulting foam cells on the vascular wall (Steinberg, 1987). *In vitro*, polypeptide or human serum albumin after glycation causes the production of superoxide and the oxidation of LDL in a phosphate-buffered solution. Such superoxide production and LDL oxidation are said to be accelerated by the addition of such transition elements as iron ion and copper ion. Copper ion, in a specific interaction with LDL, decomposes a trace of hydroperoxide contained in LDL, which leads to the initiation of an oxidative reaction of LDL. Finally, oxidized LDL is produced through the chain reaction of lipid peroxidation. In a dose-dependent manner, GBLE inhibits the increases in LDL apolipoprotein B (apo B) carbonylation, lipid peroxidation, apo B electrophoretic mobility, and LDL fluorescence, which are the products of the oxidative decomposition LDL initiated by copper ion (Yan *et al.*, 1995).

The role of necrosis and apoptosis in the cell death in various types of neuronopathy is of interest. Oyama *et al.* (1996) found that GBLE inhibited the necrosis of neurocytes induced by H_2O_2. Ni *et al.* (1996) reported that hydroxyl radicals produced by the Fenton reaction caused cerebellar neurocytes to undergo apoptosis, and that pretreatment with GBLE inhibited such apoptosis. Apoptosis is involved in an experimental model of cerebral ischemia, as well as in such degenerative nerve diseases as Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis. Studies that utilize the neurocyte-protective action of GBLE in such disorders, or in their experimental models are indicated.

Sastre *et al.* (1998) recently found that the levels of oxidative damage to mitochondrial DNA and of peroxide formation in mitochondria from old rats were both significantly higher than in those from young rats, and that treatment with GBLE partially prevented such oxidative damage to the brain and liver mitochondria from the old animals. These results suggest that GBLE exhibits beneficial effects on the aging of mitochondria by preventing chronic oxidative stress.

The inhibitory action of GBLE on vitreoretinopathy induced by intravitreal injection of xanthine and xanthine oxidase has recently been reported by Baudouin *et al.* (1999). They have demonstrated the strong pathological effects of oxygen radical production on the retina and the close relationship free radicals and inflammation-induced vitreoretinal proliferative disorders, and confirmed the preventive effect by GBLE.

Antagonism of platelet-activating factor

Platelet-activating factor (PAF) is a phospholipid found in vascular endothelial cells, leukocytes, and macrophages. It is released from the cell membrane when these cells are stimulated by various kinds of mediators. PAF is a kind of autacoid that exerts its actions at the site of its release. PAF induces platelet aggregation, thrombus formation, degranulation from neutrophils, and reactive oxygen species (ROS) production. It increases the permeability of the microvessels and causes bronchoconstriction. Braquet and Hosford (1991) reported that GBLE inhibits these actions of PAF, with such inhibitory actions being associated with ginkgolide B. Ginkgolide B inhibits erythrocyte aggregation and interferes with the linkage of PAF with platelets by binding to platelets earlier than PAF. Ginkgolide B also inhibits the effects of PAF on eosinophils, which include chemotaxis, degranulation, adherence, and cytotoxicity, all of which are involved in the inflammatory reaction. BN-52021, isolated from Ginkgo biloba leaves, showed a stronger antagonism toward PAF than ginkgolide B. PAF antagonism is considered to be associated with the efficacy of Ginkgo biloba leaves in patients with allergic asthma and rhinitis. PAF has been reported to induce functional disturbances in the circulatory system of the cerebrum and to aggravate the encephalopathy produced by ischemia. The cytoprotective action of GBLE on neurocytes is thus believed to originate from the anti-PAF action of the ginkgolide B contained in the terpene fraction. In addition, it is considered that GBLE exhibits its cytoprotective actions with the aid of free radical-scavenging action of the flavonoid fraction (Smith *et al.*, 1996).

Effects on blood flow or circulation

The effects of GBLE on vasoconstriction and vasodilatation have been studied in animals. GBLE stimulates the release of prostacyclin and endothelium-derived relaxing factor (EDRF) from rabbit aortic endothelium (Delaflotte *et al.*, 1984). By its antagonism of PAF, as described above, GBLE inhibits the aggregation of platelets and erythrocytes, increases the fluidity of erythrocytes, and inhibits the permeability of the endothelium. Any one of these actions would be considered favorable in patients with microcirculatory disturbances. GBLE is also considered to maintain vascular tone by accelerating the release of catecholamines and inhibiting their decomposition. We recently used the microchannel method of Kikuchi (1995) to assess leukocyte plugging in the capillary level. Venous blood from healthy adults was taken via venopuncture with the anticoagulant, EDTA. Each sample was passed through the microchannels of equivalent diameter 6 μm under a pressure difference of 20 cm H_2O. The transit time of 100 μl of each sample was measured and the flow behavior of the blood cells in the channels was observed with an inverted metallographic microscope. The addition of formyl-methionyl-leucyl-phenylamine (fMLP) induced the plugging of the leukocytes in the microchannels and lengthened their transit time (Fig. 5). Pretreatment with GBLE reduced the deformity of leukocytes and shortened their transit time. These findings suggest that GBLE would be effective in treating patients with microcirculatory disorders by reducing the plugging of capillaries by leukocytes.

