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REVIEW ON CURRENT TREATMENT STRATEGY IN ALZHEIMER'S DISEASE AND ROLE OF HERBS IN TREATING NEUROLOGICAL DISORDERS

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ABSTRACT

Alzheimer's disease (AD) have becomes an international threat in particular with developing countries as it progress very rapidly in aged and young adults. Increased life style modification contributes more of brain oxidative stress which triggers the event of AD and double the chances of its occurrence. Lack of proper clinical knowledge in disease identification further delays the therapy. Current goal standard treatment for AD only offers symptomatic relief. Drug belongs to the category of AChE, MAO, beta secretase inhibitors, anti-oxidants, anti-inflammatory and anti-hyperlipidemics may acts as good drug of choice for better clinical efficacy. Most of the allopathic drugs acts by single mechanism were as herbs from natural origin acts in multiple ways which tend to offers higher retrograde relief by its versatile nature of phytotherapeutics. Present review majorly focuses on recent treatment protocols available for treating AD and role of potential herbs that may acts as lead moiety in managing AD. In conclusion there is no proper cure for AD till date majorly due to irreversibility degenerated neurons. Regular usage of alternate complimentary therapy such as herbal supplements may delay and halt the progression of AD. Available preclinical data's suggested the same. Still more number of lead molecules are under clinical investigation, hope to get some unique molecule with prompt mechanism on which would prevent the AD disease progression likely to be marketed in near future.

KEY WORDS: ***Alzheimer's Disease, Phytotherapeutics, AChE, MAO, beta secretase inhibitors, anti-oxidants, anti-inflammatory and anti-hyperlipidemics***

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1. Introduction

Alzheimer's disease (AD) is one of the potential causes for neurodegeneration. Binding of extracellular amyloid and phosphorylation of intracellular tau worsen the condition of neuroinflammation. The pathophysiology of disease interlinked with several cascade mechanism. Activation of brain microglial cells triggers the inflammatory mediators. Increased expression of AChE enzyme expression depletes the level of acetylcholine which tend to cognitive dysfunction. Hyperactive monoamine oxidase enzymes degrades the substantial neurotransmitter's like dopamine and serotonin leads to motor incoordination and delay in the process of memory and learning.

2.Neurobiology of Memory And Learning

The insights gained from studying neurotransmitters related to learning and memory are particularly relevant to the study of dementia. Dementia is characterized by a progressive, irreversible deterioration of higher cognitive functions, including learning and memory .Failure of neurotransmission, particularly in regions of the brain such as the hippocampus and neocortex, is likely to be a fundamental defect responsible for cognitive impairments in dementia. Understanding the neurochemistry of learning and memory, therefore, is a first step toward relating the symptoms of dementia to underlying biochemical processes [1].

2.1.Cholinergic neurons and projections

Classic lesion studies have identified cholinergic neurons and projections that are critical for learning and memory. These neurons are located in the basal forebrain and project to the hippocampus and neocortex. The basal forebrain region includes the medial septal area (MSA) and the vertical limb of the diagonal band of Broca (dbB), which project primarily to the hippocampus, and the horizontal limb of the dbB and nucleus basalis magnocellularis (nBM), which project to the neocortex. Lesions of the MSA and nBM in rodents impair performance on a variety of mnemonic tasks including spatial reference and working memory tasks such as the Morris water maze and T-maze alternation [2].

2.2.Dopaminergic neurons and projections

Most catecholaminergic neurons originate in discrete nuclei in the brain stem that project widely to the neocortex, limbic system, and striatum. In addition to the striatum, dopaminergic neurons in the ventral tegmental area and substantia nigra project to the prefrontal cortex, anterior cingulate cortex, perirhinal and entorhinal cortices, basal forebrain, hippocampus, and amygdala. Some evidence implicates reduced DA function in the cognitive impairments common in several neurodegenerative diseases [3].

