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EGb 761
Ginkgo biloba extract, Ginkor

Abstract

EGb 761 [*Ginkgo biloba extract EGb 761, Rökan®, Tanakan®, Tebonin®*] is a standardised extract of *Ginkgo biloba* leaves and has antioxidant properties as a free radical scavenger.[1]

A standardised extract of *Ginkgo biloba* leaves is a well defined product and contains approximately 24% flavone glycosides (primarily quercetin, kaempferol and isorhamnetin) and 6% terpene lactones (2.8-3.4% ginkgolides A, B and C, and 2.6-3.2% bilobalide).

Ginkgolide B and bilobalide account for about 0.8% and 3% of the total extract, respectively. Other constituents include proanthocyanadins, glucose, rhamnose, organic acids, D-glucaric and ginkgolic acids.

EGb 761 promotes vasodilation and improves blood flow through arteries, veins and capillaries. It inhibits platelet aggregation and prolongs bleeding time. EGb 761, which was originated by Dr Willmar Schwabe Pharmaceuticals (Dr Willmar Schwabe Group), has been available in Europe as a herbal extract since the early 1990s. However, products containing EGb 761 are not approved for use by the US FDA.

As a dietary supplement, Nature's Way in the US distributes and markets a standardised extract of *Ginkgo biloba* leaves (the EGb 761 Formula) under the name Gingold Nature's Way.

The French company Beaufour-Ipsen and its German subsidiary Ipsen Pharma are co-developing EGb 761 with Dr Willmar Schwabe Group. Beaufour-Ipsen (France) is developing EGb 761 as Tanakan®, Dr Willmar Schwabe Pharmaceuticals (Germany) as Tebonin® and Ipsen Pharma (Germany) as Rökan®. Intersan was formerly developing EGb 761 in Germany, but Intersan appears to have been merged into Ipsen Pharma. However, there has been no recent development for these indications.

In the UK and other European countries, the cardioprotective effects of EGb 761 in myocardial ischaemia and reperfusion are being investigated in preclinical studies.

The psychological and physiological benefits of ginkgo are said to be based on its primary action of regulating neurotransmitters and exerting neuroprotective effects in the brain, protecting against or retarding nerve cell degeneration. Ginkgo also benefits vascular microcirculation by improving blood flow in small vessels and has antioxidant activity.

There has been conflicting evidence about the benefits of ginkgo, e.g. the ginkgo clinical trial published in August 2002 in *JAMA* concluded that a leading ginkgo supplement did not produce measurable benefits for memory in healthy adults over 60, although a month earlier, another study concluded that the same

1 This profile has been selected from *R&D Insight*™, a pharmaceutical intelligence database produced by Adis International Ltd.

ginkgo extract is effective in helping normal healthy older adults in memory and concentration. However, in December 2002, the Cochrane Collaboration, the world's most respected scientific reviewer of clinical trials in medicine, concluded that the published literature strongly supports the safety and potential benefits of ginkgo in treating memory loss and cognitive disorders associated with age-related dementia.[1]

A phase II study of EGb 761 in combination with fluorouracil is in progress in Germany in patients with pancreatic cancer. German researchers are investigating the potential of EGb 761 for the treatment of sudden deafness and tinnitus in clinical studies.

EGb 761 was undergoing preclinical development for the potential treatment of diabetes in France, diabetic neuropathies in Russia, and cancer in Brazil. However, there has been no recent development for these indications.

Beaufour-Ipsen has expressed the intention to license out its diabetes projects that may include EGb 761.

1. Profile

1.1 Adverse Events

In patients treated with EGb 761 240 mg/day PO for dementia, 7/205 discontinued treatment because of adverse events.[2]

In a double-blind study in which 309 patients were treated with EGb 761 120 mg/day or placebo for 12–52 weeks, the incidence, severity and nature of adverse events were similar in both treatment groups, with the exception of gastrointestinal side effects, which occurred slightly more often in the active treatment group.[3]

