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Review Article

STRATEGIES FOR MANAGEMENT OF ALZHEIMER'S DISEASE: A REVIEW

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ABSTRACT

Alzheimer's is the most widely recognized reason for dementia discovered by Alois Alzheimer's in 1906. Severity of Alzheimer's disease is increments with age and mostly after 65 years. It is a progressive neurodegenerative disease that damage memory and intellectual capacities. It affects 34 million people worldwide and as time goes, the pervasiveness of Alzheimer's disease continues to increase and as indicated by WHO it can reaches to 95 million by 2050. Manifestation of Alzheimer's incorporates cognitive decline that changes day by day way of life, trouble in finishing everyday errands, disarray with time or spot, misguide thinking. Most preferred drugs used for Alzheimer's are cholinesterase inhibitors like Donepezil, rivastigmine, Galantamine, Tacrine, NMDA receptor antagonist like memantine. The purpose of this review article is to provide a brief introduction, potential causes, symptoms and mechanism of action of Alzheimer's disease. This review article likewise accentuation on utilization of therapeutic plants and isolated compounds for preventing and reducing the symptoms of Alzheimer's disease.

KEYWORDS: Dementia, Amyloid plaque, ApoE, tau

INTRODUCTION

Alzheimer's is a progressive neurodegenerative disease, where degeneration of neurons in brain occurs, and it is the most widely reason for dementia[1]. As Dementia is characterized as the major neurodegenerative disorder since it meddles with both intellectual capacities and performing ordinary activities. Cognitive functions allude to memory, language, speech, thinking, planning, excursion and other reasoning capacities[2]. Alzheimer's disease was distinguished over 100 years prior yet in recent years it was perceived as the most widely recognized reason for dementia just as significant reason for death[3]. It affects 34 million people worldwide and as time goes, the predominance of Alzheimer's disease continues to increase and as per WHO it can spans to 95 million by 2050. Worldwide the expense of exhaustive consideration and treatment of dementia is added up to $818 billion[4]. According to WHO, it is estimated that 12.5% individual suffering from Alzheimer's disease are in severe stage of dementia and at this stage serious intellectual and functional deflect means individual leaving is no longer possible and the patient is under expert consideration[5]. According to Alzheimer's disease international "attitude to dementia" 2019 report

- 2 out of 3 people think dementia is caused due to normal ageing.
- 1 in 4 people think that there is nothing we can do to prevent dementia.
- 95% of people think they are suffered from dementia in their lifetime.
- 54% of respondents think lifestyle factors play a part in developing dementia.

It also showed the attitude of health care practitioner towards dementia

- 62% of health care practitioner thinks dementia as normal part of ageing.
- 40% of general public think health care practitioner ignores people with dementia[6, 7].

