Review Article

Pharmacological Review on the All Cure Plant - *Gingko biloba*

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ABSTRACT

Gingko biloba is used as a potent medicine since time immemorial. The plant is an inhabitant of Asian countries like China, Korea, and Japan. They belong to the division Ginkgophyta which has characteristics intermediate between Pteridophyta and gymnosperms and they belong to the family Ginkgoaceae. There has been an ever increasing investigation on the numerous uses of the plant. It has become a part and parcel in man's daily food supplement. It is used as a memory booster, in intermittent claudication, as an anti-inflammatory agent, antioxidant, antimicrobial, in treatment of dementia, as hypolipidemic agent, in glaucoma treatment. It is also used along with 5-flurouracil in cancer treatment. The major constituents of the plant are terpene lactones and flavonoids.

Keywords: *Gingko biloba*, Ginkgoaceae, anti-inflammatory, hypolipidemic, intermittent claudication.

INTRODUCTION

An array of plants has been adopted traditionally to cure mental as well as physical illness. These plants have been utilised in traditional Chinese, Ayurveda, Siddha, Unani and Tibetan medicines.

Traditional Chinese Medicine is an essence of China's rich heritage and culture and for last thousands of years; leaves from gingko biloba tree have been used in Chinese medicines. Gingko biloba is considered world's oldest living tree and hence is called as "living fossil" and is resistant to pollution and disease.[1]The plant was formerly called as *Salisburia adiantifolia Sm*. [2]and Pterophyllus salisburiensis.[3]Several studies have shown that it help with memory problems caused by dementia or Alzheimer's disease and various other ailments such as liver fibrosis, acute pancreatitis, intermittent claudication, sexual dysfunction, inflammation etc.

The present review aims to highlight the morphology, distribution, phytochemistry and pharmacology of Gingko biloba and its expectancy in further investigation.

Biological Source [3, 4, 5]

Biological name: *Gingko biloba*
Division: Ginkgophyta
Class:Ginkgoopsida
Order: Ginkgoales
Family: Ginkgoaceae
Genus: Gingko

Common name: Fossil tree, Kew tree, Maidenhair tree, Japanese silver apricot

Description [3, 4, 5]

The plant is a deciduous, resinous and dioecious tree. It grows up to 60m or more tall. The branches are stiff with both elongated and spur shoots. The leaves are alternately clustered, fan shaped and cut in middle. It is dichotomously veined and long petioled. The female reproductive system consists of two ovules, rarely more on a long peduncle and usually only one among them maturing. Seeds are usually plum like in appearance, yellowish and drupe like to 2.5cm long, long peduncled, outer coat is fleshy and inner coat stony.

Habitat [3, 4, 5]

The plant is widely planted in China, Korea and Japan.

Parts Used [3, 4, and 5]

Seed and leaf

Propagation [3, 4, 5]

The propagation is by seed and vegetative method.

Phytochemical Composition [1, 4, 5]

The major constituents present in the leaf extract are found to be flavonoids, terpene lactones. Flavonoids are presents as glycoside (Major – Quercetin-3-β- D-glucoside, Quercitrin, Rutin; Minor – Quercetin, Kaempferol, Isorhamnetin) and they constitute about 24% while terpene lactones (Ginkgolide A, Gingkolide B, Ginkgolide C, Bilobalide, Ginkgotoxin) constitute about 6%.

Pharmacological activities

The plant is reported to show an exquisite array of pharmacological activities. The activities are shortlisted below.

Anti-inflammatory action

The plant extract is reported to show anti-inflammatory action. The action is due to the presence of purified polysaccharides present in the plant (p-PGBL). In the study conducted by *Fei R et al* ,the methodology for study include assaying the plant extract by edema in ear and the acute peritonitis model of mice. It was henceforth concluded that its action is due to interference the p selecting – ligand interaction. [6]

In another similar study, the anti-inflammatory action of the plant was demonstrated by using purified polysaccharide (p-PGBL) on lipopolysaccharide induced inflammatory reaction. The study was performed both in vitro and in vivo.[7,8] The extract was reported to suppress TLR4/NF-κb signalling pathway. [7,8]

According to *Yan-Hong Zhou et al* gingko biloba extract have potent effect on mediators of inflammation like SOD, MDA, TNFα, NFκ, BP 65, IL-6.[9]

Intermittent claudication

Intermittent claudication[10] is generalised as the pain associated due to the narrowing or blocking of artery that carry blood to the leg. According to the meta-analysis performed by Pittler and Ernst, gingko biloba extract is more effective in treating pain due to claudication than placebo. The study was conducted based on results of randomised, placebo controlled, double blind trials.[11]In another similar study conducted by Johannes Schweizer and Christian hautmann it was observed that there was significant improvement in patient's condition as the dosage was increased from 120mg to 240mg.Both the doses were found to show high safety profile.[12]A clinical study conducted on 111 patients who were administered either with placebo or G*ingko biloba* extract proved the same.[13]

