ISSN 0975 - 6299 Vol 2 / Issue 4 / Oct - Dec 2011

International Journal of Pharma and Bio Sciences

REVIEW ARTICLE

PHARMACOLOGY

TOP THREE HERBS IN ALZHEIMER'S DISEASE - A REVIEW

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ABSTRACT

Alzheimer's is a degenerative disease characterized by the progressive death of brain cells. It is the most common form of dementia, which occurs equally in both genders. There are currently a few plant-derived drugs approved for clinical use. This is largely because most herbal medicines are complex mixtures of chemical components and have diverse biological and pharmacological actions. A considerable number of herbal extracts and constituents, most notably antidepressant and antidementia agents, possess antioxidant and neuroprotective actions, as evidenced by protection against neuronal cell death induced by exposure to excessive free radicals, excitatory toxins, toxic derivatives of amyloid precursor protein, and other neurotoxins. In this review, the antioxidant and neuroprotective effects of herbs like *Curcuma longa* (turmeric), *Bacopa monniera Wettst* (Brahmi),*Ginko biloba* (Maidenhair tree) that have great therapeutic potentials in Alzheimer's disease is discussed extensively

ISSN 0975 - 6299 Vol 2 / Issue 4 / Oct - Dec 2011

KEY WORDS

Alzheimer's disease, antioxidants, neuroprotective agents, amyloid precursor protein, herbal medicine.

INTRODUCTION

Dr. Alois Alzheimer first identified the "peculiar disease of the cerebral cortex" in 1906 and was later named after him.[1] Alzheimer described a thinned cortex speckled with unusual brown clumps and irregular knots that appeared to be growing inside the brain cells that are now called as amyloid plaques and neurofibrillary tangles. These are the hallmark signs of Alzheimer (AD) Alzheimer's is a degenerative disease characterized by the progressive death of brain cells, which occurs equally in both genders and it is the most common form of dementia. Most often, it is diagnosed in people over 65 years of age [2]. In 2006, there were 26.6 million sufferers worldwide. Alzheimer's is predicted to affect 1 in 85 people globally by 2050. [3] There are many common symptoms even though the course of Alzheimer's disease is unique for every individual.[4]When AD is suspected, the diagnosis is usually confirmed with behavioural assessments and cognitive tests, often followed by a brain scan. [5]

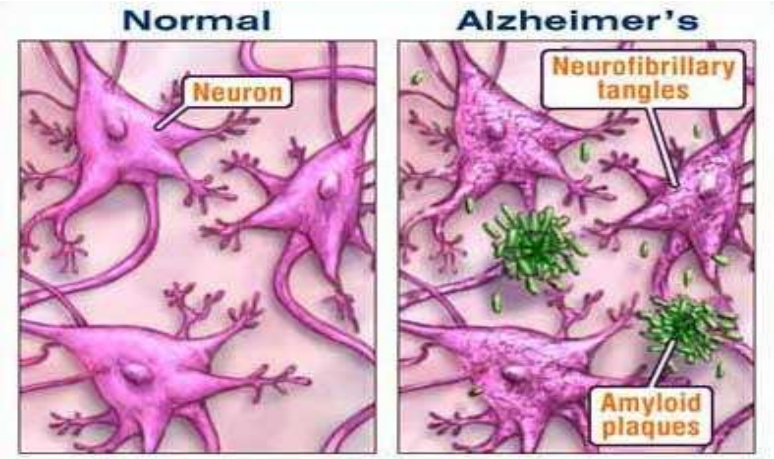

Fig. 1
Normal Neuron and Alzheimer's Neuron

In the early stages, the most common symptom of AD is the inability to acquire new memories, observed as difficulty in recalling recently observed events. As the disease advances, symptoms include confusion, irritability and aggression, mood swings, language breakdown, long-term memory loss and the general withdrawal of the sufferer as their senses decline .[6] [,7] Gradually, bodily functions are lost, ultimately leading to death. The cause and progression of Alzheimer's disease are not well understood. Research indicates that the disease is associated with plaques and tangles in the brain.[4] AD is one of the most costly diseases to society.[8,9] As AD cannot be cured and is degenerative, management of patients is essential. The impairment of central acetylcholine (ACh) neuro-transmission due to neural degeneration is believed to be a principal neuropathological