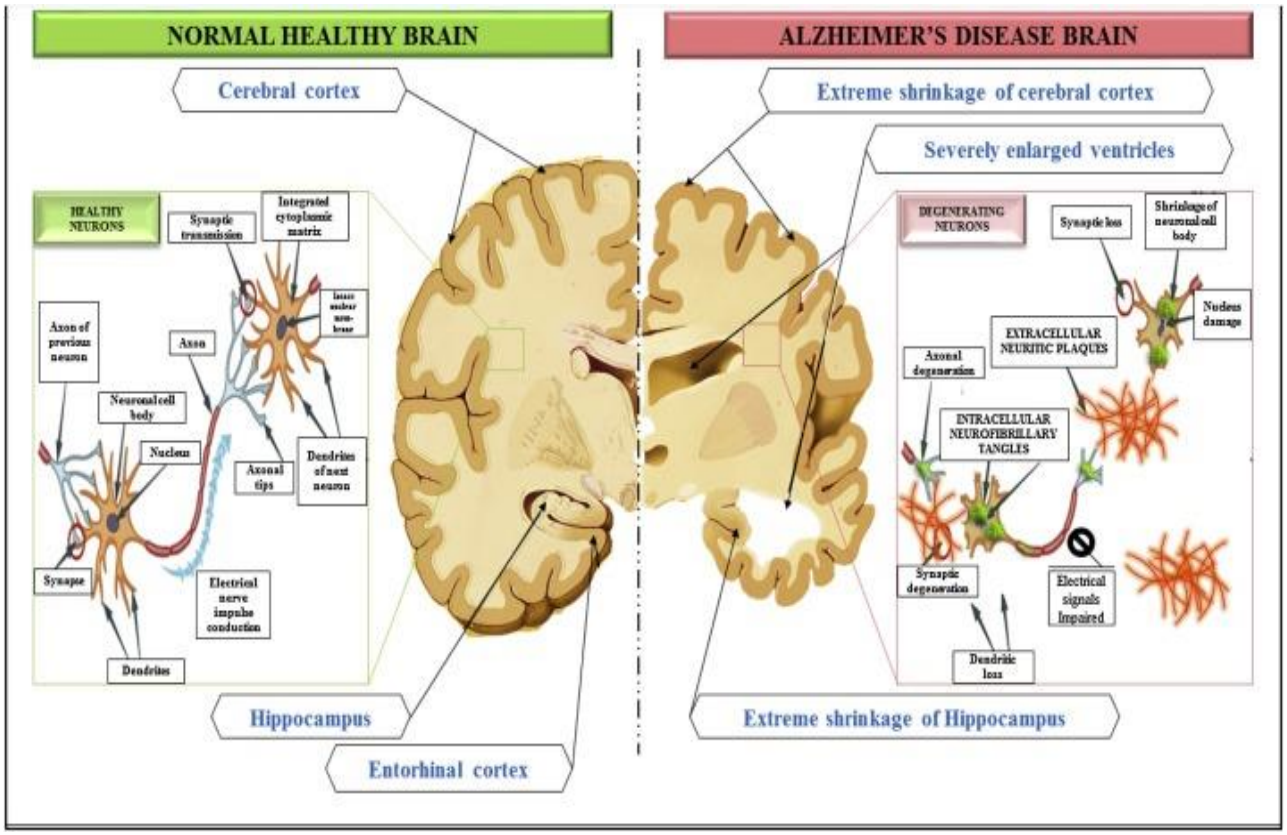

Figure 1: Schematic diagram comparing a normal healthy brain and brain at severe stage of Alzheimer's disease [8]

SYMPTOMS

Symptoms of Alzheimer's disease vary among individuals. The most widely recognized introductory symptoms are worsening ability to remember new information this occur because the neurons in brain which are involved in forming new memories are damaged and annihilated.

Early sign and symptoms include

- **Memory Loss That Changes Daily Life:** It for the most part observed in early stage, is forgetting learned information. Likewise incorporate overlooking occasions and relies upon memory aids (update notes or electronic gadgets) and furthermore asking same questions over and over.
- **Difficulty in Completing Everyday Errands:** It incorporates day by day tasks like arranging basic food list, how to play their favorite games, inconvenience driving to a known area.
- **Confusion with Spot and Time:** People with Alzheimer's disease overlook where they are or how they arrived they likewise forget dates, seasons.
- **Misplacing Things and Furthermore Losing Ability to Retrace Them:** An individual with Alzheimer's place things in a specific spot yet after some time they are unable to find the place or overlook the things they place.
- **Poor Judgment:** People with Alzheimer's experience changing in judgment or decision making like managing cash, prepping themselves[9].

Neuropsychiatric Manifestation of Alzheimer's disease

1. **Psychotic Symptoms in Alzheimer's disease:** Delusion and hallucination is reported as psychotic symptoms[10]. A study shows that in 124 demented patients, 67% had psychotic symptoms[11]. The recurrence is higher among patient with dementia with lewy body. The occurrence of hallucination is frequently less than dementia. Hallucination and dementia in Alzheimer's disease is different from that occur in schizophrenia, psychosis, depression or mania. Hallucination in Alzheimer's disease is usually visual less ordinarily auditory and rarely olfactory[12].
2. **Agitation in Alzheimer's disease:** Agitation is characterized as the excessive motor activity, or verbal or physical aggression with emotional distress. Agitation happens a great part of the time in Alzheimer's disease and related with structural and functional abnormalities of the brain region which is subject for emotional regulation[13]. Agitation and aggression are associated with decline in cholinergic and serotonergic markers, increment tau and phosphor tau[14].
3. **Apathy in Alzheimer's disease:** Apathy, depicted by lack of inspiration, impairment of voluntary muscles, emotional indifference, and it is the most notable purpose behind neuropsychiatric symptoms related with Alzheimer's disease[15] and as the illness progress conversion of ordinary cognition to mild cognitive impairment (MCI) and MCI to dementia happens. Neuroimaging investigation of preclinical or prodromal Alzheimer's sickness, apathy is related with cortical dysfunction in the posterior cingulate or inferior temporal cortex as well as atrophy, diminished metabolism in the regions. GABAergic and dopaminergic capacities have been related with apathy just as increase level of tau and phosphotau in cerebrospinal fluid[16].
4. **Depression:** Two distinct studies shows that 16% depression is found in population-based Alzheimer's disease and 44.3% in clinical based[16] and it is additionally normal in MCI. Alongside apathy, depression is moreover an indicator of progression from typical cognition to mild cognitive impairment (MCI) and MCI to dementia[17]. Tau, amyloid and vascular Sickness are found in patient with Alzheimer's illness with depression differentiated to those patients without depression and they show extreme loss of serotonin and

serotonin transporter binding, which have suggestion for therapy.

