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A COMPREHENSIVE REVIEW ON THE HERBS USED FOR TREATMENT OF ALZHEIMER'S DISEASE (AD)

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ABSTRACT

Alzheimer's disease (AD) first described by German psychiatrist Alois Alzheimer in 1906, is a disorder and is the main cause of dementia which causes degeneration of the cells in the brain and is characterized by a decline in thinking. Two main causes for AD were postulated viz. cholinergic and amyloid. In addition to these increasing age,, head injuries, genetic factors, infections, vascular diseases, and environmental factors are considered as progressive factors of AD. For the treatment of AD cholinesterase enzyme inhibitors and *N*-methyl d-aspartate (NMDA) antagonists are used to get symptomatic relief, but no curative treatment is available for AD. Herbal medicine has long been widely used to enhance the treatment of symptoms of dementia and improve cognitive impairment in East Asian countries. The review summarises pathophysiology of AD and usefulness of medicinal plants in the treatment of AD.

KEYWORDS: Alzheimer's disease, pathophysiology of AD, herbal treatments

INTRODUCTION

Alzheimer's disease (AD) is the neurodegenerative disorder most prevalent in the world, affecting about 24 million people and it is estimated that by 2050 this number will be quadrupled. Its main features are the

deposit of β-amyloid (Abeta) peptides in the extracellular surface of neurons and the formation of neurofibrillary tangles arising from the intracellular accumulation of hyper- phosphorylated Tau protein. AD is also associated with the deficit of the neurotransmitter acetylcholine (ACh) and oxidative stress caused by exacerbation of glutamatergic transmission [1,2].

PATHOPHYSIOLOGY

Even after over a century of research, the pathophysiology of Alzheimer's disease remains a mystery, and there is no treatment that causes natural recovery [3]. Nonetheless, macroscopic and microscopic markers are known to be associated with it, and they may aid in its characterisation, knowledge of disease pathophysiology, and development of potential therapies. At the macroscopic level, there is hippocampal and cerebral cortex atrophy, which is more pronounced in AD due to age. The production of amyloid plaques, also known as senile plaques, which are amorphous Abeta structures, as well as the buildup of hyperphosphorylated Tau protein, which indicates the creation of neurofibrillary tangles and widespread neuronal death, may be seen under a microscope. Other pathways have been linked to other mechanisms, according to recent study [4,5].

Genetic Mechanism

The vast majority of Alzheimer's disease cases are sporadic, meaning there is no dominant genetic cause. However, rare mutations in the APP gene, which causes familial Alzheimer's disease, and allele 4 of apolipoprotein E (ApoE), which has been shown in recent studies to be the strongest genetic risk factor related to the AD development process, may occur. Human ApoE carriers account for about one out of every five people. When it is discovered that ApoE offers a subsidy to the development of Alzheimer's disease, it is revealed that these individuals account for around 65 percent of instances of the condition, and that ApoE carriers have a threefold greater chance of getting Alzheimer's [6].

The processes that link the existence of ApoE to Alzheimer's disease are yet unknown, although it's thought that there's a decrease in Abeta clearance in the brain in such circumstances. Aside from the ApoE-related mechanism, studies show a strong link between the existence of preselinin alleles (PSEN 1 and PSEN 2) in AD patients and persons who are at risk of developing AD or other associated disorders. The detection of two different types of mutations in this gene in patients with familial AD has been documented in the literature. Although the PSEN 1 and PSEN 2 genes are uncommon in people with Alzheimer's disease, their interaction with ApoE is a crucial determinant when the disease is caused by genetic factors. They play a role in early-onset pathology, which is a rare type of cancer. PSEN 1 (chromosome 14) mutations account for 18% to 50% of these early-onset instances; mutations in PSEN 2 (chromosome 1) have been documented seldom and were predominantly found in African and European populations. The mechanism of preselinin's link with APP cleavage control has yet to be fully explored [7].

Amyloid hypothesis and Protein Tau

Abeta fragments and neurofibrillary tangles, as previously established, are crucial markers for Alzheimer's disease that describe the amyloid hypothesis. These deposits arise as a result of native proteins folding incorrectly, i.e. following an altered cleavage of the amyloid precursor protein (APP). APP is a 770-amino-acid transmembrane glycoprotein expressed by a variety of cells, including CNS neurons. The enzymes -, -,

and -secretase break APP, releasing the amyloid cascade when APP is cleaved by -secretase, resulting in insoluble peptides with 39 to 43 fragments. The A beta fragments, particularly the Abeta-42 isoform, show strong cytotoxic qualities linked to neurodegeneration, boosting the creation of oxy radicals, and being or not being directly harmful to neurons [8].

Inflammatory Mechanism and Mitochondrial Dysfunction AD

Alzheimer's disease is linked to inflammatory processes. Furthermore, various investigations have demonstrated that Tau disorders are greatly aggravated when acute and chronic inflammatory processes occur. Microglial clumps around the densest parts of Abeta plaques, high levels of pro-inflammatory cytokines, and microglial activation that occurs before the creation of a neurofibrillary tangle all play a role in these inflammatory processes. In terms of mitochondrial dysfunction, it is thought that the accumulation of Abeta fragments and abnormal Tau protein in brain cells impacts mitochondrial function, particularly mitochondrial oxidative metabolism. Benevento's research into the existence of Abeta peptides allowed him to infer, with greater specificity, that these peptides can be directly harmful [9, 10].

Oxidative Stress

Studies demonstrate that oxidative stress caused by Abeta is important in the development and progression of Alzheimer's disease, as it is present as both a cause and a consequence of inflammatory processes in general, which are common in neurodegenerative illnesses. The brain is an organ with a high energy requirement, which is met by mitochondrial oxidative phosphorylation, which can result in the synthesis of highly reactive oxygen species. Oxidative stress is caused by excessive production of these species. The protective systems are weakened in this instance, reactive oxygen species build up, and the neurons become vulnerable to excitotoxic damage. This pathway, however, is dependent on Abeta fragments, which, when collected, increase iron and brain reduction [11,12].

Cholinergic Hypothesis

The cholinergic hypothesis, which was the initial explanation connected to AD pathogenesis, is one of the most investigated mechanisms related to the development and evolution of AD. In general, AD carriers' brains show shrinkage, synaptic loss, and a lack of central neurotransmission, in addition to the previously mentioned histological indicators. Neurons in the basal forebrain are degenerating in general. Cholinergic neurons in the basal nucleus and entorhinal cortex are lost during the start of the disease, but by the end of the disease, more than 90% of the cholinergic neurons in the basal nucleus have died. According to Bartus and Emerich's cholinergic hypothesis, aberrant or impaired cholinergic system function is capable of generating depression [13].

PLANTS USED IN ALZHEIMER'S DISEASE

This literature review referred to active ingredients extracted from herbal medicines, herbal extracts that affect the AD model in vitro and in vivo. In India herbal medicines are used to treat central nervous system problems. Numerous classes of natural herbal medicines and traditional synthetic neuroprotective agents manufactured have been investigated. Some herbs are listed below.