feature of the disease.[10,11] Histological, pathological, molecular, cellular and gene expression studies of AD have revealed that multiple cellular pathways are involved in the disease progression. [12] The pathological features identified in the central nervous system in AD are amyloid plaques, neurofibrillary tangles, inflammatory processes and disturbance of neurotransmitters .[13,14] Studies with AD brains and mouse models show that abnormal metabolism of amyloid precursor protein (APP) is a key mechanism of AD pathogenesis.[15,16]Cells in the brains of AD patients exhibit abnormally high amounts of oxidatively modified proteins, lipids and DNA; such free radical-mediated molecular damage is particularly prominent in the environment of senile plaques and in neurofibrillary tangle-bearing neurons, suggesting roles for reactive oxygen species in amyloid-mediated neuronal damage and neurofibrillary pathologies. [17] Amyloid precursor proteins (APP) is an integral membrane protein of uncertain function. The cellular proteolytic processing of amyloid precursor protein (APP), can lead to the generation of amyloid β-protein (Aβ) that readily form aggregates and that have neurotoxic activities under certain conditions *in vitro* and *in vivo*. [18,19] Other than the normal treatment with allopathic medicine in general for Alzheimer's, there is acupuncture, aromatherapy, art therapy, herbal supplements, exercise – gardening – yoga, massage , pet – animal caring etc;

Numerous plants are reputed in traditional practices of medicine to alleviate the cognitive decline that can be associated with general ageing and they may be relevant in the treatment of specific cognitive disorders such as Alzheimer's disease and other dementias. This review gives an insight to some of the herbs which are easily available around us with potent effect on Alzheimer's like *Curcuma longa* (turmeric), *Bacopa monniera Wettst* (Brahmi), *Ginko biloba* (Maidenhair tree)

Curcuma longa (Turmeric)

Curcuma longa (family Zingiberaceae) is a perennial herb that grows to a height of three to five feet and is cultivated extensively in Asia, India, China and other countries with a tropical climate. It has oblong, pointed leaves and funnel-shaped yellow flowers.[20]The rhizome, the portion of the plant used medicinally, is usually boiled, cleaned and dried, yielding a yellow powder. Dried *Curcuma longa* is the source of the spice turmeric, the ingredient that gives curry powder its characteristic yellow colour. Turmeric is used extensively in foods for its flavour and colour as well as having a long tradition of use in the Chinese and Ayurvedic systems of medicine, particularly as an anti-inflammatory and for the treatment of flatulence, jaundice, menstrual difficulties, hematuria, hemorrhage and colic. Turmeric can also be applied topically in poultices to relieve pain and inflammation.[21]Current research has focused on turmeric's antioxidant, hepatoprotective, anti-inflammatory, anticarcinogenic, and antimicrobial properties, in addition to its use in cardiovascular disease and gastrointestinal disorders. Turmeric is a powerful anti-inflammatory herb. It has been shown to be helpful in the treatment of rheumatoid arthritis, osteoarthritis, injuries, trauma, and stiffness from both under activity and over activity. [22]

The rhizome contains 70% carbohydrates, 7% protein, 4% minerals and at least 4% essential oils. It also has vitamins, other alkaloids and about 1% resin .[23]The active constituents of turmeric are the flavonoid curcumin (diferuloylmethane) and various volatile oils, including tumerone, atlantone, and zingiberone. Other constituents include sugars, proteins, and resins. The best-researched active constituent is curcumin, which comprises 0.3-5.4 % of raw turmeric.[21]In its raw state, turmeric contains only 2-5% curcumin. [24] Curcumin is the substance that is responsible for the biological activity of turmeric.