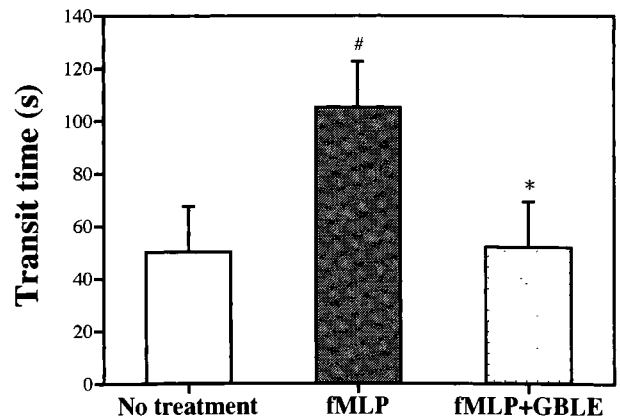

FIG. 5. Effect of GBLE on the increase in transit time of whole blood induced by fMLP. The transit time of 100 μl of each sample was measured with an inverted metallographic microscope. The addition of formyl-methionyl-leucyl-phenylamine (fMLP) induced leukocyte plugging in the microchannels and extended the transit time. #$p <$ 0.05 vs the value of no treatment group, and *$p < 0.05$ vs the fMLP group.

Other actions

The following actions of GBLE have also been reported: a normalizing action on cerebral metabolism in the ischemic state, accompanied by an inhibition of an increase in glucose consumption and by a decrease in electrolyte abnormalities; an increase in the number of cerebral muscarinic receptors; and an improving action on metabolism of norepinephrine. Such pharmacological effects could protect neurocytes against damage.

CLINICAL PHARMACOKINETICS

It is difficult to assess the pharmacokinetics of GBLE because of its many active ingredients. These ingredients show various interactions, being synergistic, additive, or antagonistic; thus, their pharmacological effects are difficult to evaluate. The pharmacodynamics of GBLE have been evaluated in a few clinical studies that determined the serum levels of elected components. Fourtillan *et al.* (1995) administered GBLE orally to 12 healthy young volunteers, and measured serum concentrations of ginkgolide A, ginkgolide B, and bilobalide. Each of these three active ingredients showed the greatest bioavailability after the oral administration of GBLE to fasting subjects as compared with either postprandial or intravenous administration. The differences in bioavailability caused by the different dosage forms of GBLE were also examined, based on serum concentrations of quercetin, kaempferol, and isorhamnetin (Wojcicki *et al.*, 1995). According to that report, there were no great differences in bioavailability among capsules, drops, and tablet when 18 healthy volunteers received three different formulations in equal an quantity, orally as a single dose at an interval of at least five days, although the capsules prolonged the time to reach the peak serum concentration as compared with drops and tablets.

CLINICAL USE OF GBLE

Clinical benefits of GBLE have been observed in patients with cerebrovascular disorders, in particular, those with tinnitis and dizziness, and in those with peripheral circulatory disturbances. Such clinical studies have been conducted mainly in Germany and France. GBLE was found to have effects on various symptoms following cerebral failure (Kleijnen and Knipschild, 1992). Its main uses appear to be in relieving the neurologic symptoms caused by cerebral ischemia following cerebral infarction, and in relieving the intermittent claudication caused by obstructive arteriosclerosis. In 1994, a standardized dry extract of Ginkgo biloba leaves was approved by the health authorities in Germany for the treatment of primary degenerative dementia and vascular dementia. While results supporting the efficacy of GBLE were also obtained in many other conditions, the effective dose, the duration of administration, and the duration of the effect have not been established.

Results of 11 double-blind, placebo-controlled, comparative trials in humans conducted since 1991 are summarized in Table 2. Three of these reports involve memory disorders (Rai *et al.*, 1991; Allain *et al.*, 1993; Semlitsch *et al.*, 1995), three dementia (Kanowski *et al.*, 1996; Le *et al.*, 1997; Maurer *et al.*, 1997), two obstructive arteriosclerosis (Mouren et al., 1994; Peters *et al.*, 1998), and one each involve tinnitis (Holgers *et al.*, 1994), acute cerebral infarction (Garg *et al.*, 1995), and the state after cardiopulmonary bypass (Pietri *et al.*, 1997b). Results in memory disorders appear to be reliable, because the effects were evaluated not only by an improvement in subjective symptoms, but also by various psychological tests and objective electrophysiological tests.

