

GINKGOSELECT PHYTOSOME®

BIOAVAILABLE STANDARDIZED EXTRACT
OF *GINKGO BILOBA* LEAVES





G*inkgo biloba* L. of the Ginkgoaceae family, is a dioecious tree up to 30 m tall, which is believed to be native to China. The leaves are deciduous, alternate or in clusters of 3-5 on short twigs, petiolated, fan-shaped and bilobed. The fleshy, yellow, foul-smelling seed contains a nut with an edible, sweet kernel. The origin of the genus *Ginkgo* dates back to about 200 million years ago; *G. biloba* is the only existing representative of the entire Ginkgophyta division.^{1,4} This beautiful tree has a very long life span and it is highly resistant to insects, bacterial and viral infections, and pollution. A specimen of ginkgo survived the atomic bombing of Hiroshima. In China and in Japan it is held sacred and is cultivated in temple gardens. *G. biloba* was introduced into Europe around 1730 and is now cultivated for ornamental purposes in streets and parks.^{3,4}

The seed and leaf of *G. biloba* are endowed with medicinal properties. This tree is actually cultivated as medicinal plant in China, Korea, France, Germany and the United States. In the traditional Chinese medicine ginkgo seeds are prescribed as a remedy against asthma, cough, bladder inflammation, blenorrhagia, leukorrhea and alcohol abuse.

Ginkgo leaves are used for treating cardiovascular and lung disorders.⁵ In Europe only leaf extracts are used for medicinal purposes.

The major therapeutic indications for the standardized extract of *G. biloba* leaves (GBE; according to German Commission E Monographs*), occurring in many medicinal proprietary products, concern cerebral insufficiency and peripheral vascular disorders.⁴ The term "cerebral insufficiency" indicates a collection of symptoms concerning the cerebral functions, such as impairment of recent memory, confusion, change in social behavior, lack of initiative, affective and somatic troubles.

These symptoms can be associated with impaired cerebral circulation and ageing. They are considered early signs of senile dementia both of the degenerative type (Alzheimer's disease - AD) and vascular origin (multi-infarct dementia - MID). Since 1986 the standardized extract of *G. biloba* leaves has been used for the treatment of slight to moderate forms of senile dementia (AD or MID).^{4,6} AD represents about 50-60% of the cases of senile dementia, MID about 15-20% of cases. The incidence of this senile disease is related to the increase in the number of elderly people.⁷

* 22-27% *ginkgo flavanol glycosides*, 5-7% *terpene trilactones*, less 5 ppm *ginkgolic acids*

Today the standardized extract of the leaves of *G. biloba* (120-240 mg, p.o., daily) is considered a drug of choice for the treatment of senile dementia. Some significant and reliable clinical trials have recently been performed, in which the efficacy and the tolerability of this extract have been confirmed.^{8,9}

Different mechanisms of action, such as antioxidant activity, platelet-activating factor (PAF)-antagonism and modulation of neurotransmitters, seem to underlie the pharmacological activity of the extract.

This is due to the fact the extract contains several active substances, such as ginkgo flavanol glycosides and terpene trilactones that can act singly or in combination. The pharmacokinetic studies carried out on healthy volunteers have shown that the extract has a low bioavailability, in particular regarding the flavonoidic components.

Terpene trilactones are better absorbed, even though in an incomplete fraction.³

To increase the bioavailability of GBE a complex with soy phospholipids has been prepared (GINKGOSELECT PHYTOSOME®). It is known that the complexation with phospholipids may improve the oral bioavailability of some natural compound.¹⁰

GINKGOSELECT PHYTOSOME®

GINKGOSELECT PHYTOSOME®
is obtained by reacting a
stoichiometric amount of soy
phospholipids with the GBE
(US 5,043,323).



PHARMACOLOGICAL AND PHARMACOKINETIC STUDIES

Experimental investigations, concerning the antioxidant and anti-bronchospastic activities, as well as two studies of the pharmacokinetics have been performed in order to investigate whether the complexation with phospholipids, by increasing the bioavailability of GBE, could improve its pharmacological activity.

It is reported that the flavonoidic components of the extract are responsible for the antioxidant activity, whereas the terpene trilactones, being strong PAF-antagonists, are inhibitors of induced bronchoconstriction.³

Antioxidant activity

The antioxidant activity has been investigated according to the experimental protocol reported in Table 1.¹¹

GINKGOSELECT PHYTOSOME® induced a more marked increase in the

total plasma and brain antioxidant capacity in rats, in comparison with GBE (Fig. 1, 2).