1.2 Pharmacodynamics

1.2.1 Alzheimer's Disease and Cognition Disorders

EGb 761 protects neuronal cell membranes from free radical damage *in vitro*. It has been suggested that this effect may mediate the drug's beneficial effects on cognitive function, since the presence of free radicals may reduce neuronal membrane fluidity, which in turn may be a major mechanism of age-related functional decline. However, although 3 weeks' treatment with EGb 761 (100 mg/kg) significantly improved short-term memory and neuronal membrane fluidity in aged female NMRI mice, there was no significant correlation between the two parameters.[4]

Studies in mice and rats showed that EGb 761's neuroprotective effects, including its therapeutic effects on cognitive impairment, may be a result of its actions on modifying gene expression. For example, EGb 761 or one of its many constituents was shown to inhibit the expression of the peripheral benzodiazepine receptor in the adrenal cortex and decrease circulating levels of corticosterone in the rat (anti-stress effects), decrease the expression of inducible nitric oxide synthase (iNOS) and upregulate several genes that encode vital antioxidant enzymes.[5]

1.2.2 Arrhythmias

The incidence of reperfusion-induced ventricular fibrillation (VF) and ventricular tachycardia (VT) was dose-dependently reduced in the hearts of rats treated for 10 days with EGb 761 (25–200 mg/kg/day). EGb 761 ± superoxide dismutase and superoxide dismutase + catalase significantly decreased the incidence of VF and VT, but monotherapy with either superoxide dismutase or catalase was ineffective. The formation of free radicals was abolished by EGb 761 but was maintained by superoxide dismutase and catalase.[6]

Table I. Features and properties

WHO ATC code	C04A (Peripheral Vasodilators) B01A-C (Platelet Aggregation Inhibitors excl. Heparin) S02D (Other Otologicals) C01E-B (Other cardiac preparations) A10B (Oral Blood Glucose Lowering Drugs) G04B-E (Drugs used in erectile dysfunction) N07X (Other Nervous System Drugs) L01 (Antineoplastic Agents)
EphMRA ATC code	C1X (All Other Cardiac Preparations) S2D (Other Otologicals) C4A (Cerebral and Peripheral Vasotherapeutics) G4B3 (Erectile dysfunction products) B1C (Platelet Aggregation Inhibitors) N7D9 (All other anti-Alzheimer products) A10B (Oral Antidiabetics) N6D (Nootropics) L1 (Cytostatics)
Originator	Dr Willmar Schwabe Pharmaceuticals, Germany
Licensee companies	Beaufour-Ipsen: Brazil, France, Germany, Mexico, United Kingdom, USA; Ipsen Pharma: Germany
Highest development phase	Phase Clinical (Germany)
Properties	
Mechanism of action	Platelet-activating factor antagonists
Pharmacodynamics	Antioxidant effects; antiarrhythmic effects; inhibited neoplastic cell growth; memory-enhancing effects; inhibits platelet aggregation
Route	Unknown route
Adverse events	Occasional gastric disorders
Adis rating	Alzheimer's disease, PO: 54 Peripheral arterial occlusive disorders, IV: 56 Peripheral arterial occlusive disorders, PO: 66

1.2.3 Cancer

Preclinical studies: the influence of EGb 761 on the growth of normal cells compared with epidermal carcinoma cells (Hep-2) derived from the human larynx was investigated using ^{3}H-thymidine DNA incorporation. EGb 761 inhibited 45% of Hep-2 cell growth without effect on normal cells.[7]

1.2.4 Diabetes

Oral treatment with EGb 761 significantly increased liver and muscle glycogen levels, and partially attenuated impairment of glucose utilisation in rats with streptozocin-induced type 2 diabetes mellitus. Rats received repeated oral treatment with EGb 761 (50 mg/kg/day) for 15 days. The effects of EGb 761 in this study may have been due to scavenging of free radicals associated with the cytotoxic activity of streptozocin.[8]

1.2.5 Ischaemic Heart Disease

Preclinical studies: in bovine aortic endothelial cells, EGb 761 was protective against damage induced by oxidative stress; EGb 761 decreased intracellular free Ca^{2+} and inhibited caspase 3 activity.[9]

EGb 761 improved contractile function after global ischaemia in an isolated working rat heart by attenuating the formation of oxygen free radicals.[10]

In an isolated rat heart model of ischaemia/reperfusion, EGb 761 inhibited nitric oxide production.[11]

