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Medicinal Potentials of Ginkgo Biloba on Learning, Memory Enhancement - Review

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Abstract**—***Ginkgo biloba extract is considered as neuroprotective and cognitive enhancing agent which has medicinal potentials. In Ayurveda and herbal medicine, nutrient based neuro protective plant extracts are used to treat neurodegenerative disorders. However, Ginkgo biloba is such a plant, which reverse and minimize the memory impairment. mGluR5 is a type of metabotropic glutamate receptor that significantly influences the adjustment of synaptic plasticity in the hippocampus of the brain. Ginkgo biloba boosts the anti-cholinesterase activity in that way impacts the learning and memory function. This review may encourage to further in future clinical trials which explores beneficial effects of Ginkgo biloba extract in learning and memory to develop and approach for better therapeutic agents in neurodegenerative disorders.*

Keywords**—** *Ginkgo biloba extract, Neurodegeneration, Memory, learning.*

I. Introduction

Ginkgo biloba is commonly cultivated as a Chinese medicinal plant. It has neuroprotective, antioxidant, free radical scavenging, anti-apoptotic and memory enhancing properties. *Ginkgo biloba* belongs to ginkgoacece family, and its leaf extract is composed of flavone glycosides, 24% (quercetin, kaempferol, isorhamnetin) and terpene lactones, 6% (ginkgolides and bilobalide) [1]. G*inkgo* biloba *extract* (GBE) has neuromodulatory and cognitive enhancement property that can influence on neurotransmission and anti-apoptotic functions. Pharmacological actions of these active constituents have been extensively studied and has been found to exhibit free radical scavenging properties [2]. GBE enhances the mental and cognitive functions in experimental animals and human [3]. GBE has the protective role in several conditions like hypoxia, ischemia, seizures and peripheral nerve damage [4]. Multicentric trials established that GBE enhanced the cognitive ability in a clinically related manner in people suffering from dementia [5]. GBE significantly ameliorated the amnesic effect of scopolamine in mice, an animal model of memory dysfunction related with Alzheimer ‘s disease [6]. *Ginkgo biloba* leaf extract contains flavonoids, glycosides and terpenoids (*Ginkgolides and bilobalides*) and its extracts have been used pharmaceutically as anti-inflammatory, anti-apoptotic, and anti-aging agent [7].

II. Materials & Methods

A comprehensive review of the literature was conducted, focusing on studies that discuss about beneficial efficacy of G*inkgo* biloba extract on enhancing the capacity of learning and memory. Google Scholar, ScienceDirect, Web of Science, PubMed/Medline and Research Gate were used to collect data as evidence from available literature.

III. Discussion

1. Efficacy of Ginkgo biloba extract on neuro protection and enhancing learning and memory function:

Plant extracts with potential antioxidant capacity could offer neuroprotection. Previous studies have established the possible effects of antioxidants on neurodegenerative disorders in animal models [8]. GBE might enhance the short-term retention of spatial memory and progress cognition in humans and animals [9]. The highest administered dose of GBE (200 mg/kg) notably enhanced the spatial learning and memory capabilities of rats poisoned with aluminum by reducing the formation of insoluble beta amyloid fragments [10].

Ginkgo biloba (GBE) enhanced the spatial memory in rats by modulating the neurotransmitters levels in various regions of the brain [11]. High sustained Gz Exposure was Reduces AChE activity in rat brain and it was ameliorated by treatment with three different doses of GBE at 50, 100, and 200 mg/kg respectively [12]. Cholinergic neurotransmitter regulates the cognitive functions in brain. *Ginkgo biloba* enhances the anti-cholinesterase activity in that way influences the learning and memory [13]. Extracts of *Ginkgo biloba* leaves have been widely used to treat cerebro vascular insufficiency, symptoms associated with dementia as well as cognitive decline and neuro sensory impairments associated with aging and senility [14]. GBE affects the dorsal hippocampus and amygdala complex and enhances memory [15]. GBE when administered (150 mg/kg) in adult rats for two months resulted in protection against rotenone-induced neurotoxicity [16]. Long-term ingestion of GBE at 50, 100 and 150 mg/kg per day improved the spatial memory [17]. Scopolamine induced amnesia was effectively reversed by supplementation of *Ginkgo biloba* [18]. Previous study proved that GBE was potential cognitive enhancer for the treatment of Alzheimer ‘s disease [19]. 100 mg/kg GBE treated rats showed a decline in the neurotoxic effects of neurodegenerative disease like Parkinson`s disease

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[20]. The flavonoid part of GBE had antioxidant effects and acting directly on reactive oxygen species (ROS) [21].

