

A patented* Ginkgo biloba
Phospholipid Complex

.....
Phytosome[®] improved
bioavailability

.....
Developed to ameliorate
cerebral functions and
peripherals vascular
disorders

.....
Clinical and
pharmacological data
support its efficacy

.....
A safe product, devoid of
any side effect



Ginkgoselect[®]
Phytosome[®]

Ginkgo biloba leaves

■ Although the medicinal properties of *Ginkgo biloba* L. have been known in China since the most ancient times, a systematic pharmacological and clinical study of this plant only began in Europe in the last decades.¹

Often defined as a “**living fossil**”, the *Ginkgo biloba* tree is the only survivor of a genus originated 150 millions years ago. It derives its name from a wrong transcription of the Japanese Yin-Kwo, meaning “silver fruit”.

In an extensive review by DeFeudis² in 1991, the activity of *Ginkgo biloba* is described as “**polyvalent**”, as its pharmacological action is due to the combined activity of several actives.

The major therapeutic indications for the standardized *Ginkgo biloba* leaves extract concern **cerebral insufficiency** and **peripheral vascular disorders**.¹ The term “cerebral insufficiency” indicates a collection of symptoms concerning the cerebral functions, such as impairment of short term memory, confusion, change in social behavior, lack of initiative, affective and somatic troubles. These symptoms may be associated with impaired cerebral circulation and ageing. Considered as early signs of senile dementia both of degenerative type and vascular origin, the symptoms are treated with *Ginkgo biloba* extract (**GBE**) which is considered a **drug of choice** in the growing area of senile dementia.

A natural cognition enhancer

The cognition enhancing properties of the plant are attributed to the **flavonoids** fraction which are responsible for:

- ◇ enhancement of the release of catecholamines and other neurotransmitters
 - ◇ inhibition of biogenic amine intake
 - ◇ inhibition of catechol-O-methyl transferase and MAO
- The unique **terpenoids ginkgolides** and **bilobalide** exert vaso- and tissue-protective activity as:
- ◇ relaxation of blood vessels in spastic conditions
 - ◇ contraction increasing the tone of abnormally relaxed vessels
 - ◇ protection against increase in capillary permeability
 - ◇ inhibition of platelet aggregation
 - ◇ anti-ischemic and anti-oedema properties

The content of GBE

- ≥ 24% of ginkgoflavonglucosides
- ≥ 6% of ginkgolides and bilobalide
- ≤ 5 ppm of ginkgoic acids

To further improve its bioavailability, GBE has been **complexed** with soy phospholipids (1:2 w/w), thus obtaining **Ginkgoselect[®] Phytosome[®]**.

Pharmacokinetic data on human volunteers support the bioavailability improvement in Ginkgoselect[®] Phytosome[®], while its activity is supported by **clinical trials**,^{3,4} with **pharmacokinetic**^{5,6} and **pharmacological data**.^{1,7}

Clinical studies

Ginkgo biloba extract is reputed to be potent in circulatory and other disorders. Because of the interest in its use, a number of clinical trials have been carried out evaluating cognitive functions, such as memory disturbances and dementia, and classical disorders of the circulation such as intermittent claudication.

Within vascular disorders, the Raynaud's disease is a common and painful condition characterized by episodic digital ischemia produced by emotion and cold. Clinically it manifests as blanching caused by artery vasospasm, cyanosis as the remaining blood becomes deoxygenated, and rubor by the reactive hypercirculation following the ischemia.⁸ The treatment of the Raynaud's disease by vasodilator drugs is notoriously difficult because of the high incidence of side effects; it is a common disease and is estimated to afflict 10-20% of young women.⁹

The efficacy of Ginkgoselect® Phytosome® in the treatment of the Raynaud's disease was verified in a double-blind, placebo-controlled trial.³ It was proven **effective in improving vascular disorders and in counteracting the symptoms of digital ischemia.**

This initial study is of interest as it shows a highly statistically significant reduction of the number of attacks of Raynaud's disease per day due to the improvement of peripheral circulation. A similar mechanism of action may be associated with the **cognition enhancing activity** of Ginkgoselect® Phytosome®.