2.3.Pathophysiology of Alzheimer's Disease

Alzheimer's disease is associated with brain shrinkage and localised loss of neurons, mainly in the hippocampus and basal forebrain. The loss of cholinergic neurons in the hippocampus and frontal cortex is a feature of the disease, and is thought to underlie the cognitive deficit and loss of short-term memory that occur in AD. Two microscopic features are characteristic of the disease, namely extracellular amyloid plaques, consisting of amorphous extracellular deposits of β-amyloid protein (known as Aβ), and intraneuronal neurofibrillary tangles, comprising filaments of a phosphorylated form of a microtubule-associated protein (Tau). Both of these deposits are protein aggregates that result from misfolding of native proteins, as discussed above. They appear also in normal brains, although in smaller numbers. The early appearance of amyloid deposits presages the development of AD, although symptoms may not develop for many years. Altered processing of amyloid protein from its precursor is now recognized as the key to the pathogenesis of AD. This conclusion is based on several lines of evidence, particularly the genetic analysis of certain, relatively rare, types of familial AD, in which mutations of the APP (Amyloid precursor protein) gene, or of other genes that control amyloid processing, have been discovered. The APP gene resides on chromosome 21, which is duplicated in Down's syndrome, in which early AD-like dementia occurs in association with overexpression of Amyloid precursor protein APP.

2.4. Role of Inflammation in AD

The participation of the local inflammatory reaction is confirmed especially by the results of studies dealing with activated microglia, reactive astrocytes, complement system, cytokines, reactive astrocytes, complement system, cytokines, reactive mediators of oxygen and nitrogen (free radicals), all

of which participate significantly in inflammatory processes. These inflammatory markers are locally produced by brain cells, and occur in close proximity of Aβ deposits [4]. In AD pathogenesis, the chronic inflammation might be an essential co-factor involving reactive microglia, astrocytes and proinflammatory cytokines. The astrocytes are the predominant neuroglial cells of the central nervous system (CNS) and play an important role in regulation of immune and inflammatory responses by producing cytokines, Chemokine, and effector molecules [5]. Aβ peptide induces the pro-inflammatory cytokine and Chemokine secretion in rat.

2.5. Treatment Strategy Followed In Alzheimer's Disease

There is currently no cure for Alzheimer's disease. Currently available medications offer relatively small symptomatic benefit for some patients but do not slow disease progression.

2.5.1.Cholinesterase Inhibitors

Cholinesterase inhibitors are the only drugs currently approved for treatment of cognitive deficits in AD. They are the only type of drug with consistently demonstrated efficacy in well-designed large-scale clinical studies of individuals with mild to moderate AD. Overall, approximately one-half of patients show modest but significant cognitive and functional benefit from cholinesterase inhibition. Cholinesterase inhibitors vary primarily in side effect and dosing profiles rather than in efficacy. Age, gender, and/or apoE genotype do not seem to determine the response to treatment.

2.5.1.1.Physostigmine

Physostigmine, a natural alkaloid containing a tertiary amine, is a reversible nonselective cholinesterase inhibitor that is absorbed by the gastrointestinal tract, subcutaneous tissue, and mucous membranes. It is hydrolyzed and inactivated within 2 hours, thus requiring multiple doses each day. Acute parenteral [6] continuous intravenous [7], transdermal [8] and oral administration of physostigmine has yielded cognitive improvement in some AD patients. Long-term treatment with physostigmine may delay deterioration in AD [9]. A meta-analysis of 15 randomized, controlled trials involving four different methods of delivery led to the conclusion that evidence for physostigmine's effectiveness was limited, while adverse effects and a high rate of withdrawal were common . Physostigmine is not currently in clinical use.