The complex also proved to be more effective than the uncomplexed extract in protecting rat isolated heart against

ischemia/reperfusion damages (Fig. 3). The recovery of the heart activity expressed as left ventricular developed pressure, was 76% in GINKGOSELECT PHYTOSOME® and 52% in GBE treated animals.

Table 1 Antioxidant activity of GBE and GINKGOSELECT PHYTOSOME®.

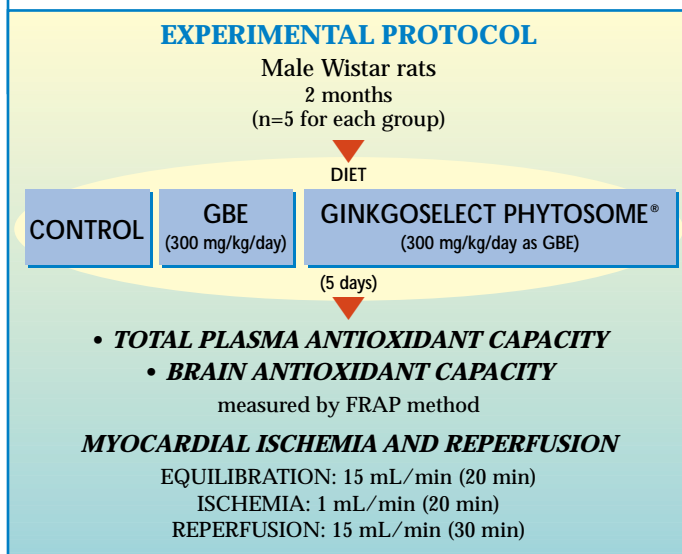


Fig. 1 Total plasma antioxidant capacity in rats.

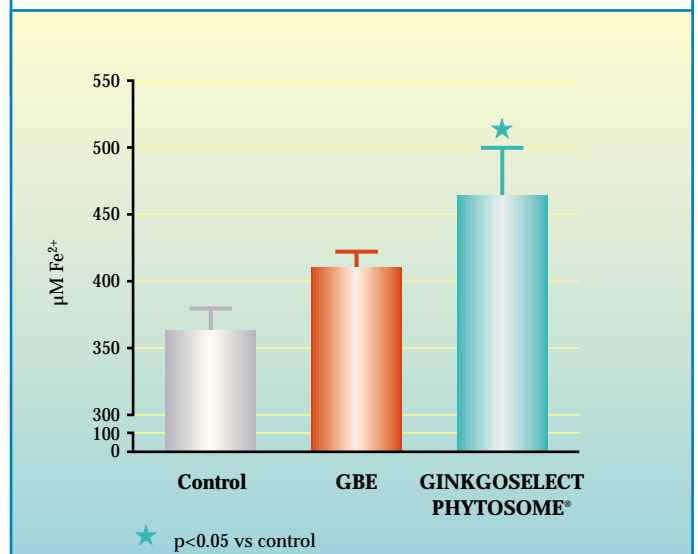


Fig. 2 Total brain antioxidant capacity in rats.

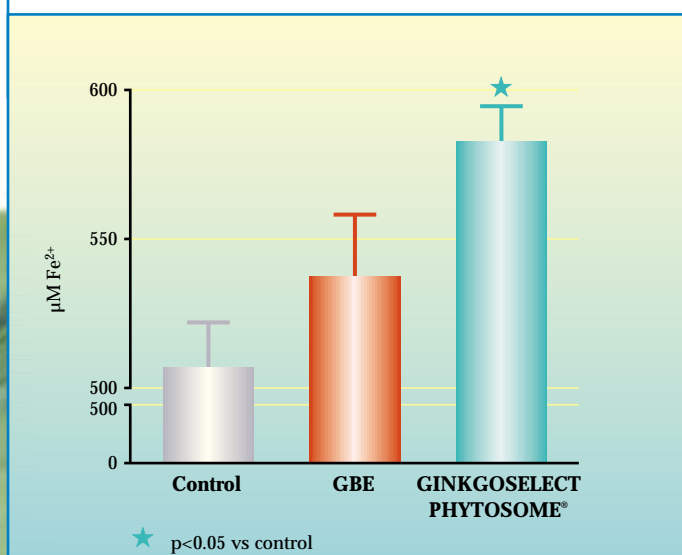
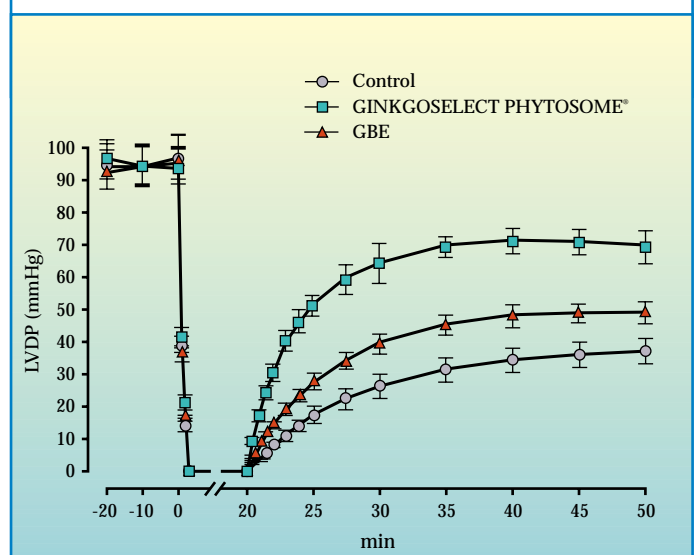


