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Medicinal Effects of Ginkgo Biloba in Animal Models

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Abstract

Ginkgo biloba is a living fossil tree that is researched on extensively regarding its medicinal properties. The leaves have bioactive flavonol glycosides (~24%), and terpene lactones (~6%) (e.g. ginkgolides, bilobalide) (1), which are thought to mediate its action. The therapeutic value of Ginkgo has been investigated in animal studies in different body systems. Key findings include: Cognitive and Neurological: An enhanced memory and synaptic plasticity of rodents with neurodegeneration or injury (2, 3). Cardiovascular: Ischemia-reperfusion injury and hypertrophy protection, enhanced autonomic balance, and hemodynamics (1, 4). Antioxidant: Decrease in oxidative stress indicators and boosting antioxidant enzymes in the brain and heart tissues (1, 5). Anti-inflammatory: antiregulation of pro-inflammatory cytokines and immune activation in colitis and brain inflammatory model (6, 7). Safety: In animal models, high dosage can cause adverse effects (e.g. gastrointestinal upset, seizures, cardiovascular depression) and increase in interaction with other drugs (7, 8). These results are explained further below and in-text citations of peer-reviewed publications are provided.

Introduction

Cognitive and Neuroprotective Effects

Neuroprotective effects of Ginkgo extracts have been reported throughout animal studies. Chronic treatment using EGb 761 (20-30mg/kg) significantly enhanced learning and memory tasks in a transgenic model of Alzheimer disease (5xFAD). Hippocampal EGb761 decreased the amyloid-b plaque burden, augmented

hippocampal neurogenesis, and amplified hippocampal dendritic branching and thickness (2). GBE50 (7.5-15g/L) enhanced spatial learning, re-established antioxidant enzyme activities (superoxide dismutase, glutathione peroxidase) and suppressed neuronal apoptosis (elevating Bcl-2, reducing cytochrome C release and caspase-3) in an Alzheimer like rat model induced by hippocampal Ab injection (9). Equally, EGb761 attenuated the occurrence of infarcts and neurological impairment in a rat model of ischemic stroke (middle cerebral artery occlusion) probably due to its ability to induce autophagy and lysosomal clearance of necrotic proteins (3). Ginkgo too improved the mood and behavior of cardiac stress models: e.g. in a mouse model of heart failure, GBE decreased the levels of TNF-a and IL-1b in the hippocampus and improved depressive-like behavior as well as cardiac performance (7). The combination of these data points to the fact that neuroprotective effects of Ginkgo, such as improved cognition, decreased neurodegeneration, and stabilization of mood are mediated by antioxidant, anti-apoptotic, and anti-inflammatory processes (2, 3).

Cardiovascular Effects

Ginkgo biloba extracts have protective effects on heart injury in cardiovascular models. GEBE50 decreased the size of infarcts and serum evidence of cardiac damage (AST, LDH, CK) and increased myocardial Na +/K +-ATPase and Ca 2 +/Mg 2 +-ATPase in rats that received myocardial ischemia-reperfusion. GBE50 also reduced the oxidative stress in the reperfused myocardium and enhanced antioxidant defenses (1). GBE inhibited pathological remodeling in models of hypertension or b-adrenergic overstimulation: e.g. isoproterenol-induced cardiac hypertrophy and fibrosis was inhibited by co-treatment with GBE (100 mg/kg). Notably, in these rats, GBE made the autonomic balance normal: isoproterenol alone induced sympathovagal imbalance (LF/HF ratio, baroreflex sensitivity), but GBE treatment completely restored the heart rate variability and baroreflex activity (4). GBE further caused cardiac receptors (stopping upregulation of muscarinic M2 and downregulation of b1-adrenergic receptors) and endothelial nitric oxide synthase (eNOS) levels and activity to be restored (4). Such activities (antioxidant, anti-inflammatory, and cholinergic/NO-mediated) are probably the basis of cardioprotection of Ginkgo in animals.