POSSIBLE CAUSES OF ALZHEIMER'S DISEASE

There are three likely purposes behind Alzheimer's disease. Research recommends that a specific allele of the apoE gene is liable for the neurodegeneration found in Alzheimer's disease[18]. Another hypothesis is that the mechanism of Alzheimer's disease is identified with prion-mediated protein mis-folding. Aside from these two causes study also shows that ecological factors likewise play a role in neuropathology of Alzheimer's disease.

The brain tissue of an Alzheimer's disease shows significant shrinkage and characteristic amyloid plaques and neurofibrillary tangles[19]. Amyloid plaque comprises of β amyloid oligomers that stick together. This β-amyloid unites to form transmembrane protein called amyloid precursor protein (APP).

Various enzymes named as α-secretase, β-secretase and γ-secretase follow up on the amyloid precursor protein and cleave it from different places causing various outcomes.

In a healthy person α-secretase cleave fragments called sAPPα, which end up being valuable for the neurons.

In a harmful pathway, amyloid precursor protein is cleaved by β-secretase and release sAPPβ and the residual fragments is cleaved by γ-secretase and released as amyloid β. These amyloid fragments accumulate and form amyloid plaque which is found in Alzheimer's disease and it is dangerous for neurons.

In healthy neurons, there is a protein 'tau' which typically assists with supporting the interior structure of the neurons. As neurons contain microtubules, which support them and help in transporting nutrients. These microtubules are attached by 'tau' protein which provides stabilization in normal person. In Alzheimer's disease the 'tau' protein is hyper phosphorylated which causes detachment of 'tau' protein from microtubules and tangle together with other 'tau' threads. As a result, the microtubule breakdown and because of this the neuron transport system fails, and the capacity of neurons to communicate is diminished.

ROLE OF ApoE ON THE EXPANSION OF SENILE PLAQUE

Numerous potential reasons for Alzheimer's disease are under investigation. Recent research shows the genetic factors of the disease.
There is a apolipoprotein E (ApoE) gene which exist in few allele, and it is the particular contributor to the biochemical mechanism of Alzheimer's disease[20]
Alzheimer's is characterized by the development of senile plaque composed by amyloid β, made up of 40-42 amino acid long peptide derived from amyloid precursor protein.

Aside from senile plaque formation another feature is the neurofibrillary tangles that emerge from the hypophosphorylated protein 'tau', which leads to a compromised cytoskeleton and cell death. The ApoE gene encodes for the ApoE protein produced by astrocytes in the brain and it is a significant cholesterol transporter which is related with the transport of lipid and injury repair. ApoE exists in three alleles: ApoE2, ApoE3 and ApoE4 and ApoE are 299 amino acid proteins and the difference between the isoforms is at amino acid 112 and 158 where either cysteine or arginine is present[21]. This slight contrast is sufficient to change the tertiary structure of protein which influences its capacity to bind lipids, receptors and amyloid β.

Among all the allele forms ApoE2 is the most well-known allele and ApoE2 is associated with decrease risk of Alzheimer's disease[22] while ApoE4 is associated with increased risk of Alzheimer's disease as it is the hypolipidated version of the protein. In late–onset and irregular Alzheimer's huge measure of ApoE4 is available. In inconsistent Alzheimer's sickness there currence of apoE4 is more prominent than 50% and each duplicate of allele decline the illness onset 7-9 years. Patient having large amount of ApoE4 shows a higher level of accumulated amyloid β and hyperphosphorylated 'tau' as well as decrease neural plasticity and neuropathology[23] and presence of ApoE4 allele affect the binding of ApoE4 to lipid, leading the proposal that the disease is caused by lipid related mechanism[24].