***Abrus precatorius* (Jequirity bean or rosary pea)**

Abrus precatorius is commonly known as Jequirity bean. It belongs to the family Fabaceae. It is native to Asia and Australia. Santhi Krupa extracted the flavonoid from the dried root of *Abrus Pectoris* using a hydroalcoholic mixture and studied the anti-Alzheimer's activity by using D-Galactose model, in the elevated plus maze, morris water maze and antioxidant potential alongwith estimation of antioxidant parameters like Lipid peroxidation, Superoxide Dismutase, Catalase, and Glutathione reductase of the *Abrus pectoris* root extract (APRE). In the protective groups III and IV, simultaneous administration of D-Galactose with APRE resulted in a considerable rise in total body weight. The APRE treatment groups' reduced transfer latency in the raised plus maze and morris water maze could be due to memory enhancement. A considerable decrease in LPO level, as well as a significant increase in SOD, CAT, and GSH levels, were detected after 90 days of APRE supplementation, indicating the antioxidant status of APRE [14].

Bacopa monnieri (Brahmi)

Bacopa monnieri is commonly known as Brahmi. It belongs to the family Plantaginaceae. It is native to the wetlands of southern and Eastern India. Kunte KB et al studied anti-Alzheimer's properties of *Bacopa monniera* plant extract (BME) on the cholinergic system of AD-induced mice. In AD-induced mice, BME dramatically increased ACh levels and decreased AChE activity, demonstrating that *Bacopa monniera* has a cholinergic system counteracting effect. In the frontal cortex and hippocampus, *Bacopa monniera* has been shown to reverse neurotoxic and colchicine-induced depletion of acetylcholine and suppression of cholinesterase activity and muscarinic receptor binding. Furthermore, it has been shown to inhibit AChE activity in a dose-dependent manner and change the expression of the NMDA receptor's NRI subunit. According to the findings, *Bacopa monniera* contains anti-components Alzheimer's and can be prescribed as a safe and effective treatment for Alzheimer's disease [15].

Camellia sinensis

It is commonly known as tea plant, tea shrub belonging to family Theaceae. The plants were originally native to Southeast Asia (southern China, north India, Myanmar and Cambodia) but today are also cultivated in Sri Lanka and Japan. Alzheimer's disease (AD) is one of the most common types of neurodegenerative disorders. The accumulation of Aβ plaques in the hippocampus contributes primarily to memory impairment. Green tea polyphenols prevent brain aging. In this study, green tea extract was used to prevent the generation of Aβ plaques in a rat model of AD induced by hen egg-white lysozyme (HEWL). Rats are divided into 2 groups control and the positive control group received normal saline and scopolamine, respectively; the lesion group received HEWL, and the treated groups received a mixture of HEWL and green tea extract at three doses into the hippocampus. Twenty days after injection, spatial memory was assessed by Morris water maze. Treated rats showed a significant decrease in escape latency, compared with lesion and positive control groups, indicating improvement in spatial memory. The AD groups showed a significant decrease in escape latency than the control group, indicating impairment of spatial memory. Histological analysis revealed more number of Aβ plaques in the hippocampus of the injured group than that in the treated animals. Results suggest that the green tea extract is effective in preventing amyloid fibril formation and lysozyme fibrillization that in turn

results in the improvement of memory deficits in the rat model of AD. The results of amyloid plaque staining are consistent with previous reports that indicated that green tea polyphenol (-)-epigallocatechin gallate reduces neuronal cell damage and upregulation of MMP-9 activity in the hippocampal CA1 and CA2 areas following transient global cerebral ischemia. Lim et al. showed that green tea catechin leads to global improvement among AD-related phenotypes in NSE/hAPP-C105 Tg mice [16].

Carissa edulis

It is commonly known as Currant Bush, Conker berry, Bush Plum, Burrum Bush belonging to family Apocynaceae. *Carissa edulis* is a medicinal plant that grows particularly in Kenya.The present study is aimed to evaluate the properties of *Carissa edulis* aqueous extract on a Scopolamine mouse model as an attempt to search for new compounds against Alzheimer's disease-related memory impairment. Memory impairment was induced by administration of 1 mg/kg (i.p.) of Scopolamine for 7 days, and mice were treated with Carissa edulis aqueous extract. Behavioral studies were performed using T-maze and novel object recognition tasks for assessing learning and memory and open field tests for locomotion. Brain acetylcholinesterase enzyme (AChE) activity was measured to evaluate the central cholinergic system. The level of MDA, glutathione and catalase activity were measured to evaluate the oxidative stress level. Administration of Scopolamine shows a decrease in learning and memory enhancement during behavioral studies. A significant decrease in the time spent in the preferred arm of T-maze, in the time spent in the exploration of the novel object, and in the discrimination index of the familiar object was also observed. The significant impairment of the central cholinergic system was characterized in mice by an increase of AChE activity to 2:55 ± 0:10 mol/min/g with an increase in oxidative stress. Treatment with the different doses of Carissa edulis (62.8, 157, 314, and 628 mg/kg orally administrated) significantly increased the memory of mice in T-maze and novel object recognition tests and also ameliorated locomotion of mice in the open field. Carissa edulis aqueous extract treatment also decreases the AChE activity and brain oxidative stress. It is concluded that administration of Carissa edulis aqueous extract enhances the memory of mice by reducing AChE activity and demonstrating antioxidant properties. This could be developed into a novel therapy against memory impairment related to Alzheimer's disease [17].

Carthamus tinctorius L

It is commonly known as Safflower. It belongs to family Asteraceae. It is native to parts of Asia, the Middle East, and Africa. It was grown mainly for its flowers, which were used in making dyes for clothing and food.We investigated the synergistic effects of *Carthamus tinctorius* L. seed (CTS), Taraxacum core num (TC), and their combination on the Aβ25-35-infused mice. In the T-maze test and novel object recognition test, the combination improved the spatial memory and object recognition capacity compared with their single treatments. In the Morris water maze test, the combination groups performed better spatial memory, indicating a synergistic effect on improving learning and memory ability in Aβ25-35-infused mice. We also investigated the Aβ-related protein expressions, suggesting the combination administration attenuated amyloidogenesis by regulating the metabolism of Aβ. Therefore, the combination might provide a positive synergistic effect on AD protection by the metabolism of Aβ. CTS-ad- ministered group significantly reduced the expression of acetylcholinesterase and the production of reactive oxygen species, indicating the potential protective ability

of CTS in cholinergic dysfunction, also reported that the treatment with TC extract reduced the lipid peroxide level and inhibited nitric oxide activity in Aβ- induced AD mouse model, indicating the relation between oxidative stress and Aβ metabolism. Therefore, administrations of CTS and TC, or their combination might regulate cognitive dysfunction in AD via cholinergic or inflammatory pathways, although the further study has to be supported to elucidate the protective mechanisms clearly [18].

Centella asiatica (Gotu kola)

Centella Asiatica is commonly known as Gotu Kola. It belongs to the family Apiaceae. It is native to wetlands in Asia. To investigate the potential use of *Centella Asiatica* in Alzheimer's disease (AD), we examined the effects of a water extract of *Centella Asiatica* in the Tg2576 mouse, a murine model of Alzheimer's disease with the high β-amyloid burden. Orally administered water extract of *Centella Asiatica* attenuated β-amyloid-associated behavioral abnormalities in these mice. water extract of *Centella Asiatica* protected SH-SY5Y cells and MC65 human neuroblastoma cells from toxicity induced by exogenously added and endogenously generated β-amyloid, respectively. water extract of *Centella Asiatica* prevented intracellular β-amyloid aggregate formation in MC65 cells. water extract of *Centella Asiatica* did not show anticholinesterase activity or protect neurons from oxidative damage and glutamate toxicity, mechanisms of current Alzheimer's Disease therapies. water extract of *Centella Asiatica* is rich in phenolic compounds and does not contain Asiatic acid, a known *Centella Asiatica* neuroprotective triterpene. *Centella Asiatica* thus offers a unique therapeutic mechanism and novel active compounds of potential relevance to the treatment of Alzheimer's Disease [19].