Antioxidant Properties

Ginkgo extracts have been shown to be good antioxidants in animals. An example is in a rat model of lead neurotoxicity, GbE (50-100 mg/kg) helped to eliminate lead-induced oxidative stress: reactive oxygen species, lipid peroxidation and protein carbonyl levels (enhanced by lead) were partially returned to normal by Ginkgo treatment (5). Similarly, Ginkgo treatment increased levels of catalase, SOD and GSH-Px and decreased H 2 O 2 accumulation similar to the case above brain ischemia and Alzheimer models[11]. GBE50 lowered H2O2 and enhanced antioxidant enzyme activities in the ischemia-reperfusion injury in the heart (9). Better antioxidant defenses were associated with better tissue outcome (smaller infarcts, intact neurons) (3). Therefore, the flavonoids of Ginkgo seem to eliminate free radicals and enhance the native antioxidants, decreasing the oxidative stress of the brain and heart tissues(1, 5).

Anti-inflammatory effects

Ginkgo also has anti-inflammatory effects on animal data. EGb761 inhibited the activation of macrophages and the expression of inflammatory response (iNOS, COX-2, TNF-a, p53 stress signals) in a mouse model of ulcerative colitis and decreased inflammatory processes in the colon (6). EGb761 was also found to induce death of pathogenic T cells (CD4+) in the colon, which caused more relieved inflammation (6).

With neuroinflammatory models, Ginkgo also decreased cytokines: E.g. hippocampal TNF-a and IL-1b, were decreased in heart-failure mice receiving GBE, in step wise with enhanced behavioral results (7). GE50 was also observed to reduce myocardial activity of myeloperoxidase and the level of IL-8, TNF-a and IL-1b in the blood following ischemia-reperfusion, which represents an evidence of reduced inflammation in the heart (1). To conclude, the bioactive compounds of Ginkgo attenuate NF-kB and other associated inflammatory cascades in vivo, which is likely to explain its therapeutic efficacy in disease models of inflammation(1, 6).

Side Effects and Interactions

Although Ginkgo is typically safe at moderate doses, animal research points to potential adverse effects at a high dose or during drug interactions. Big oral doses in animals may result in gastrointestinal (vomiting, diarrhea) and CNS agitation (7). Huge doses can cause seizures: a genetic rat model of absence epilepsy shows that 400 mg/kg EGb761 had a significant pro-epileptic effect, i.e. it increased the release of spikes (9). In the old hypertensive rats, long-term GBE (100 mg/kg) actually decreased heart rate and impaired the peripheral blood flow (10), indicating that cardiovascular depression could take place at the high level of exposure. Another interaction of ginkgo with other drugs was also reported: it was discovered that when GBE761 (100 mg/kg) was co-administered with the antibiotic amikacin (600 mg/kg) in young rats, the effect was different and suggested a pharmacodynamic or pharmacokinetic interaction (10). Furthermore, the mild MAO-inhibitory effect of Ginkgo is also potentially dangerous in combination with SSRIs, as the case reports indicate, and as the increased levels of serotonin have been reported with GBE (7). Altogether, animal evidence recommends caution: high doses of Ginkgo could induce neurologic or cardiovascular side effects and co-administration with some drugs (antibiotics, anticoagulants or serotonergic drugs) should be followed closely (7, 8).

Conclusion

The traditional uses of Ginkgo biloba are supported by preclinical research in the animal models. Standardized leaf extracts (e.g. EGb 761 or GBE50) have a neuroprotective, cardioprotective, antioxidant and anti-inflammatory effect on rodents (1, 2). These are in the form of better cognitive performance, decreased tissue damage in stroke models or heart injury models and decreased oxidative/inflammatory indicators throughout systems. To achieve these advantages, the active flavonoids and terpenoids seem to have a variety of target pathways (free radicals, apoptotic proteins, cytokines, neurotransmitters). However, such studies in animals also highlight the safety boundaries: extremely large doses may lead to negative nervous and cardiac outcomes and drug interactions have been reported (7, 8).

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