2.5.1.2.Tetrahydroaminoacridine (Tacrine)

Tacrine the first drug approved for treating AD, was investigated on the basis that enhancement of cholinergic transmission might compensate for the cholinergic deficit. Trials showed modest improvements in tests of memory and cognition in about 40% of AD patients, but no improvement in other functional measures that affect quality of life. Tacrine has to be given four times daily and produces cholinergic side effects such as nausea and abdominal cramps, as well as hepatotoxicity in some patients, so it is far from an ideal drug. Later compounds, which also have limited efficacy but are more effective than tacrine in improving quality of life, include donepezil, rivastigmine and galantamine. These drugs produce a measurable, although slight, improvement of cognitive function in AD patients, but this may be too small to be significant in terms of everyday life [10].

There is some evidence from laboratory studies that cholinesterase inhibitors may act somehow to reduce the formation or neurotoxicity of Aβ, and therefore retard the progression of AD as well as producing symptomatic benefit. Clinical trials, however, have shown only a small improvement in cognitive function, with no effect on disease progression [11].

2.5.1.3.Memantine

The other drug currently approved for the treatment of AD is memantine, an orally active antagonist at NMDA receptors, with weaker blocking actions on various other amine receptors. It was originally introduced as an antiviral drug, and resurrected as a potential inhibitor of excitotoxicity. It produces-surprisingly-a modest cognitive improvement in moderate or severe AD, but does not appear to be neuroprotective. It causes few side effects, and has a long plasma half-life [12].

2.5.1.4.Donepezil

Donepezil inhibits acetylcholinesterase in a mixed competitive/noncompetitive manner. It is well absorbed after oral administration, A relatively long half-life of this drug permits single daily dosing. Several large-scale double-blind, placebo-controlled studies have demonstrated that donepezil, 5 or 10 mg/day, improves cognition [13]. While both doses

of donepezil are superior to placebo, the 10 mg/day dose appears to be somewhat more effective than the lower dose. In a 240-week open-label extension of a 14-week study, patients on donepezil displayed clinical improvement in cognitive and overall dementia severity scores for 6 to 9 months [14]. While the scores deteriorated gradually after this point, the decline was less than would be expected had the patients never been treated. There is some evidence that donepezil may be efficacious in the treatment of moderate to severe AD.

Donepezil's side-effect profile is superior to that of tacrine. In general, side effects (e.g., nausea, diarrhea, sedation, sleep disturbance) are usually mild and transient and occur mostly on initiation of drug therapy. Liver toxicity is not associated with the medication.

2.5.1.5.Rivastigmine

Rivastigmine is a pseudoirreversible inhibitor of acetylcholinesterase. The drug's half-life necessitates twice-daily dosing. Randomized, controlled trials to date have supported significant improvements from baseline in cognition, global outcomes, behavior, and function with 6 to 12 mg/day doses of rivastigmine compared to placebo. Reported side effects include nausea, vomiting, diarrhea, headaches, and fatigue. Side effects are usually mild to moderate and transient; gradual titration may improve patient tolerance [15].

2.5.1.6.Metrifonate

Metrifonate was withdrawn from further development in 2000; it is discussed here due to the success of several trials prior to the cessation of testing. Metrifonate is a prodrug that is converted enzymatically to a 2.2, dimethyl dichlorovinyl phosphate, which is an irreversible cholinesterase inhibitor. The compound has been used to treat schistosomiasis for over 30 years [16].

2.5.1.7.Galantamine

Galantamine, a tertiary amine of the phenthrene group, has been used clinically since the early 1960s in the treatment of myasthenia gravis. It is a competitive inhibitor of acetylcholinesterase and a nicotinic agonist at an allosteric nicotinic receptor site. Consequently, the drug produces more cholinomimetic enhancement than would be produced by cholinesterase inhibition alone. Galantamine is rapidly absorbed after oral administration. Cerebral concentrations that are three times higher than plasma levels are observed after administration. Since galantamine has a half-life of 7 hours, dosing should occur twice daily, with an optimal dose of 24 mg/day [17].