Fig. 2
Curcuma longa

The active properties of curcumin are best known for protective properties. The same components that prevent deterioration of food, protect living tissue from degenerating, possibly extending the life span of our bodies. [23] Clinical and laboratory research indicates that diets that include turmeric or curcumin stabilize and protect biomolecules in the body at the molecular level, which is shown in its anti-oxidant, anti-mutagenic and anti-carcinogenic action. [25] These components may work by protecting a person directly, by shielding the biomolecules, or indirectly, by stimulating the natural detoxification and defense mechanisms of the body, helping the body to heal and preserve itself naturally. [23]
It has been noted that people taking anti-inflammatory medication for arthritis are less likely to develop Alzheimer's Disease.[25] Alzheimer's disease is found to be 4.4 times less common among older adults in India than in the United States. [24]

In vitro and *in vivo* studies substantiated that curcumin has anticancer, antiviral, antiarthritic, anti-amyloid, antioxidant and anti-inflammatory properties. They found to involve in the regulation of diverse molecular targets, including transcription factors (such as nuclear factor-κ B), growth factors (such as vascular endothelial cell growth factor), inflammatory cytokines (such as tumor necrosis factor, interleukin 1 and interleukin 6), protein kinases (such as mammalian target of rapamycin, mitogen-activated protein kinases, and Akt) and other enzymes (such as cyclooxygenase 2 and 5 lipoxygenase). Its ability to regulate multiple targets and its safety for human use, made curcumin an amenable therapeutic agent for the prevention or treatment of various malignant diseases, arthritis, allergies, Alzheimer Disease and other inflammatory illnesses.[26]

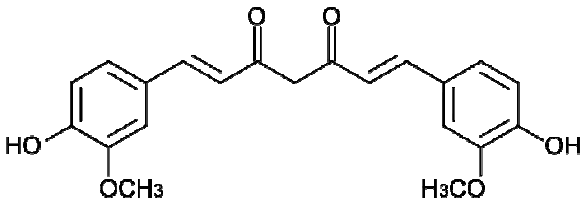

Fig. 3
Structure of curcumin ($C_{21}H_{20}O_6$)

The consumption of curcumin is associated with multiple health benefits like apparent reduction in the formation of amyloid-beta or Aß, an abnormal protein found in the brains of Alzheimer's patients.[26] Inflammation is believed to play a major role in the progression of Alzheimer's, resulting in the aggregation of tangled nerve bundles and Aß plaques in the brains of affected individuals. Experts suggest that the consumption of curcumin might offer protection from the inflammation that triggers neurodegenerative diseases such as Alzheimer's. Researchers believe that curcumin targets a variety of inflammatory pathways, which could be useful in cancer, arthritis, cardiovascular disease and Alzheimer's dementia. Like many polyphenols, curcumin appears to interfere with the activity of inflammatory transcription factors, growth factors, cytokines and enzymes. Furthermore, a study has demonstrated that curcumin binds directly to Aß plaques which could contribute to its protective properties.[27]One important consideration in the use of medications or nutraceuticals is whether they cross the blood-brain barrier and studies shows that it does cross the blood-brain barrier in mammals.[28]

Bacopa monniera Wettst ((**Brahmi)**

Bacopa monniera Wettst (family Scrophulariaceae) is commonly known as *Herpestis monniera*, water hyssop or Brahmi. [29,30,31] It is found throughout India, Nepal, Sri Lanka, China, Taiwan, Vietnam and Florida, Hawaii and some other southern states of USA. Bacopa is a small tropical, creeping, succulent, marshy herb with short, petiolated, oblong leaves, rooting at nodes. Stem is 10-30 cm long, 1-2 mm thick, with soft, glabrous ascending branches. Leaves are 0.6-2.5cm long and 3-8mm broad. Flowers are blue or white with purple veins, axillary and solitary on long pedicels. Capsule is ovoid, glabrous, up to 5mm long. Flowers and fruit appear in summer and the entire plant is used medicinally.[32,33] It has no distinct odour but taste is slightly bitter. [30]