Interesting results in dementia were obtained in two large-scale comparative trials (Kanowski *et al.*, 1996; Le *et al.*, 1997). Kanowski *et al.* (1996) administered GBLE (240 mg/day) or a placebo for 24 weeks to 216 patients with Alzheimer's-type dementia or multi-infarct dementia, and evaluated efficacy by three objective tests. Treatment was completed by 156 patients. Significantly more patients in the GBLE group showed a favorable response to treatment, the same as that obtained by an intent-to-treat analysis. Using a double-blind design, Le *et al.* (1997) administered GBLE (120

TABLE 2. RESULTS OF 11 DOUBLE-BLIND, PLACEBO-CONTROLLED, RANDOMIZED TRIALS OF GBLE (1991–1998)

Disorder[a]	*Number of patients*	*Dose (mg/day)*	*Evaluation method*[a]	*Results*	*Reference*
Memory impairment	31	120	Psychometric test	Effective	Rai *et al.*, 1991
Memory impairment	18 600	320	Dual-cording test	Effective	Allain *et al.*, 1993
Atherosclerotic arterial occlusive disease	20	320	Size of ischemic area	Decrease	Mouren *et al.*, 1994
Tinnitus	20		Patients' symptoms	NS	Holgers *et al.*, 1994
Memory impairment	48	120	Latency of P300	Decrease	Semlitsch *et al.*, 1995
Acute cerebral infarction	55 (21/26)	160	Mathew's scale	NS	Garg *et al.*, 1995
Dementia (DAT, MID)	216	240	CGI Item 2 SKT NAB	Effective	Knowski *et al.*, 1996
Dementia (DAT, MID)	309	120	ADAS-Cog GERRI CGIS	Effective Effective NS	Le *et al.*, 1997
Cardiopulmonary bypass	15	320	Clinical outcome Oxidative stress Myoglobin leakage	NS Decreased Decreased	Pietri *et al.*, 1997b
Dementia (DAT)	20	240	SKT	Effective	Maurer *et al.*, 1997
Intermittent claudication	111	3p	Pain-free walking distance Maximum walking distance	Effective Effective	Peters *et al.*, 1998

[a]P300, auditory event-related potentials in age-associated memory; DAT, dementia of the Alzheimer type; MID, multi-infarct dementia; CGI Item 2, Clinical Global Impression; SKT, Syndrom-Kurztest for the patients attention and memory; NAB, Nurnberger Alters-Beobachtungsskala; ADAS-Cog, Alzheimer's Disease Assessment Scale-Cognitive subscale; GERRI, Geriatric Evaluation by Relative's Rating Instrument; CGIS, Clinical Global Impression of Change.

mg/day) for 52 weeks to 309 patients with Alzheimer's-type dementia or multi-infarct dementia. Of these cases, 202 provided evaluable data for analysis at the 52-week end point. The GBLE group showed significant improvement according to the judgment criteria for dementia, such as Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog) or Geriatric Evaluation by Relative's Rating Instrument (GERRI). In addition, there was no serious adverse effects or aggravation of symptoms in either trials, indicating the safety of GBLE. Results of these two large double-blind comparative studies strongly support the efficacy of GBLE. Maurer *et al.* (1997) reported that the administration of GBLE (240 mg/day) for 3 months to patients with dementia significantly increased the psychopathological (Clinical Global Impression) levels as well as the EEG topographic findings, which can be interpreted as providing evidence of the effectiveness of GBLE in dementia. Itil *et al.* (1998) also confirmed the efficacy of GBLE in treating dementia by a study of GBLE vs. tacrine using computer-analyzed EEGs to evaluate efficacy. Results showed that a greater number of patients receiving 240 mg of GBLE had typical "cognitive activator" EEG profiles (8 of 18 patients), compared with 40 mg of tacrine (3 of 18 patients). The latter agent (tetrahydroaminoacrine) has been approved in the United States for treating Alzheimer's disease.

In 1998, a multicenter, randomized, placebo-controlled double-blind study of ginkgo biloba extract was conducted in patients with peripheral occlusive arterial disease, Fontaine stage IIb (Peters *et al.*, 1998). Both the pain-free walking distance and the maximum walking distance were significantly greater in the GBLE-treated group. The authors concluded that GBLE treatment of patients with peripheral occlusive arterial disease, Fontaine stage IIb, is safe and effective, causing both a statistically significant, and a clinically relevant, prolongation of walking distance (Peters *et al.*, 1998).

FUTURE CLINICAL USE

It is now known that ROS, or free radicals, are intimately involved in various biological reactions. At a normal rate of generation, some free radicals are useful in the human body. However, when the generation of oxygen radicals exceeds the capacity of the body's antioxidative defenses, the result is oxidative stress. Oxidative stress occurs in many diseases and may make a significant contribution to their pathogenesis. GBLE shows a very strong scavenging action on free radicals, and is thus considered to be useful for the treatment of diseases related to the production of free radicals, such as ischemic heart disease, cerebral infarction, chronic inflammation, and aging.

ABBREVIATIONS

AAPH, 2,2-Azo *bis*(2-amidino propane) hydrogen dichloride; AMVN, 2,2-azo *bis*(2,4-dimethyl valero nitrile); apo B, apolipoprotein B; DMPO, 5,5′-dimethyl-1-pyrroline-*N*-oxide; DPPH, diphenyl-*p*-picrylhydral; EPR, electron paramagnetic resonance; ERDF, endothelium-derived relaxing factor; fMLP, formyl-methionyl-leucyl-phenylamine; GBLE, Ginkgo biloba leaf extract; H_2O_2, hydrogen peroxide; LDL, low-density lipoprotein; NO, nitric oxide; PAF, platelet activating factor; pc, phosphatidyl choline; ROS, reactive oxygen species; SOD, superoxide dismutase.

