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Review Article

Ginkgo Biloba in Alzheimer's Disease

Dash SK*
Apollo Hospital, Dhaka, Bangladesh

***Corresponding author:** Dash SK, Apollo Hospital, Dhaka, Bangladesh, Tel: +8801713047523; Fax: +880-2-8401161; Email: drskdash@yahoo.co.in

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Abstract

Alzheimer's disease (AD) is a chronic and most prevents disease, affecting millions of people worldwide and causes a great burden to the society. Besides hyperphosphorylated tau and neurofibrillary tangles, various other mechanisms like oxidative stress, mitochondrial dysfunctions, Aβ production, neurofibrillary tangle accumulation, calcium mishandling, and hormonal imbalance also play a role in causing the neuronal loss and the disease process. Various studies have shown a beneficial role of ginkgo biloba in Alzheimer's disease, although some have refuted its role in AD. In the absence of effective therapy in dementia particularly in AD, Ginkgo biloba seems to have a therapeutic value in dementia and it needs further clinical trial to recommend it as an effective drug in AD. In this review various studies pertaining to the role of ginkgo biloba on memory and various mechanism of action of ginkgo biloba in improving memory function have been discussed.

Keywords: Ginkgo biloba; EGb761; Alzheimer's disease; Dementia

Abbreviations

VaD: Vascular Dementia; MAO: Mono Amino Oxidase Inhibitor; PD: Parkinson's disease; APP: Amyloid Precursor Protein; AB: Amyloid Beta; BACE 1: Beta site APP Cleaving Enzyme 1; TNFα: Tumor Necrosis Factor Alpha; MMSE: Mini Mental State Examination

Introduction

Dementia especially Alzheimer's disease is a chronic disabling disease most prevalent among the neurodegenerative diseases. It affects millions of people worldwide causing a great burden to the society. It's a leading cause of disability and long-term care placement. There are many mechanisms proposed to cause degeneration and Alzheimer's disease. Here we describe the various mechanisms of ginkgo biloba in improving cognition in Alzheimer's disease.

The etiology of Alzheimer's disease is multi factorial, and advanced age is the greatest risk factor. As the average lifespan of humans are increasing the prevalence of Alzheimer's disease is also increasing. It is expected that one person in every 85 individuals will suffer from Alzheimer's disease by 2050 [1]. Hyperphosphorylated tau and neurofibrillary tangles are the pathological hallmarks of Alzheimer's disease. Besides Aβ and phosphorylated tau, various deranged mechanisms like oxidative stress, mitochondrial dysfunction, Aβ production, neurofibrillary tangles accumulation, inflammation, calcium mishandling, and hormonal imbalance also play a role in the disease process thereby causing neuronal loss.

The Standardized preparation of ginkgo leaves contain flavonoids (24%) and terpene lactones (6%), as well as a variety of unknown substances 13% of dry weight [2]. The 24% of flavonoid of EGb 761 are flavones, flavonols, tannis, biflavones, glycosides like quercetin, kaempferol, isohamentin, mycertin and 3 methyl mycertin [3]. It is one of the most commonly used neutraceuticals marketed in Europe and used for various problems relating to mental health and wellbeing. Ginkgo biloba is found to be useful in Alzheimer's disease, normal aging, multi infarct dementia, stroke, traumatic brain injury, cerebral edema, cerebral insufficiency, and glutamate toxicity [4]. Some studies have related a beneficial role of Egb761 in dementias and in Alzheimer's disease. Various mechanisms like its anti oxidative [5], free radical scavenging [6], anti amyloidogenic [7], anti apoptic properties [8] are believed to be responsible for the prevention and treatment of Alzheimer's disease.

Clinical studies on memory function of ginkgo biloba. There are studies showing the beneficial effect of Egb761 on memory in humans whereas others have shown that it has no beneficial effect. In a double-blind, placebo controlled study of Ginkgo biloba extract ('tanakan') in 50 elderly outpatients with mild to moderate memory impairment; it was found that ginkgo biloba extract had a beneficial effect on cognitive function. Performance on the digit copying subtest of the Kendrick battery was significantly improved at both 12 and 24 weeks, while the median speed of response on a computerized version of a classification task also showed a significant superiority over placebo at 24 weeks [9]. To assess the efficacy of EGb 761 in mild to moderate dementia with neuropsychiatric features, a randomized, placebo-controlled, double-blind clinical trial with 400 patients aged 50 years or above with Alzheimer's disease (AD) or vascular dementia (VaD), randomized to receive EGb 761 or placebo for 22 weeks, it was seen that EGb 761 was significantly superior to placebo on all secondary outcome measures, including the NPI and an activities-of-daily-living scale. Treatment results were essentially similar for AD and VaD subgroups [10]. In a 20-year follow-up population-based study, to see the effect of Ginkgo biloba extract and long-term cognitive decline, a significant difference in MMSE decline over the 20-year follow-up was observed in the EGb761® and piracetam treatment groups compared to the 'neither treatment' group [11]. In a randomized, placebo-controlled, double-blind, multi-center trial to explore the efficacy and safety of Ginkgo biloba extract EGb 761 in mild cognitive impairment with neuropsychiatric symptoms, it was found that EGb 761 improved NPS and cognitive performance in patients with MCI. The drug was safe and well tolerated [12].