Further research on how ApoE4 is identified with Alzheimer's disease has demonstrated that how other factors play a role in disease process. Other than causing the development of senile plaque, the ApoE4 protein can likewise affect the body's means of eliminating it. Generally amyloid plaque and neurofibrillary tangles are taken out from the brain by a process known as autophagy[25]. Autophagy eliminates cellular debris for e.g. dysfunctional organelles, old protein, and aggregated protein. In normal person astrocytes produce ApoE in the central nervous system which generally protect the brain from harmful protein buildup but in case of Alzheimer's disease as, the disease progress the mechanism become faulty and impaired autophagy become harmful because the accumulated protein can cause synaptic degeneration in the hippocampus neurons

ENVIRONMENTAL FACTORS AND THEIR ROLE IN ALZHEIMER'S DISEASE

Environmental factors play a significant role to influence brain structure and function. Lifestyle elements for e.g. nutrition's, physical exercise, smoking, diet, exposure to chemicals and social interaction significantly impact the brain structure and function. The primary risk factors for late onset Alzheimer's disease is way of life changes that incorporates the social detachment, infrequent participation in intellectual activities, poor nutritional intake[26]. Individual who participates in intellectually invigorating action, such as, reading article, playing indoor, outdoor games, crossword puzzles, singing songs, playing musical instruments, daily social interaction show reduced risk of Alzheimer's disease[27]. Physical activity is additionally seeming to be useful for reducing the risk of Alzheimer's disease[27]. Physical exercise is likewise associated with decreased rate of dementia also physical exercise reduces the symptoms in Alzheimer's disease patients[28, 29]. Diet likewise assumes a significant role in the management of Alzheimer's disease, people who maintain a healthy diet reduces the risk of Alzheimer's disease[30]. Individual who takes diet rich in saturated fats and simple carbohydrates like mono and disaccharide have a higher risk of Alzheimer's disease[31]. People who take diet rich in flavonoid for e.g. cocoa, red wine and tea may diminish the risk of Alzheimer's disease[32].

DIAGNOSIS

Alzheimer's disease is normally diagnosed with the help of patient's medical history, a close behavioral observation, information from family relative and neighbors. A physician can diagnose Alzheimer's disease with the help of neurologist. Neurological and Neuropsychological characters assume a significant role and apart from these presence and absence of alternative condition are likewise supportive[33, 34]. Progression in the field of medical science finds various approaches to diagnose

Alzheimer's illness with the help of CT scan, or MRI and furthermore with single photon emission computed tomography and positron emission tomography (PET). These techniques are utilized to eliminate cerebral pathology and subtype of dementia[35] and with the assistance of these techniques the neurologist additionally predicts the conversion from mild cognitive impairment to Alzheimer's disease[36].

In 1984, the National institute of neurological and communicative disorders and stroke (NINCDS) and the Alzheimer's disease and related disorder association (ADRDA) now known as Alzheimer's association established the most commonly used NINCDS-ADRDA criteria for diagnosis of Alzheimer's disease[37] which were updated in 2007[38].

Apart from the diagnosis tools histopathological affirmation including a microscopic examination of brain tissue is additionally required. Good statistical reliability and validity have been appeared between diagnostic criteria and histopathological examination[39]. Neurological assessment of patients in beginning stage of Alzheimer's illness will usually provide ordinary outcomes and get crucial in the differential diagnosis of Alzheimer's disease and other diseases[40].

Information from the family members regarding patient condition, his behavior is likewise utilized in the evaluation of the disease; caregivers also give data regarding patient mental health, daily living abilities, and patient's memory in regard to date or time, propensity for misplacing things and furthermore loosing ability to retrace it[41]. In Alzheimer's disease a caregiver viewpoint plays an important role for the diagnosis, treatment of the disease, since the patient is unaware of his own situation[42].

TREATMENT

There is no specific measure which is compelling in forestalling Alzheimer's disease [44] conflicting outcomes are produced by the worldwide investigations of measures to forestall or delay the onset of Alzheimer's illness. Epidemiological studies proposed connection between certain modifiable factors for e.g., diet, cardiovascular risk, and pharmaceutical product but on further research including clinical trials demonstrates whether these factors help to prevent Alzheimer's disease[43].

Non-Pharmacological Treatment

The primary motivate behind non-pharmacological treatment is keeping up or improving intellectual capacities, capacity to perform activities of day by day living or the quality of life. The goal of non-pharmacological treatment is reducing behavioral symptoms such as depression, apathy, sleep disturbance, agitation and aggression.

Example includes art therapy, activity-based therapy and memory training. Non-pharmacological therapies have not been shown to alter the course of Alzheimer's disease. Methodical surveys of distributed examination on pharmacological therapies have discovered that some, for example, exercise, and intellectual action (gardening, word games, tuning in to music and cooking) show advantageous outcomes[44].

Pharmacological Treatment for Alzheimer's Disease

There are five prescribed medication which is used in the treatment of Alzheimer 'disease endorsed by the U.S food and drug administration. They are prescribed to treat the symptoms of Alzheimer's illness. Example of drugs affirmed by the U.S food and drug administration incorporates

- Donepezil
- Galantamine
- Rivastigmine
- Memantine

Donepezil, Galantamine and rivastigmine belongs to the class of cholinesterase inhibitor. These medications are utilized to prevent the breakdown of chemical messenger in the brain that assumes a significant role in learning and memory.

