

## Ginkgo biloba- an appraisal

Dubey AK<sup>1</sup>, Shankar PR<sup>1</sup>, Upadhyaya D<sup>2</sup>, Deshpande VY<sup>3</sup>

<sup>1</sup>Assist. Prof., <sup>2</sup>Lecturer, <sup>3</sup>Professor, Dept. of Pharmacology, Manipal College of Medical Sciences, Pokhara

### Abstract

Ginkgo biloba has been used in traditional Chinese medicine for about 5000 years. A standardized preparation, EGb 761 has been recently prepared. The pharmacologically active constituents, flavonol glycosides and the terpene lactones are standardized. The terpene lactones comprise of ginkgolides A, B, C and bilobalides. The extract scavenges excess free radicals and pretreatment with EGb 761 reduces damage by free radicals in patients undergoing coronary bypass surgery. The action of platelet activating factor is antagonized and platelet aggregation is reduced. Blood flow is increased. Release of prostacyclines and nitric oxide was shown to be stimulated. Ginkgo biloba has been found to be useful in the treatment of Alzheimer's disease and cognitive impairment. EGB 761 has shown beneficial effect in aging and mild cognitive impairment. Bilobalide has been shown to be protective against glutamate-induced excitotoxic neuronal death. Early studies indicate a potential role in age-related macular degeneration and some types of glaucoma. Anticancer action is related to antioxidant, anti-angiogenic and gene regulatory actions. Ginkgo biloba has shown overall improvement in about 65% of patients with cerebral impairment and a similar percentage suffering from peripheral vascular diseases. A recent study suggested that phytoestrogens in Ginkgo biloba may have a role as alternative hormone replacement therapy. Recent trials have not shown a beneficial effect of Ginkgo biloba in tinnitus and acute mountain sickness. Ginkgo biloba increased the bioavailability of diltiazem. The extract has been shown to protect against doxorubicin-induced cardiotoxicity and gentamicin-induced nephrotoxicity in animals. Ginkgo biloba inhibits microsomal enzymes and has a potential for drug interactions. Further studies to establish the efficacy of Ginkgo biloba are required.

**Key words:** Dementia, Drug interactions, Ginkgo biloba extract, Neuroprotection, Peripheral vascular disease

In developing countries like Nepal, a large proportion of the population relies heavily on traditional practitioners and medicinal plants to meet health care needs.<sup>1</sup> Very few plant species have been scientifically evaluated for their possible medical applications. Ginkgo biloba is a plant species with multitude of medicinal properties.

Ginkgo biloba is a dioecious tree which has been used in traditional Chinese medicine for about 5000 years. It is native to China, but is commercially cultivated in France and United States of America.<sup>2</sup> The scientific description of Ginkgo biloba is as follows:

Ginkgo biloba L

Family: Ginkgoaceae

Mantissa Plantarum 1771;2:313-314.

Synonyms: *Pterophyllus salisburiensis*, *Salisburia adiantifolia*, *Salisburia macrophylla*

The seeds are commonly employed in traditional Chinese medicine. Recently extracts from leaves of Ginkgo biloba have been used as a standardized preparation EGb 761. The pharmacologically active constituents, flavonol glycosides and terpene

lactones are kept within a narrow range of 22 to 27% and 5 to 7% respectively by standardization.<sup>3</sup>

The mixture of active ingredients gives the whole extract a complex range of activities.

### Effects of ginkgo biloba

#### *Scavenging of oxygenated free radicals:*

The most important effect of Ginkgo biloba extract (GBE), exhibited at cellular membranes, is scavenging of oxygenated free radicals produced during arachidonic acid metabolism. Under normal conditions, endogenous enzymes rapidly deactivate these free radicals. During ischemia, however, the excess of free radicals generated overwhelms these natural defenses leading to peroxidation and damage of lipid membranes.

### Correspondence

Dr. P.Ravi Shankar

Department of Pharmacology

Manipal College of Medical Sciences

P.O.Box 155, Deep Heights Pokhara, Nepal.

E-mail: [ravi\\_p\\_shankar001@hotmail.com](mailto:ravi_p_shankar001@hotmail.com)

GBE scavenges these excess free radicals.<sup>4</sup> Pretreatment with EGb 761 has been shown to reduce free radical induced oxidative damage in patients undergoing coronary bypass surgery.<sup>5</sup> Recent studies have shown that GBE protects mitochondria from oxidative stress.<sup>6</sup> Mitochondrial abnormalities may constitute a part of the spectrum of chronic oxidative stress in Alzheimer's disease. A role has been suggested for electromagnetic radiation induced oxidative damage in tissues caused by mobile phones. Ginkgo biloba prevents the mobile phone induced oxidative stress and preserves antioxidant activity in brain tissue.<sup>7</sup>

#### ***Platelet activating factor (PAF) antagonism and platelet aggregation***

Biological actions of PAF include induction of platelet aggregation and oxygen radical production leading to increased microvascular permeability and bronchoconstriction.<sup>4,8</sup> Ginkgo biloba antagonizes skin and platelet responses to PAF in man.<sup>8</sup> GBE has been shown to significantly reduce platelet aggregation in healthy subjects and in subjects suffering from type 2 diabetes mellitus.<sup>9</sup> However, a recent study in healthy volunteers failed to show evidence of an inhibition of blood coagulation and platelet aggregation by EGb 761. There was no evidence of a causal relationship between EGb 761 administration and hemorrhagic complications.<sup>10</sup> Further studies are required.