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In a systemic review to discuss new evidence on the clinical and adverse effects of standardized ginkgo biloba extract EGb761 for cognitive impairment and dementia, it was found that in the meta-analysis, the weighted mean differences in change scores for cognition were in favor of EGb761 compared to placebo (-2.86, 95%CI -3.18; -2.54); the standardized mean differences in change scores for activities in daily living (ADLs) were also in favor of EGb761 compared to placebo (-0.36, 95%CI -0.44; -0.28); Peto OR showed a statistically significant difference from placebo for Clinicians' Global Impression of Change (CGIC) scale (1.88, 95%CI 1.54; 2.29). All these benefits are mainly associated with EGb761 at a dose of 240 mg/day. For subgroup analysis in patients with neuropsychiatric symptoms, 240 mg/day EGb761 improved cognitive function, ADLs, CGIC, and also neuropsychiatric symptoms with statistical superiority than for the whole group. For the Alzheimer's disease subgroup, the main outcomes were almost the same as the whole group of patients with no statistical superiority. In conclusions it is EGb761 at 240 mg/day is able to stabilize or slow decline in cognition, function, behavior, and global change at 22-26 weeks in cognitive impairment and dementia, especially for patients with neuropsychiatric symptoms [13]. Similarly in a review to assess the effects of Ginkgo biloba in Alzheimer's disease as well as vascular and mixed dementia covering a variety of outcome domains, it was found in the meta-analysis, the SMDs in change scores for cognition were in favor of ginkgo compared to placebo (-0.58, 95% confidence interval [CI] -1.14; -0.01, p = 0.04), but did not show a statistically significant difference from placebo for activities in daily living (ADLs) (SMD = -0.32, 95% CI -0.66; 0.03, p = 0.08). Heterogeneity among studies was high. For the Alzheimer subgroup, the SMDs for ADLs and cognition outcomes were larger than for the whole group of dementias with statistical superiority for ginkgo also for ADL outcomes (SMD = -0.44, 95% CI -0.77; -0.12, p = 0.008). Drop-out rates and side effects did not differ between ginkgo and placebo, suggesting ginkgo biloba appears more effective than placebo though the effect sizes were moderate, while clinical relevance is, similar to other dementia drugs, difficult to determine [14]. However in Cochrane database Syst Review 2010 it was found that there is a lack of convincing evidence to show a cognitive enhancing effect of Panax ginseng in healthy participants and no high quality evidence about its efficacy in patients with dementia. However in this review all of these trials investigated the effects of ginseng on healthy participants. Pooling the data was impossible owing to heterogeneity in outcome measures, trial duration and ginseng dosage. Results of the analysis suggested improvement of some aspects of cognitive function, behavior and quality of life [15], was of the opinion that all of these trials investigated the effects of ginseng on healthy participants. Pooling the data was impossible owing to heterogeneity in outcome measures, trial duration, and ginseng dosage. Results of the analysis suggested improvement of some aspects of cognitive function, behavior and quality of life and randomized, double-blind, placebo-controlled, parallel group trials with large sample sizes are needed to further investigate the effect of ginseng on cognition in different populations, including dementia patients. In a systemic review to assess the efficacy and safety of ginkgo biloba for dementia or cognitive decline, it was seen that most trials tested ginkgo biloba in different doses and the recent trials showed in consistent results for cognition, activities of daily living, mood, depression and care burden. A subgroup analysis including only patients diagnosed with Alzheimer's disease (925 patients from nine trials) also showed inconsistent pattern of benefit associated with ginkgo biloba [16]. Four randomized, controlled trials investigating the effects of ginkgo biloba extract EGb 761 in dementia with neuropsychiatric features, it was found, one thousand, and two hundred and ninety-four patients were analyzed for efficacy. Patients treated with EGb 761 showed improvement of cognitive performance and behavioral symptoms that were associated with advances in activities of daily living and a reduced burden to caregivers. Placebo-treated patients, on the other hand, showed only minimal improvements or signs of progression. In each placebo-controlled trial, EGb 761 was significantly superior in all mentioned domains ($p < 0.01$). In the actively controlled trial, EGb 761 and donezepil as well as a combination of both drugs had similar effects, supports the efficacy of EGb 761 in age-related dementia with neuropsychiatric features. The drug was safe and well-tolerated [17]. In a randomized placebo-controlled double blind study, comparing the efficacy of ginkgo biloba with a cholinesterase inhibitor (Donepezil) in patients with dementia of AD type , it was found that there was no differences in the efficacy of EGb761 and donepezil in the treatment of mild to moderate Alzheimer's dementia and the use of both substances can be justified [18]. The GINDEM –NP, GOTADAY and GOT IT studies showed that 240mg/day EGb761 improved cognitive function, neuropsychiatric symptoms, activities of daily living, and quality of life in patients with mild to moderate dementia compared to placebo, with results reproducible in independent trials. A combination of 240mg/day EGb761 and 10 mg/day donepezil was also more effective than either drug alone [19]. In a multi- center, double blind, randomized, placebo controlled 24 week trial with 410 patients it was seen that patients treated with EGb 761 showed improvement in both SKT and NPI scores in comparison to placebo [20]. In a randomized placebo controlled trial to study the long term use of standardized ginkgo biloba extract for the long term prevention of Alzheimer's disease (GuidAge) it was found that ginkgo biloba did not reduce the risk of progression of Alzheimer's disease compared with placebo [21]. The strength of this study was the active involvement of primary care physician in recruitment and follow up of participants. But the limitation of the study was that the number of dementia events was much lower than expected, leading to a lack of statistical power to detect the effects and also some evidence of selection bias in the trial. To determine effectiveness of ginkgo biloba vs. placebo in reducing the incidence of all-cause dementia and Alzheimer's disease (AD) in elderly individuals with normal cognition and those with mild cognitive impairment (MCI), in a randomized, double-blind, placebo-controlled clinical trial conducted in 5 academic medical centers in the United States between 2000 and 2008 with a median follow-up of 6.1 years ginkgo biloba at 120 mg twice a day was not effective in reducing either the overall incidence rate of dementia or AD incidence in elderly individuals with normal cognition or those with MCI [22]. All these trials did not show evidence for reducing the overall incidence of dementia or AD with Ginkgo biloba extract in elderly individuals with or without memory complaints. Due to the particularly long pre-dementia phase, expecting a preventive effect of ginkgo biloba on the incidence of dementia over a period of 3–6 years may be over optimistic. In an expert meeting on ageing brain meeting on ginkgo biloba special extract EGb 761, it was noted that symptomatic efficacy has been

Table 1: Effect of Ginkgo biloba on memory in various studies.