Memantine belongs to the category of NMDA receptor antagonist that likewise assumes significant role in learning and memory by regulating the activity of different chemical messengers also there is a combination of the cholinesterase inhibitor (Donepezil) with NMDA receptor antagonist (memantine).

Inhibition of β and γ secretase pathways (amyloidogenic pathways of proteolytic cleavage of APP) and incitement of α secretase pathway have been the most encouraging systems for neuro protection in Alzheimer's disease within this research focus[45].

Cholinesterase Inhibitors

Three different types of cholinesterase inhibitors are commonly prescribed

- Donepezil: medication used to treat all stages of Alzheimer's illness
- Galantamine: medication used to treat mild to moderate stages of Alzheimer's illness
- Rivastigmine: Approved for mild to moderate stage of Alzheimer's disease as well as mild to moderate dementia associated with Parkinson's disease.

The principal motivation behind treatment for Alzheimer's disease is to inhibit the degradation of acetylcholine within the synapse and to increase cholinergic transmission.

Tacrine was approved as the first acetylcholinesterase inhibitors used to treat mild to moderate stages of Alzheimer's disease over 15 years ago but due to its poor tolerability and risk of hypertoxicity it is no longer prescribed now[46].

US-FDA approved three second generation acetylcholinesterase inhibitors for the treatment of mild to moderate Alzheimer's disease. These agents differ in their pharmacological actions, particularly in relation to enzyme specificity. Donepezil selectively inhibits acetylcholinesterase, rivastigmine inhibits both acetylcholinesterase and butylcholinesterase and Galantamine inhibits acetylcholinesterase but also has activity as an allosteric modulator of nicotinic acetylcholine receptor[47]

Mechanism of Action of Cholinesterase Inhibitors

Acetylcholinesterase acts as a neurotransmitter which is associated with memory, judgment, thinking, language and other thought process.
Cholinesterase inhibitors act by increasing the level of acetylcholine by inhibiting the degradation of acetylcholine inside the neural connection. Certain part of brain cells releases acetylcholine, which causes in conveying message to different cells when the message spans
to the getting cell, different other chemicals, including an enzyme acetylcholinesterase, break acetylcholine down so it can be recycled.
In Alzheimer's disease the cell which is liable for production and use of acetylcholine is damaged and destroyed thereby reducing

the amount available to carry messages. Cholinesterase inhibitors works by eases back the breakdown of acetylcholine by blocking the activity of acetylcholinesterase. By keeping up acetylcholine levels, the medications may help make up for the loss of working synapses.

Table 1: Characteristics of acetylcholinesterase inhibitors and NMDA receptor antagonist [48]

CHARACTERISTICS	DONEPEZIL	RIVASTIGMINE	GALANTAMINE	MEMANTINE
Primary mechanism of action	Selective and Reversible AChE-I	Pseudo-irreversible AChE-I	Selective and Reversible AChE-I	NMDA receptor Antagonist
Secondary mechanism of action	None	BuChE-I	Nicotine modulator	5-HT3 receptor antagonist
Starting dose	5 mg daily	1.5 mg bd (oral) (or 4.6mg/24 hrs patch)	4 mg bd 5 mg daily or 8 mg XL daily	5 mg daily
Maximum dose	10mg daily	6mg bd(oral) Or 9.5mg/24 hrs patch	12 mg bd (or 24 mg XL daily	20 mg daily or (10mg bd)
Metabolism	Substrate at 3A4 and 2D6	Non-hepatic metabolism	Substrate at 3A4 and 2D6	Primarily non-hepatic metabolism renal elimination
Effects on plasma level (increased by)	Ketoconazole Itraconazole Erythromycin Quinidine Fluoxetine	Metabolic interactions appear unlikely Rivastigmine may inhibit the butyryl- succinylcholine - type muscle relaxants, cholinergic cholinesterase mediated metabolism of other substances e.g. cocaine	Ketoconazole Erythromycin Ritonavir Quinidine Fluoxetine Fluvoxamine amitriptyline	Cimetidine Ranitidine Procainamide Quinidine Quinine Nicotine
Effects on plasma level (decreased by)	Rifampicin Phenytoin Carbamazepine Alcohol	Metabolic interaction appears unlikely	None known	None known (possibility of reduced Serum level of hydrochlorothiazide's when co-administered with memantine

