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Review article

The neuroprotective properties of the *Ginkgo biloba* leaf: a review of the possible relationship to platelet-activating factor (PAF)

Paul F. Smith*[a], Karyn Maclennan[a], Cynthia L. Darlington[b]

[a]*Department of Pharmacology, School of Medical Sciences, University of Otago Medical School, Dunedin, New Zealand*
[b]*Department of Psychology and the Neuroscience Research Centre, University of Otago, Dunedin, New Zealand*

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Abstract

Ginkgo biloba (Ginkgoaceae) is an ancient Chinese tree which has been cultivated and held sacred for its health-promoting properties. There is substantial experimental evidence to support the view that *Ginkgo biloba* extracts have neuroprotective properties under conditions such as hypoxia/ischemia, seizure activity and peripheral nerve damage. Research on the biochemical effects of *Ginkgo biloba* extracts is still at a very early stage. One of the components of *Ginkgo biloba*, ginkgolide B, is a potent platelet-activating factor (PAF) antagonist. Although the terpene fraction of *Ginkgo biloba*, which contains the ginkgolides, may contribute to the neuroprotective properties of the *Ginkgo biloba* leaf, it is also likely that the flavonoid fraction, containing free radical scavengers, is important in this respect. Taken together, the evidence suggests that *Ginkgo biloba* extracts are worthy of further investigation as potential neuroprotectant agents.

Keywords: *Ginkgo biloba*; Ginkgolides; Neuroprotection; Neural damage

1. Introduction

Ginkgo biloba (Michel, 1985) (Ginkgoaceae) is an ancient tree which, for centuries, the Chinese have cultivated and held sacred for its health-promoting properties. Although it was threatened with extinction during the ice age, fossils of the *Ginkgo biloba* tree date back more than 200 million years and individual trees have been known to live for as long as 1000 years (Anonymous, 1988).

In recent decades, concentrated extracts of *Ginkgo biloba* leaves have been marketed in Western countries as herbal medicines which enhance cerebral blood flow and improve memory (e.g EGB 761, 24% *Ginkgo*-flavone glycosides and 6% terpenoids). Although the evidence supporting their enhancement of memory in healthy animals and humans is limited and controversial (Winter,

* Corresponding author.

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1991), there is substantial evidence to support the view that these extracts have neuroprotective properties (Rodriguez de Turco et al., 1993). Since few reviews have been published on the potential neurological applications of *Ginkgo biloba*, and there have been many recent studies, the aim of this review is to evaluate critically the available data on its neuroprotective properties with a view to stimulating further studies.

2. Chemical composition of the *Ginkgo biloba* leaf

Ginkgo biloba leaves contain a number of flavonoids (e.g kaempferol, quercetin and isohamnetin derivatives) and terpenes (e.g ginkgolides and bilobalide) (van Beek et al., 1991; Sticher, 1993). The specific concentrations of these substances in the leaves varies with season, and different *Ginkgo biloba* extracts also use different formulations (van Beek et al., 1991; Sticher, 1993). At present, it is not known which of the various constituents of *Ginkgo biloba* is/are responsible for its beneficial effects, although attention has focussed on the flavonoids (Tighilet and Lacour, 1995) and ginkgolides (Maclennan et al., 1995b); the latter include potent PAF antagonists such as ginkgolide B (see Braquet, 1987; Braquet et al., 1987, 1991; Snyder, 1990; Nojima, 1991; Lindsberg et al., 1991; Shimizu et al., 1992; Venable et al., 1993; Koltai et al., 1994 for reviews).

3. *Ginkgo biloba* as a 'smart drug'

The evidence supporting the view that *Ginkgo biloba* extracts have memory-enhancing properties in healthy animals and humans is best described as inconclusive at this stage. Relatively few well-controlled studies have been conducted and so the status of *Ginkgo biloba* as a 'smart drug' is premature and potentially misguided.

A number of semi-anecdotal studies of the cognitive effects of *Ginkgo biloba* in humans have been published (see Warburton, 1986 for review); however, there have been few well-controlled studies. Using a battery of psychological tests, Subhan and Hindmarch (1984) evaluated the effects of the *Ginkgo biloba* extract, EGB 761, on cognitive function in healthy humans. Aside from causing a reduction in reaction time on the Sternberg memory scanning test at the highest dose used (600 mg, oral), the drug had no significant effects (Table 1). However, since this study incorporated a randomized, double-blind crossover design, it does provide some evidence that EGB 761 may reduce response time, via effects on attention, memory or motor activity.