Authors	Symptoms	Method	Outcome measures	Dose	Outcome
Rai et al. [9]	Memory impairment	n-27 RPC, DB Researching article	KDC, KDL task, digit recall	40 mg TID	KDL26.8.placebo 24.3. KDL 106.6, Placebo 94.5.Digit recall error 47.92, placebo 3. 273
Napryeyenko O et al. [10]	Dementia with AD	n 400 RCT, DB	SKT		Improved 3.2 in SKT neuropsychiatry feature
Amieva H et al. [11]	Cognitive decline	20 year follow MMSE, original prospective Cohort study.			Cognitive decline lower in EGb 761
Gavrilova SI et al. [12]	Cognition in MCI	DB, MC,RCT N160 NPS, Researching article		EGb 761 249	Improvement 78.8%
Tan MS et al. [13]	ADL,CGIC	review of 9 trials n2561 Review and meta analysis		EGb761 240 mg	Improvement in ADL,CGIC
Weinmann et al. [14]	Cognition, ADL	review of 9 trials n372 Review and meta analysis		EGb761	Improvement in cognition (-0.58,95%ci), for AD, Cognition and ADL, (SMD=0.44,95% CI)
Geng J, Dong J, Ni H [15]	Cognition	reviewed 9 trials systemic review	DBSB, RCT	Gineseng	Pooling the data impossible due to heterogeneity in trials. Healthy sub, 1AAMI (Age associated memory impairment)
Birks J, Evans JG [16]	Cognitive impairment	9 trials, n 2016 systemic review			Significant benefit for people with dementia or cognitive impairment is inconsistent and unreliable
Ihl R RCT [17]	Dementia with no symptoms	n 1294 review 4 RCT	SKT, NPI	EGb761 240mg	Improvements of cognitive performance and behavioral symptoms
Mazza M et al. [18]		Syndron kuzz test SKT, MMSE	DB, RCT	EGb761 160mg+ Donepezil 5 mg	Improvement in SKT
Ihl R et al. [19]	Dementia	n-410 RCT, DB Research article	SKT, NPI, ADCS	240 mg	SKT,NPI, ADCS-CGIC improvement
Herrschaft H et al. [20]	Dementia	n -410 RCT DB multicentric study	SKT	240 mg	Improved 2.2+3.5 on SKT with neuro psychiatric features. NPI improved 4.6 ± 7.1
Vellas B et al. [21]	Memory impairment patients 70 years or more	n 1406 MMSE, CDR, FCSRT	DB RCT Guidage trial		Did not prevent risk of AD in 5 yrs. Trail making test, verbal fluency, ADL
DeKosky ST et al. [22]	Dementia prevention	n1545	DB,RCT multi centric	240 mg 3.3/100 person in EGb, 2.9/100 person	Prevention dementia, no effect on the rate of progressing to dementia with MCI
Lautenschlager NT(Nicola) et al. [23]	AD and cognitive decline	expert meeting "The Ageing Brain"	Review		Effective in dementia and mild cognitive impairment (MCI), methodological problems in dementia prevention trials
Zhang SJ et al. [24]		N80 VCIND Patients Montreal cognitive assessment	RCT original study	Ginkgo Biloba 120mg	Improvement in cognitive ability
Jiang L, Su L[25]	Dementia	n1917 PC Systemic review, meta analysis	RCT		May be effective persons under 75 years of age with dementia

Abbreviations: KDC: Kendrick Digit Copy; KDL: Kendrick Digit Learning; SKT: Short Cognitive Performance Test (Syndrom–kurz test); NPS: Neuro Psychiatric Symptoms; NPI: Neuro Psychiatric Inventory; CGIC: Clinicians Global Impression of Change; SMD: Standardized Mean Difference; ADCS: Alzheimer's Disease Cooperative Study; MCI: Mild Cognitive Impairment; VICND: Vascular Cognitive Impairment of None Dementia

demonstrated in dementia and mild cognitive impairment, but interpretation of data from dementia prevention trial is complicated by important methodological issues, and it was concluded that there is plenty of promising data, both preclinical and clinical, to consider future research with the compound targeting cognitive impairment in old age as worthwhile activity [23]. Similarly in a study to evaluate the effect of combined treatment with aspirin and ginkgo biloba in patients of vascular cognitive impairment of none dementia, it was found that after 3 months of combined treatment in 40 patients, it was found that the scores of executive ability, attention, abstract, delayed memory orientation in the Montreal cognitive assessment were significantly increased compared with those before treatment and those in the control group. This study suggested that ginkgo biloba extract EGb can improve the therapeutic efficacy and improve cognitive ability and cerebral blood flow in patients with vascular cognitive impairment of none dementia (VCIND) [24]. To assess the effects of ginkgo biloba in AD as well as in vascular and mixed dementia in a systemic review and Meta analysis of 9 trials, of 12 to 52 weeks including 2372 patients, it was found ginkgo biloba appears to be more effective than placebo. In the meta analysis the standardized mean differences in the change score for cognition were in favor of gingko compounds than placebo (-0.58, 95% confidence interval -1.14, -0.01, p=0.04) [14]. To discuss new evidence on the clinical and adverse effects of ginkgo biloba extract EGb761 for cognitive impairment and dementia in a recent systemic review and Meta analysis of 9 trials including 2561 patients with 22-26 weeks duration, it was found that EGb 761 was able to stabilize and slowed the cognitive decline. In the study, it was found the mean change scores for cognition were in favor of EGb 761 compared to placebo (-2.86, 95% CI-3.18, -2.54) [13]. In a meta analysis on ginkgo biloba extract for dementia highlighted serious weaknesses in the studies and showed it may be effective in people under 75 years of age with dementia, but further trials focusing on milder forms of dementia ,comparing different doses of ginkgo biloba and follow up for longer periods are needed to confirm this [25].