Table 2: Adverse effects and pharmacodynamic interaction of medication used in Alzheimer's disease [48]

CHARACTERISTICS	DONEPEZIL	RIVASTIGMINE	GALANTAMINE	MEMANTINE
Adverse effects Very common: ≥ 1/10 and common: ≥ 1/100	Diarrhea, nausea, headache, common cold, anorexia, hallucination, agitation, aggressive behavior, abnormal dreams and Nightmares, syncope, dizziness, insomnia, vomiting, abdominal pain, rash, pruritis, muscle cramps, urinary incontinence, fatigue and pain	Anorexia, dizziness, nausea, vomiting diarrhea, agitation, confusion, anxiety, headache, somnolence, tremor, abdominal pain And dyspepsia, sweating fatigue and asthenia, malaise and weight gain	Nausea, vomiting, decreased appetite, anorexia, hallucination, syncope, tremor, depression, lethargy, bradycardia, hypertension, dyspepsia, diarrhea, muscle spasm, asthenia, malaise, and weight loss	Drug hypersensitivity somnolence, dizziness, balance disorders, hypertension, dyspnoea, constipation, elevated liver function test and headache
Pharmacodynamic interactions	Antagonistic with anticholinergic drugs. Synergistic activity with cholinomimetics such as Neuro-muscular blocking and peripherally Acting cholinergic agonists and peripherally acting cholinesterase inhibitors e.g. neostigmine.	Antagonistic effects with anticholinergic and additive effects cholinomimetics drugs, succinylcholine – type muscle relaxants, cholinergic agonists e.g. bethanechol or peripherally acting cholinesterase inhibitors e.g. neostigmine. Synergistic effects on cardiac conduction with beta blockers, amiodarone, and calcium channel blockers.	Antagonistic effects with anticholinergic and additive effects with cholinomimetics, succinylcholine – type muscle relaxants, cholinergic inhibitors e.g. neostigmine. Possible interaction with agents that significantly reduce heart rate like digoxin, beta blockers, certain calcium channel blockers and amiodarone. Caution with agents that cause torsades de pointes.	May enhanced effects of L-dopa, dopaminergic agonists and anticholinergic. May reduce the effects of barbiturates and neuroleptics. Avoid concomitant use with amantadine, ketamine and dextromethorphan as there is risk of pharmacotoxic psychosis. Dosage adjustment is necessary for antispasmodic agents, dantrolene or baclofen when administered with memantine

ROLE OF MEDICINAL PLANT IN THE TREATMENT OF ALZHEIMER'S DISEASE

Medicinal plant appeared to have beneficial effects on decreasing the progress and symptoms of various diseases including Alzheimer's disease[49]. Medicinal plant as well as isolated compounds show results in preventing and reducing symptoms of Alzheimer's disease. Numerous studies show the beneficial effect of complete medicinal plant extract as well as a single isolated active compound in Alzheimer's disease[50]. Compounds like tannins, flavonoids, lignans, polyphenol, triterpenes, alkaloids and sterols shown various pharmacological activities like anti-inflammatory, anti-amyloidogenic, anticholinestrase and antioxidant which are important for the prevention of Alzheimer's disease[49]. Medicinal compound such as aged garlic extract, curcumin, melatonin, resveratrol, *Ginkgo biloba* extract, green tea, vitamin C and E is also used in patients with Alzheimer's disease and yielded positive results[51, 52].

LIST OF MEDICINAL PLANT USED IN TREATMENT OF ALZHEIMER'S DISEASE

- *Curcuma longa* (Turmeric)
- *Bacopa monnieri* (Brahmi)
- *Centella asiatica* (Indian pennywort or Asiatica pennywort)
- *Convolvulus pluricaulsis* (Shankhapusphi)
- *Ginkgo biloba* (Maidenhair tree)
- *Zingiber officinale* (Ginger)

Others Include

- Quercetin
- Resveratrol
- Berberine
- Luteolin
- Rosmarinic acid

***Curcuma Longa* (Turmeric)**

Curcuma longa (turmeric) is a rhizomatous plant belongs to family zingiberaceae. Curcuminoid (water insoluble) are the active components responsible for the majority of the medicinal properties of turmeric, and they consist of a mixture of curcumin (75–80%), demethoxy curcumin (15–20%), and Bidemethoxy curcumin (3–5) and they are available commercially[53, 54].
Yellow color of curcumin is due to presence of curcumin[55]. Curcumin shows anti-inflammatory, antioxidant, anti-tumor, and anti-bacterial activities[56, 57].
A past review has indicated that curcumin might be a promising compound for the treatment of Alzheimer's disease[58]. Other studies show that mice with β-amyloid plaque when treated with curcumin shows decrease amount of plaque deposition[59] and curcumin also decrease the oxidative stress in brain[60].