One of the few well-controlled animal studies of the effects of EGB 761 on memory was conducted by Winter (1991), who used the performance of mice in an operant conditioning task as an index of memory. Using a dose of 100 mg/kg per day, administered orally for 4 or 8 weeks prior to training and then for 10 weeks until a retention test, Winter reported that EGB 761 treatment reduced the time to acquisition and enhanced performance on the task, in terms of the number, the effectiveness and the retention of correct responses. On the other hand, Porsolt et al. (1990) reported that EGB 761 treatment (50 or 100 mg/kg per day, oral) for 5 days did not affect the performance of rats or mice in a passive avoidance test, although it did seem to reduce learned helplessness, possibly due to anxiolytic effects.

These few studies suggest that *Ginkgo biloba* extracts are worthy of further investigation in memory tasks, particularly with a view to possible application to the treatment of neurodegenerative disorders such as senile dementia of the Alzheimer's type (SDAT). In this context, the evidence that EGB 761 and related drugs can reduce neural damage is particularly important (see below).

4. *Ginkgo biloba* as a neuroprotectant

Le Poncin Lafitte et al. (1980) used the microembolization technique to investigate the effects of EGB 761 on cerebral blood flow and energy metabolism following microinfarctions in rats. EGB 761 treatment (100 mg/kg per day, administered osophageally) for 21 days prior to microembolization resulted in an increase in blood flow, and in an increase in ATP, glucose and lactate levels in the embolized hemisphere, relative to controls (which received an i.p injection of NaCl).

Karcher et al. (1984) examined the effects of

Table 1
Examples of studies in which *Ginkgo biloba* extracts have been shown to promote recovery from neural damage

Reference	Extract	Species	Model	Dose/Route/Frequency
Le Poncin Lafitte et al. (1980)	EGB 761	Rats	Microembolization	100 mg/kg (os) per day, 21 days
Karcher et al. (1984)	EGB 761	Rats	Hypoxia	100 mg/kg (i.p.), single
Karcher et al. (1984)	EGB 761	Rats	Hypoxia	200 mg/kg (oral) per day, 14 days
Subhan and Hindmarch (1984)	EGB 761	Humans	Sternberg scanning test	120, 240, 600 mg (oral), single
Denise and Bustany (1989)	EGB 761	Rats	Vestibular compensation	50 mg/kg (i.p) per day, 10 weeks
Attella et al. (1989)	EGB 761	Rats	Frontal cortex lesions	100 mg/kg (i.p) per day, 60 days
Porsolt et al. (1990)	EGB 761	Rats, mice	Operant task	50, 100 mg/kg (oral) per day, 14–18 weeks
Winter (1991)	EGB 761	Mice	Passive avoidance, learned helplessness	100 mg/kg (oral) per day, 5 days
Lacour et al. (1991)	EGB 761	Cats	Vestibular compensation	50 mg/kg (i.p.) per day, 30 days
Rodriguez de Turco et al. (1993)	EGB 761	Rats	Electroconvulsive shock	100 mg/kg (os) per day, 14 days
Tighilet and Lacour (1995)	EGB 761 non-terpenic	Cats	Vestibular compensation	25 mg/kg (i.p) per day, 40 days

os, osophageal; i.p, intraperitoneal.

EGB 761 (100 mg/kg i.p, single injection 30 min pre-treatment) on cerebral energy metabolism in rats exposed to hypobaric or hypoxic hypoxia. Animals treated with EGB 761 survived hypobaric hypoxia for a longer period of time than controls; they also retained higher cerebral glucose levels and exhibited a slower breakdown of high-energy phosphates relative to controls. In a second experiment, Karcher et al. (1984) pre-treated rats with an average daily oral dose of 200 mg/kg EGB 761 for 14 days prior to hypobaric hypoxia. In this case, the EGB 761-treated animals survived the hypoxia for a longer period of time; however, brain energy metabolism was not significantly affected.

Attella et al. (1989) studied the effects of EGB 761 on recovery from a penetrating brain injury in rats. Animals received 100 mg/kg per day i.p for 30 days, were trained on a delayed spatial alternation task and then subjected either to a sham operation or to bilateral frontal cortex lesions using aspiration. Sham-operated animals then received daily saline injections for 30 days while the frontal cortex lesioned animals received either daily saline injections or EGB 761 (100 mg/kg i.p) for 30 days post-op. Compared to the saline controls, EGB 761 was found to significantly reduce the behavioral deficits resulting from frontal cortex lesions, as indicated by measurements of delayed spatial alternation retention.