1.2.6 Thromboses

Preclinical studies: in normal rats, EGb 761 (40 mg/kg), ticlopidine (200 mg/kg) and EGb 761 (40 mg/kg) + ticlopidine (50 mg/kg) inhibited platelet aggregation *ex vivo* 54, 98 and 96%, respectively. In a rat model of thrombosis, the antithrombotic effects of combination therapy were more effective than with ticlopidine alone.[12]

Table II. Drug development history

Apr 1995	Preclinical development for Cancer in Brazil (Unknown route)
Jun 1996	Clinical Phase Unknown for Alzheimer's disease in Germany (PO)
Aug 1996	Preclinical development for Arrhythmias in United Kingdom (IV)
Aug 1996	Preclinical development for Myocardial ischaemia in United Kingdom (IV)
Aug 1996	Clinical Phase Unknown for Peripheral vascular disorders (PO)
Apr 1997	Clinical Phase Unknown for Peripheral arterial occlusive disorders in France (Unknown route)
Oct 1997	Preclinical development for Type-2 diabetes mellitus in France (PO)
Oct 1997	Preclinical development for Thrombosis in South Korea (Unknown route)
Oct 1997	Clinical Phase Unknown for Dementia in Mexico (PO)
Nov 1997	Clinical Phase Unknown for Alzheimer's disease in US (PO)
Jun 1998	Clinical Phase Unknown for Erectile dysfunction in Germany (PO)
Aug 1998	Clinical Phase Unknown for Peripheral arterial occlusive disorders in Germany (PO)
Mar 1999	Clinical Phase Unknown for Alzheimer's disease in Mexico (PO)
Mar 2000	Preclinical development for Reperfusion injury in Europe (Unknown route)
Mar 2000	Phase II for Pancreatic cancer in Germany (IV-infusion)
Jul 2001	Clinical trials in Deafness in Germany (Unknown route)
Jul 2001	Clinical trials in Tinnitus in Germany (unspecified route)
Apr 2002	Phase III in Alzheimer's disease in USA (PO)
Apr 2002	Phase III in Alzheimer's disease in Mexico (PO)
Apr 2002	Phase III in Alzheimer's disease in Germany (PO)
Apr 2002	Phase III in Alzheimer's disease in France (PO)
Apr 2003	No development reported - Preclinical for Arrhythmias in United Kingdom (IV)
Apr 2003	No development reported - Preclinical for Type-2 diabetes mellitus in France (PO)
Apr 2003	No development reported - Clinical Phase Unknown for Peripheral arterial occlusive disorders in Germany (PO)
Apr 2003	No development reported - Preclinical for Thrombosis in South Korea (unspecified route)
Apr 2003	No development reported - Clinical Phase Unknown for Peripheral arterial occlusive disorders in France (unspecified route)
Apr 2003	No development reported - Clinical Phase Unknown for Erectile dysfunction in Germany (PO)
Apr 2003	No development reported - Preclinical for Cancer in Brazil (unspecified route)

1.3 Therapeutic Trials

1.3.1 Alzheimer's Disease and Cognition Disorders

EGb 761 240 mg/day PO bid displayed efficacy in the treatment of patients with dementia of the Alzheimer's type and multi-infarct dementia when administered over a period of 24 weeks.[2]

EGb 761 has shown efficacy against impaired memory, as well as vertigo and tinnitus, co-morbidities often present in patients with dementia. However, the drug was not beneficial in advanced cases of dementia. 187 patients with DSM-IV criteria for dementia, or with clinically diagnosed vertigo or tinnitus received EGb 761 120 mg/day PO tid for 12 weeks in an open study design. Dementia was absent in 15% of patients at 12 weeks, compared with no patients at baseline. Dementia was mild in 32% of patients at 12 weeks, compared with 5% of patients at baseline. At baseline, severe or very severe tinnitus was present in 55% of patients; after 12 weeks' treatment with EGb 761, the symptom resolved completely in 25% of patients and was rated as mild in 60%. At baseline, severe or very severe vertigo was present in 68% of patients; after 12 weeks' treatment with EGb 761, the symptom resolved completely in 42% of patients and was rated as mild in 38%. No significant adverse effects were observed.[13]