Fig.4
Bacopa monniera

Bacopa's chief chemical constituents include alkaloids brahmine, herpestine and nicotine,saponin monierin, hersaponin , bacoside A1, A2 , A3 and B and four saponin bacogenin A1 to A4.[34-38] It also contains betulinic acid .A milestone in the elucidation of the pharmacologically active principles in Bacopa monnieri or brahmi was achieved by Chatterji and coworkers .[39-40]Analysis of the leaves and stalks showed moisture, 88.4; protein, 2.1 fat, 0.6; carbohydrates,5.9; crude fiber,1.05; and ash, 1.9 g / 100g. calcium,202.0; phosphorus, 16.0; iron, 7.8; ascorbic acid, 63.0;nicotinic acid 0.3 mg /100 g; and energy, 38 cal / 100 g. The leaves contain a sterol $C_{26}H_{46}O.H_2O$.[41]

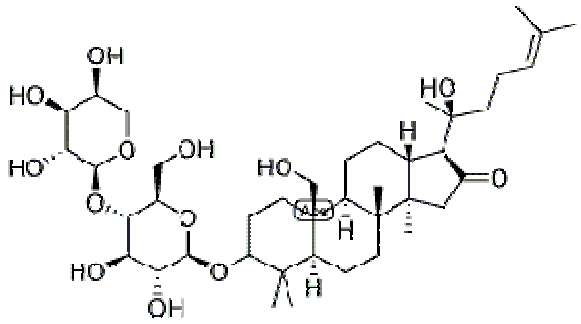

Fig. 5
Structure of Bacoside A ($C_{41}H_{68}O_{13}$)

Brahmi has been used in the Ayurvedic system of medicine for centuries. Traditionally, it was used as a brain tonic to enhance memory development, learning, and concentration, and to provide relief to patients with anxiety or epileptic disorders. The plant has also been used in India and Pakistan as a cardiac tonic, digestive aid, and to improve respiratory function in cases of bronchoconstriction.[32,42,43] It is listed as a nootropic, a drug that enhances cognitive ability. In India, this plant has also been used traditionally to consecrate newborn babies in the belief that it will open the gateway of intelligence. Laboratory studies on rats indicate that extracts of the plant improve memory capacity and motor learning ability.[44] Recent studies suggest Bacopa may improve intellectual activity.[45,46,47] The sulfhydryl and polyphenol components of *Bacopa monniera* extract have also been shown to impact the oxidative stress cascade by scavenging reactive oxygen species, inhibiting lipoxygenase activity and reducing divalent metals. This mechanism of action may explain the effect of *Bacopa monniera* extract in reducing beta-amyloid deposits in mice with Alzheimer's disease.[48]

Bacopa's primary therapeutic use is to enhance cognitive function, most research has focused on the mechanism behind these properties. The triterpenoid saponins and their bacosides are responsible for Bacopa's ability to enhance nerve impulse transmission. The bacosides aid in repair of damaged neurons by enhancing kinase activity, neuronal synthesis, and restoration of synaptic activity and ultimately nerve impulse transmission.[49] Loss of cholinergic neuronal activity in the hippocampus is the primary feature of Alzheimer's disease.[50] Based on animal study results, bacosides appear to have antioxidant activity in the hippocampus, frontal cortex, and striatum.[51] Animal research has shown Bacopa extracts modulate the expression of certain enzymes involved in generation and scavenging of reactive oxygen species in the brain.[52] *In vitro* research has shown Bacopa exerts a protective effect against DNA damage in astrocytes and human fibroblasts.[53,54]