Fig. 3 Left ventricular developed pressure (LVDP) in rat isolated hearts.



Anti-bronchospastic activity

GINKGOSELECT PHYTOSOME® showed a more marked protective activity against histamine-induced bronchoconstriction in guinea pigs, when compared with GBE.

The two compounds significantly reduced the intratracheal pressure by 81% and 38% respectively. Comparable reductions of the release of thromboxane in blood were also observed (Fig. 4).

Similar interesting results have been obtained in another model of bronchoconstriction, ovalbumin-sensitized guinea pigs test (Fig. 5).¹²

Fig. 4 Effect of GBE and GINKGOSELECT PHYTOSOME® on histamine-induced bronchoconstriction in guinea pigs.

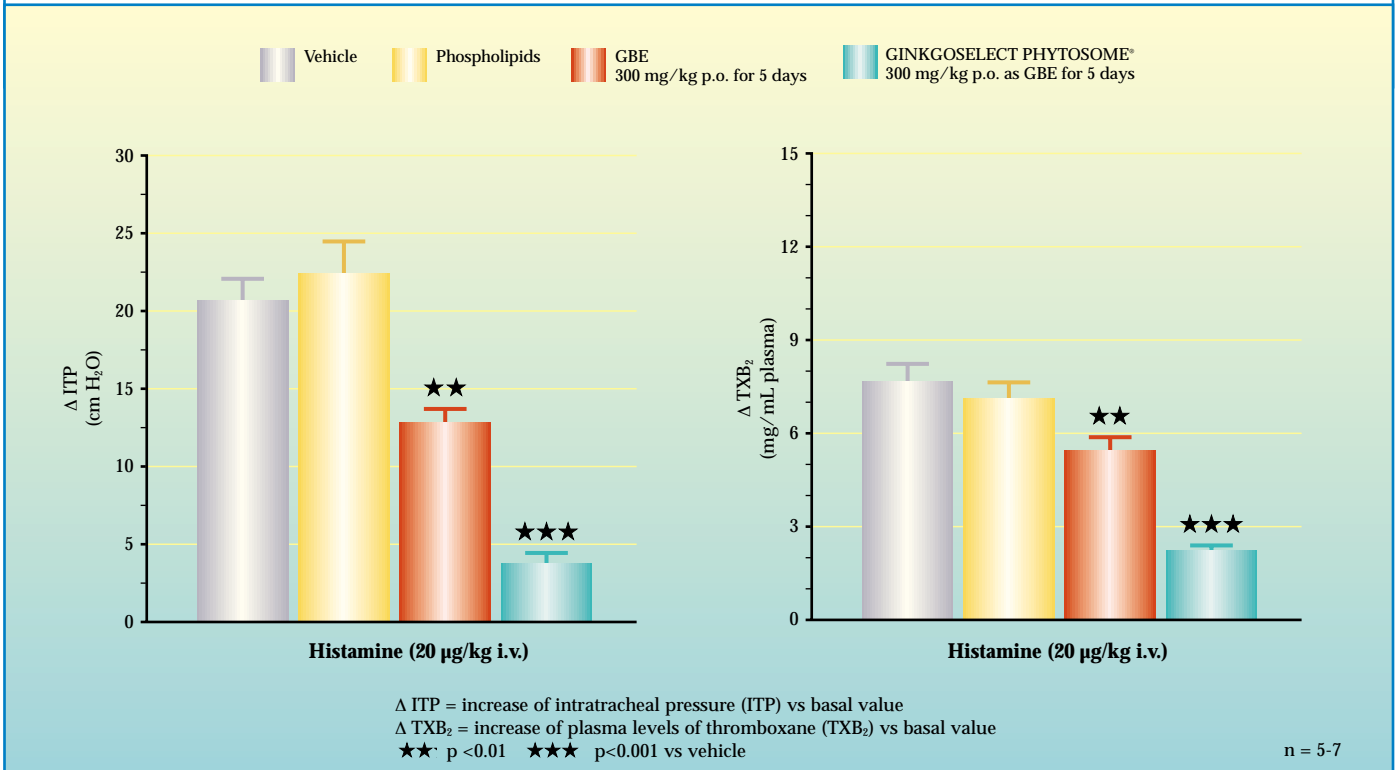
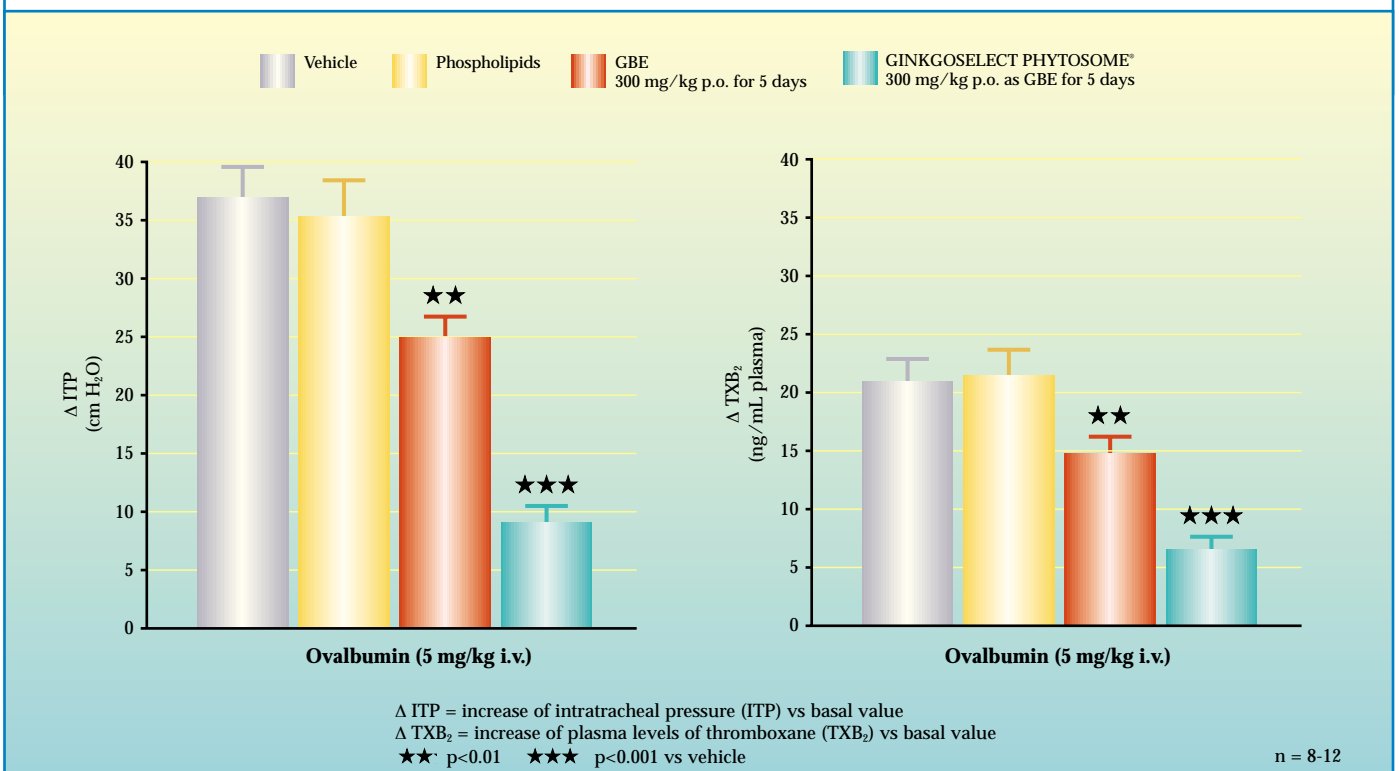


Fig. 5 Effect of GBE and GINKGOSELECT PHYTOSOME® on ovalbumin-sensitized guinea pigs.



Pharmacokinetic data

A more marked urinary excretion of phenolic metabolites, degradation products of flavonoids, was found in human healthy volunteers after administration of GINKGOSELECT

PHYTOSOME[®] than after administration of GBE (Fig. 6).¹³ This finding confirms that the complexation with phospholipids improves the bioavailability of the flavonoidic components of the extract.