#### ***Circulatory effects***

GBE has been shown to increase blood flow in vivo. GBE reduces whole blood viscosity and elasticity. Release of prostacyclines and endothelium derived relaxing factor (EDRF), potent vasodilators were shown to be stimulated by GBE.<sup>11</sup> Vasodilating actions of GBE and bilobalide (a constituent) could be due to inhibition of Ca<sup>2+</sup> influx through the Ca<sup>2+</sup> channel and activation of nitric oxide release.<sup>12</sup> As detailed later these effects may be helpful in the treatment of peripheral arterial diseases but further studies are required.

#### ***Cerebral metabolism, behaviour and learning***

GBE has been shown to increase cerebral glucose uptake and consumption. GBE, in a dose of 100 mg/kg, in rats kept in a hypoxic environment (a model for normal cerebral aging) and in other animals subjected to clamping of the carotid arteries to produce ischaemia, enhanced glucose uptake and consumption, when compared to untreated animals.<sup>13</sup> GBE significantly attenuated the amnaesic effect of scopolamine in mice, an animal model of memory dysfunction associated with Alzheimer's disease.<sup>14</sup> These properties might

be useful in the treatment of Alzheimer's disease. A comparison of effectiveness of second-generation anticholinesterases (donepezil, rivastigmine) and GBE showed significantly better results compared to placebo. However, anticholinesterases were superior to GBE.<sup>15</sup>

EGb 761 has shown a beneficial effect in aging and mild cognitive impairment.<sup>16</sup> Animal studies have shown that EGb 761 inhibits neuronal toxic effects of levodopa in Parkinson's disease in rats. Therefore combined use of levodopa and EGb 761 may be a workable method for treatment of Parkinson's disease and may be better than levodopa alone.<sup>17</sup> Bilobalide has been shown to be protective in global brain ischaemia and against glutamate-induced excitotoxic neuronal death.<sup>18</sup> The neuroprotective actions of bilobalide may be because of its ability to decrease the release of excitotoxic amino acids, particularly glutamate.<sup>19</sup> In rats, prenatal exposure to EGb 761 has been shown to alter the expression of genes in the hippocampus and changes in enzymes activated by these genes may underlie its neuroprotective properties.<sup>20</sup> An intent-to-treat analysis of a multi-centre trial confirmed that EGb 761 improved cognitive function in a clinically relevant manner in patients suffering from dementia.<sup>21</sup>

#### ***Age-related macular degeneration, retinal occlusion and glaucoma***

Limited data indicate a potential clinical role for GBE in the treatment of age-related macular degeneration.<sup>22</sup> However, the question as to whether people with age-related macular degeneration should take GBE has not been answered.<sup>22</sup> The efficacy of Ginkgo biloba has also been demonstrated in patients with retinal vein occlusion.<sup>23</sup> EGb 761 was an effective neuroprotectant on pretreatment and early posttreatment in a rat model of chronic glaucoma.<sup>24</sup> Ginkgo biloba has been linked with improvements in pre-existing field damage in some patients with normal tension glaucoma.<sup>25</sup>

#### ***Cancer***

Ginkgo biloba has been shown to affect gene expression.<sup>26</sup> The anticancer (chemopreventive) properties are related to its antioxidant, anti-angiogenic and gene-regulatory actions.<sup>27</sup> In humans, GBE inhibits the formation of radiation-induced clastogenic factors and ultraviolet light-induced oxidative stress.<sup>27</sup>

### ***Tinnitus***

Ginkgo biloba is commonly used in the treatment of tinnitus of vascular origin.<sup>28</sup> However, a recent review suggests that Ginkgo biloba did not demonstrate an effect in tinnitus which was a primary complaint.<sup>29</sup> There was no reliable evidence to address the question of use of Ginkgo biloba for tinnitus associated with cerebral insufficiency.<sup>29</sup>

### ***Diabetic neuropathy***

GBE has also shown a beneficial effect in patients with diabetic neuropathy. In a preliminary double blind placebo controlled study in 40 patients with diabetic neuropathy, GBE along with folic acid significantly increased nerve conductivity.<sup>30</sup>