More recently, Rodriguez de Turco et al. (1993) have examined the effects of EGB 761 treatment (100 mg/kg per day, osophageally, for 14 days) on the neurochemical effects of electroconvulsive shock treatment (ECS) in rats. Sham control animals received identical treatment except that they received vehicle (6.6 ml/kg 5% ethanol) rather than EGB 761. ECS caused a rapid accumulation of free fatty acids and an increase in diacylglycerols in both the hippocampus and cerebral cortex. EGB 761 treatment reduced free fatty acid levels in the hippocampus and delayed the increase in diacylglycerol concentrations in the hippocampus and cerebral cortex. In addition, the size of the diacylglycerol increase was reduced in the hippocampus of EGB 761-treated rats and the rate of the decrease in diacylglycerol levels over time was increased. Seizures result in a remodelling of membrane phospholipids through the activation of the phospholipid degradative enzymes, phospholipases C (PLC) and A_2/A_1 (PLA_2/A_1), caus-

ing an accumulation of free fatty acids and diacylglycerol; EGB 761 treatment appears to reduce the extent and duration of this remodelling (Rodriguez de Turco et al., 1993).

Kleijnen and Knipschild (1992) reviewed 40 studies in which *Ginkgo biloba* was used to treat cerebral insufficiency in humans. The majority of these studies involved EGB 761; the remaining ones used another *Ginkgo biloba* extract containing 25% *Ginkgo*-flavone glycosides and 6% terpenoids. Of the 40 trials evaluated, Kleijnen and Knipschild found 8 that were, in their view, well designed and conducted. Common shortcomings in the other studies included small numbers of patients, lack of double-blind procedures, and poor measurement techniques. The authors concluded that, on the basis of the 8 well controlled studies, there is ample justification for further assessment of *Ginkgo biloba* extracts in relation to the treatment of cerebral insufficiency in humans.

Several studies have examined the effects of EGB 761 on behavioral recovery following unilateral deafferentation of the vestibular nerve (UVD). Since this recovery process, known as 'vestibular compensation', is associated with neuronal plasticity in the brainstem vestibular nuclei (VN), it also consititutes a form of central nervous system (CNS) plasticity (see Smith and Curthoys, 1989 for review). Ez-Zaher and Lacour (1989) and Lacour et al. (1991) reported that EGB 761 treatment (50 mg/kg per day i.p) for 30 days following UVD in cats resulted in an acceleration of postural and locomotor compensation, as well as an increase in the rate of recovery of spontaneous neuronal activity in the ipsilateral lateral vestibular nucleus. Immunohistochemical studies indicated that synaptic reoccupation of the ipsilateral VN also occurred more rapidly in EGB 761-treated animals. Denise and Bustany (1989) have reported similar results using rats. Using 50 mg/kg per day EGB 761 i.p for 10 weeks, compensation of both the postural symptoms and spontaneous ocular nystagmus developed more rapidly than in rats that did not receive EGB 761. Unfortunately, in both the Lacour et al. (1991) and Denise and Bustany (1989) studies, control animals did not receive any vehicle injections; therefore, these studies were inadequately controlled.

In an attempt to determine what component of the EGB 761 was responsible for the enhancement of the vestibular compensation process, Tighilet and Lacour (1995) compared the effects of EGB 761 with and without the terpene component, which contains PAF antagonists such as ginkgolide B. Tighilet and Lacour reported that administration of non-terpenic EGB 761 (25 mg/kg per day, i.p) for up to 40 days following UVD resulted in an acceleration of vestibular compensation which was comparable to the same dose of the standard EGB 761 extract. The authors concluded that the non-terpenic fraction of EGB 761, containing flavonol heterosides, is mainly responsible for the beneficial effects of EGB 761 on vestibular compensation. However, Maclennan et al. (1995) have reported that a single 25 mg/kg i.p injection of ginkgolide B, administered at the time of a UVD in guinea pigs, caused an acceleration of spontaneous nystagmus compensation relative to vehicle controls. Since the terpenic fraction of EGB 761 contains ginkgolides, including ginkgolide B, these results suggest, contrary to those of Tighilet and Lacour (1995), that the terpenic fraction of EGB 761 may have beneficial effects on at least some aspects of vestibular compensation. At present, the mechanism(s) by which EGB 761 accelerates vestibular compensation is/are unknown. Yabe et al. (1992) have reported that unilateral injection of EGB 761 into the guinea pig VN results in a labyrinthine syndrome which is the opposite to that produced by a UVD, suggesting that EGB 761 causes a neuronal hyperactivity in the ipsilateral VN. By contrast, in vitro electrophysiological studies suggest that both EGB 761 and ginkgolide B have a hyperpolarizing effect on VN neurons in guinea pig brainstem slices (Vidal et al., 1993.