2. *Effects of Ginkgo biloba extract in regulations of mGluR5 gene expression to boosting learning and memory function*

mGluR5 is a subtype of the group I metabotropic glutamate receptor and is essential for the regulation of synaptic plasticity. The function of mGluRs in synaptic plasticity and synaptic transmission are responsible for the source of learning and memory, characterized in the hippocampus [22]. Fluoride intoxication to Spraque Dawley rats caused striking reduction in the levels of mGluR5 gene expression in the cortex and hippocampus of brain regions to impair learning and memory functions [23]. In cases of lead exposure, the levels of mGluR5 mRNA and protein were found to decline in a dose-dependent manner [24]. The expression of mGluR5 mRNA and protein also steadily decreases with age [25]. *In vitro* studies showed reduced mGluR5 mRNA expression and protein levels dose-dependently in lead exposure, which was further established by the results of in vivo studies [26]. Lack of mGluR5 in the mice affected hippocampal long-term potentiation and hence attributed for spatial learning impairments and fear conditioning [27,28]. Maternal mice were exposed to fluoride during gestation and lactation period and the results showed no significant changes in hippocampal mGluR5 expression levels [29]. Ionotopic glutamate receptors play a vital role in excitotoxic cell death and related with neurodegeneration [30]. mGluRs is important factor that showed processing in synaptic plasticity that maintain neuronal development for learning and memory [31]. mGluRs is instead of playing direct role in excitatory glutama tergic synaptic transmission it modulates that function. mGluR5 signaling changes were noticed in various neurodegenerative diseases like Parkinson ‘s disease, Huntington ‘s disease and Alzheimer ‘s disease (AD) [32]. mGluR5 are found in the neurons and glia cells all over the CNS including the cortex and the hippocampus [33]. Inhibition of mGluR5 expression can impaired the spatial learning in experimental rats [34].

3. *Effect of Ginkgo biloba on neuronal changes in hippocampus mediated learning and memory*

Bilobalide and quercetin constituents of *Ginkgo biloba* had significantly increased the brain derived neurotrophic factor level that enhanced neurogenesis in the hippocampal neurons [35]. *Ginkgo biloba* was found to increase the cell proliferation and neuroblast differentiation in the mouse dentate gyrus [36]. The flavonoid composition found in Ginkgo biloba extract possesses antioxidant capabilities that safeguard the hippocampal neurons from damage caused by β amyloid [37]. *Ginkgo biloba* prevents the excitotoxicity induced cell death and offers neuro protection [38]. *Gingko biloba* extract reduced the apoptosis in hydroxyl radicals induced apoptosis in rat cerebellar granule cells and oxidative stress induced apoptosis [39,40]. Mice treated with Ginkgo biloba displayed enhancement in neuronal harm caused by acrylamide in the hippocampus, and this improvement was truly due to the encouragement of the neuronal healing process [41]. Ischemia induced hippocampal neurodegeneration *was* delayed by administration of *Ginkgo biloba* [42]. GBE 100 mg/kg/d treated for 8 weeks to rats showed morphometrical changes in hippocampal pyramidal cells in aged rats that confirmed the long-term administration of EGB may improve the memory [43]. *Gingko biloba* extract protects neurons of hippocampus from oxidative stress, ischemia and staurosporine induced neuronal apoptosis [44]. GBE has the potentials to promote regeneration of neural cell apoptosis in various target neural structures in rats [45]. Prenatal exposure of GBE promotes cell survival in fetal hippocampus of rat by altering the hippocampal gene expression levels [46].

4. *Mechanism of action of Ginkgo biloba extract on enhancing learning and memory function*

Ginkgo biloba contains terpene lactones like ginkgolides and diterpenes, as well as ginkgo flavone glycosides such as ginkgetin and bilobetin in various concentrations. *Ginkgo biloba* extract EGb 761 is the standardized extract of *ginkgo biloba* mostly used in experiments, which comprises 6% terpenoids and 24% flavonoid glycosides. Animal experiments have shown that action and mechanisms of *ginkgo biloba* on numerous brain structures and functions and modulating the neurotransmitter pathways. Flavones constituent of *ginkgo biloba* action was observed in some animal studies showed to inhibits lipid peroxidation, inhibit the uptake of neurotransmitters like serotonin, dopamine, and norepinephrine and inhibit the platelet aggregation [47]. *Ginkgo biloba* extract may inhibit the amyloid-β neurotoxicity and protects against hypoxic effects and increased oxidative stress and reversibly inhibits monoamine oxidase A and moderately reduces anticholinesterase activity [48]. *Ginkgo biloba* extract can regulate the apoptotic pathway and mitochondrial function in dementia by improving of energy metabolism, stabilization of mitochondrial membrane potential, inhibition of cytochrome c release, upregulation of anti-apoptotic Bcl-2 protein and downregulation of pro-apoptotic Bax protein and inhibits level of caspase 9 and caspase 3 after oxidative stress and finally decrease of apoptotic cell death [49,50].

IV. Conclusion

In this study we conducted a research review on medicinal values of *Ginkgo biloba* mainly focused on enhancing memory, learning abilities in experimental animals and other sources from previous published data. Flavone glycosides like quercetin, kaempferol, isorhamnetin and terpene lactones like ginkgolides and bilobalide can improve the memory, learning impairments due to various pathological reasons of hippocampal at micro molecular levels. Phytochemicals, bioactive constituents which includes flavonoids, biflavonoids, terpenoids in *Ginkgo biloba* can mitigates the memory, learning defects.

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