***Bacopa Monnieri*(Brahmi)**

Bacopa monnieri which is also known as water hyssop, Brahmi, herb of grace, and Indian pennywort is an important medicinal plant belongs to family scrophulariaceae. The main compounds of *Bacopa monnieri* are saponins and triterpenoids. Other compounds, including alkaloids, sterols, betulic acid, polyphenols, and sulfhydryl, polyphenols which show antioxidant activity have, additionally been found in *Bacopa monnieri*[61]. Conventional medication has utilized brahmi for improving memory and cognitive functions[62]. Numerous examinations related to neuro pharmacological impact of brahmi extracts have been conducted extensively[63]. In the hippocampus, brahmi, increase protein kinase action, this gives a nootropic action[64]. Animal Alzheimer's model, in rats feed with *Bacopa monnieri* extract indicated decrease cholinergic degeneration and exhibited perception improving impact[65]. Another study detailed that brahmi inhibited the Ache activity and increase the level of acetylcholine[66]. Clinical trials result of patient suffering from Alzheimer's disease shows that polyherbal formulation contain extract of Indian pennywort adequately improved the psychological capacities and also shown to decrease level of inflammation and oxidative stress[67].

***Convolvulus Pluricaulis* (shankhpushpi)**

The photochemical present in *Convolvulus pluricaulis* uncover that it might contain active compounds like triterpenoids, flavonol glycosides, anthocyanins, and steroids. They give the nootropic and memory enhancing activity for *Convolvulus pluricaulis*[68]. Another study announced that shankhpushpi may calm the nerves by regulating stress hormones adrenaline and cortisol levels in the body[69]. Oral administration of shankhpushpi additionally eased the neurotoxic impact of scopolamine by diminishing the induction of protein and mRNA levels of tau and AβPP[70].

***Centella Asiatica* (Gotu Kola)**

Conventional medication has utilized *Centella asiatica*for rejuvenating the neuronal cells. Asiatic acid and asiaticoside have been separated from *Centella asiatica* and these compounds have indicated the ability to diminish H2O2 – initiated cell cytotoxicity, decrease free radical levels, and hinder β-amyloid cell damages in vitro. *Centella asiatica* extracts reduced the β-amyloid pathology and decrease the oxidative stress response in the brains of a mice model of Alzheimer's disease[71]. It has just been accounted that *Centella asiatica*ethanol extract can protect neuronal cells against Aβ1-40 prompted neurotoxicity. These activities propose the significant job of *Centella asiatica* for the counter action and treatment of Alzheimer's disease[72].

***Ginkgo Biloba* (Maidenhair Tree)**

Leaves of *Ginkgo biloba* have been utilized in conventional medicines as an agent for improving memory and age-related disintegration. The photochemical of *Ginkgo biloba* leaf extracts contain flavonoids, organic acids, and terpenoids, which give neuroprotective movement. The defensive mechanism of *Ginkgo biloba* leaf extract against β-amyloid has been appeared to prompt cytotoxicity and might be identified with the ability to rummage free radicals, reduce mitochondrial dysfunction, activate JNK and ERK pathway and forestall neuronal apoptosis[73]. *Ginkgo biloba* has been appeared to decrease the declaration of P53, Bax, and caspase-3 protein just as inhibit ROS induced apoptosis in PC12 cells[74].

***Zingiber Officinale* (Ginger)**

Zingiber officinale also known as ginger is broadly utilized in food supplements and also used as ingredients of ginger tea. The main Phytochemical such as gingerols, shagols, bisabolene, zingiberene and monoterpenes have been isolated form *Zingiber officinale*[75]. In vitro assays in the ACHE inhibitory action of *Zingiber officinale* by inhibiting the Ache enzyme, the level of acetylcholine on the synapses increase, augments the activity of cholinergic pathway, and upgrades intellectual capacities in Alzheimer's disease patients. Moreover, *Zingiber officinale* has the ability to inhibit lipid peroxidation and give the defensive impact against Alzheimer's disease[76].

Quercetin

Quercetin which is a flavonoid compound and found in wide assortment of medicinal plants, for e.g. apple, onion, berries,

green tea, and red wine. Quercetin acts as a strong antioxidant by scavenging reactive oxygen species[77]. At a dose of 10µm quercetin shows anti-amyloidogenic activity[78]. Quercetin likewise diminished the Aβ instigated apoptosis in neuronal cells. In any case, at a higher dose (40µm), quercetin may incite cytotoxicity[79].