2.6. Cholinergic Agonists

The use of postsynaptic agonists is of interest because of the observed depletion of presynaptic (M2) receptors in conjunction with the relative preservation of postsynaptic (M1) sites in AD. Activation of the M1, M3, and M5 receptors causes cellular excitation, whereas activation of the M2 and M4 subtypes produces inhibitory effects. Most mRNA located in the cerebral cortex and hippocampus is for M1 and M3 receptors, making these sites potentially most important for pharmacological enhancement of cognition. The nicotinic and muscarinic systems appear to jointly modulate performance in learning and memory. Animal data suggest that presynaptic nicotinic receptors mediate a positive feedback mechanism that modulates cholinergic activity.

2.6.1.Bethanechol

Bethanechol is a synthetic methyl analogue of acetylcholine with agonist effects on M1 and M2 cholinergic receptors. Studies conducted on AD patients have reported modest improvement with this agent. Bethanechol must be administered by an intracerebroventricular (icv) route, because it does not cross the blood-brain barrier. This carries substantial risks, including perioperative complications, pneumocephalus, seizures, and chronic subdural hematoma. Thus, icv bethanechol treatment is not a viable option for cholinergic enhancement in AD patients [18].

2.6.2.Xanomeline

Xanomeline is a selective M1 and M4 muscarinic agonist. A 6-month double-blind, placebo-controlled trial with 343 subjects demonstrated that xanomeline administration significantly improved Alzheimer's Disease Assessment Scale (ADAS) cognitive subscale scores and reduced behavioral disturbances in AD patients . A transdermal patch form of xanomeline has been developed in order to avoid cholinergic side effects; phase II trials of the patches are underway. It has been suggested that xanomeline may be neuroprotective of cholinergice neurons [19].

2.7. Monoamine Oxidase Type B (Mao-B) Inhibitors

2.7.1.L-Deprenyl (Selegiline)

L-Deprenyl has been used for the treatment of depression and Parkinson's disease. L-Deprenyl, a levorotatory acetylenic derivative of phenethylamine, is an irreversible monoamine oxidase inhibitor (MAOI) that selectively inhibits MAOB at low doses. Double-blind, placebo-controlled trials with small patient samples suggest that subchronic treatment with 10 mg/day L-deprenyl improves aspects of cognition, behavior, and performance [20].

2.7.2. Glycine Site Inhibitors

The glycine-B allosteric site on the N-methyl-D-aspartate (NMDA) receptor is a positively modulating site. Glycine has been shown to act together with glutamate in the stimulation of the NMDA receptor. Antagonism of the glycine modulatory site of the NMDA receptor could decrease neurotoxicity mediated by glutamate. One-hydroxy-3-amino-2-pyrrolidone (HA-966) and L-aminocyclobutane (ACB) appear to inhibit NMDA-specific binding and block NMDA responses [21]. Antagonism at the glycine site may be of therapeutic importance by interfering with glutamate's neurotoxicity without causing cognitive impairment.

2.8. Anti-inflammatory Agents

Like all neuroprotective agents, anti-inflammatory agents have not been widely tested in the treatment of AD. However, basic science and epidemiological findings suggest the utility of these agents for AD treatment. Several lines of evidence demonstrate the involvement of the immune system and inflammation in AD, refuting the long-held belief that the brain is immunologically privileged. The inflammatory response may lead to neuronal death. Markers of inflammation, including increased numbers of reactive glia and microglia, tumor necrosis factor, interleukins, antichymotripsin (ACT), acute phase proteins, and activated T lymphocytes have been seen in AD subjects [22]. The immune response in the CNS has been shown to localize with senile plaques, and inflammatory cytokines and ACT may stimulate abnormal processing of amyloid precursor protein (APP), suggesting a role for the immune response in the patho-physiology of AD.