■ *improvement of the vascular disorders associated to the Raynaud's disease*³

Ginkgoselect® Phytosome® was administered at a dosage of 360 mg/day (120 mg three times per day) to 22 subjects affected by the Raynaud's disease in a double-blind, placebo-controlled trial.

Patients were required to record the frequency and duration of any vasospastic attack, also completing a scoring scale of the overall perception of the severity of the episodes.

Patients were reviewed after two, four and ten weeks of treatment.

This pilot study showed the efficacy of Ginkgoselect® Phytosome® in promoting a clear and highly statistically significant reduction in the frequency (56%) and severity of Raynaud's attacks per day (chart 1, table 1).

The free radical scavenging properties and antiplatelet effects of Ginkgoselect® Phytosome® contribute to improve peripheral circulation disorders

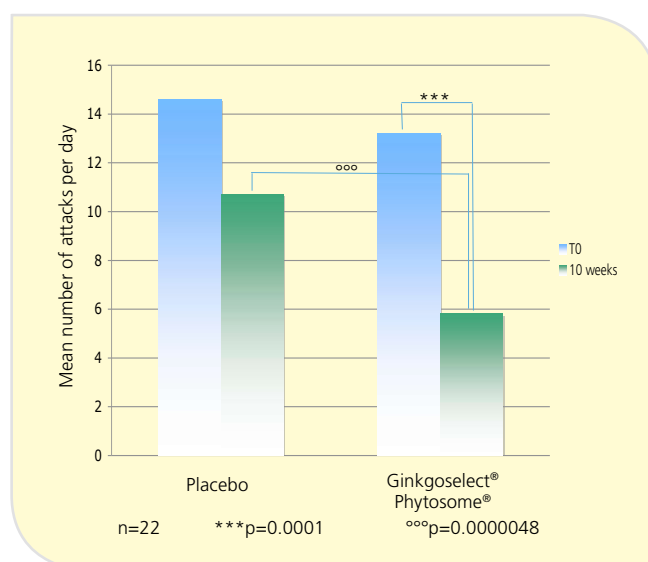


Chart 1: effect of Ginkgoselect® Phytosome® on mean number of attacks of Raynaud's disease per week

	Placebo		Ginkgoselect® Phytosome®	
	T0	10 weeks	T0	10 weeks
Median number of attacks/week [range]	13 [1-30]	9 [0-38]	8 [3-63]	4 [0-32]
Mean duration of attacks	28.0 min	17.0 min	27.8 min	10.3 min
Reduction in severity scores	11%		25%	

Table 1: effect of Ginkgoselect® Phytosome® on median number, duration and severity of attacks of Raynaud's disease per week

■ *improvement of the vascular disorders associated to the Raynaud's phenomenon*⁴

Twelve patients with Raynaud's phenomenon received 180 mg of Ginkgoselect® Phytosome® daily for 6 days. After a 5 days washout period, they received 120 mg of GBE. Upon microscopic examination of nailbed, the Phytosome® preparation made visible capillary loops just under the skin that were not visible before, thus indicating an appreciable improvement of blood flow in capillary loops.



Pharmacokinetics

The pharmacokinetic profile of Ginkgoselect® Phytosome® has been defined in experimental animals and in human volunteers. Its bioavailability has been compared to GBE.

■ *increase in plasma levels of total ginkgolides (A and B) and bilobalide in healthy volunteers*⁵

Fifteen healthy volunteers were randomly divided into two groups and administered respectively 160 mg of free formulation of GBE (corresponding to 9.6 mg of terpene lactone) and 160 mg of Ginkgoselect® Phytosome® (corresponding to the same amount of terpene lactone). The subjects switched formulations after a week of wash out. Blood samples were collected at 30, 60, 120, 180, 240, 300 and 400 min after ingestion. Terpene lactone detection was performed by means of liquid chromatography/atmospheric pressure chemical ionization mass spectrometry (LC/APCI-ITMS).

Ginkgolides A, B and bilobalide were absorbed to a higher extent (about threefold) after administration of Ginkgoselect® Phytosome®. As an example, chart 2 reports plasma concentrations of ginkgolide A which, according to AUC, shows a 3.5 folds higher absorption of the Ginkgoselect® Phytosome®.