Most of the *Ginkgo biloba* literature is consistent with the view that *Ginkgo biloba* extracts have the capacity to protect against the effects of neural damage (i.e. they have 'neuroprotective' properties). However, it is unclear to what extent these neuroprotective properties are a function of direct actions on CNS neurons (e.g. modulation of gluta-

mate release or excitatory amino acid receptors in the case of ECS or deafferentation) versus indirect effects on the CNS via modulation of blood flow (e.g. in the case of neuronal damage caused by hypoxia/ischemia). It is worth noting that, on a mg/kg basis, the effective doses of EGB 761 in animal studies are often at least ten times larger than those used in human studies (see Table 1); why this is the case is unclear. Although ginkgolide B and other potent PAF antagonists are known to have neuroprotective properties (see Braquet, 1987; Braquet et al., 1987, 1991; Feuerstein et al., 1990; Hosford and Braquet, 1990; Koltai et al., 1994; Lindsberg et al., 1991; Prescott et al., 1990; Shimizu et al., 1992; Venable et al., 1993; Ward et al., 1991 for reviews), it must be recognized that other components of *Ginkgo biloba*, such as the flavonoids (Brailowsky et al., 1993, 1995; Tighilet and Lacour, 1995) and bilobalide (Sancesario and Kreutzberg, 1986), have also been demonstrated to possess such properties, and therefore may contribute to the beneficial effects.

5. Ginkgolides and other PAF antagonists as neuroprotectants

PAF is an alkylphospholipid produced by a variety of cells, including basophils, neutrophils, monocytes, platelets and endothelial cells. It is one of the most potent lipid mediators known, producing effects at concentrations as low as 10^{-14} M (see Snyder, 1990 for review). The term 'platelet-activating factor' was introduced by Benveniste et al. (1972) when they discovered a soluble substance, released from immunoglobulin E-stimulated basophils, that could aggregate platelets. Later, Muirhead et al. (1980) identified a similar factor in the renal medulla that lowered blood pressure, which they called 'antihypertensive polar renal lipid' (APRL). By 1979, three independent groups had determined that PAF and APRL were in fact identical and the chemical structure of what was to become known as 'PAF' was described. However, because PAF is widespread throughout the body, its name is really inappropriate (see Snyder, 1990 for review).

Specific PAF receptors have been identified in the CNS, localized both to synaptic endings and to intracellular membranes (Marcheselli et al., 1990b). PAF concentrations are known to increase in the brain during trauma (Kumar et al., 1988), which results in an increase in free intracellular Ca^{2+} concentrations (Kornecki and Ehrlich, 1988, 1991).

PAF appears to augment neurotransmission involving excitatory amino acids (Clark et al., 1990). In one of the few electrophysiological studies of PAF, Clark et al. (1992) examined the effect of a PAF analogue on excitatory synaptic transmission in cultured hippocampal neurons. PAF was found to enhance glutamatergic excitatory synaptic transmission and increase the frequency of spontaneous miniature excitatory synaptic events without affecting their amplitude or duration; these effects were blocked by a PAF receptor antagonist. PAF had no effect on GABA-mediated inhibition. Clark et al. (1992) concluded that PAF enhances excitatory synaptic transmission in the hippocampus by activating presynaptic PAF receptors, although the precise details of its mechanism of action remain to be elucidated. Consistent with this evidence, Del Cerro and Lynch (1990) have reported that a PAF antagonist prevented the development of stable long-term potentiation (LTP) in hippocampal slices (see Bliss and Collingridge, 1993 for review). More recently, Wieraszko et al. (1993) have reported that PAF can induce LTP in the hippocampal slice and that this effect can be blocked by either PAF antagonists or *N*-methyl-D-aspartate (NMDA) receptor antagonists.