Data suggest that the target of anti-inflammatory therapy in dementia could be either cyclo-oxygenase-1 (COX-1) or cyclo-oxygenase-2 (COX-2). Cyclo-oxygenase-2 has a more restricted tissue distribution than COX-1 and has enhanced expression in the brain. Cyclo-oxygenase-2 has a high level of expression in the hippocampal formation, temporal and frontal cortices, and microglial cells of AD patients [23],neuronal COX-2 content increases with the progression of dementia [24]. Cyclo-oxygenase-1 is expressed in hippocampal neurons and select other brain regions, and is widely expressed in brain microglia. Cyclo-oxygenase-1-microglia are associated with amyloid plaques, and are found in greater density in the fusiform cortices of AD patients than in controls [25]. Animal studies indicating a protective role for COX-2 in stressed neurons have led to the suggestion that COX-1, rather than COX-2, is the appropriate target of nonsteroidal anti-inflammatory drug (NSAID) therapy. Both COX-1 and COS-2 may play different roles in the pathogenesis of AD. The inability of NSAIDs to selectively inhibit brain COX-1, combined with the more restricted expression of COX-2, may make COX-2 inhibitors a more attractive target for clinical trials.

2.9. Antioxidants

Free radicals are capable of mediating neuronal degeneration. Several lines of evidence suggest that in AD there is increased oxidative stress, which may play a role in the pathophysiology of the illness [26]. Patients with AD display significantly increased oxidizability of cerebro Spinal fluid (CSF) and plasma lipoproteins, as well as lower levels of CSF and plasma ascorbate (a hydrophilic antioxidant), CSF polyunsaturated fatty acids (the substrate for lipid oxidation), and plasma alpha-carotene and alpha-tocopherol [27]. Antioxidants such as alpha-tocopherol protect CNS cell cultures and clonal cell lines from amyloid protein toxicity, suggesting that one pathway of amyloid protein cytotoxicity involves free radical damage . These findings support the use of antioxidant treatments to slow oxidation in the brain, thereby attenuating the clinical course of AD.

A large prospective study (n = 633, average followup 4.3 years) of the incidence of AD among persons age 65 and older suggested that high-dose vitamin E or vitamin C supplements may lower the risk of AD [28]. A double-blind, placebo-controlled

2-year study determined that alpha tocopherol and deprenyl administration significantly delayed disease progression compared to placebo.

2.10. Estrogen

It has been known for several years that the brain is responsive to estrogen, and that estrogen is neurotrophic and neuroprotective. The hippocampus contains receptors for estrogen, and estrogen priming is associated with increased dendritic spine density in the CA1 region. Preclinical studies with rodents demonstrate that estrogen-deprived animals perform worse on learning tasks than animals that receive estrogen replacement therapy. Estrogen is a free radical scavenger, protective against lipid peroxidation. Women are at increased risk for AD compared to men; it has been suggested that the loss of estrogen production in women after menopause may play a role in the pathophysiology of AD.Some epidemiological studies indicate that women who take estrogen after menopause are at decreased risk for development of AD compared to estrogen nonusers [29]. Estrogen replacement therapy has been associated with superior cognition at baseline and with the maintenance of cognition in non-demented postmenopausal women, as well as superior short-term visual memory in the nondemented [30].

2.11. Anti-amyloid Therapy

There is substantial evidence that overproduction and cerebral deposition of amyloid (1-42) peptide plays an early and significant role in the pathogenesis of AD. That amyloid (1-42) peptide may thus be pathogenic has led to a number of therapies designed to reduce the amyloid peptide burden in the brain, thereby preventing or ameliorating the disease [31].

2.12.Beta-secretase inhibitors

Amyloid peptides are created by the cleavage of amyloid precursor protein (APP) by two proteases, beta-secretase and gamma-secretase. Gamma-secretase appears to stimulate amyloid (1-42) production at low concentrations, limiting its clinical utility. However, beta-secretase is a prime therapeutic target. A human transmembrane apartic protease, beta-site APP-cleaving enzyme (BACE), with all the known characteristics of beta-secretase, was recently cloned. Overexpression of this enzyme increased beta-secretase cleavage products, while inhibition of BACE reduced these products. Beta-site APP cleaving enzyme knockout mice display reduced amyloid peptides without severe phenotypic effects [32]. Development of a BACE inhibitor for ultimate use in AD continues with some success.