### ***Peripheral arterial diseases***

The optimal treatment of intermittent claudication has not yet been identified. A meta-analysis of the efficacy of GBE suggests that the extract is modestly superior to placebo in the symptomatic treatment of claudication.<sup>31</sup>

Raynaud's phenomenon is a common and painful condition characterized by episodic digital ischaemia produced by emotion and cold. Ginkgo biloba may be effective in reducing the number of attacks per week in patients suffering from Raynaud's disease.<sup>32</sup> A recent review showed that EGb 761 increased the pain-free walking distance compared to placebo in patients with peripheral arterial occlusive disease.<sup>33</sup>

### ***Estrogenic activity***

GBE contains 24% of phytoestrogens. A recent study has provided evidence of potential estrogenic activity of GBE and it could be useful as an alternative hormone replacement therapy.<sup>34</sup> However more studies are required.

### ***Acute mountain sickness***

Oxidative stress has been suggested to be involved in the pathophysiology of acute mountain sickness (AMS). The anti-oxidant property of Ginkgo biloba led to its evaluation as prophylaxis against AMS. However, a recent large trial showed that ginkgo is not effective in preventing AMS when compared to placebo.<sup>35</sup>

Laboratory experiments conducted during the past two decades have revealed many effects of Ginkgo biloba- vasoregulatory, antioxidant, neuroprotective, as well as effects on learning and memory.<sup>36</sup>

### ***Place of ginkgo biloba extract in therapy***

GBE has been demonstrated to be helpful in well-designed comparative trials in patients with impaired cerebral function and peripheral vascular disease. More recently, several preliminary studies have investigated the efficacy of GBE in patients with diabetic neuropathy and age-related macular degeneration. Cerebral impairment is the main indication showing an overall improvement in about 65% of patients. A similar percentage of patients of peripheral vascular disease responded to treatment.<sup>36</sup>

### ***Dosage Forms***

The constituents of EGb761 have been already described.<sup>3</sup> The terpene lactones comprise approximately 2.8-3.4% of ginkgolides A, B and C and 2.6-3.2% bilobides. It is available as coated tablets and solutions prepared from standardized purified extract.<sup>3</sup>

### ***Adverse effects and toxicity***

In the daily dose range of 120-140 mg in two to three divided doses, GBE has shown minimal adverse effects. Nausea, headache, stomach upset, diarrhoea, allergy, anxiety and insomnia have been reported.<sup>37</sup>

### ***Contraindications***

Hypersensitivity to Ginkgo biloba preparation.

The safety of Ginkgo biloba has not been established in pregnant ladies and lactating mothers.<sup>37</sup>

Investigations with GBE have shown no effects that were mutagenic, carcinogenic, or toxic to reproduction.<sup>37</sup>

### ***Drug Interactions***

Ginkgo biloba, because of its antiplatelet properties, should not be used along with other antiplatelet drugs or any other anticoagulants. In rats Ginkgo biloba extract increased the bioavailability of diltiazem by inhibiting its intestinal and hepatic metabolism.<sup>38</sup> Concomitant use of Ginkgo biloba and digoxin did not appear to have any significant effect on the pharmacokinetics of digoxin in healthy volunteers.<sup>39</sup> In mice, GBE has been shown to protect against doxorubicin-induced cardiotoxicity.<sup>40</sup> The extract has been shown to ameliorate gentamicin-induced nephrotoxicity in rats.<sup>41</sup> In subjects suffering from type 2 diabetes mellitus ingestion of GBE may increase the hepatic metabolic clearance of not only insulin but also the hypoglycaemic agents. There is reduced insulin-mediated glucose metabolism and elevated blood glucose.<sup>42</sup> The prevalence of herbal

preparations use among cancer patients varies from 13 to 63%. EGb 761 was tested for its ability to inhibit human cytochrome P450 enzymes (CYPs). The terpenoidic fraction inhibited CYP2C9 whereas the flavonoidic fraction inhibited CYP2C9, CYP1A2, CYP2E1 and CYP3A4.<sup>43</sup> Because of this activity the potential for pharmacokinetic interactions of Ginkgo biloba with anticancer drugs should be kept in mind.<sup>44</sup>

### Conclusion

Dr. Willmar Schwabe III, a German physician–pharmacist, introduced Ginkgo biloba leaf extracts into allopathic medical practice in 1965.<sup>36</sup> The standardized extract named EGb 761 was developed. Clinical studies during the last two decades have revealed that EGb 761 is useful in treating early cognitive decline and more severe types of senile dementia of primary degenerative, vascular and mixed origin, as well as peripheral arterial occlusive diseases and various neurosensory disorders.<sup>36</sup>

Because of its various pharmacological activities, Ginkgo biloba is definitely not a fleeting success. Further studies are required to explore the clinical potential of these encouraging leads to firmly establish their efficacy.

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