Mechanism of Action

EGb 761 can be considered as a multi target compound with demonstrated activity on distinct pathophysiological pathways in AD and age related cognitive decline [24]. The action of flavonoids

are due to a number of biological process like their interactions with neuronal and signaling pathways that are important for neuronal survival [26,27], Free radical biology, expression of proteins required for synaptic plasticity and repair [28], their ability to cause changes in CBF (Cerebral Blood Flow) [29], inhibition of neuropathological process in certain brain regions [30,31]. A number of studies using transgenic mouse models of AD pathology have shown beneficial effects of flavonoids in cognition and memory. It is shown that oral administration of the green tea flavonoids for 6 months to mice over expressing the Swedish mutation of APP tg 2576 reduced amyloid β pathology as well as improved cognition [32]. Similarly long term green tea administration improved spatial learning and memory in senescence's prone mice [33]. The mechanism underlying these might be due to increased activity of alpha secretase [34] or it might be due to EGCG reduces Aβ plaque pathology by inhibiting protein aggregation and fibrillization either as a result of metal chelation activity [35,36]. In addition to the protective effects on Aβ, EGb761 has been shown to prevent amyloidogenesis. It was demonstrated that on hippocampal slices, EGb761 can shift he amyloid precursor protein (APP) towards alpha secretase pathway, thereby increasing the release of soluble forms of APP [37,38]. In a transgenic AD mouse model Tg 2576, it was found that Tg 2576 mice exhibited an enhancement of spatial learning and memory comparable to wild mice [38,39]. EGb 761 inhibits the production of brain Aβ levels by lowering cholesterol, as free and circulating free cholesterols and intracellular cholesterols could affect the APP processing and amyloidogenesis [38,40-43]. EGb 761 may also influence the formation of Aβ fibrils by increasing gene expression of transthyretin [44], as transthyretin has been shown to prevent Aβ aggregation in vitro by sequestrating Aβ monomers [45].

It has been reported that certain flavonoids and flavones act as BACE1 inhibitors and suppress BACE1 expression [46,47]. The beneficial effects of flavonoids may be due to its action on tau phosphorylation and fibrillization. It has been noted that a number of flavonoids inhibit heparin induced tau aggregation [48].

Clinical trials on the effects of EGb 761 in AD suggested that the use of EGb 761 as an AD stabilizer [49]. It is seen that addition of standardized extract of EGb 761 together with the Aβ protein, prevented in a dose dependant manner, the Aβ induced free radical production, increased glucose uptake, apoptosis and cell death [50]. The deposition of Aβ peptide by inducing neuronal oxidative stress, inflammation and apoptosis, plays an important roles in neurodegeneration in AD. In an AD model of rats [51], it was found that ginkgo biloba significantly protected against learning and memory impairments induced by Aβ 25-35 in Morris water maze, in addition attenuated the neuronal damage and apoptosis in frontal cortex and hippocampus CA1 rats and also inhibition of TNF alpha and Aβ1-40 is also involved in the action mechanism of bilobide, thus providing an experimental basis for the clinical application of ginkgo biloba in AD. Apoptosis has been implicated in the pathogenesis of AD and in neurodegenerative diseases. EGb 761 prevents apoptosis by maintaining the integrity of mitochondrial membrane; prevent cytochrome C release from the mitochondria, thereby blocking the formation of the apoptosomes and the apoptosis cascades. In a study [52] to investigate the neuro protective effects of ginkgolide B against Aβ 25-35 induced apoptosis in cultured hippocampal neurons it was found to be effective in attenuating apoptosis and the up regulation of BDNF seen when the cells were subjected to Aβ 25-35, suggesting the neuro protective effects may be due to brain derived neurotrophic factor up regulation. In a study it was demonstrated that pretreating cerebellar granule cells with the antioxidant EGb 761 (Ginkgo biloba extract) effectively attenuated oxidative damage induced by H2O2/FeSO4, and prevented cells from apoptotic cell death. The results suggested that EGb 761 might be used as a potential drug for neuronal diseases associated with the excessive production of reactive oxygen species [53].

One of the common hall marks of neurodegenerative disease is the formation of aberrant protein aggregates [54]. Misfolded proteins are removed through proteasomes or if their degradation fails, these proteins accumulate and form protein aggregates. Poly Q aggregates assemble to insoluble inclusion bodies, containing amyloid like fibers of poly q Proteins numerous cytoplasmic proteins and proteins to form the ubiquitin proteosome system, (UPS). The withdrawal of protein from UPS decreases the efficiency of protein degradation. The aberrant monomeric and oligomeric expanded poly Q proteins can promote further pathologic cellular deregulations and toxicity [55]. In a study of the effects of EGb 761 on the enzymatic activity of the proteasomes and associated protein degradation, it was demonstrated that EGb 761 has a novel activity on protein aggregates by enhancing proteosomal protein degradation, suggesting a therapeutic role in neurodegenerative disease with disturbed protein homeostasis [56].

Oxidative stress and mitochondrial failure promote altered protein degradation, reduced neurotransmission, synapse loss and tau/hyperphosphorylation, which are early stages in the development of Alzheimer's disease (AD). A growing volume of data confirms that ginkgo biloba extract (GBE) reduces oxidative stress and improves mitochondrial respiration and thus may be useful in preventing or slowing down the progression of AD. A respiratory experiment indicated that ginkgo biloba extract was able to rescue Aβ-induced defects in energy metabolism, with results suggesting long-term regulatory effects on mitochondria. Ginkgo biloba extract also had a selective effect on the activities of mitochondrial enzymes that assemble the electron transport system. The flavonoids, bilobalide and some of the ginkgolides (B and J) had a high protective capacity, indicating that a combination of several compounds within standardized gingko biloba extracts contribute disproportionately for these protective effects [57]. Similarly in a study to investigate whether standardized ginkgo biloba extract LI 1370 (GBE) is able to rescue Aβ-induced defects in energy metabolism. It was found that there was a beneficial effect of ginkgo biloba on the cellular OXPHOS (Oxidative phosphorylation) performance and restoration of Aβ-induced mitochondrial dysfunction, although the underlying molecular mechanisms of the mode of action of ginkgo biloba remain to be determined [58]. Bilobide an extract of ginkgo biloba has been shown to have neuro protective effects. It was demonstrated that bilobide treatment reduced generation of two β secretase cleavage products of APP, The amyloid β and soluble APP β via PIK3 dependant pathway. In addition GSK3, β signaling might be involved in bilobide induced Aβ reduction as a downstream target of the activated PI3K pathway. Bilobide induced reduction Aβ reduction was probably mediated through modulation of cathepsin B [59]. This study suggests bilobide may offer an approach to combat AD.