2.13.Statins

Epidemiological data suggest an association between high cholesterol levels and the development of AD. The apolipoprotein E4 susceptibility gene for AD has been associated with elevated cholesterol levels [33] .Clinical studies suggest a decreased prevalence of AD among individuals using statins to treat hypercholesterinemia . Numerous studies support a role for cholesterol in the modulation of amyloid production and suggest that cholesterol depletion inhibits amyloid production. Simvastatin and lovastatin reduced intracellular and extracellular levels of amyloid peptides in cultures of rat hippocampal and mixed cortical neurons, while guinea pigs treated with simvastatin showed significantly reduced cerebral amyloid levels in CSF and brain homogenate. A randomized clinical trial of humans with elevated low-density lipoprotein cholesterol found that lovastatin produced a significant dose-dependent reduction in serum amyloid peptide [34]. Clinical trials investigating the therapeutic benefit of statins in AD are underway.

2.14.Tau-aggregation inhibitor therapy

Leuco-methylthioninium bishydromethanesulfonate (LMTM) acts as a selective inhibitor of tau protein aggregation both in vitro and in transgenic mouse models. LMTM is new class of compound currently under trial for establishing the safety and efficacy in humans [35].

2.15.Stem Cell Therapy

There are several preclinical studies justifies the potential of transplanted stem cells in rejuvenating the lost neural network. But still now there is no proper trial outcome to evident the stem cell therapy in treating neurodegenerative conditions in humans. Further elucidation of mechanism on which stem cells acts is still under investigation [36].

3 .Herbs and Alzheimer's Disease

Bacopa monnieri which richly grows in India along the Gangetic plains contains bacosides and has tested anticholinesterase and antioxidant effects in vitro [37] and in rodents are hypothesized

to be the potential mechanisms among others of its utility in AD.

Salvia lavandulaefolia have shown inhibitory activity on the enzyme acetylcholinesterase in-vitro and in vivo which is relevant to the treatment of AD. Other activities relevant in this context are its antioxidant, anti-inflammatory effects. Several other phytochemicals from different herbs e.g. Acorus calamus, Epimedium coreanum peels of Citrus medica , Salvia lerrifolia , Phagnalon saxatile which possess significant anticholinesterase activity which warrant a detailed follow up with clinical trials [38,39].

Ginkgo biloba leaf extract has shown strong beneficial effects in treating neurodegenerative diseases like AD, geriatric complaints like vertigo and psychiatric disorders like schizophrenia. This multitude of activities of Ginkgo leaf extract may work through various mechanisms. The proposed mechanisms of the extract containing EGb 761 are its antioxidant effect, inhibition of beta amyloid peptide (Aβ) aggregation to reduce Alzheimer's progression [40] .

The dietary omega-3 fatty acid docosahexaenoi acid (DHA) is another promising member in this category with proven beneficial effects in mitigating oxidative damage and synaptic cognitive deficits in transgenic rodent models of AD [41].

3.1.Bio-active phytoconstituents and their relationship to Alzheimer's disease

Neuroinflammation is now recognized as a fundamental response of the CNS not only to acute injury, but also to chronic neurodegenerative disease. This is perhaps no better demonstrated than in AD, where the severity of the neuroinflammatory response parallels the disease course [42].

3.1.2.Phenols and Polyphenol

Phenolic compounds in foods have attracted great interest since the 1990s due to growing evidence of their beneficial effect on human health. Evidence from in-vitro, in-vivo studies and clinical trials has shown that polyphenols from apple, grape, and citrus fruit juices possess a stronger neuroprotection than antioxidant vitamins. The phenolic compounds (catechins and epicatechins) of green tea are capable to protect neurons against a range of oxidative and metabolic insults, which includes protection of dopaminergic neurons from damage.