An open label, prospective, uncontrolled, non-randomized trial was conducted by Goswami *etal* to evaluate the effect of *Bacopa monnieri* on cognitive functions in Alzheimer's disease patients. Study population included all newly diagnosed patients of Alzheimer's disease in the psychiatry outdoor patient department between 60-65 years of age. Subsequently all patients took 300 mg of *Bacopa monniera* standardized extract, orally twice a day for 6 months. Study patients showed statistically significant improvements in various components including orientation of time, place and person, attention and in their language component in

terms of reading, writing and comprehension at the end of trial. The patients involved in this trial also reported improvement in their quality of life and decrease in the irritability and insomnia. So the researchers concluded that administration of *Bacopa monnieri* standardized extract for 6 months showed improvement in some aspects of cognitive functions in geriatric patients suffering from Alzheimer's disease. [55]

To evaluate the effect of *Bacopa monniera* extract (BME) on amyloid (Abeta) pathology in PSAPP mice, two doses of BME (40 or 160 mg/kg/day) were administered starting at 2 months of age for either 2 or 8 months. From this study data, Holcomb *etal* suggested that BME has potential application in Alzheimer's disease therapeutics as it lowers Abeta 1-40 and 1-42 levels in cortex by as much as 60%, and reverses Y-maze performance and open field hyper locomotion behavioral changes present in PSAPP mice.[56]

Jyoti A and Sharma D investigated the neuroprotective effect of Bacopa extract against aluminium-induced changes in peroxidative products, such as thio-barbituric acid-reactive substance (TBA-RS) and protein carbonyl contents and superoxide dismutase (SOD) activity. Effect on lipofuscin (age pigments) accumulation and ultra structural changes were also studied. Bacopa effects were compared with those of l-deprenyl. Co-administration of Bacopa extract during aluminium treatment significantly prevented the aluminium-induced decrease in SOD activity as well as the increased oxidative damage to lipids and proteins. Protective effect was also observed at microscopic level. Fluorescence and electron microscopic studies revealed considerable inhibition of intraneuronal lipofuscin accumulation and necrotic alteration in the CA1 region of the hippocampus. Observations showed that Bacopa's neuroprotective effects were comparable to those of l-deprenyl at both biochemical and microscopic levels.[57]

Anbarasi *et al* [58] has conducted a study to evaluate the antioxidant role of bacoside A against chronic cigarette smoking induced oxidative damage in rat brain. Bacoside A administration improved the antioxidant status and maintained the levels of trace elements. Antioxidant status of the brain was assessed from the levels of reduced glutathione, vitamin C, vitamin E and vitamin A and the activities of superoxide dismutase, catalase, and glutathione peroxidase and glutathione reductase. The levels of copper, iron, zinc and selenium in brain and serum ceruloplasmin activity were also measured. Oxidative stress was evident from the diminished levels of both enzymatic and non-enzymatic antioxidants. Alterations in the levels of trace elements with accumulation of copper and iron, and depletion of zinc and selenium were also observed. These results suggest that chronic cigarette smoke exposure enhances oxidative stress, thereby disturbing the tissue defense system and bacoside A protects the brain from the oxidative damage through its antioxidant potential.

Kishore and Singh investigated the effect of bacosides (alcoholic extract of brahmi) on scopolamine (3 mg kg(-1), ip), sodium nitrite (75 mg kg(-1), ip) and BN52021 (15 mg kg(-1), ip) induced experimental amnesia in mice, using Morris water maze test, all the agents were administered 30 min before the acquisition trials on each day and repeated for 4 consecutive days, and on 5th day during the retrieval trials. On the basis of the study results they have concluded that bacosides facilitate anterograde memory and attenuate anterograde experimental amnesia induced by scopolamine and sodium nitrite possibly by improving acetylcholine level and hypoxic conditions, respectively. Beside this bacosides also reversed BN52021 induced retrograde amnesia, probably due to increase in platelet activating factor (PAF) synthesis by enhancing cerebral glutamate level. [59]

Ginkgo biloba:

Ginkgo biloba, also known as Maidenhair Tree, is often planted as an ornamental tree which grows to a height of 120 feet. The tree has an

angular crown and long, somewhat erratic branches and is usually deep rooted and resistant to wind and snow damage. Young trees are often tall and slender, and sparsely branched; the crown becomes broader as the tree ages. The leaves are unique, being fan-shaped with veins radiating out into the leaf blade, sometimes bifurcating. The leaves are usually 5–10 cm. The old popular name "Maidenhair tree" is because the leaves resemble some of the pinnae of the Maidenhair fern *Adiantum capillus-veneris*. Ginkgos are dioecious, with separate sexes, some trees being female and others being male.[60] Ginkgo seeds and leaves have been used in traditional Chinese medicine for over 5,000 years.

Fig. 6
Ginkgo biloba

In modern botanical medicine, extracts are made from the distinctive, fan-shaped leaves. Ginkgo biloba extracts , utilized in clinical trials (EGb 761 and LI1370) contain approximately 24-percent flavone glycosides (primarily composed of quercetin, kaempferol, and isorhamnetin) and 6-percent terpene lactones (2.8-3.4% ginkgolides A, B, and C, and 2.6-3.2% bilobalide). Other constituents include proanthocyanadins, glucose, rhamnose and organic acids (hydroxykinurenic, kynurenic, protocatechic, vanillic, shikimic) D glucaric acid and ginkgolic acid and related alkylphenols.[61]

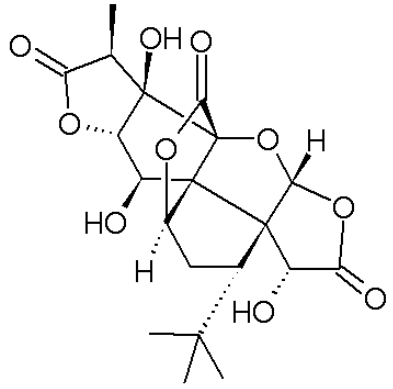

Fig. 7
Structure of Ginkgolide B ($C_{20}H_{24}O_{10}$)

Ginkgo is believed to have nootropic properties, and is mainly used as memory and concentration enhancer [62] and as anti-vertigo agent. Ginkgo exhibits anti-inflammatory, neuroprotective and

antithrombotic effects. Flavonoid glycosides and ginkgolide B may inhibit the oxidization of lipoprotein formation, platelet aggregation and platelet adherence. Flavonoid glycosides may exert antioxidant effects. The free radical scavenging actions on superoxide anions may increase the half-life of endothelium-based relaxing factors and cause relaxation of blood vessels. Ginkgo extract may increase cerebral blood flow, and protect neural and retinal tissue from oxidative or hypoxic injury. In addition, the ginkgo extract may offer intestinal mucosa protection against ischemic injury by decreasing neutrophil infiltration and lipid peroxidation, stimulate choline uptake and prevent declination of age-related muscarinic receptors, and decrease blood viscosity. [63-65]

The mechanism of action of ginkgo is believed to be produced by its functions as a neuroprotective agent, an antioxidant, a free-radical scavenger, a membrane stabilizer, and an inhibitor of platelet-activating factor via the terpene ginkgolide B.[66-69] Other pharmacologic effects includes endothelium relaxation mediated by inhibition of 3',5'-cyclic GMP (guanosine monophosphate) phosphodiesterase [70,71] , inhibition of age-related loss of muscarinergic cholinoceptors and α-adrenoceptors; and stimulation of choline uptake in the hippocampus .[72, 73]Ginkgo extract also has been shown to inhibit beta-amyloid deposition[74] Ginkgo has been proposed as a treatment for Alzheimer's disease on the basis of positive preclinical results in mice[75] .A study conducted by Mazza *et al* revealed that 160 mg of ginkgo extract is as effective as a daily 5 mg dose of the cholinesterase inhibitor donepezil in human subjects.[76] Ginkgo is found effective in treating mild to moderate dementia at a dose of 240 mg daily.[77] A recent meta-analysis of nine studies of ginkgo for use in the treatment of dementia concluded that it was more effective than placebo although, like other dementia drugs, the clinical significance of these moderate effects was difficult to quantify.[78]