Citrus aurantium

In this study, we examined the protective effects of CA flowers extract (CAFE) against memory impairments induced by Aβ. Adult male Sprague-Dawley rats assigned to three groups (n=8) of control (Aβ, 3 µl intracerebroventricular, ICV), vehicle (normal saline, 3 µl ICV), and CAFE pre-treated groups (300 mg/kg, IP, for 21 days). Twelve days after Alzheimer induction, behavioral analysis Morris Water Maze (MWM), as well as, western blot and morphological studies were carried out to explore the CAFE effect on male rats of Alzheimer's. Administration of CAFE significantly restored memory and learning impairments induced by Aβ in the MWM test. CAFE significantly decreased the cytochrome-c expression level in the pre-treated group. CAFÉ is a rich source of flavonoids including nobiletin. naringin and hesperidin. These flavonoids have various pharmacological activities such as anti-inflammatory and anti-oxidant. Naringin, a prominent flavonoid of CAFE, has antioxidant, anti-inflammatory, and anti-apoptotic activities. Nobiletin can pass through the blood-brain barrier. It has a potential therapeutic advantage of dementia including Alzheimer's disease. It has been shown that Nobiletin can improve dizocilpine-memory impairments by activating extracellular signal-regulated kinase signaling in mice hippocampus. Although the used extract demonstrated some protective effects, further studies need to be done to identify the exact mechanism of it [20].

Cissampelos pariera

The present study was undertaken to investigate the effects of *Cissampelos pariera* on learning and memory in mice. Elevated plus maze and passive avoidance paradigm were employed to test learning and memory. To delineate the mechanism by which CPE exerts nootropic activity, the effect of CPE on whole-brain AChE

activity was also assessed. CPE also decreased whole brain acetylcholinesterase activity. Anti-inflammatory and antioxidant properties of *C.pariera* may be contributing favorably to the memory enhancement effect. Here, Piracetam (200 mg/kg, i.p) was used as a standard nootropic agent. Hence *C.pariera* appears to be a promising candidate for improving memory and it would be worthwhile to explore the potential of this plant in the management of dementia and Alzheimer's disease. However, further studies are necessitated to identify the exact mechanism of action. AChE inhibitory activity has been detected and has been traced to the benzylisoquinoline alkaloids. The roots of *C.pariera* contain benzylisoquinoline alkaloids that may be responsible for memory enhancing activity. *C. pariera* has been reported to possess antioxidant properties as well 15. The neuroprotective effect of CPE may be attributed to its antioxidant property by the virtue of which susceptible brain cells get exposed to less oxidative stress resulting in reduced brain damage and improved neuronal function. Results suggested that *C.pariera* appears to be a promising candidate for improving memory and it would be worthwhile to explore the potential of this plant in the management of dementia and Alzheimer's disease. However, further studies are necessitated to identify the exact mechanism of action [21].

***Clitoria ternatea* (Asian pigeonwings)**

Clitoria ternatea is commonly known as bluebellvine. It belongs to the family Fabaceae. It is native to India. Examined the effectiveness of alcoholic extracts of aerial and root parts of *C. ternatea* at 300 and 500 mg/kg doses orally in rats in attenuating electroshock-induced amnesia. The aerial parts produced significant retention of memory, and also increased the Ach content of the brain. This confirms the beneficial effect of the aerial parts 300 mg/kg of *C. ternatea* in amnesia, and also its relationship with cholinergic activity. Again, the AchE activity was also increased parallel to increased acetylcholine results suggest that *C. ternatea* extracts increase rat brain acetylcholine content and acetylcholinesterase activity similar to the standard Cerebro protective drug Pyritinol [22].

Cocos nucifera* *(Coconut)

The current study evaluated the neuroprotective effects of virgin coconut oil (VCO) on amyloid beta (Aβ)-induced cell injury. The total phenolic content (TPC) and total flavonoid content (TFC), 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical scavenging and total antioxidant activity were measured. Rats were randomly divided into six groups: control; sham; sham receiving normal saline; Alzheimer’s rats (received Aβ 1 - 40); Alzheimer’s rats + 8% VCO and Alzheimer’s rats + 10% VCO. After 8 weeks, the levels of TNF-α protein, TNF-α and iNOS gene expression in the hippocampus, the nitric oxide level, thiol group, catalase, superoxide dismutase (SOD) and glutathione peroxidase (GPx) activity were measured. The morphological changes in the regions of the hippocampus and Aβ plaque formation were determined. Phosphorylated tau proteins were also determined by immunohistochemistry. Results: VCO showed potential antiradical and antioxidant activity after in vitro treatment. VCO also significantly increased the thiol content, catalase, SOD and GPx activity and decreased the cholinesterase and nitric oxide levels. TNF-α and iNOS gene expression and protein levels decreased significantly after administration of VCO. This study initially established that VCO treatment strongly attenuates damage to nerve cells. It was shown that TNF-α, iNOS, AChE and oxidative stress decreased markedly in the VCO-treated AD rats compared to the AD rats. These findings strongly

suggest that VCO can potentially attenuate damage to nerve cells and improve AD pathogenesis by suppressing the inflammatory response [23].

Coriandrum sativum (coriander)

Coriandrum sativum is commonly known as Coriander. It belongs to the family Apiaceae. It is native to India. The present investigation aims to clarify the role of coriander seed aqueous extract as a protective and therapeutic agent against neurodegenerative disorders and Alzheimer's disease induced by AlCl3 on the pyramidal cells in the cerebral cortex of male albino rats. potent antioxidant activity of coriander seed aqueous extract, its ability to increase antioxidant enzymes and to promote oxygen to the brain could prevent oxidative damage caused by interaction between the aluminum cation and unstable oxygen from abnormal mitochondria and protect pyramidal cells in the cerebral cortex against damage induced by aluminum chloride overload. Meanwhile, coriander seed aqueous extract could provide some protective mechanism after stopping aluminum chloride and proved an improvement in the therapeutic action. The results show that coriander seed aqueous extract showing protection and an improvement in therapeutic action on pyramidal cells in the cerebral cortex against neurodegenerative disorders and Alzheimer's disease induced by aluminum chloride treatment [24].