■ *improvement of DHBA urinary excretion in healthy volunteers*⁶

Ginkgoselect® Phytosome® (120 mg/day as GBE) or GBE were administered for 5 days to 6 healthy volunteers in a cross-over study. Urine samples were collected and analyzed twice daily and metabolite 3,4-dihydrobenzoic acid (DHBA) was determined by HPLC. Volunteers were asked to refrain from consuming flavonoids-rich foods for the duration of the study.

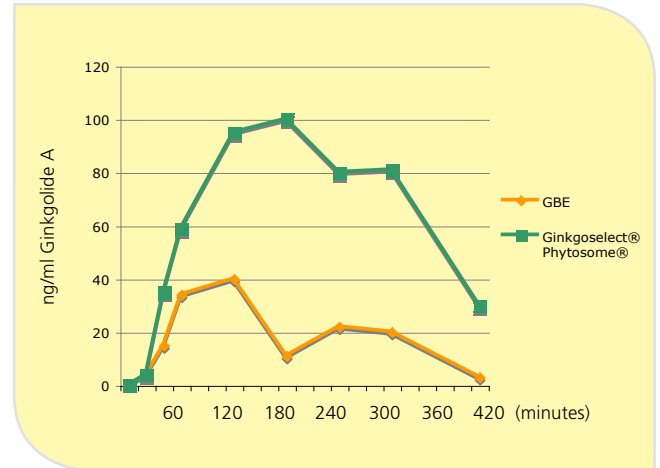


Chart 2: plasma concentrations of ginkgolide A in healthy volunteers

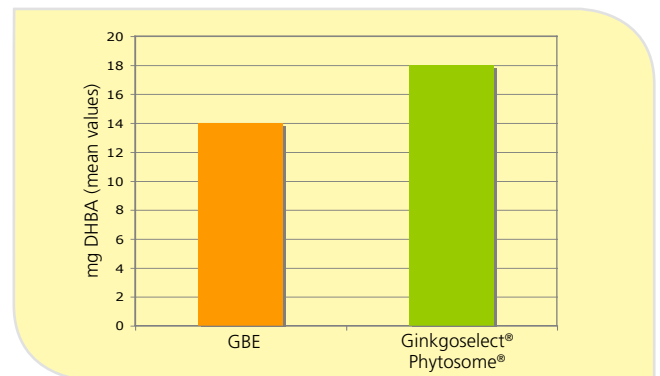


Chart 3: urinary excretion of metabolite DHBA in healthy volunteers

Pharmacology

The pharmacological profile of Ginkgoselect® Phytosome® has been defined by extensive *in vitro* and *in vivo* experimental studies. It is reported that the flavonoidic components of the extract are responsible for the antioxidant activity,⁸ whereas the terpene lactones, being strong PAF-antagonists, are inhibitors of induced bronchoconstriction,⁹ thus suggesting possible anti-asthma applications.

• *antioxidant activity*⁷

GBE and Ginkgoselect® Phytosome® demonstrated their effective antioxidant capacity by increasing total plasma and brain antioxidant capacity in rats, according to the experimental protocol described below. Ginkgoselect® Phytosome®, though, induced a higher antioxidant protection compared to GBE.

GBE and Ginkgoselect® Phytosome® have been administered to a group of 5 rats respectively (plus a control group) at 300 mg/kg/day (and 300 mg/kg/day as GBE for the complexed form). The total plasma antioxidant capacity and the brain antioxidant capacity have been measured by FRAP method.

Ginkgoselect® Phytosome® total plasma antioxidant capacity in rats resulted 27.9% higher compared to GBE (chart 4).

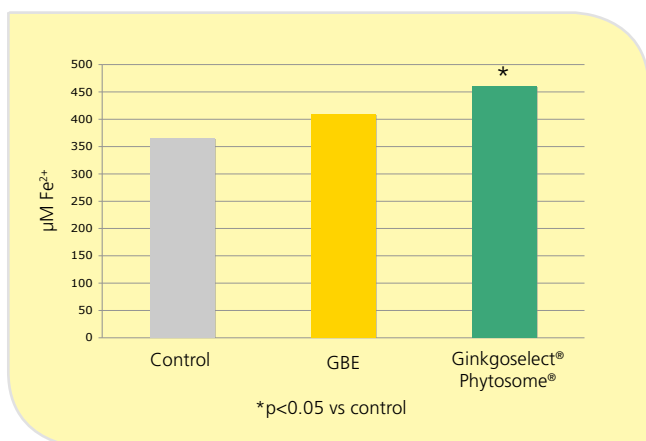


Chart 4: total plasma antioxidant capacity in rats (FRAP: ferric reducing ability of plasma)