Oxidative stress has long been thought to play a major role in causing AD. The beneficial action of EGb 761 is mainly due to its action on free radical scavenging action, as demonstrated in various studies [60]. In a study using two AD models, Aβ expressing neuroblastoma cell line N2a and Aβ expressing transgenic Caenorhabditis elegans, EGb 761 was found to be able to attenuate the basal as well as the induced levels of H_2O_2 related reactive oxygen species (ROS) [60,61]. Besides attenuation of ROS, EGb 761 may also stabilize the cellular redox state by up regulation of the protein levels and activity of super oxide dismutase and catalase in rat hippocampus and rat ileum [62-64]. The flavonoid fraction is suggested to be mainly responsible for the antioxidant properties of EGb 761. The flavonoid fraction evokes anti oxidant effects via direct scavenging ROS, chelating pro-oxidant transitional metal ions and increase in antioxidant proteins like SOD and GSH [60,65,66].

Age, hypertension, atherosclerosis, diabetes mellitus and APOε4 are risk factors for cognitive decline. By modulating these, flavonoids are known to lessen the cognitive decline. Epidemiological data suggests that flavonoids are capable of preventing many forms of cerebro vascular disease including those associated with stroke and dementia [67,68]. Ginkgo biloba has been shown to exert constrictive or dilatory effects on blood vessels in a state dependant manner in a rabbit model, the vasodilator effects appear to be endothelial dependant. The alternative mechanisms may involve MAO inhibition, prostacyline release, beta adrenoreceptor agonism, increased intracellular calcium sequestration, increased nitric oxide synthase activity, or decreased lipid peroxidation [69]. Ginkgo biloba appears to inhibit platelet aggregation by increasing the concentration of endothelium derived nitric oxide and prostacycline and improve endothelial functions [70]. Due to these, there is increased cerebrovascular function which facilitates adult neurogenesis in the hippocampus [71]. Angiogenesis is accompanied by production of endothelium derived nitric oxide and vasodilatation [72]. The vascular effects of flavonoids are mediated by their ability to produce endothelial derived nitric oxide [73]. Increased vascularization in hippocampus is likely to stabilize the presence of new neurons [74].

Inflammation has been implicated in AD. EGb 761 has been demonstrated to have anti inflammatory effects [75]. These effects are due to ginkgolides and flavonoids. The anti inflammatory action may be associated with their PAF (Platelet activating factor) antagonistic activity. Studies have provided evidences regarding the role of PAF as a regulator of cytokines in inflammatory responses [76]. PAF can be synthesized in neurons following stimulation with neurotransmitters such as NMDA and glutamic acid and plays various roles in neuronal functions and brain development [77]. However an increased concentration of PAF has been implicated in neurodegenerative diseases like AD [78] Ginkgolides have a specific and potent antagonistic effects against PAF .In a study it was found that ginkgolide B could completely block PAF induced decrease of cell viability in SH-SY-5Y cells. It was also found that Quercetin a flavonoid constituent of EGb 761 may also be involved in EGb 761 s PAF antagonist activity [79]. In addition it has inhibitory effects on pro-inflammatory cytokines TNF α and interleukin 1 production.

The ginkgo biloba extract EGb 761 improves memory loss and cognitive impairments in patients with senile dementia. Ginkgo biloba extract treatment promotes neural stem cell proliferation and migration in the subventricular zone of PD mice [80], induces neural stem cell proliferation and differentiation in the hippocampus and improves learning and memory in young epileptic rats [81]. In a rat model of vascular model of vascular dementia, it was seen EGb 761 enhanced proliferation of neural stem cells in the subventricular zone and dentate and dentate gyrus and improved learning and memory [82]. Possible mechanisms for neural stem cell proliferation in rat model of vascular model of rats include inhibition of neural stem cells apotosis, antilipid peroxidation and excito-toxicity, changes in redox state in neural stem cells, regulate growth of neural stem cells and promote gene regulation.

Conclusion

Various studies have supported the usefulness of ginkgo biloba extract EGb 761 in the treatment and prevention of AD and in dementia. However in some of the review of clinical trials it as found as not effective in preventing nor improving the cognitive impairment. The various possible mechanisms for improving cognition of ginkgo biloba are amyloidogenesis and prevention of Aβ aggregation, anti oxidantant, anti inflammatory, modulation of tau phosphorylation, induction growth factors and neuroplasticity. Still the clinical efficacy still remains controversial. However the effect of long-term therapy with ginkgo biloba will be clarified through further clinical trials and investigations. In the absence of effective treatments of dementia, ginkgo biloba may still help, appearing to be safe and will not harm the patient. As there is overlap between different types of dementia and mixed pathologies, ginkgo biloba appears to be safe in a multi targeted approach treatment.

References

1. Brookmeyer R, Johnson E, Ziegler-Graham K, Arrighi HM. Forecasting the global burden of Alzheimer's disease. Alzheimers Dement. 2007; 3: 186-191.
2. van Beek TA. Chemical analysis of Ginkgo biloba leaves and extracts. J Chromatogr A. 2002; 967: 21-55.
3. Kleijnen J, Knipschild P. Ginkgo biloba. Lancet. 1992; 340: 1136-1139.
4. Diamond BJ, Shiflett SC, Feiwel N, Matheis RJ, Noskin O, Richards JA, et al. Ginkgo biloba extract: mechanisms and clinical indications. Arch Phys Med Rehabil. 2000; 81: 668-678.
5. Horáková L, Licht A, Sandig G, Jakstadt M, Duracková Z, Grune T. Standardized extracts of flavonoids increase the viability of PC12 cells treated with hydrogen peroxide: effects on oxidative injury. Arch Toxicol. 2003; 77: 22-29.
6. Maitra I, Marcocci L, Droy-Lefaix MT, Packer L. Peroxyl radical scavenging activity of Ginkgo biloba extract EGb 761. Biochem Pharmacol. 1995; 49: 1649-1655.
7. Brunetti L, Orlando G, Menghini L, Ferrante C, Chiavaroli A, Vacca M. Ginkgo biloba leaf extract reverses amyloid beta-peptide-induced isoprostane production in rat brain in vitro. Planta Med. 2006; 72: 1296-1299.
8. Smith JV, Burdick AJ, Golik P, Khan I, Wallace D, Luo Y. Anti-apoptotic properties of Ginkgo biloba extract EGb 761 in differentiated PC12 cells. Cell Mol Biol (Noisy-le-grand). 2002; 48: 699-707.
9. Rai GS, Shovlin C, Wesnes KA. A double-blind, placebo controlled study of Ginkgo biloba extract ('tanakan') in elderly outpatients with mild to moderate memory impairment. Curr Med Res Opin. 1991; 12: 350-355.
10. Napryeyenko O, Borzenko I; GINDEM-NP Study Group. Ginkgo biloba special extract in dementia with neuropsychiatric features. A randomised, placebo-controlled, double-blind clinical trial. Arzneimittelforschung. 2007; 57: 4-11.