Evodia rutaecarpa

It is known as Euodia or Bee bee tree . It belongs to family Rutaceae. This plant is native to northern China and Korea, although it is cultivated as an ornamental landscaping plant in many other places in the world. Evodiamine, a major component of *Evodia rutaecarpa*, has been reported to possess various pharmacological activities, including anti-inflammatory, antioxidative stress, and neuroprotective effects. The present study was designed to investigate the neuroprotective mechanism and therapeutic potential of evodiamine against intracerebroventricular streptozotocin (ICV-STZ)-induced experimental sporadic Alzheimer's disease in mice. STZ was injected twice intracerebroventricularly (3 mg/kg ICV) on alternate days (day 1 and day 3) in mice. Daily oral administration with evodiamine (50 or 100 mg/kg per day) starting from the first dose of STZ for 21 days showed an improvement in STZ induced cognitive deficits as assessed by novel object recognition and Morris water maze test. Evodiamine significantly decreased STZ induced elevation in acetylcholinesterase activity and malondialdehyde level, and significantly increased STZ induced reduction in glutathione activities and superoxide dismutase activities in the hippocampus compared to to to control. Furthermore, evodiamine inhibited significantly glial cell activation and neuroinflammation (TNF-a, IL-1b, and IL-6 levels) in the hippocampus. Moreover, evodiamine increased the activity of the AKT/GSK-3b signaling pathway and inhibited the activity of nuclear factor-kB. The study suggests that evodiamine can be a novel therapeutic agent for the management of sporadic AD [25].

Evolvous Alsinoside

It is commonly known as dwarf morning-glory and slender dwarf morning-glory, is flowering plant from the family Convolvulaceae.It has a natural pantropical distribution encompassing tropical and warm-temperate regions of Australasia, Indomalaya, Polynesia, Sub-Saharan Africa and the Americas. The objective of the present study was to investigate and compare the neuro-pharmacological effects of Evolvulus alsinoides plant extract on the cholinergic system and Histopathological aspects in the AD-induced rat model. Ethanolic

extract of Evolvulus alsinoides Linn (EAE) was prepared and administered to rats orally at a dose of 200 mg/kg body weight. To evaluate the anticholinergic potential of the plant extract, selected regions of the brain viz. The cerebral Cortex, Hippocampus, Pons medulla, and cerebellum were used. As a corollary to these, Histopathological experiments only on two selected regions of the brain viz. cerebral cortex and hippocampus were conducted in all groups of rats on the 60th day of experimentation to assess the extent of cytoarchitectural changes in neurons brought out by AD induction and the reversal efficiency of EAE. A common observation was made i.e., Evolvulus alsinoides (EAE) extract exhibited a positive stimulatory effect on the cholinergic system in all groups of rats in general and induced rats in particular. This was further reiterated by Histopathological experiments changes in the neurons of the cerebral cortex and hippocampus of ADinduced rat brains have been restored to the near-normal condition after administration of EAE to AD-induced rats. Given this, it was concluded that EAE has a neuroprotective effect on the cholinergic system which would pave new vistas in the discovery of safe and novel anti-Alzheimer's compounds. The present study demonstrated that consecutive i.p. injection of Legal (120 mg/kg/d) for 2 months produced AD-like disorders, including neurodegenerative evidence, Cortex & hippocampus neuron abnormalities, etc, which can be nullified with simultaneous treatment of AD-induced with EAE. The biochemical studies on the cholinergic system estimations indicate the neuroprotective effect of EAE. Histopathological studies stand as perfect evidence for the above results by reverting the cell damages with oral administration of EAE [26].

Ficus racemosa (cluster fig, red river fig or gular)

Ficus racemosa is commonly known as cluster fig. It belongs to the family Moraceae. It is native to Australia and tropical Asia. This research aimed to define neural influences of the chronic administration of the mixture Figs *(Ficus carica)* and Olive oil *(Olea europaea)* as medicinal plants to delay cholinergic abnormality and oxidative stress in amnesia induced by Scopolamine as a model of Alzheimer's disease in the hippocampus region of male Albino Rats. The findings showed that the combination of dried Figs and Olive oil produced a considerable decrease in AchE levels in the hippocampus. The outcomes suggested that the daily administration of the mixture *F. carica* and Olive oil resulted in the enhancement of behavioral activities and reduction in the levels of AchE due to the antioxidant properties and protective benefits of the mixture. learning and memory-enhancing activity of Ficus carica may be due to its antioxidant a ctivity and some compounds. Polyphenolic contents that were found in Ficus carica were responsible for AChE inhibition as was mentioned. Hence, AchE inhibitory activities of the mixture (Figs with Olive oil) could be a possible source of emerging accepted medications for Alzheimer's disease. The current work on *Ficus carica* extract has revealed significant AChE inhibitory effects. *Ficus carica* fruit exhibited the potential for the treatment of Alzheimer's disease. Results obtained by the maze test for the *Ficus carica* treated male albino rats indicated a gradual improvement in memory formation as their latency to reach the food at the end decreased. The findings of this work described that feeding Figs markedly improved learning and memory disorders induced by scopolamine [27].

Glycyrrhiza Glabra

The present study was undertaken to investigate the effects of *Glycyrrhiza glabra* root extract on learning and memory in three months old male Wistar albino rats. The aqueous extract of the root of *Glycyrrhiza glabra*

was administered orally in three doses (75, 150, and 300 mg/kg) for 4 weeks. Elevated plus-maze and Morris water maze tests were conducted to evaluate the learning and memory parameters and served as the exteroceptive behavioral models. The aqueous extract of the root of *Glycyrrhiza glabra* showed improvement in learning and memory in a dose-dependent manner. However, in the dose of 150mg/kg, it has shown a significant ($p<0.01$) enhancement in learning and memory which is comparable to control. Hence *Glycyrrhiza glabra* appears to be a promising drug for improving memory. Furthermore, pretreatment with aqueous root extract of Gg given for 4 weeks protected the animals from learning and memory impairment produced by interoceptive stimuli (Diazepam). Additionally, the aqueous root extract of Gg in the dose of 150mg/kg significantly ($p<0.01$) increased learning and memory in rats compared to control. The neuroprotective effect of aqueous root extract of Gg may be attributed to its antioxidant property by the virtue of which susceptible brain cells get exposed to less oxidative stress resulting in reduced brain damage and improved neuronal function. However further extensive studies are needed to know the exact mechanism of action as a potent and efficacious nootropic agent [28].

Melissa officinalis

It is commonly known as Lemon balm. Its belongs to family Lamiaceae. It is native to south-central Europe, the Mediterranean Basin, Iran, and Central Asia, but now naturalized in the Americas and elsewhere. we studied the potential therapeutic effect of *M. officinalis* in intracerebroventricular (i.c.v) amyloid-β (Aβ) model of Alzheimer's disease Male Wistar rats weighing 260-330 g received the hydro-alcoholic extract of *M. officinalis* (50, 100, 200, 400 mg/kg; P.O), chronically for 30 consecutive days. The control group received the solvent of the drug. Memory retrieval was assessed, using the passive avoidance task. Three groups of the rats received Aβ (1-42; 10 µg/rat bilaterally; i.c.v). One group received DMSO 1% (2 µL/rat; i.c.v). Twenty days later memory retrieval was assessed. The Aβ-treated rats, received *M. officinalis* (50, 100 mg/kg; P.O) or saline (1 mL/kg; P.O), chronically for 30 consecutive days. The DMSO 1%-treated rats received saline (1 mL/kg; P.O). The hydro-alcoholic extract of M. officinalis (50, 100, 200, 400 mg/kg; P.O) did not have a significant effect on step-through latency (STL). Aβ impaired memory retrieval by decreasing STL and increasing the time spent in the dark compartment (TDC). *M. officinalis* (50, 100 mg/kg; P.O) improved memory retrieval in AD rats by increasing STL and decreasing TDC, significantly. current study indicated potential therapeutic effects of the hydroalcoholic extract of *M. officinalis* in the i.c.v Aβ model of AD. The anti-inflammatory, antioxidant, neuroprotective, and anti-cholinesterase activities of the extract are proposed to be involved in the observed results. Further studies are required to clarify the mechanisms of this activity and identify the responsible components of the extract [29] .