Clark et al. (1992) have speculated that PAF may amplify excitotoxicity produced by excessive glutamate release during neuronal injury. Consistent with this view, PAF antagonists have been shown to reduce the activation of immediate early gene proteins such as *c fos* and *c jun* which are induced in the brain following trauma, even in the case of a single seizure (Squinto et al., 1989; Marcheselli et al., 1990a; Marcheselli et al., 1991; see Bazan et al., 1991 for a review).

Numerous studies have shown that PAF antagonists, including ginkgolide B, protect against neuronal damage following trauma (Kornecki and

Ehrlich, 1988). Ginkgolide B (BN52021) has been demonstrated to reduce the accumulation of free polyunsaturated fatty acid during ischemia and electroconvulsive shock in the mouse (Birkle et al., 1988). Consistent with this finding, Panetta et al. (1987) reported that ginkgolide B reduced free fatty acid levels and increased blood flow in the gerbil brain following ischemia-reperfusion-induced injury. Gilboe et al. (1991) have reported that other PAF antagonists also enhance the recovery of cerebral metabolic and electrophysiological activity following ischemia in dogs. Furthermore, Bielenberg et al. (1992) have reported that a PAF antagonist reduces the infarct volume in rats following occlusion of the left middle cerebral artery.

The exact mechanisms by which PAF antagonists produce their neuroprotectant effects are unclear at present. PAF appears to have little effect on cerebral blood flow or metabolism under normal circumstances (Kochanek et al., 1990). One possibility is that following trauma, the increase in brain concentrations of PAF results in the modulation of neurotransmitters/neuromodulators and their receptors. There is evidence for an interaction between PAF and several neurotransmitter/neuromodulator systems. For example, Sogos et al. (1990) have reported that, in cultured human fetal brain cells, PAF production is stimulated by acetylcholine and reduced by the acetylcholine receptor antagonist, atropine. Takehara et al. (1990) have shown that the specific PAF receptor antagonist, Y-24180, binds with low affinity to benzodiazepine receptors in synaptosomal membranes in the rat cerebral cortex. It has also been reported that PAF causes a decrease in adrenocorticotrophic hormone (ACTH) concentrations in the anterior lobe of the pituitary gland (Blasquez et al., 1990). Since short ACTH fragments have been shown to protect against neural damage (see van Rijzingen et al. (in press) for review), it is possible that PAF antagonists exert their neuroprotective effects indirectly by increasing available short ACTH fragments (Maclennan et al., 1995). However, it is also likely that PAF antagonists have direct neuroprotective actions. For example, Faden and Tzendzalian (1992) have reported that PAF antagonists reduced glycine levels following fluid percussion-induced traumatic brain injury in rats. Braquet (1987) has proposed that one way in which PAF antagonists reduce neuronal damage is by reducing PAF-induced increases in intracellular Ca^{2+} which cause phospholipase C-induced mobilization of Ca^{2+} from its internal pools. PAF antagonists are also likely to protect against neural damage by reducing the activation of protein kinase C via Ca^{2+}/diacylglycerol (Braquet, 1987) and by reducing excitatory amino acid receptor function (Clark et al., 1990, 1992; see Lindsberg et al., 1991 for review).

6. Conclusions

Research on the biochemical effects of *Ginkgo biloba* extracts is still at a very early stage. However, there is sufficient experimental evidence to support the view that such extracts do have neuroprotective properties under conditions such as hypoxia/ischemia, seizure activity and peripheral nerve damage. Further studies on other kinds of neural damage are clearly merited. The fact that one of the components of *Ginkgo biloba*, ginkgolide B, is a potent PAF antagonist makes it tempting to speculate that *Ginkgo biloba*'s neuroprotective properties are due mainly to the terpene fraction that contains this ginkgolide. Indeed, Bazan, Braquet and colleagues have demonstrated that such PAF antagonists have impressive neuroprotective properties; however, it would be premature at this stage to conclude that the flavonoids were less important, given the known neuroprotective action of free radical scavengers (Tighilet and Lacour, 1995). The sesquiterpene, bilobalide, also has neuroprotective properties (Sancesario and Kreutzberg, 1986). We believe that both the flavonoid and terpene fractions of *Ginkgo biloba* are worthy of further investigation in the context of neuroprotective pharmacology.

Note added in proof

Further evidence for the utility of EGB 761 in

the treatment of Senile Dementia of the Alzheimer's Type has been reported by Hofferberth, B. (1994) The efficacy of EGB 761 in patients with Senile Dementia of the Alzheimer Type, a double-blind, placebo-controlled study on different levels of investigation. *Human Psychopharmacology*, 9, 215–222.

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