REFERENCES

ALLAIN, H., RAOUL, P., LIEURY, A., LECOZ, F., GANDON, J.M., and d'ARBIGNY, P. (1993). Effect of two doses of ginkgo biloba extract (EGb 761) on the dual-coding test in elderly subjects. Clin. Ther. **15,** 549–558.

BAUDOUIN, C., PISELLA, P.J., ETTAICHE, M., GOLDSCHILD, M., BECQUEST, F., GASTAUD, P., and DROY-LEFAIX, M.T. (1999). Effects of EGb761 and superoxide dismutase in an experimental model of retinopathy generated by intravitreal production of superoxide anion radical. Graefes Arch. Clin. Exp. Ophthalmol. **237,** 58–66.

BRAQUET, P., and HOSFORD, D. (1991). Ethnopharmacology and the development of natural PAF antagonists as therapeutic agents. J. Ethnopharmacol. **32,** 135–139.

DELAFLOTTE, S., AUGUET, M., DEFEUDIS, F.V., BARANES, J., CLOSTRE, F., DRIEU, K., and BRAQUET, P. (1984). Endothelium-dependent relaxations of rabbit isolated aorta produced by carbachol and by Ginkgo biloba extract. Biomed. Biochim. Acta **43,** 8–9.

DRIEU, K. (1988). Preparation and definition of Ginkgo biloba extract. In *Roken (Ginkgo biloba). Recent Results in Pharmacology and Pharmacology and Clinic.* E.W. Funfgeld (ed.). (Springer-Verlag, New York) pp. 32–36.

DROY-LEFAIXT, L.M., CLUZEL, J., MENERATH, J.M., BONHOMME, B., and DOLY, M. (1995). Antioxidant effect of a Ginkgo biloba extract (EGb 761) on the retina. Int. J. Tissue React. **17,** 93–100.

DUMONT, E., D'ARBIGNY, P., and NOUVELOT, A. (1995). Protection of polyunsaturated fatty acids against iron-dependent lipid peroxidation by a ginkgo biloba extract (EGb 761). Methods Find. Exp. Clin. Pharmacol. **17,** 83–88.

FOURTILLAN, J.B., BRISSON, A.M., GIRAULT, J., INGRAND, I., DECOURT, J.P., DRIEU, K., JOUENNE, P., and BIBER, A. (1995). Pharmacokinetic properties of Bilobalide and Ginkgolides A and B in healthy subjects after intravenous and oral administration of Ginkgo biolba extract (EGb 761). Therapie **50,** 137–144.

GARG, R.K., NAG, D., and AGRAWAL, A. (1995). A double blind placebo controlled trial of ginkgo biloba extract in acute cerebral ischaemia. J. Assoc. Physicians India **43,** 760–736.

HARAMAKI, N., AGGARWAL, S., KAWABATA, T., DROY, L.M., and PACKER, L. (1994). Effects of natural antioxidant ginkgo biloba extract (EGB 761) on myocardial ischemia-reperfusion injury. Free Radic Biol Med **16,** 789–794.

HOLGERS, K.M., AXELSSON, A., and PRINGLE, I. (1994). Ginkgo biloba extract for the treatment of tinnitus. Audiology **33,** 85–92.

ITIL T.M., ERALP, E., AHMED, I., KUNITZ, A., ITIL, K.Z. (1998). The pharmacological effects of ginkgo biloba, a plant extract, on the brain of dementia patients in comparison with tacrine.

KANOWSKI, S., HERRMANN, W.M., STEPHAN, K., WIERICH, W., and HORR, R. (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 **29,** 47–56.

KIKUCHI, Y. (1995). Effect of leukocytes and platelets on blood flow through a parallel array of microchannels: micro- and macroflow relation and rheological measures of leukocyte and platelet activities. Microvasc. Res. **50,** 288–300.

KLEIJNEN, J., and KNIPSCHILD, P. (1992). Ginkgo biloba. Lancet **340,** 1136–1139.

KOBUCHI, H., DROY, L.M., CHRISTEN, Y., and PACKER, L. (1997). Ginkgo biloba extract (EGb 761): inhibitory effect on nitric oxide production in the macrophage cell line RAW 264.7. Biochem. Pharmacol. **53,** 897–903.

KOSE, K., and DOGAN, P. (1995). Lipoperoxidation induced by hydrogen peroxide in human erythrocyte membranes. 2. Comparison of the antioxidant effect of Ginkgo biloba extract (EGb 761) with those of water-

soluble and lipid-soluble antioxidants. J. Int. Med. Res. **23,** 9–18.

KOSE, K., DOGAN, P., ASCIOGLU, M., and ASCIOGLU, O. (1997). In vitro antioxidant effect of Ginkgo biloba extract (EGb 761) on lipoperoxidation induced by hydrogen peroxide in erythrocytes of Behcet's patients. Jpn. J. Pharmacol. **75,** 253–258.

LE, B.P., KATZ, M.M., BERMAN, N., ITIL, T.M., FREEDMAN, A.M., and SCHATZBERG, A.F. (1997). A placebo-controlled, double-blind, randomized trial of an extract of Ginkgo biloba for dementia. North American EGb Study Group. J. Am. Med. Assn. **278,** 1327–1332.