Moringa oleifera (Drumstick tree)

Moringa oleifera is commonly known as Drumstick. It belongs to the family Moringaceae. It is native to India. the study, the effect of *Moringa oleifera* (MO), a naturally occurring plant with high antioxidative, anti-inflammatory, and neuroprotective effects, was evaluated on hyperhomocysteinemia (HHcy) induced AD-like pathology in rats. found that MO decreased the level of oxidative stress and neurodegeneration induced by hyperhomocysteinemia. Most importantly MO decreased the hyperhomocysteinemia induced tau hyperphosphorylation and Amyloid Beta pathology. As previously reported Hcy and oxidative stress both

lead to inactivation of PP2A and activation of GSK3beta. We also found a decrease in the methylation of PP2A as well as an increase in the activity of GSK3beta which were both recovered by MO administration. However, we also observed an increase in the protein level of CDK5, recovered by MO. MO might also influence Amyloid Beta clearance as suggested by the result where MO decreased Amyloid Beta protein level in the brain lysates of the treated animals. More especially, the immunofluorescence result showed a decrease in Amyloid Beta aggregates in the brain of MO-treated animals. Results showed that *Moringa oleifera* can cure Alzheimer's Disease [30].

Ocimum sanctum (Holy basil or Tulsi)

Ocimum sanctum is commonly known as Tulsi. It belongs to the family Lamiaceae. It is native to India. the present study has been undertaken to evaluate the possible role of OS in experimental AD in rats. Experimental AD in rats was produced by a nucleus basalis magnocellular lesion with ibotenic acid (IB) and intracerebroventricular (i.c.v) administration of colchicine (Col). Various behavioral tests and biochemical analyses were performed to explore the possible role of OS in AD. OS exhibited anxiolytic activity in an open field test. In an elevated plus-maze test, OS significantly alleviated IB, and Col induced anxiety and depression in the Porsolt's swim test. In Morris' water maze test, OS pretreatments improved reference memory, working memory, and spatial learning. Both IB and Col induced deficits in active avoidance learning and retention of learned behavior, which were significantly reversed by OS. IB and Col induced increased lipid peroxidase activity, which was significantly reversed by OS (as seen from the reductions in the malondialdehyde level) and stabilized the rise in superoxide dismutase activity, but it did not affect the acetylcholinesterase activity. OS might be effective in clinical AD by its cognition enhancement, antidepressant, and anti-anxiety properties, which are the primary needs to be addressed in AD. OS has reversed the decrease in ambulations induced by IB and ameliorated the decrease in immobility induced by IB and Col in the open-field test indicating anxiolytic activity. It is interesting to note that although OS showed anxiolytic activity in neurotoxin-treated rats, it did not show any anxiolytic activity. OS treatment significantly reversed the decrease in the open arm to closed arm ratio induced by IB and Col indicating anxiolytic activity. OS alleviated the neuropsychological symptoms associated with animal models of AD. The beneficial effect observed with OS can be attributed to its antioxidant activity [31].

Olea europaea L

It is commonly known as olive tree. It belongs to family Oleaceae. It is native to southern Europe, northern Africa and western Asia. African olive (*Olea europaea* subsp. Cuspidata) is native to Africa, Madagascar, the Mascarenes, western Asia, the Indian sub-continent and western China. this study intended to analyze the neuroprotective effects of ethanolic extract of Olea Europaea fruits in alloxan-induced cognitive impairment and brain tissue oxidative stress in mice by using the Hole Cross (HC) test, Open Field (OF) test, Free Exploration (FE) test, Y- Maze (YM) test and contents of thiobarbituric acid reactive substances (TBARS) in brain tissue homogenates of mice. Ethanolic extract of Olea Europaea fruits (200 and 400 mg/kg b.w.) was administered to alloxan-induced mice for 21 days. The neuroprotective effect of these fruit extracts was examined by using behavioral studies such as HC test, OF test, FE test, YM test, and biochemical study such as lipid peroxidation (TBARS) assay. n HC test, administration of ethanolic extract of Olea Europaea on 14th

and 21st day was remarkably ($P < 0.05$, $P < 0.01$) increased the number of holes crossed from one chamber to another by mice as compared to the disease control group. Administration of ethanolic extract of *Olea europaea* significantly ($P < 0.01$) increased the number of squares traveled by mice on the 21st day concerning that of the disease control group in OF test. In the FE test ethanolic extract of *Olea Europaea* considerably ($P < 0.05$, $P < 0.01$) increased the number of entries to the novel area and time spent in the novel area of the mice on the 7th, 14th, and 21st day as compared to the disease control group. The administration of ethanolic extract of *Olea europaea* significantly ($P < 0.05$, $P < 0.01$) increased the percentage of spontaneous alternation behavior of the mice on the 14th and 21st day as compared to that of the disease control group in the YM test. EEOE administration for successive days markedly ($P < 0.05$) decreased TBARS level in the brain tissue homogenates of mice concerning the disease control group. The present study demonstrated that ethanolic extract of *Olea Europaea* has a near defensive effect and revealed significant improvement of cognition, spatial memory, and learning in alloxan-induced diabetic mice. Our findings showed the neurological justification for the traditional use of OE in the treatment of neurodegenerative disorders more specifically AD, further studies are needed to characterize the active compounds with their mechanism of action that is predominantly accountable for their beneficial effects [32].

Phyllanthus Emblica

The study was aimed at examining the effect of ethanolic extracts of *Phyllanthus Emblica* (EEPE) ripe (EEPEr) and EEPE unripe (EEPEu) fruits on cognitive functions, brain antioxidant enzymes, and acetylcholinesterase (AChE) activity in the rat. The present study shows that EEPE fruit possesses an excellent source for natural cognitive enhancers which could be developed in the treatment of AD and other neurodegenerative diseases. Our results pro- jected that administration of EEPEr fruit, especially higher dose (i.e., 200 mg/kg b.w.) and both lowest and highest doses of EEPEu fruit (i.e., 100 mg and 200 mg/ kg, b.w.) for 12 days increased the levels of superoxide dismutase, catalase, glutathione peroxidase, glutathione reductase, reduced glutathione, glutathione-S-transferase and decreased the levels of thiobarbituric acid reactive substances (TBARS) and AChE activity in rat brain tissue homogenates. the study demonstrates that EEPE fruits showed marked beneficial effects for improving the learn- ing, memory, and antioxidant potential. Among ripe and unripe fruits, significant cognitive-enhancing effects were observed by unripe fruit which is comparable with the standard. Thus, this plant extract can be useful in the treatment of various cognitive disorders, dementia, and neurodegenerative disorders, especially AD [33].