Berberine

Berberine is a quaternary ammonium salt and a sort of isoquinoline alkaloids, which is isolated from coptis chinensts[80]. Berberine has numerous biological activities, for e.g. anti-oxidant activity, restraint of AChE and cholesterol bringing down action[81]. Tg mice took care of with berberine at a dose of 100 mg\kg through oral administration indicated significantly expanding learning and spatial memory[80]. BV2 microglia cells treated with berberine essentially diminished the β-amyloid initiated articulation of IL-6; COX, and INOS [82.] moreover, berberine likewise unequivocally diminished the expression of NF-RB by restraining the PI3K\ protein kinase B and MAPK pathways[83]. An ongoing report has demonstrated that berberine can altogether enhance memory impedance, diminish Aβ and APP levels, and reduce Aβ plaque deposition in the hippocampus[84] and forestall the expansion of AChE activity[85].

Resveratrol

Resveratrol belongs to a group of stilbenes and it is a polyphenolic compound. It can be found in red wine, nuts and the skin of grapes and different organic products[86]. Resveratrol has an intense antioxidant activity by rummaging ROS, expanding glutathione levels; what's more, improving the endogenous antioxidants. Resveratrol can likewise reduce the level of β-amyloid by initiating the non-amyloidogenic cleavage of APP and upgrading the leeway of β-amyloid[87]. Resvesatrol at a dose of 14, 45, 135 mg\kg additionally repressed AChE action in neuronal cells[88]. A randomized, double-blind, placebo controlled preliminary of resvesatrol for Alzheimer's disease gave proof that it is safe, well tolerated and decrease the CSF Aβ40 and plasma Aβ40 levels[89].

Luteolin

Luteolin is a flavonoid compound found in numerous therapeutic plants, for e.g., Magnoliophyta, Pteridophyta, Bryophyta and Pinophyta[90]. Luteolin diminish the zinc-induced hyperphospho rylation of the tau-protein, the mechanism of which might be clarified by the anti-cancer action and ability to direct the tau phosphatase\kinase system[91]. Besides, luteolin can diminish the expression of amyloid precursor protein and decreased the development of β-amyloid[92]. Luteolin can likewise moreover restrain apoptosis by diminishing intracellular ROS generation, improving cell reinforcement endogenous framework for e.g. augmenting SOD, CAT and GPx activities; and actuating the NRF2 pathway[93]. In another examination, luteolin additionally improve the cognizance capacity and memory on a streptozotocin induced Alzheimer's disease rat model[94]. Further clinical trial data are expected to confirm the defensive impact of luteolin against Alzheimer's disease.

Rosmarinic Acid

Rosmarinic acid is a type of polyphenol carboxylic acid existed in numerous lamiaceae species[95]. Rosmarinic acid may altogether forestall β-amyloid instigated cognitive decline, the mechanism of which might be ascribed to its ability to inhibit NF-k band TNF-α expression[96]. Rosmarinic acid has additionally been appeared to secure neuronal PC12 cells to keep away from β-amyloid initiated cytotoxicity. Moreover, it might diminish the hyperphosphorylation of the tau protein. Hindering apoptotic pathways by rosmarinic acid might be disclosed because of its ability to hinder ROS arrangements, caspase3 activation, and DNA fragmentations rosmarinic acid may likewise forestall locomotors activity, momentary spatial memory, and biochemical changes of mind tissue found in rodent model of Alzheimer's disease by diminishing lipid peroxidation and inflammatory process[97].

CONCLUSION

Alzheimer's was discovered by Alois Alzheimer's over a century prior, much advancement has been made in comprehension the pathophysiology, clinical aspects of the disease. Numerous significant advances have been made in describing pre-dementia phase of Alzheimer's disease, much as MCI and improving the diagnostic and therapeutic option accessible for treating Alzheimer's disease. Cure of Alzheimer's disease at last depend not just on having a precise perspective on the cellular and molecular processes yet in addition on having ideal biomarkers for early diagnosis and timely therapeutic intervention in at-risk individuals. Neuroimaging and different biomarkers are utilized for early detection of Alzheimer's disease. The pharmacological management of Alzheimer's disease is testing zone for the prescriber. AchEIs and memantine remains the main medications affirmed for the utilization in Alzheimer's disease. Aside from the allopathic drugs Ayurvedic herbs additionally assumes a significant role in treating Alzheimer's disease. Numerous significant restorative plants can be applied to reduce dementia and treat Alzheimer's. Chemical compounds for e.g. alkaloids, flavonoid have demonstrated to be effective against Alzheimer's disease.

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