LEE, S.L., WANG, W.W., LANZILLO, J., GILLIS, C.N., and FANBURG, B.L. (1998). Superoxide scavenging effect of Ginkgo biloba extract on serotonin-induced mitogenesis. Biochem. Pharmacol. **56,** 527–533.

LUGASI, A., HORVAHOVICH, P., and DWORSCHAK, E. (1999). Additional information to the in vitro antioxidant activity of Ginkgo biloba leaf. Phytother. Res. **13,** 160–162.

MAITRA, I., MARCOCCI, L., DROY, L.M., and PACKER, L. (1995). Peroxyl radical scavenging activity of Ginkgo biloba extract EGb 761. Biochem. Pharmacol. **49,** 1649–1655.

MAURER, K., IHL, R., DIERKS, T., and FROLICH, L. (1997). Clinical efficacy of Ginkgo biloba special extract EGb 761 in dementia of the Alzheimer type. J. Psychiatr. Res. **31,** 645–655.

MIYAJIMA, M., YOSHIKAWA, T., ICHIKAWA, H., MINAMIYAMA, Y., TSUJIGIWA, M., NAKAHASHI, Y., TAKAHASHI, S., and KONDO, M. (1994). Anti-oxidative properties of Ginkgo biloba extract (GBE). In *Frontiers of Reactive Oxygen Species in Biology and Medicine.* K. Asada and T. Yoshikawa (eds.). (Elsevier Science B.V., Amsterdam) pp. 341–342.

MOUREN, X., CAILLARD, P., and SCHWARTZ, F. (1994). Study of the antiischemic action of EGb 761 in the treatment of peripheral arterial occlusive disease by TcPo2 determination. Angiology **45,** 413–417.

NI, Y., ZHAO, B., HOU, J., and XIN, W. (1996). Preventive effect of Ginkgo biloba extract on apoptosis in rat cerebellar neuronal cells induced by hydroxyl radicals. Neurosci. Lett. **214,** 115–118.

NODA, Y., ANZAI, K., MORI, A., KOHNO, M., SHINMEI, M., and PACKER, L. (1997). Hydroxyl and superoxide anion radical scavenging activities of natural source antioxidants using the computerized JES-FR30 ESR spectrometer system. Biochem. Mol. Biol. Int. **42,** 35–44.

NOGUCHI, N., NISHINO, K., and NIKI, E. (1997). Antioxidant action of Gingko biloba extract. J. Jpn. Oil. Chem. Soc. **46,** 1481–1488.

OYAMA, Y., CHIKAHISA, L., UEHA, T., KANEMARU, K., and NODA, K. (1996). Ginkgo biloba extract protects brain neurons against oxidative stress induced by hydrogen peroxide. Brain Res. **712,** 349–352.

PETERS, H., KIESER, M., and HOLSCHER, U. (1998). Demonstration of the efficacy of ginkgo biloba special extract EGb 761 on intermittent claudication—a placebo-controlled, double-blind multicenter trial. Vasa **27,** 106–110.

PIETRI, S., MAURELLI, E., DRIEU, K., and CULCASI, M. (1997a). Cardioprotective and anti-oxidant effects of the terpenoid constituents of Ginkgo biloba extract (EGb 761). J. Mol. Cell. Cardiol. **29,** 733–742.

PIETRI, S., SEGUIN, J.R., D'ARBIGNY, P., DRIEU, K., and CULCASI, M. (1997b). Ginkgo biloba extract (EGb 761) pretreatment limits free radical-induced oxidative stress in patients undergoing coronary bypass surgery. Cardiovasc. Drugs Ther. **11,** 121–131.

RAI, G.S., SHOVLIN, C., and WESNES, K.A. (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,** 350–355.

RONG, Y., GENG, Z., and LAU, B.H. (1996). Ginkgo biloba attenuates oxidative stress in macrophages and endothelial cells. Free Radic. Biol. Med. **20,** 121–127.

SASTRE, J., MILLAN, A., GARCIA, DE, LA, ASUNCION, J., PLA, R., JUAN, G., PALLARDO, O'CONNOR, E., MARTIN, J.A., DROY, L.M., and VINA, J (1998). A Ginkgo biloba extract (EGb 761) prevents mitochondrial aging by protecting against oxidative stress. Free Radic. Biol. Med. **24,** 298–304.

SCHOLTYSSEK, H., DAMERAU, W., WESSEL, R., and SCHIMKE, I. (1997). Antioxidative activity of ginkgolides against superoxide in an aprotic environment. Chem. Biol. Interact. **106,** 183–190.

SEIF, EL, NASR, M., and EL, F.A. (1995). Lipid peroxide, phospholipids, glutathione levels and superoxide dismutase activity in rat brain after ischaemia: effect of ginkgo biloba extract. Pharmacol. Res. **32,** 273–278.

SEMLITSCH, H.V., ANDERER, P., SALETU, B., BINDER, G.A., and DECKER, K.A. (1995). Cognitive psychophysiology in nootropic drug research: effects of Ginkgo biloba on event-related potentials (P300) in age-associated memory impairment. Pharmacopsychiatry **28,** 134–142.