Hepatoprotective action

In a preliminary study conducted on gingko biloba composite (GBC) it was suggested that GBC was effective in halting the development of liver fibrosis of chronic hepatitis.[14, 15] In a study conducted by K. Ashok Shenoy et al it was demonstrated that Gingko biloba can also be used to protect the liver from carbon tetrachloride damage by providing protection against the oxidative damage by carbon tetrachloride.[16]

Acute pancreatitis

Acute pancreatitis is an inflammatory condition of the pancreas. The plant extract is demonstrated to be highly advantageous in case of acute pancreatitis. The extract reduces serum amylase as well as lipase level. This action of the extract is dependent on the oxygen radical scavenger effect.[17]

For sexual dysfunction

Gingko biloba extract have shown positive result on sexual dysfunction. In an open trial study conducted by A. J Cohen and B. Barlick it was concluded that the extract is potent in treating sexual dysfunction which is induced due to intake of antidepressant drugs. The impotency is considered to be due to selective serotonin reuptake inhibitors (SSRI), serotonin and nor epinephrine reuptake inhibitors (SNRI), monoamine oxidase inhibitor (MAOIs), and tricyclics. They are proved effective in all four phases of sexual response cycle.[18]A study was performed for the complete evaluation of the short term as well as the long term effects of the extract on women dysfunction. 99 women of age group 18- 65 who were suffering from sexual arousal disorder participated and both physiological as well as subjective measures were assessed. A limited but significant effect was shown physiologically by a single dose of 300mg GBE and no effect was produced subjectively on all 99 women. In 68 sexually dysfunctional women who were given 8 week treatment of either GBE, placebo, sex therapy emphasising on training women to attend genital sensation or sex therapy plus GBE witnessed long term effect of GBE. On combination with sex therapy the extract was effective for sexual response arousal.[19,20]

Neuroprotective function

Numerous studies conducted on the plant extract has concluded that the plant is an effective neuroprotectant. Several in vitro as well as in vivo studies conducted using standardized ginkgo biloba extract has proven this effect. In the study conducted by J. Krieglstein et al, the constituents of the plants such as gingkolides and bilobalides were evaluated.[21] 5mg/kg bilobalide subcutaneously given thirty minutes prior to ischemia has reduced the infarct area on mouse brain .A dose of 100mg/kg of gingkolide B or a dose of 50mg/kg of gingkolide A produced the same effect. The in vivo neuromodulatory effect of the plant was performed by Watanabe et al using twenty adult female mouse who were categorized as control and gingko biloba fed group. Later on the hippocampi and the cortex were dissected to study the transcriptional effects using oligonucleotide microarrays.[22]The effectiveness of the plant extract in treating cerebral ischemia was addressed by Salem et al. The study suggest that heme oxygenase support the plant extract in its neuroprotective role.[23]Studies reveal that the flavonoids and terpenoids present in the plant also possess neurological value and the extract is effective in treatment of cerebral hypoxia.[24]

Nootropic effect

The efficacy of the plant in treating Alzheimer's disease as well as senile dementia was addressed by Weinmann et al.The extract was better than placebo in treating patients with alzheimer's disease was justified by the meta-

analysis conducted using standardized extract EGb761[25] in 2372 patients[26] and a similar study was conducted in 2,561patients for 22-26 weeks, thus proving the efficacy of the extract in treating cognitive function and dementia with emphasis on patients with neuropsychiatric disorder.[27]In the study conducted by Alhemeyer, it was henceforth concluded that the plant protects the brain tissue and Gingkolide B and bilobalide, the main terpene lactones of the plant provide the protective role.[28]A recent research has suggested that the Alzheimer's disease is due to the building up of β-amyloid (Aβ)-derived peptides and a small proportion of free radicals in the hippocampal neurons of the patients. The flavonoid present in the plant plays the shielding role against the toxicity induced by Aβ derived peptides.[29] in the study headed by Zhan-You Xue et al, the *Gingko biloba* tablet was found efficacious in enhancing the cognitive ability as well as the cerebral blood flow supply of vascular cognitive impairment, no dementia (VCIND) candidates.[30]

For Glaucoma treatment

Gingko biloba has shown its impact on glaucoma patients by enhancing ocular blood flow. The methodology for evaluation includes a placebo controlled trial in eleven volunteers. Pre-trial and post-trial ocular blood flow was evaluated using Doppler imaging. The extract elevates the ophthalmic artery end diastolic velocity and do not produce any effect on systemic arterial blood pressure, intra ocular pressure or heart rate.[31]