Punica granatum

The present work was undertaken to assess the effect of ethanolic extract of *Punica granatum* seeds on cognitive performance of aged and scopolamine-treated young mice using one trial step-down type passive avoidance and elevated plus maze task. Aged or scopolamine-treated mice showed poor retention of memory in step-down type passive avoidance and elevated plus maze task. Chronic administration (21 days) of *Punica granatum* extract and vitamin C significantly ($p < 0.05$) reversed the age-induced or scopolamine-induced retention deficits in both the paradigms. *Punica granatum* extract also significantly lowered lipid peroxidation level and increased antioxidant glutathione level in brain tissues. *Punica granatum* preparations could be protective in the treatment of cognitive disorders such as dementia and Alzheimer's disease. how that chronic

treatment of *Punica granatum* seeds extract alleviates age-dependent and scopolamine-induced cognitive deficit of mice on passive avoidance and elevated plus-maze tasks, which could be due to its antioxidant action. Results show that *Punica granatum* may be protective in cognitive dysfunctions. Our results suggest that the antiamnesic effect of *Punica granatum* seeds extract in the present study could be due to its antioxidant action [34].

Salvia officinalis (Garden sage, culinary sage)

Salvia officinalis is commonly known as garden sage. It belongs to the family Lamiaceae. It is native to the Mediterranean region. The present study is done to evaluate *Salvia officinalis*, for in vivo study on Alzheimer's disease-induced mice. Memory Enhancing Activity, Conditioned avoidance test, Y-maze spontaneous alternation test, Elevated Plus Maze, Morris Water Maze, Measurement of Locomotor Activity was done to assess memory & cognitive functioning. The elevated level of enzymes and decreased level of tissue antioxidant markers were observed in treatment compared to the piracetam treatment group. While 300 mg/kg extract significantly reduced the elevated levels of the enzymes and also significantly increased the tissue antioxidant levels, while decreased the glutathione levels when compared with the control. The histopathological study confirmed the recovery. The herbal extract (150 and 300 mg/kg) has shown effectiveness against Alzheimer's disease [35].

Terminalia chebula

It is commonly known as chebulic myrobalan. It belongs to family Combretaceae. It is native to South Asia from India and Nepal east to southwest China (Yunnan), and south to Sri Lanka, Malaysia, and Vietnam. To evaluate the neuroprotective activity of *Terminalia chebula* Retz against ethanol-induced cognitive impairment and oxidative stress in rats brain. The learning and memory-enhancing activity of *Terminalia chebula* Retz extract was investigated in Sprague Dawley rats for 21 days and its effects on learning and memory were examined by using an 8-arm radial maze (or) radial arm maze (RAM) and histopathological studies. *Terminalia chebula* showed a cholinesterase inhibitor mechanism at an effective dose of 100 mg/kg against ethanol-induced cognitive impairment. *Terminalia chebula* ethanolic extract showed comparatively significant effect exerted to standard drug donepezil hydrochloride in the finding of time taken to reach paired arm (sec) & several entries in baited arms and non- baited arms (i.e. learning and memory activity). Time taken to reach paired arm (sec) & several entries in baited arms and non-baited arms were recorded after administration of ethanol at different days and graphs were plotted according to the results obtained. The histopathological study showed that ethanol-induced apoptosis neurodegeneration and the treatment of ethanolic extract of *Terminalia chebula* with ethanol decreased ethanol-induced apoptotic neurodegeneration in the rat brain. This effect is attributed to its ability to improve the levels of acetylcholine that are decreased in Alzheimer's disease .

the study was to identify the potential of *Terminalia chebula* as a protective and therapeutic agent against Alzheimer's disease. The learning and memory-enhancing activity of *Terminalia chebula* fruit extracts were investigated in rats by using the ethanol-induced cognitive impairment and diazepam-induced amnesia and its effects on learning and memory were examined by using the Morris water maze (MWM) test. All the groups showed a significant (P-value is<0.01 and <0.05) decrease in transfer latency at all periods as compared to the

ethanol and diazepam-inducing group. *Terminalia chebula* showed a cholinesterase inhibitor mechanism at an effective dose of 100 mg/kg against ethanol-induced cognitive impairment and diazepam-induced amnesia in rats. *Terminalia chebula* ethanolic extract showed a comparatively significant effect exerted to standard drug donepezil hydrochloride in the finding of transfer latency in sec (i.e. learning and memory activity). Transfer latency was recorded after administration of ethanol and diazepam on different days and graphs were plotted according to the results obtained. This effect is attributed to its ability to improve the levels of acetylcholine that are decreased in Alzheimer's disease [36].

Thymus vulgaris

It is commonly known as Thyme. It belongs to family Lamiaceae .Thyme is native to Eurasia and is cultivated throughout the world.To investigate the effect of *Thymus vulgaris* (*T. Vulgaris*) on learning and memory functions in scopolamine-induced memory deficit in rats. Memory enhancing activity in scopolamine-induced amnesic rats was investigated by assessing the Morris water maze and passive avoidance paradigm. Our results suggested that the anti-amnesic effect of *T. Vulgaris* extract on scopolamine-induced memory impairment may be related to the antioxidant activity of extract or mediation of the cholinergic nervous system [32–34]. Therefore, other plants which have antioxidant activity [35–39] might reduce amnesia. *T. Vulgaris* extract has to repair effects on memory and behavioral disorders produced by scopolamine and may have beneficial effects in the treatment of Alzheimer's disease [37].

Ulmus pumila L

In the current study, *Ulmus pumila* L. leaves alcoholic extract was investigated for its neuroprotective activity in AlCl3-induced AD in rats. Rats were orally treated with AlCl3 (17 mg/kg) for 4 weeks followed by *U. pumila* extract (150 mg/kg b.wt.) for another 6 weeks. Treatment of neuro-intoxicated rats with *U. pumila* extract resulted in a significant regulation in neurotrophic factors; brain derived neurotrophic factor and transforming growth factor-β and pro-inflammatory cytokine; TNF. It also induced an elevation in serum levels of monoamine neurotransmitters; norepinephrine, dopamine and serotonin and a decline in brain acetlycholinesterase activity. *U. pumila* extract also showed potent antioxidant activity as indicated by the declined malondialdehyde and elevated reduced glutathione, catalase and super oxide dismutase levels in AD rats‘ brains. Histological improvement was detected in the cerebral cortex, the hippocampus and striatum of the treated rats. The phytochemical analysis of U. pumila extract revealed high contents of flavonoids and phenolics and the major compounds were isolated and chemically characterized. Additionally, *U. pumila* extract and the isolated compounds exerted a prominent activity in in-vitro acetylcholinesterase inhibition assay with kaempferol-3-O-β-glucoside being the most potent compound showing IC50 of 29.03 0.0155 μM. Treatment with *U. pumila* extract significantly reduced the AChE activity in rats' brains as compared to the AlCl3 treated animals. It reveals that inhibition of AChE activity by the plant extract had a protective role in acetylcholine degradation and improved the cholinergic neurotransmission. Additionally, *U. pumila* extract and the major isolated compounds; kaempferol 3-o-β-D-glucoside, kaempferol 3-o-robinobioside, quercetin-3-O-β-D-gulucopyranoside, catechin and epicatechin, exerted a significant acetylcholinesterase inhibitory action in in-vitro assay [38].