11. Amieva H, Meillon C, Helmer C, Barberger-Gateau P, Dartigues JF. Ginkgo biloba extract and long-term cognitive decline: a 20-year follow-up population-based study. PLoS One. 2013; 8: e52755.

12. Gavrilova SI, Preuss UW, Wong JW, Hoerr R, Kaschel R, Bachinskaya N; GIMCIPlus Study Group. Efficacy and safety of Ginkgo biloba extract EGb 761 in mild cognitive impairment with neuropsychiatric symptoms: a randomized, placebo-controlled, double-blind, multi-center trial. Int J Geriatr Psychiatry. 2014; 29: 1087-1095.

13. Tan MS, Yu JT, Tan CC, Wang HF, Meng XF, Wang C, et al. Efficacy and adverse effects of ginkgo biloba for cognitive impairment and dementia: a systematic review and meta-analysis. J Alzheimers Dis. 2015; 43: 589-603.

14. Weinmann S, Roll S, Schwarzbach C, Vauth C, Willich SN. Effects of Ginkgo biloba in dementia: systematic review and meta-analysis. BMC Geriatr. 2010; 10: 14.

15. Geng J, Dong J, Ni H, Lee MS, Wu T, Jiang K, et al. Ginseng for cognition. Cochrane Database Syst Rev. 2010; CD007769.

16. Birks J, Evans JG. Ginkgo biloba for cognitive impairment and dementia. Cochrane Database Syst Rev. 2009; CD003120.

17. Ihl R. Effects of Ginkgo biloba extract EGb 761 ® in dementia with neuropsychiatric features: review of recently completed randomised, controlled trials. Int J Psychiatry Clin Pract. 2013; 17: 8-14.

18. Mazza M, Capuano A, Bria P, Mazza S. Ginkgo biloba and donepezil: a comparison in the treatment of Alzheimer's dementia in a randomized placebo-controlled double-blind study. Eur J Neurol. 2006; 13: 981-985.

19. Ihl R. Gingko biloba extract EGb 761®: clinical data in dementia. Int Psychogeriatr. 2012; 24: S35-40.

20. Herrschaft H, Nacu A, Likhachev S, Sholomov I, Hoerr R, Schlaefke S. Ginkgo biloba extract EGb 761® in dementia with neuropsychiatric features: a randomised, placebo-controlled trial to confirm the efficacy and safety of a daily dose of 240 mg. J Psychiatr Res. 2012; 46: 716-723.

21. Vellas B, Caley N, Ousset PJ, Berrut G, Dartigues JF, Dubois B, et al. Long term use of standardized ginkgo biloba extract for the prevention of Alzheimer's disease (GuidAge): a randomized placebo controlled trial. Lancet Neurol. 2012; 11: 851-859.

22. DeKosky ST, Williamson JD, Fitzpatrick AL, Kronmal RA, Ives DG, Saxton JA, et al. Ginkgo biloba for prevention of dementia: a randomized controlled trial. JAMA. 2008; 300: 2253-2262.

23. Lautenschlager NT, Ihl R, Müller WE. Ginkgo biloba extract EGb 761® in the context of current developments in the diagnosis and treatment of age-related cognitive decline and Alzheimer's disease: a research perspective. Int Psychogeriatr. 2012; 24: S46-50.

24. Zhang SJ, Xue ZY. Effect of Western medicine therapy assisted by Ginkgo biloba tablet on vascular cognitive impairment of none dementia. Asian Pac J Trop Med. 2012; 5: 661-664.

25. Jiang L, Su L, Cui H, Ren J, Li C. Ginkgo biloba extract for dementia: a systematic review. Shanghai Arch Psychiatry. 2013; 25: 10-21.

26. Spencer JP. Beyond antioxidants: the cellular and molecular interactions of flavonoids and how these underpin their actions on the brain. Proc Nutr Soc. 2010; 69: 244-260.

27. Williams RJ, Spencer JP, Rice-Evans C. Flavonoids: antioxidants or signalling molecules? Free Radic Biol Med. 2004; 36: 838-849.

28. Spencer JP. The impact of flavonoids on memory: physiological and molecular considerations. Chem Soc Rev. 2009; 38: 1152-1161.

29. Dinges DF. Cocoa flavanols, cerebral blood flow, cognition, and health: going forward. J Cardiovasc Pharmacol. 2006; 47: S221-223.

30. Rezai-Zadeh K, Shytle D, Sun N, Mori T, Hou H, Jeanniton D, et al. Green tea epigallocatechin-3-gallate (EGCG) modulates amyloid precursor protein cleavage and reduces cerebral amyloidosis in Alzheimer transgenic mice. J Neurosci. 2005; 25: 8807-8814.

31. Wang J, Ho L, Zhao W, Ono K, Rosenweig C, Chen L, et al. Grape derived polyphenolic prevents Abeta oligomerization and attenuate cognitive deterioration in a mouse model of Alzheimer's disease. J Neurosci. 2008; 28: 6388-6392.

32. Rezai-Zadeh K, Arendash GW, Hou H, Fernandez F, Jensen M, Runfeldt M, et al. Green tea epigallocatechin-3-gallate (EGCG) reduces beta-amyloid mediated cognitive impairment and modulates tau pathology in Alzheimer transgenic mice. Brain Res. 2008; 1214: 177-187.