SHEN, J.G., and ZHOU, D.Y. (1995). Efficiency of Ginkgo biloba extract (EGb 761) in antioxidant protection against myocardial ischemia and reperfusion injury. Biochem. Mol. Biol. Int. **35,** 125–134.

SHI, H., and NIKI, E. (1998). Stoichiometric and kinetic studies on Ginkgo biloba extract and related antioxidants. Lipids **33,** 365–370.

SMITH, P.F., MACLENNAN, K., and DARLINGTON, C.L. (1996). The neuroprotective properties of the Ginkgo biloba leaf: a review of the possible relationship to platelet-activating factor (PAF). J. Ethnopharmacol. **50,** 131–139.

STEINBERG, D. (1987). Lipoproteins and atherosclerosis. A look back and a look ahead. Atherosclerosis **3,** 283–301.

SZABO, M.E., DROY, L.M., and DOLY, M. (1997). Direct measurement of free radicals in ischemic/reperfused diabetic rat retina. Clin. Neurosci. **4,** 240–245.

TOSAKI, A., DROY-LEFAIX, M.T., PALI, T., and DAS, K.D. (1993). Effects of SOD, catalase, and a novel antiarrhythmic drug. EGB 761, on reperfusion-induced arrhythmias in isolated rat hearts. Free Radic. Biol. Med. **14,** 361–370.

WOJCICKI, J., GAWRONSKA, S.B., BIEGANOWSKI, W., PATALAN, M., SMULSKI, H.K, SAMOCHOWIEC, L., and ZAKRZEWSKI, J. (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. **27,** 141–146.

YAN, L.J., DROY, L.M., and PACKER, L. (1995). Ginkgo biloba extract (EGb 761) protects human low density lipoproteins against oxidative modification mediated by copper. Biochem. Biophys. Res. Commun. **212,** 360–366.

Address reprint requests to:
Dr. Toshikazu Yoshikawa
First Department of Medicine
Kyoto Prefectural University of Medicine
Kyoto 602-8566, Japan
E-mail: toshi@koto5.kpu-m.ac.jp

This article has been cited by:

1. Limei Han, Yan Fu, Adam J. Cole, Jie Liu, Jianxin Wang. 2012. Co-encapsulation and sustained-release of four components in ginkgo terpenes from injectable PELGE nanoparticles. *Fitoterapia* **83**:4, 721-731. [CrossRef]
2. Tarek Kamal Motawi, Sherine Maher Rizk, Ahmed Hassan Shehata. 2012. Effects of curcumin and Ginkgo biloba on matrix metalloproteinases gene expression and other biomarkers of inflammatory bowel disease. *Journal of Physiology and Biochemistry* . [CrossRef]
3. Michael J Stanger, Lauren A Thompson, Andrew J Young, Harris R Lieberman. 2012. Anticoagulant activity of select dietary supplements. *Nutrition Reviews* **70**:2, 107-117. [CrossRef]
4. Andy Suter, Wolfgang Niemer, Rainer Klopp. 2011. A New Ginkgo Fresh Plant Extract Increases Microcirculation and Radical Scavenging Activity in Elderly Patients. *Advances in Therapy* . [CrossRef]
5. Chul Ho Jang, Yong Bum Cho, Jun Sung Kim, Sung Woo Cho, Hyung Chae Yang, Kee Hong Jung, Jae Young Kim, Cheol Hee Choi, Yong Lim, Haekyun Park, Sung In Kang. 2011. Effect of Ginkgo biloba extract on endotoxin-induced labyrinthitis. *International Journal of Pediatric Otorhinolaryngology* . [CrossRef]
6. Giovanni D'Andrea, Davide Colavito, Maurizio Dalle Carbonare, Alberta Leon. 2011. Migraine with aura: conventional and non-conventional treatments. *Neurological Sciences* **32**:S1, 121-129. [CrossRef]
7. Ting Hua Yang, Yi Ho Young, Shing Hwa Liu. 2010. EGb 761 (Ginkgo biloba) protects cochlear hair cells against ototoxicity induced by gentamicin via reducing reactive oxygen species and nitric oxide-related apoptosis#. *The Journal of Nutritional Biochemistry* . [CrossRef]
8. Sandra Trompezinski, Marlène Bonneville, Ingrid Pernet, Alain Denis, Daniel Schmitt, Jacqueline Viac. 2010. Gingko biloba extract reduces VEGF and CXCL-8/IL-8 levels in keratinocytes with cumulative effect with epigallocatechin-3-gallate. *Archives of Dermatological Research* **302**:3, 183-189. [CrossRef]
9. Serdar F#L#Z, #ükriye Bilge GÜRSEL, Pelin CO#TUR BIYIKSIZ, Sava# YÖRÜKER, Süheyla GONCA, Elif GELENL#, Hakk# DALÇIK. 2010. Immunohistochemical Evaluation of the Protective Effect of Ginkgo Biloba, Probiotic Saccharomyces Boulardii and N-Acetylcysteine on Radiation-Induced Small Intestine Injury. *Turkiye Klinikleri Journal of Medical Sciences* **30**:5, 1433-1440. [CrossRef]
10. Kunmei Ji, Jiajie Chen, Meng Li, Zhigang Liu, Lixin Xia, Chunbo Wang, Zhengke Zhan, Xuli Wu. 2009. Comments on serious anaphylaxis caused by nine Chinese herbal injections used to treat common colds and upper respiratory tract infections. *Regulatory Toxicology and Pharmacology* **55**:2, 134-138. [CrossRef]
11. Vijay K. Kapoor, Janhvi Dureja, Renu Chadha. 2009. Herbals in the control of ageing. *Drug Discovery Today* **14**:19-20, 992-998. [CrossRef]
12. Chiu-Ling Hsu, Yuh-Lin Wu, Gau-Jun Tang, Tzong-Shyuan Lee, Yu Ru Kou. 2009. Ginkgo biloba extract confers protection from cigarette smoke extract-induced apoptosis in human lung endothelial cells: Role of heme oxygenase-1. *Pulmonary Pharmacology & Therapeutics* **22**:4, 286-296. [CrossRef]
13. Jing He, Juan Lin, Jing Li, Jian-Hong Zhang, Xue-Min Sun, Cheng-Ming Zeng. 2009. Dual Effects of Ginkgo biloba Leaf Extract on Human Red Blood Cells. *Basic & Clinical Pharmacology & Toxicology* **104**:2, 138-144. [CrossRef]
14. Shikai Yan, Bin Wu, Zhongying Lin, Huizi Jin, Jianhua Huang, Yun Yang, Xinmin Zhang, Ziyin Shen, Weidong Zhang. 2009. Metabonomic characterization of aging and investigation on the anti-aging effects of total flavones of Epimedium. *Molecular BioSystems* **5**:10, 1204. [CrossRef]
15. Elham Satvat, Paul E. Mallet. 2009. Chronic administration of a Ginkgo biloba leaf extract facilitates acquisition but not performance of a working memory task. *Psychopharmacology* **202**:1-3, 173-185. [CrossRef]
16. Zeynep Kizilkaya Kaptan, Hatice Emir, Hakan Gocmen, Hakki Uzunkulaoglu, Alparslan Karakas, Mehmet Senes, Erdal Samim. 2009. Ginkgo biloba, a free oxygen radical scavenger, affects inflammatory mediators to diminish the occurrence of experimental myringosclerosis. *Acta Oto-laryngologica* **129**:8, 826-831. [CrossRef]
17. Jan E. Leuendorf, Andreas Genau, Agnieszka Szewczyk, Sutton Mooney, Christel Drewke, Eckhard Leistner, Hanjo Hellmann. 2008. The Pdx1 family is structurally and functionally conserved between Arabidopsis thaliana and Ginkgo biloba. *FEBS Journal* **275**:5, 960-969. [CrossRef]
18. Natural Therapies to Preserve and Enhance Cognition and Memory 248-257. [Citation] [Full Text PDF] [Full Text PDF with Links]