Hypolipidemic activity

According to the study conducted by Dubey et al (2005), Gingko biloba extract can be used as hypolipidemic agent though not as effective as the cholesterol lowering agent-lovastatin. The flavonoid content of the plant is assumed to be responsible for their hypolipidemic action and the plant is estimated for their hypolipidemic action and the plant is estimated to contain 24% flavonoids. The study was conducted on albino white rats and they were grouped as normal control, cholesterol control, group fed with cholesterol and lovastatin and three other groups fed with cholesterol and doses of gingko biloba- 25mg/kg, 50mg/kg, 100mg/kg. As the study progressed it was witnessed that the groups treated with gingko biloba extract has shown percent decline in cholesterol from 9.51 to 16.31 though the decline percent was not proportionate to the elevated doses of the plant extract.[32]

Antibacterial activity

The methanolic, ethanolic, chloroform, and hexane extract of the plant was evaluated in strains of Agrobacterium tumefaciens, bacillus subtilis, Echerichia coli, *Erwinia chrysanthemi, Xanthomonas phaseoli*. Both disc diffusion and broth dilution assays were done.[33]The activity was in the order:

Methanol> Ethanol> Chloroform> Hexane

The antibacterial activity of the plant extract was reported by KaurAman Deep et al (2012). The study was proven effective against all strains of bacteria by agar well diffusion, minimum zone of inhibitory concentration (MIC), relative percentage inhibition. Accordingly Streptococcus faecalis showed the maximum zone of inhibition and E.coli showed the least.The effective antimicrobial dose was found to be 50mg/ml. a 77.4% maximum relative percent inhibition was shown by Streptococcus faecalis and 42.03% by *Proteus vulgarus* which was found to be the least.[34]

Antioxidant activity

Fermino et al in 2015 demonstrated that the plant extracts (EGb 761) has potent antioxidant activity and it was also confirmed to have low toxicity. The flavonoids present in the plant is responsible for the antioxidant activity.[35] R. Bridi et al demonstrated that there was significant increase in the activity of antioxidant enzymes, catalase, superoxide dismutase in the hippocampus, striatum and substantianigra of the EGb 761 treated rats.[36]In the study conducted by S. R Naik et al, the phytosomes, which is the complex of natural ingredients present in the plant, elevated the superoxide dismutase activity, calalase activity, Glutathione peroxidase activity, glutathione reductase activity in the frontal cortex, cerebellum, hippocampus, striated region etc.[37]Kaur Aman Deep et al (2012)proved that Gingko biloba was a potent antioxidant. Various test which include 1, 1-diphenyl-2-picryl hydrazyl (DPPH), hydrogen peroxide and reducing power scavenging activity was carried out. Result of Gingko biloba by DPPH was 40µg/ml while the standard ascorbic acid was 20.4µg/ml.

Result of the plant extract by hydrogen peroxide was 105µg/ml and the standard was 95µg/ml.[34]

Antidiabetic property

Antidiabetic activity of the plant was evaluated by Shankar et al in his study using Albino wistar rats who were induced with Streptozotocin.[38]Streptozotocin is a chemical that has devastating effect on the β cells which produce insulin.[39] It was observed that the plant extract in a dose of 100mg/kg was effective in decreasing the fasting blood sugar (FBS) and they also elevated the blood glutathione (GSH). It was assumed that the antioxidant activity of the extract plays a key role in the antidiabetic property of the plant. In another study conducted by T Sugiyama et al it was observed that the plant extract was useful in modifying the hypoglycemic action of the drug tolbutamide. Tolbutamide is a first generation sulfonylurea. The modification in tolbutamide's efficiency was due to the hepatic cytochrome P450 mediated mechanism.[40]

Cancer treatment

5- Fluorouracil in combination with GBE 761 ONC (Special extract of Ecb 761) increases the effectiveness and acceptability of the drug as a second line treatment in

metastatic colorectal cancer. The dose of GBE 761 ONC required to produce the effect was found to be 350mg while the drug. Dose was found to be 500mg/m^2.[41]

Platelet activating factor antagonist

Platelet activating factor is a phospholipid which act as a activator as well as a mediator in many leucocyte function, platelet aggregation and inflammatory process. In the study conducted by Braquet P and Hosford D in 1991, Gingolide which is the terpene present in the plant has been reported with unique platelet activating factor antagonist activity.[42]Brikle et al made use of the potent gingkolide BN52021, to study its effect on the accumulation of free fatty acid and diacyl glycerol as well as the decrease in the fatty acid content of phosphatidylinositol-4,5-bisphosphate (PIP2) in the brain of mouse. The mouse was treated with BN52021 prior to electroconvulsive shock. The reports showed that BN52021 pretreated mouse showed diminishing accumulation of palmitic acid and docosahexaenoic acid and no particular impact on fatty acid of diacyl glycerol or loss of PIP2.[43]

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