Ginkgo biloba Oral administration can prevent the decline in muscarinic (cholinergic) receptor density in the hippocampus of rats [79] and might inhibit degradation of acetyl-choline by acetyl-cholinesterase. The anti-stress and neuroprotective effects of *Ginkgo biloba* extract might also be related to its effect on glucocorticoid biosynthesis. Ginkgo extract and specifically its components ginkgolide A and B decreases corticosteroid synthesis.[80] *Ex vivo* treatment with Gingko extract has resulted in a 50-percent reduction of ACTH-stimulated corticosterone production by adrenocortical cells.[81]

A 52 week, randomized doubled-blinded, placebo-controlled, parallel-group, multicenter trial was conducted to assess the efficacy and safety of EGb 761 extract of *Ginkgo biloba* in patients with multi-infarct dementia (MID) and Alzheimer disease. The study population included both men and women, 45 years of age or older, who was diagnosed with uncomplicated dementia. 327 patients have been enrolled in the study, where 251 patients had AD. 166 patients were randomly assigned to receive EGb 120mg QD for 52 weeks and 161 assigned to matching placebo. The study concluded that EGb appears to be safe and effective in improving the cognitive performance and social functioning of patients with dementia.[82]

CONCLUSION

Alzheimer's patients are currently treated with drugs like tacrine and donepezil (AChE inhibitors). The other measures which may be used include prevention of h-amyloidogenesis via antioxidant action; protection against neurotoxicity and neuronal death induced by endogenous neurotoxins, e.g. excitatory transmitters and ACh; elevation of neurotrophic levels e.g., nerve growth factor, modulation of neurotransmitter-receptor systems. The use of complementary medicines such as plant extracts in dementia therapy varies

according to the different cultural traditions. The herbal constituents for which the behavioral effects and pharmacological properties have been well characterized, may be good candidates for further investigations that may ultimately result in clinical use.

Curcumin present in turmeric benefits by apparent reduction in the formation of amyloid-beta or Aß, an abnormal protein found in the brains of Alzheimer's patients. Its anti-inflammatory potential is believed to play a major role in AD. Inflammation leads to progression of Alzheimer's, resulting in the aggregation of tangled nerve bundles and Aß plaques in the brains of affected individuals. Curcumin targets a variety of inflammatory pathways, which could be instrumental in Alzheimer's dementia. Curcumin appears to interfere with the activity of inflammatory transcription factors, growth factors, cytokines and enzymes. Curcumin binds directly to Aß plaques, which could contribute to its protective properties.

Study demonstrates that *B. monniera* extract enhances the learning ability and is known to reduce the level of amyloid especially Abeta 1-40 and 1-42 .Its cognition-facilitating effect of *B. monniera* has been due to bacoside-A and bacoside-B. Betulinic acid present in it, attenuates interleukin-6 production and exerts anti-inflammatory effect**.** *B. monniera* promotes cell survival in response to oxidative stress by suppressing the formation of reactive oxygen species and any change in the activity of redox regulated proteins involved in the pathophysiology of Alzheimer's disease.

The mechanism of action of ginkgo is believed to be produced by its functions as a neuroprotective agent, an antioxidant, a free-radical scavenger, a membrane stabilizer, and an inhibitor of platelet-activating factor via the terpene ginkgolide B. Inhibition of age-related loss of muscarinic cholinoceptors , stimulation of choline uptake in the hippocampus and inhibition beta-amyloid deposition explains its benefit in Alzheimer's.

ACKNOWLEDGMENT

The authors are grateful to the authors/editors of all those articles, journals and books from where the data for this article has been reviewed and discussed.

Conflict of Interest: Nil.

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