19. Chris D. Meletis , Nieske L. Zabriskie , Robert Rountree Clinical Natural Medicine Handbook . [Abstract] [Full Text PDF] [Full Text PDF with Links]
20. G LIPPI, G TARGHER, G GUIDI. 2007. Ginkgo biloba, inflammation and lipoprotein(a). *Atherosclerosis* **195**:2, 417-418. [CrossRef]
21. Xinyan Huang, Craig A. Whitworth, Leonard P. Rybak. 2007. Ginkgo Biloba Extract (EGb 761) Protects Against Cisplatin-Induced Ototoxicity in Rats. *Otology & Neurotology* **28**:6, 828-833. [CrossRef]
22. Elaine A Irving, Neil Upton. 2007. Symptomatic treatment of Alzheimer's disease: identification of biomarkers to aid translation from bench to bedside. *Biomarkers in Medicine* **1**:1, 93-110. [CrossRef]
23. Satoshi Akiba, Hidenori Yamaguchi, Satomi Kumazawa, Mayuko Oka, Takashi Sato. 2007. Suppression of Oxidized LDL-Induced PDGF Receptor .BETA. Activation by Ginkgo Biloba Extract Reduces MMP-1 Production in Coronary Smooth Muscle Cells. *Journal of Atherosclerosis and Thrombosis* **14**:5, 219-225. [CrossRef]
24. Patricia AmmonMultiple Sclerosis 169-176. [CrossRef]
25. Danna Park, Melinda RingPeripheral Vascular Disease 309-321. [CrossRef]
26. Young-Mi Park, Jong-Heon Won, Kyung-Jin Yun, Jong-Hoon Ryu, Yong-Nam Han, Seung-Ki Choi, Kyung-Tae Lee. 2006. Preventive Effect of Ginkgo biloba Extract (GBB) on the Lipopolysaccharide-Induced Expressions of Inducible Nitric Oxide Synthase and Cyclooxygenase-2 via Suppression of Nuclear Factor-#B in RAW 264.7 Cells. *Biological & Pharmaceutical Bulletin* **29**:5, 985-990. [CrossRef]
27. Bradford Frank, Sanjay Gupta. 2005. A Review of Antioxidants and Alzheimer's Disease. *Annals of Clinical Psychiatry* **17**:4, 269-286. [CrossRef]
28. E. YAGMUR, A. PIATKOWSKI, A. GRÖGER, N. PALLUA, A.M. GRESSNER, P. KIEFER. 2005. Bleeding complication under Gingko biloba medication. *American Journal of Hematology* **79**:4, 343-344. [CrossRef]
29. Siegfried Wolffram, Rainer CermakEffect of Ginkgo biloba Extract EGb 761 on Differential Gene Expression in the Brain **20055079**, 341-352. [CrossRef]
30. Chris I. Wright, Christine I. Kroner, Richard Draijer. 2005. Raynaud's Phenomenon and the Possible Use of Foods. *Journal of Food Science* **70**:4, R67-R75. [CrossRef]
31. I ILIEVA. 2004. The effects of Ginkgo biloba extract on lipopolysaccharide-induced inflammation in vitro and in vivo. *Experimental Eye Research* **79**:2, 181-187. [CrossRef]
32. Satoshi Akiba, Masahiro Chiba, Yuki Mukaida, Akira Tamura, Takashi Sato. 2004. The leaf extract of Ginkgo Biloba L. suppresses oxidized LDL-stimulated fibronectin production through an antioxidant action in rat mesangial cells. *British Journal of Pharmacology* **142**:3, 419-424. [CrossRef]
33. Gerald Rimbach, Rainer Cermak, Siegfried WolfframGene Regulatory Activity of Ginkgo biloba L **20045272**, 105-119. [CrossRef]
34. A. Kurz, B. Van Baelen. 2004. Ginkgo biloba Compared with Cholinesterase Inhibitors in the Treatment of Dementia: A Review Based on Meta-Analyses by the Cochrane Collaboration. *Dementia and Geriatric Cognitive Disorders* **18**:2, 217-226. [CrossRef]
35. N Zeybek. 2003. The effects of gingko biloba extract (EGb 761) on experimental acute pancreatitis. *Journal of Surgical Research* **115**:2, 286-293. [CrossRef]
36. David Mantle , Richard M. Wilkins , Muhamed Asim Gok . 2003. Comparison of Antioxidant Activity in Commercial Ginkgo biloba Preparations. *The Journal of Alternative and Complementary Medicine* **9**:5, 625-629. [Abstract] [Full Text PDF] [Full Text PDF with Links]
37. Steven T. DeKosky. 2003. Pathology and Pathways of Alzheimer's Disease with an Update on New Developments in Treatment. *Journal of the American Geriatrics Society* **51**:5s2, S314-S320. [CrossRef]
38. Shu-Ying Chung, Ming-Fu Wang, Jing-Ying Lin, Ming-Cheng Lin, Hui-Ming Liu, Fu-Chou Cheng. 2003. Effect of One Week Treatment with Ginkgo biloba Extract (EGb761) on Ischemia-Induced Infarct Volume in Gerbils. *The American Journal of Chinese Medicine* **31**:04, 533-542. [CrossRef]
39. C. Michiels, J. Remacle, N. Bouaziz. 2002. Endothelium and venotropic drugs in chronic venous insufficiency: A review. *Phlebology* **17**:3-4, 145-150. [CrossRef]
40. Cynthia Brewer, Fanny Bonin, Paula Bullock, Marie-Christine Nault, Jennifer Morin, Sophie Imbeault, T. Y. Shen, D. J. Franks, Steffany A. L. Bennett. 2002. Platelet activating factor-induced apoptosis is inhibited by ectopic