Resveratrol (trans-3,4′,5-trihydroxystilbene), a naturally occurring polyphenol mainly found in grapes and red wine, markedly lowers the levels of secreted and intracellular amyloid-β (Aβ) peptides produced from different cell lines. It promotes proteasome dependent intracellular degradation of Aβ and is a potential candidate molecule against AD Catechins are polyphenols exhibiting neuroprotective activities that are mediated, in part, by activation of protein kinase C (PKC) and transcription factors that induce the expression of cell-survival genes [43].

3.1.3.Flavonoids

Dietary intervention studies in several mammalian species, including humans, using flavonoid rich plant or food extracts have indicated an ability to improve memory and learning, by protecting vulnerable neurons, enhancing existing neuronal function or by stimulating neuronal regeneration. Flavanones such as hesperetin, naringenin and their in-vivo metabolites, along with some dietary anthocyanins, cyanidin-3-rutinoside and pelargonidin-3-glucoside, have been shown to traverse the blood brain barrier (BBB) in relevant in vitro and in situ models [44].

3.1.4.Alkaloids

Ergot alkaloids have marked effects on blood flow, which was originally thought to be the main mechanism of action. Tropane alkaloids like atropine, hyoscyamine and scopolamine from Datura affect the spinal cord and CNS. Iso-quinoline alkaloid such as morphine, which is isolated from Papaver somniferum (opium poppy) is a highly potent analgesic and a narcotic drug. Morphin's mechanism of action is strong binding to the μ-opioid receptor (MOR) in the central nervous system, resulting in an increase of Gamma aminobutyric acid (GABA) in the synapses of the brain [45].

3.1.5.Terpenoids and Saponins

Many plant-derived essential oils, such as wormwood, have been known for over a century to have convulsant properties. The rhizome of valerian (Valerian officinalis) contains two pharmacologically active ingredients: Valepotriates and sesquiterpenes (valerenic acid and acetoxyvalerenic acid). Sedating effects of the active agents have been demonstrated in mice. Valerian crude extract, however, is noted to

have GABA(B) receptor binding properties and GABA uptake inhibition in rat synaptosomes [46].

3.1.6.Diarylheptanoid

Curcumin from Curcuma longa, apart from exerting its anti-AD effects through many different mechanisms has a very important and potent anti-inflammatory effect. Curcumin inhibits Aβ-induced expression of Early growth response protein 1 (Egr-1) and Egr-1 DNA-binding activity in human monocytic cells (THP-1). By inhibition of Egr-1 DNA-binding activity by curcumin, it attenuates inflammation. The chemotaxis of monocytes, which can occur in response to chemokines from activated microglia [47].

3.1.7.Omega-3 fatty acid

Omega-3 linolenic acid from Perilla frutescens seed oil (PFSO), a rich source of unsaturated fatty acids, especially of which is commonly used as herbal food supplement for vascular health has come up with encouraging results in guinea pigs. It was found to decrease reactive oxygen species,stabilize mitochondrial membrane potential on dissociated neuronal cells [48].

3.1.8.Steroid glycosides

Ginsenoside from Ginkgo Biloba has been used in traditional Chinese medicine for the improvement of memory loss associated with abnormalities in the blood circulation [49].The herb shows memory enhancing action by increase the supply of oxygen, and helps the body to eliminate free radicals thereby improving memory.

4. Conclusion

T Since many decades the measure of developing prompt therapy towards treatment of AD continues , but still now there is no proper cure for AD this is majorly due to delay in identification and lack of gold standard treatment. Several categories of drug which reveals potential activity in preclinical level fails to achieve the same in clinical trials. Secondly the neurons once degenerated will be difficult to retrieve back to the original stature. Furfure the actual results of trial drug under investigation are yet to be released. In near future these trial outcomes may render some beneficial therapy for management of AD. Herbs are playing very crucial role in delaying the progression of the neurodegeneration, but on the other hand there is no proper documentary clinical evidence which substantiate the use of herbs as an ailment for AD therapy is not established. By considering the potential of phytotherapeutics there are several possibilities for discovery of new lead from the herbal origin in near future.

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