33. Li Q, Zhao HF, Zhang ZF, Liu ZG, Pei XR, Wang JB, et al. Long term green tea catechin administration prevents spatial learning and memory impairment in senescence accelerated mouse prone -8 mice by decreasing Aß -42 oligomers and up regulating synaptic plasticity related proteins in the hippocampus. Neuroscience. 2009; 163: 741-749.

34. Obregon DF, Rezai-Zadeh K, Bai Y, Sun N, Hou H, Ehrhart J, et al. ADAM10 activation is required for green tea (-)-epigallocatechin-3-gallate-induced alpha-secretase cleavage of amyloid precursor protein. J Biol Chem. 2006; 281: 16419-16427.

35. Amit T, Avramovich-Tirosh Y, Youdim MB, Mandel S. Targeting multiple Alzheimer's disease etiologies with multimodal neuroprotective and neurorestorative iron chelators. FASEB J. 2008; 22: 1296-1305.

36. Mandel S, Amit T, Bar Am O, Youdin MB. Iron dysregulation in ALZHEIMERS disease: multimodal brain permeable iron chelating drugs, possessing neuroprotective-neurorescue and amyloid precursor protein –processing regulatory activities as therapeutic agents. Prog Neurobiol. 2007; 82: 348-360.

37. Colciaghi F, Borroni B, Zimmermann M, Bellone C, Longhi A, Padovani A, et al. Amyloid precursor protein metabolism is regulated toward alpha-secretase pathway by Ginkgo biloba extracts. Neurobiol Dis. 2004; 16: 454-460.

38. Ramassamy C. Emerging role of polyphenolic compounds in the treatment of neurodegenerative diseases: A review of their intracellular targets. Eur J Pharmacol. 2006; 545: 51-64.

39. Stackman RW, Eckenstein F, Frei B, Kulhanek D, Nowlin J, Quinn JF. Prevention of age-related spatial memory deficits in a transgenic mouse model of Alzheimer's disease by chronic Ginkgo biloba treatment. Exp Neurol. 2003; 184: 510-520.

40. Yao ZX, Han Z, Drieu K, Papadopoulos V. Ginkgo biloba extract (Egb 761) inhibits beta-amyloid production by lowering free cholesterol levels. J Nutr Biochem. 2004; 15: 749-756.

41. Bodovitz S, Klein WL. Cholesterol modulates alpha-secretase cleavage of amyloid precursor protein. J Biol Chem. 1996; 271: 4436-4440.

42. Howland DS, Trusko SP, Savage MJ, Reaume AG, Lang DM, Hirsch JD, et al. Modulation of secreted beta-amyloid precursor protein and amyloid beta-peptide in brain by cholesterol. J Biol Chem. 1998; 273: 16576-16582.

43. Simons M, Keller P, De Strooper B, Beyreuther K, Dotti CG, Simons K. Cholesterol depletion inhibits the generation of beta-amyloid in hippocampal neurons. Proc Natl Acad Sci U S A. 1998; 95: 6460-6464.

44. Watanabe CM, Wolffram S, Ader P, Rimbach G, Packer L, Maguire JJ, et al. The in vivo neuromodulatory effects of the herbal medicine ginkgo biloba. Proc Natl Acad Sci U S A. 2001; 98: 6577-6580.

45. Tsuzuki K, Yamaguchi H, Tateno M, Imai K, Fujii N, Yamauchi T, et al. Transthyretin binds amyloid beta peptides, A BETA 1-42 and A beta 1-40 to form complex in the autopsied human kidney possible role of thransthyretin for abeta sequestration. Neurosci Lett. 2000; 281: 171-174.

46. Shimmyo Y, Kihara T, Akaike A, Niidome T, Sugimoto H. Epigallocatechin-3-gallate and curcumin suppress amyloid beta-induced beta-site APP cleaving enzyme-1 upregulation. Neuroreport. 2008; 19: 1329-1333.

47. Shimmyo Y, Kihara T, kaike A, Niidome T, Sugimoto H. Flavonoids and flavones as BACE1 inhibitors: structure activity relationship in cell free: cell based and in silico studies reveal novel pharmacophore features. Biochem Biophys Acta. 2008; 1780: 819-825.

48. Taniguchi S, Suzuki N, Masuda M, Hisanaga S, Iwatsubo T, Goedert M, et al. Inhibition of heparin-induced tau filament formation by phenothiazines, polyphenols, and porphyrins. J Biol Chem. 2005; 280: 7614-7623.

49. Le Bars PL, Katz MM, Berman N, Itil TM, Freedman AM, Schatzberg AF. A placebo-controlled, double-blind, randomized trial of an extract of Ginkgo biloba for dementia. North American EGb Study Group. JAMA. 1997; 278: 1327-1332.

50. Yao Z, Drieu K, Papadopoulos V. The Ginkgo biloba extract EGb 761 rescues the PC12 neuronal cells from beta-amyloid-induced cell death by inhibiting the formation of beta-amyloid-derived diffusible neurotoxic ligands. Brain Res. 2001; 889: 181-190.

51. Yin Y, Ren Y, Wu W, Wang Y, Cao M, Zhu Z, et al. Protective effects of bilobalide on Aβ(25-35) induced learning and memory impairments in male rats. Pharmacol Biochem Behav. 2013; 106: 77-84.

52. Xiao Q, Wang C, Li J, Hou Q, Li J, Ma J, et al. Ginkgolide B protects hippocampal neurons from apoptosis induced by beta-amyloid 25-35 partly via up-regulation of brain-derived neurotrophic factor. Eur J Pharmacol. 2010; 647: 48-54.

53. Wei T, Ni Y, Hou J, Chen C, Zhao B, Xin W, et al. Hydrogen peroxide-induced oxidative damage and apoptosis in cerebellar granule cells: protection by Ginkgo biloba extract. Pharmacol Res. 2000; 41: 427-433.