expression of the platelet activating factor G-protein coupled receptor. *Journal of Neurochemistry* **82**:6, 1502-1511. [CrossRef]

41. Didier Morin, Vassilios Papadopoulos, Jean-Paul Tillement. 2002. Prevention of cell damage in ischaemia: novel molecular targets in mitochondria. *Expert Opinion on Therapeutic Targets* **6**:3, 315-334. [CrossRef]
42. Lauren T Bonner, Elaine R Peskind. 2002. Pharmacologic treatments of dementia. *Medical Clinics of North America* **86**:3, 657-674. [CrossRef]
43. N Bouaziz. 2002. Mitochondrial respiratory chain as a new target for anti-ischemic molecules. *European Journal of Pharmacology* **441**:1-2, 35-45. [CrossRef]
44. Sheila A Doggrell. 2001. Pharmacotherapy of intermittent claudication. *Expert Opinion on Pharmacotherapy* **2**:11, 1725-1736. [CrossRef]
45. Chris D. Meletis , Ben Bramwell . 2001. Natural Therapies to Preserve and Enhance Cognition and Memory. *Alternative and Complementary Therapies* **7**:5, 273-276. [Citation] [Full Text PDF] [Full Text PDF with Links]
46. Gerald Rimbach, Kishorchandra Gohil, Seiichi Matsugo, Hadi Moini, Claude Saliou, Fabio Virgili, Stefan U. , Lester Weber Packer. 2001. Induction of glutathione synthesis in human keratinocytes by Ginkgo biloba extract (EGb761). *BioFactors* **15**:1, 39-52. [CrossRef]