- antibronchospastic activity⁹

Ginkgoselect® Phytosome®, administered at 300 mg/kg/die (as GBE) for 5 days in guinea pigs, was proven to prevent bronchoconstriction induced by three different agonists (histamine, PAF and acetylcholine). The bronchospastic inhibition was measured at the maximum peak, expressed as variation versus the basal values (cmH₂O as intra-tracheal pressure) (chart 5).

The results obtained indicate that Ginkgoselect® Phytosome® can not only counteract direct bronchoconstriction, but also it may reduce the TXA₂ mediated bronchoconstriction of histamine and PAF, thus suggesting a possible indication in allergen induced bronchospasm.

GBE and Ginkgoselect® Phytosome® also proved their efficacy in protecting rat isolated hearts against ischemia/reperfusion damages. The recovery of the heart activity expressed as left ventricular developed pressure was 76% in Ginkgoselect® Phytosome® and 52% in GBE treated animals.⁷

Ginkgoselect® Phytosome® has free radical scavenging potential that has shown to contribute to promote cardiovascular protection

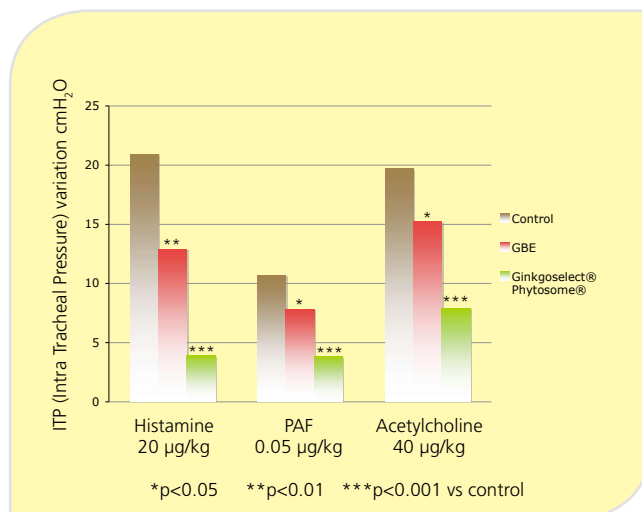


Chart 5: effect of Ginkgoselect® Phytosome® on induced bronchospastic activity in guinea pigs

Toxicology

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.¹⁰ Moreover, in the template test in rats, the complex (Ginkgoselect® Phytosome®), as well as GBE, did not induce significant changes in the bleeding time¹¹ (table 2).

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	50	129.5 ± 15.6
100	127.0 ± 11.0	100	136.5 ± 9.3
150	124.5 ± 8.0	150	141.5 ± 15.1
300	116.5 ± 3.3	300	125.0 ± 11.3

Table 2: effect of GBE and Ginkgoselect® Phytosome® on bleeding time (template test) in rats

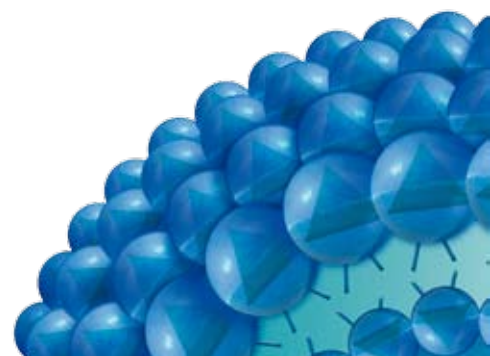
Conclusive remarks

Ginkgoselect® Phytosome® was proven able to be effective in the treatment of disorders of **cerebral function** and **peripheral vascular insufficiency**. The complexation of GBE in the phospholipid complex (Ginkgoselect® Phytosome®) resulted successful in improving the bioavailability of the actives, thus improving the efficacy of the ingredient.

Terpene lactones as ginkgolides and bilobalide and flavonoids are responsible for the biological action of Ginkgoselect® Phytosome®.

References

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