54. Ross CA, Poirier MA. Protein aggregation and neurodegenerative disease. Nat Med. 2004; 10 Suppl: S10-17.

55. Takahashi T, Katada S, Onodera O. Polyglutamine diseases: where does toxicity come from? what is toxicity? where are we going? J Mol Cell Biol. 2010; 2: 180-191.

56. Strk M, Behl C. The ginkgo biloba extract EGb761 modulates proteosome activity and polyglutamine protein aggregation. Evid Based Complement Alternat Med. 2014; 2014: 940186.

57. Eckert A. Mitochondrial effects of Ginkgo biloba extract. Int Psychogeriatr. 2012; 24: S18-20.

58. Rhein V, Giese M, Baysang G, Meier F, Rao S, Schulz KL, et al. Ginkgo biloba extract ameliorates oxidative phosphorylation performance and rescues abeta-induced failure. PLoS One. 2010; 5: e12359

59. Shi C, Zheng DD, Wu FM, Liu J, Xu J. The phosphatidyl inositol 3 kinase-glycogen synthase kinase 3β pathway mediates bilobalide-induced reduction in amyloid β-peptide. Neurochem Res. 2012; 37: 298-306.

60. Smith JV, Luo Y. Studies on molecular mechanisms of Ginkgo biloba extract. Appl Microbiol Biotechnol. 2004; 64: 465-472.

61. Wu Y, Wu Z, Butko P, Christen Y, Lambart MP, Klein WL, et al. Amyloid beta induced pathological behaviors are suppressed by ginkgo biloba extract EGb761 and ginkgolides in transgenic Caenorhabditis elegans. J Neurosc. 2006; 26: 13102-12113.

62. Ahlemeyer B, Krieglstein J. Neuroprotective effects of Ginkgo biloba extract. Cell Mol Life Sci. 2003; 60: 1779-1792.

63. Bridi R, Crossetti FP, Steffen VM, Henriques AT. The antioxidant activity of standardized extract of Ginkgo biloba (EGb 761) in rats. Phytother Res. 2001; 15: 449-451.

64. Colak O, Sahin A, Alataş O, Inal M, Yaşar B, Kiper H. The effect of Ginkgo biloba on the activity of catalase and lipid peroxidation in experimental strangulation ileus. Int J Clin Lab Res. 1998; 28: 69-71.

65. Smith JV, Luo Y. Elevation of oxidative free radicals in Alzheimer's disease models can be attenuated by Ginkgo biloba extract EGb 761. J Alzheimers Dis. 2003; 5: 287-300.

66. Rimbach G, Gohil K, Matsugo S, Moini H, Saliou C, Virgili F, et al. Induction of glutathione synthesis in human keratinocytes by Ginkgo biloba extract (EGb761). Biofactors. 2001; 15: 39-52.

67. Dai Q, Borenstein AR, Wu Y, Jackson JC, Larson EB. Fruit and vegetable juices and Alzheimer's disease: the Kame Project. Am J Med. 2006; 119: 751-759.

68. Commenges D, Scotet V, Renaud S, Jacqmin-Gadda H, Barberger-Gateau P, Dartigues JF, et al. Intake of flavonoids and risk of dementia. Eur J Epidemiol. 2000; 16: 357-363.

69. Barth SA, Inselmann G, Engemann R, Heidemann HT. Influences of Ginkgo biloba on cyclosporin A induced lipid peroxidation in human liver microsomes in comparison to vitamin E, glutathione and N-acetylcysteine. Biochem Pharmacol. 1991; 41: 1521-1526.

70. Heiss C, Finis D, Kleinbongard P, Hoffmann A, Rassaf T, Kelm M, et al. Sustained increase in flow-mediated dilation after daily intake of high-flavanol cocoa drink over 1 week. J Cardiovasc Pharmacol. 2007; 49: 74-80.

71. Gage FH. Mammalian neural stem cells. Science. 2000; 287: 1433-1438.

72. Cooke JP. NO and angiogenesis. Atheroscler Suppl. 2003; 4: 53-60.

73. Heiss C, Jahn S, Taylor M, Real WM, Angel FS, Wong ML, et al. Improvement of endothelial function with dietary flavanols is associated with mobilization of circulating angiogenic cells in patients with coronary artery disease. J Am Col Cardiol. 2010; 56: 218-224.

74. Zhao C, Deng W, Gage FH. Mechanisms and functional implications of adult neurogenesis. Cell. 2008; 132: 645-660.

75. Baequet P. The ginkgolides: Potent platelet activating factor antagonist isolated from ginkgo biloba L chemistry, pharmacology and clinical applications Drugs Future. 1987; 42: 643-688.

76. Maclennan KM, Darlington CL, Smith PF. The CNS effects of Ginkgo biloba extracts and ginkgolide B. Prog Neurobiol. 2002; 67: 235-257.

77. Aihara M, Ishii S, Kume K, Shimizu T. Interaction between neurone and microglia mediated by platelet-activating factor. Genes Cells. 2000; 5: 397-406.

78. Bate C, Tayebi M, Williams A. Ginkgolides protect against amyloid-beta1-42-mediated synapse damage in vitro. Mol Neurodegener. 2008; 3: 1.

79. Shi C, Zhao L, Zhu B, Li Q, Yew DT, Yao Z, et al. Protective effects of Ginkgo biloba extract (EGb761) and its constituent's quercetin and ginkgolide B against beta-amyloid peptide-induced toxicity in SH-SY5Y cells. Chem Biol Interact. 2009; 181: 115-123.

80. Sun HM, Zhang L, Guan T. Study of GBE on promoying proliferation of neural stem cell in the subventricular zone in mice of Parkinson's disease. SHIJE zHONGXYjie Zaxhi. 2006; 3: 518-520.

81. Li R, Yuan BQ, Fan QP ET AL. Effect of ginkgo biloba extract on learning and memory of developing rats with kindled seizure by pentelene tetrazole and proliferatin and differentiation of hippocampal neural stem cells. Shiyong Erke Linehang Zahi 2011; 26: 1821-1824.

82. Wang J, Chen W, Wang Y. A ginkgo biloba extract promotes proliferation of endogenous neural stem cells in vascular dementia rats. Neural Regen Res. 2013; 8: 1655-1662.

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