Vitis vinifera

It is commonly known as Grape Vine. It belongs to family Vitaceae. Native to Asia near the Caspian Sea, it has been imported to Europe since before recorded history. In this study, we investigated the behavioral and biochemical effects of aluminum in Sprague-Dawley rats and the activity of *Vitis vinifera* related to Alzheimer's disease. Animals were exposed to aluminum chloride (100 mg/kg/day) orally for 8 weeks. Vitis was given in doses of 250 mg/kg and 500 mg/kg for 16 weeks and the possible effects of *Vitis vinifera* on the expression of Tau and amyloid precursor protein were evaluated by PCR analysis and the possible activities of lipid peroxidation, inflammation, and anti-cholinesterase activity were evaluated. The findings of the present study revealed the significant neuroprotective actions of *Vitis vinifera* by modifying the biochemical parameters and inhibited the mRNA expression of Amyloid Precursor Protein and Tau, which are the key pathological hallmarks of Alzheimer's disease, which was further confirmed by histopathological observations. Treatment with Vitis has shown a significant protective effect which may be due to reduction in oxidative stress, inflammation and also showed alteration in gene expression of APP and Tau. The neuroprotection offered by *V. vinifera* against Al-induced AD was confirmed by the histopathological studies. The findings of the present study revealed that Vitis markedly reduced the formation of amyloid plaques, Tau tangles and also reduced the oxidative stress, inflammation, and improved cholinergic actions. This work suggests that *V. vinifera* may prove to be the useful entity in the treatment of AD [39].

Zataria Multiflora

It is commonly known as Avishan-e-Shirazi. It belongs to family lameaceae. Native to southwestern Asia (Iran, Afghanistan, Pakistan, Kashmir).The present study aimed at clarifying plausible effects and related mechanism(s) of *Zataria Multiflora* Essential Oil (ZMEO) against memory impairment in a rat model of the AD. Methods: Forty male adult rats were categorized into four groups and treated as follows: The Negative Control (NC): no treatment, Sham control (sham): distilled water by Intracerebroventricular (ICV) injection, The AD control (AD): Aβ 1-42 by ICV injection; and 4. The ZMEO group: Aβ 1-42 by ICV injection and ZMEO at 100 µL/kg/d orally for 20 days. After Congo red staining of the hippocampus, a relative decrease in amyloid deposits was observed in the ZMEO group. Moreover, rats showed better outcomes in Morris Water Maze (MWM) test, reduced hippocampal acetylcholinesterase (AchE) activity, and higher Brain-Derived Neurotrophic Factor (BDNF) content as compared with the AD group (P0.05). ZMEO has a protective effect against memory impairment in rats with AD at least partly via reducing hippocampal AchE activity and enhancement of BDNF levels without a change in antioxidant status. These findings can pave the way for future studies on the usefulness of this herb in AD prevention [40].

Zizyphus jujube

It is commonly known as common jujube. It belongs to family Rhamnaceae. *Ziziphus jujuba* Mill is a native plant of China. Its fruits have been used in traditional Chinese medicine for more than two thousand years. This study investigates the effect of *Zizyphus jujube* extract in intact male Wistar rats and a rat model of AD. The learning and memory performance was assessed using the passive avoidance paradigm, and the memory cognition for spatial learning and memory was evaluated by Morris's water maze. The learning and memory performance was assessed using the passive avoidance paradigm, and the memory cognition for spatial

learning and memory was evaluated by Morris's water maze. In the shuttle box test, *Zizyphus jujube* extract (500 and 1,000 mg) significantly increased step-through latency in AD *Zizyphus jujube* groups compared with the AD group. In the Morris water maze test (in probe day), *Zizyphus jujube* groups receiving extract (500 and 1,000 mg) demonstrated a significant preference for the quadrant in which the platform was located on a preceding day as compared with the AD group. Results suggested that *Zizyphus jujube* has to repair effects on memory and behavioral disorders produced by nucleus basalis of Meyner lesion in rats and may have beneficial effects in the treatment of AD patients [41].

REFERENCES

1. Dos Santos Picanco LC, Ozela PF, de Fatima de Brito Brito M, Pinheiro AA, Padilha EC, Braga FS, de Paula da Silva CHT, Dos Santos CBR, Rosa JMC, da Silva Hage-Melim LI. Alzheimer's Disease: A Review from the Pathophysiology to Diagnosis, New Perspectives for Pharmacological Treatment. Curr Med Chem. 2018;25(26):3141-3159.

2. Forestier A, Douki T, De Rosa V, Béal D, Rachidi W. Combination of Aβ Secretion and Oxidative Stress in an Alzheimer-Like Cell Line Leads to the Over-Expression of the Nucleotide Excision Repair Proteins DDB2 and XPC. Int J Mol Sci. 2015;16(8):17422-44.

3. Liu J, Liu Z, Zhang Y, Yin F. A novel antagonistic role of natural compound icariin on neurotoxicity of amyloid β peptide. Indian J Med Res. 2015;142(2):190-5.

4. Perl DP. Neuropathology of Alzheimer's disease. Mt Sinai J Med. 2010;77(1):32-42.

5. Hendrie HC, Hake A, Lane K, Purnell C, Unverzagt F, Smith-Gamble V, Murrell J, Ogunniyi A, Baiyewu O, Callahan C, Saykin A, Taylor S, Hall K, Gao S. Statin Use, Incident Dementia and Alzheimer Disease in Elderly African Americans. Ethn Dis. 2015;25(3):345-54.

6. Stancu IC, Vasconcelos B, Terwel D, Dewachter I. Models of β-amyloid induced Tau-pathology: the long and "folded" road to understand the mechanism. Mol Neurodegener. 2014:18;9:51.

7. Zhu L, Zhong M, Elder GA, Sano M, Holtzman DM, Gandy S, Cardozo C, Haroutunian V, Robakis NK, Cai D. Phospholipid dysregulation contributes to ApoE4-associated cognitive deficits in Alzheimer's disease pathogenesis. Proc Natl Acad Sci U S A. 2015;112(38):11965-70.

8. Hardy JA, Higgins GA. Alzheimer's disease: the amyloid cascade hypothesis. Science. 1992;256 (5054):184-5.

9. Jonsson T, Stefansson H, Steinberg S, Jonsdottir I, Jonsson PV, Snaedal J, Bjornsson S, Huttenlocher J, Levey AI, Lah JJ, Rujescu D, Hampel H, Giegling I, Andreassen OA, Engedal K, Ulstein I, Djurovic S, Ibrahim-Verbaas C, Hofman A, Ikram MA, van Duijn CM, Thorsteinsdottir U, Kong A, Stefansson K. Variant of TREM2 associated with the risk of Alzheimer's disease. N Engl J Med. 2013 ;368(2):107-16.

10. Bhaskar K, Konerth M, Kokiko-Cochran ON, Cardona A, Ransohoff RM, Lamb BT. Regulation of tau pathology by the microglial fractalkine receptor. Neuron. 2010;68(1):19-31.

11. Schwab C, McGeer PL. Inflammatory aspects of Alzheimer disease and other neurodegenerative disorders. J Alzheimers Dis. 2008;13(4):359-69.

12. Barnham KJ, Masters CL, Bush AI. Neurodegenerative diseases and oxidative stress. Nat Rev Drug Discov. 2004;3(3):205-14.