In a second study on human healthy volunteers the plasma levels of total ginkgolides (A and B) and bilobalide were markedly increased after intake of GINKGOSELECT PHYTOSOME[®] (Fig. 7).¹⁴

Fig. 6 Urinary excretion (24 hours) of 3,4-dihydroxybenzoic acid (DHBA) in healthy volunteers.

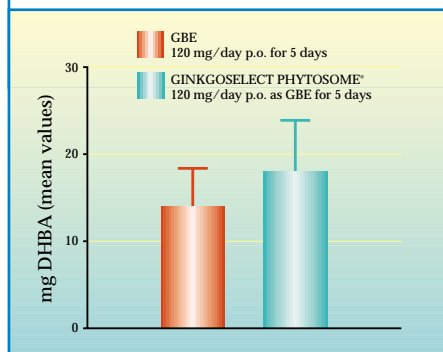
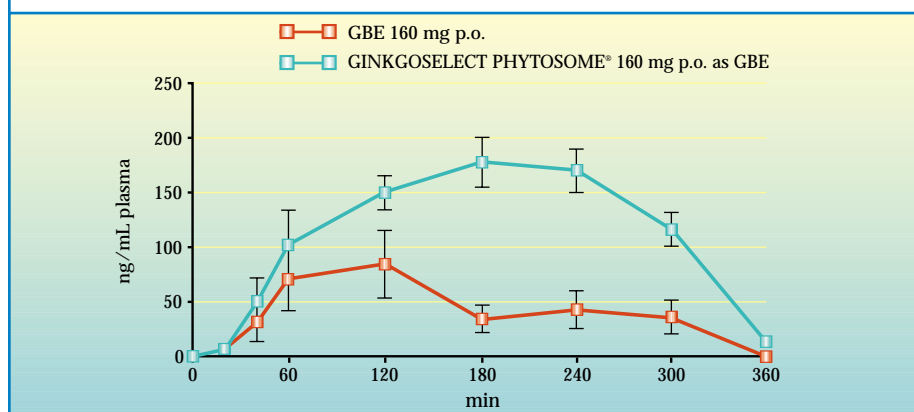


Fig. 7 Plasma levels (LC-MS) of total ginkgolides (A and B) and bilobalide in healthy volunteers.



TOXICOLOGICAL INVESTIGATIONS

In a 30-day sub-chronic toxicity study in rats, GINKGOSELECT PHYTOSOME[®] orally administered at the daily dose of 3.5 g/kg, proved to be well tolerated. No mortality or toxic effects that could be attributed to the treatment were observed.¹⁵ Moreover, in the template test in rats, the complex, as well as GBE, did not induce significant changes in the bleeding time (Table 2).¹⁶

Table 2 Effect of GBE and GINKGOSELECT PHYTOSOME[®] on bleeding time (template test) in rats.

| GBE | | GINKGOSELECT PHYTOSOME [®] | |
|-------------------|---------------------------|-------------------------------------|---------------------------|
| Dose (mg/kg) p.o. | Time (sec) | Dose (mg/kg) p.o. | Time (sec) |
| Control | 107.5 ± 6.4 | Control | 118.0 ± 7.7 |
| 50 | 107.0 ± 4.4 (- 0.5%) | 50 * | 129.5 ± 15.6 (+ 9.7%) |
| 100 | 127.0 ± 11.0 (+ 18.0%) | 100 * | 136.5 ± 9.3 (+ 16.0%) |
| 150 | 124.5 ± 8.0 (+16.0%) | 150 * | 141.5 ± 15.1 (+ 19.0%) |
| 300 | 116.5 ± 3.3 (+ 8.4%) | 300 * | 125.0 ± 11.3 (+ 5.8%) |

* mg/kg p.o. as GBE

CONCLUSIVE REMARKS

The results of the pharmacological and pharmacokinetic studies indicate that under the experimental conditions adopted:

- GINKGOSELECT PHYTOSOME[®], is endowed with superior and more constant pharmacological activity in comparison with GBE
- the complexation of GBE with phospholipids enhances the absorption of the flavonoidic components as well as the bioavailability of terpene trilactones
- the complex is well tolerated and does not influence the bleeding time in rats

It has been reported that superoxide radicals and PAF are involved in the mechanism of the brain ischemia and related neuronal damages, associated with ageing and senile dementia.

GINKGOSELECT PHYTOSOME[®], an easily absorbable form of the standardized extract of *G. biloba* leaves, constitutes an appropriate aid in situations of reduced cerebral performance. Moreover, due to its better bioavailability, this compound is suitable for long term treatments, in which a lower dosage is advisable.

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