Patients treated with EGb 761 exhibited improved cognitive impairment and daily living and

social behaviour in a double-blind, placebo-controlled study involving 327 patients with DSM-III-R criteria for uncomplicated dementia of the Alzheimer's type or multi-infarct dementia. Patients were randomised to therapy with EGb 761 120 mg/day or placebo for 52 weeks. 236 patients were included in the intention-to-treat analysis, which revealed treatment differences significantly favouring EGb 761 recipients on the Alzheimer's Disease Assessment Scale Cognitive subscale (ADAS-Cog) and the Geriatric Evaluation by Relative's Rating Instrument (GERRI). There was no significant difference between treatment groups as measured by the Clinical Global Impression of Change (CGIC). Similar results were observed in the 202-patient evaluable population. At 52 weeks, 50% of EGB 761 recipients had an improvement in ADAS-Cog by ≥2 points, compared with 29% of placebo recipients. This approximate 2-fold difference was maintained when the improvement threshold was set at 4 ADAS-Cog points.[3]

Two hundred and fourteen patients with mild to moderate dementia of the Alzheimer's type, vascular dementia or substantial age-associated memory impairment were randomised to therapy with EGb 761 240 mg/day, EGb 761 160 mg/day or placebo. After completing the first 12-week treatment period, patients exposed to EGb 761 were randomised either to continue EGb 761 for another 12 weeks or to placebo therapy. Patients receiving placebo for the first 12 weeks went on to receive placebo for the next 12 weeks. Outcome measures included neuropsychological testing, clinical assessment, depressive mood, self-perceived health and memory status, and behavioural assessment. There were no systematic or clinically meaningful effects of EGb 761 on any of the outcome measures.[14]

1.3.2 Cancer

Clinical studies: of the 48 evaluable patients with pancreatic cancer who received EGb 761 + fluorouracil, four (8%) had a partial response, eight (17%) had stable disease, and 22 (46%) experienced disease progression. The mean survival of this patient population was 4.9 months, and, according to the researchers conducting this phase II study, there was no substantial change in QOL during treatment. Patients received EGb 761 350 mg/day by IV infusion over 6 consecutive days every 3 weeks. Fluorouracil was administered at a dosage of 500 mg/m^2/day concurrently with EGb 761 for 5 days q3w. Patients received 1–12 treatment courses.[15]

1.3.3 Diabetes

In an open study in 41 patients with type 2 diabetes mellitus and diabetic neuropathies, EGb 761 120 mg/day PO for 6 weeks significantly improved blood supply and peripheral nerve functions compared with baseline.[16]

1.3.4 Ear, Nose and Throat Disorders

In a randomised, double-blind study, 72 patients with sudden deafness were treated with EGb 761 (n = 37) or pentoxifylline (35). Both treatments were therapeutically equivalent for improvement or return to normal of auditory thresholds, return to normal of speech discrimination and reduction of tinnitus. Patient's assessment of treatment with regard to hearing improvement and reduction in tinnitus favoured EGb 761 over pentoxifylline.[17]

1.3.5 Men's Health

The efficacy of EGb 761 was not confirmed in a double-blind, placebo-controlled trial in 32 men with erectile dysfunction. No significant subjective success was observed. It had been shown to be effective in an earlier pilot study.[18]

1.3.6 Thromboses

Patients with Fontaine stage IIb peripheral occlusive arterial disease were randomised to receive EGb 761 or placebo for 24 weeks. EGb 761 significantly increased pain-free walking distance vs placebo at 24 weeks. Maximum walking distance was also significantly greater in EGb 761- vs placebo-treated patients.[19] In another trial, 74 patients with peripheral arterial disease were randomised to receive EGb 761 as Rökan® 120 or 240 mg/day for 24 weeks. EGb 761 240 mg/day significantly improved pain free and maximum walking distances compared with the 120 mg/day dosage.[20]

1.3.7 Vascular Disorders

Patients with Fontaine stage IIb peripheral occlusive arterial disease were randomised to receive EGb 761 or placebo for 24 weeks. EGb 761 significantly increased pain-free walking distance vs placebo at 24 weeks. Maximum walking distance was also significantly greater in EGb 761- vs placebo-treated patients.[19]

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