13. Bartus RT, Emerich DF. Cholinergic markers in Alzheimer disease. JAMA. 1999; 282(23):2208-9.

14. D SK, Lochana C, Padmalatha K. Antialzheimer's Potential of Abrus pectoris hydroalcoholic root extract. J. Pharm. Sci. & Res. 2020;12(7):914–9.

15. Kunte KB, Kutagolla P, Kuna Y. Evaluation of Anti-Alzheimer's s properties of Bacopa monniera extract on Morphometric, Behavioral aspects and Cholinergic system in albino mice. BioMedRx. 2013;1(2):176–87.

16. Mahmoodzadeh T, Haji Khasem Kashani M, Ramshini H, Moslem A, Mohammad-Zadeh M. Effect of Camellia sinensis on Spatial Memory in a Rat Model of Alzheimer's Disease. J Biomed. 2016;1(1).

17. Yadang FSA, Nguezeye Y, Kom CW, Bette Ph.D., Mamat A, Tchokouaha LRY, et al. Scopolamine-Induced Memory Impairment in Mice: Neuroprotective Effects of Carissa edulis (Forssk.) Vale (Apocynaceae) Aqueous Extract. Int J Alzheimers Dis. 2020;2020.

18. He MT, Kim JH, Kim JH, Park CH, Cho EJ. Combination of Carthamus tinctorius L. seed and Taraxacum core num exerts synergistic effects on learning and memory function by regulating the metabolism of amyloid-beta in mice. J Funct Foods. 2020;72:104048.

19. Soumyanath A, Zhong YP, Henson E, Wadsworth T, Bishop J, Gold BG, et al. Centella Asiatica extract improves behavioral deficits in a mouse model of Alzheimer's disease: Investigation of a possible mechanism of action. Int J Alzheimers Dis. 2012;2012.

20. Sanjari N, Kalantaripour TP, Esmaeilpour K, Oloumi H. Beneficial Effects of Citrus aurantium Extract in Animal Model of Alzheimer's Disease. 2018;6(5):355–60.

21. Niranjan C. Memory enhancing the activity of cissampelos pariera in mice. 2016;

22. Taranalli AD, Cheeramkuzhy TC. Influence of Clitoria ternatea extracts on memory and central cholinergic activity in rats. Pharm Biol. 2000;38(1):51–6.

23. Fatemeh Mirzaei 1, Mozafar Khazaei 2, Alireza Komaki 3, Iraj Amiri 4 and Cyrus Jalili 2. Multitarget Effects of Coconut Oil (Virgin Type) on Aβ-Induced Alzheimer's Disease Animal Model. 2019; 6(2):e85715

24. Khalil A. Study the Possible Protective and Therapeutic Influence of Coriander (Coriandrum sativum L .) Against Neurodegenerative Disorders and Male Albino Rats. 2010;2(8).

25. Wang D, Wang C, Liu L, Li S. Protective effects of evodiamine in the experimental paradigm of Alzheimer's disease. Cogn Neurodyn. 2018;12(3):303–13.

26. Mukesh kumar yadav, Santosh kumar singh, Manish singh . Neurocognitive values of Evolvulus alsinoids and Centella asiatica on Scopolamine induced Amnesia in mice. 2019:6(1:15): 1-9.

27. Alharthy NA, Bawazir AE. Pharmacophore. Effects of the mixture dried figs (ficus carica) and olive oil on amnesia model of alzheimer ' s induced by scopolamine in male albino rats. 2019;10(4):62–71.

28. Chakravarthi KK, Avadhani R, Narayan RS. Effect of glycyrrhiza glabra root extract on learning and memory in Wistar albino rats. Int J Pharm Pharm Sci. 2012;4(4):199–202.

29. Beheshti S, Shahmoradi B. Therapeutic effect of Melissa officinalis in an amyloid-β rat model of Alzheimer's disease. J HerbMed Pharmacol. 2018;7(3):193–9.

30. Mahaman YAR, Huang F, Wu M, Wang Y, Wei Z, Bao J, et al. Moringa Oleifera Alleviates Homocysteine-Induced Alzheimer's Disease-Like Pathology and Cognitive Impairments. J Alzheimer's Dis. 2018;63(3):1141–59.

31. Raghavendra M, Maiti R, Kumar S, Acharya SB. Role of Ocimum sanctum in the experimental model of Alzheimer′s disease in rats. Int J Green Pharm. 2009;3(1):6–15.

32. AM A, Uddin MS, Wahid F, AI M, Rahman MM. Neurodefensive Effect of Olea europaea L. in Alloxan-Induced Cognitive Dysfunction and Brain Tissue Oxidative Stress in Mice: Incredible Natural Nootropic. J Neurol Neurosci. 2016;7:1–9.

33. Uddin S, Mamun A, Akter F. Exploring the Effect of Phyllanthus Emblica L . on Cognitive Performance, Brain Antioxidant Markers and Acetylcholinesterase Activity in Rats : Promising Natural Gift for the Mitigation of Alzheimer's Disease. 2016;1213:218–29.

34. Kumar S, Maheshwari KK, Singh V. Protective effects of Punica granatum seeds extract against aging and scopolamine-induced cognitive impairments in mice. African J Tradit Complement Altern Med. 2009;6(1):49–56.

35. Akhondzadeh S, Noroozian M, Mohammadi M, Ohadinia S, Jamshidi AH, Khani M. Salvia officinalis extract in the treatment of patients with mild to moderate Alzheimer's disease: A double-blind, randomized and placebo-controlled trial. J Clin Pharm Ther. 2003;28(1):53–9.

36. K L, SK K, J GC, M MR, A NB, N BK. Neuroprotective Activity of Terminalia Chebula Retz Against Ethanol Induced Cognitive Impairment and Oxidative Stress in Rats: Promising for Regimentation the Risk of Alzheimer'S Disease. Int J Res Ayurveda Pharm. 2018;9(4):90–3.

37. Rabiei Z, Mokhtari S, Asgharzade S, Gholami M, Rahnama S, Rafieian-kopaei M. Inhibitory effect of Thymus vulgaris extract on memory impairment induced by scopolamine in the rat. Asian Pac J Trop Biomed. 2015;5(10):845–51.

38. Rehab A. Hussein, Ahmed H. Afifi , Khairy M.A. Zoheir , Khaled M. Mahmoud. Neuroprotective activity of Ulmus pumila L. in Alzheimer's disease in rats; role of neurotrophic factors. Heliyon . 2020;6 (12) : 1-13.

39. Rapaka D, Bitra VR, Vishala TC, Akula A. Vitis vinifera acts as anti-Alzheimer's agent by modulating biochemical parameters implicated in cognition and memory. J Ayurveda Integr Med. 2019;10(4):241–7.

40. Eskandari-Roozbahani N, Shomali T, Taherianfard M. Research paper: Neuroprotective effect of Zataria multiflora essential oil on rats with Alzheimer disease: A mechanistic study. Basic Clin Neurosci. 2019;10(1):85–97.

41. Rabiei Z, Rafieian-Kopaei M, Heidarian E, Saghaei E, Mokhtari S. Effects of Zizyphus jujube extract on memory and learning impairment induced by bilateral electric lesions of the nucleus basalis of meynert in the rat. Neurochem Res. 2014;39(2):353–60.