Journal of Young Pharmacists, 2023; 15(1):13-30.
www.jyoungpharm.org

Review Article

Management of Alzheimer's Disease: A Review of Herbal Drugs Having Potential Pharmacological and Therapeutic Activity

Mrunali S Potbhare[1,2,*], Rakesh Barik[3], Deepak S Khobragade[2]

[1]Institute of Pharmacy, GITAM University, Vizag, Andhra Pradesh, INDIA.
[2]Datta Meghe College of Pharmacy, Datta Meghe Institute of Medical Sciences (DU), Sawangi (M), Wardha, Maharashtra, INDIA.
[3]School of Pharmacy, GITAM University, Hyderabad, Telangana, INDIA.

ABSTRACT

Alzheimer's disease (AD), the most common type of dementia, is a progressive neuro-degenerative disease severely affecting memory and cognitive function. It causes linguistic and visuo-spatial deficiencies, and behavioral problems like indifference, aggressiveness and depression as disease progresses advanced stages. No cure is available for Alzheimer's, though symptomatic treatment improves memory and other symptoms. Natural products ease the symptoms of many kinds of diseases and offer a treatment option for many diseases at least successfully slowing the progress. Medicinal plants and plant products have been historically employed to improve brain function and treat memory disorders like amnesia, dementia. Though, various studies have described the utility of plants for treatment of Alzheimer's, but with limited scientific evidence. Though, it has been reported that early start of utilization memory enhancing agents and brain tonics can be beneficial in AD. The present review is to summaries the herbal medicines which have reported to have some kind of CNS activity and may be utilized for slowing progression, symptomatic treatment and research in the treatment of Alzheimer's disease (AD) and its related symptoms.

Keywords: Alzheimer's disease, Dementia, Acetylcholine, Memory, Medicinal plants.

Correspondence:
Prof. Mrunali S Potbhare
Institute of Pharmacy, GITAM University, Vizag -530045, Andhra Pradesh, INDIA.
Email id: mrunalipotbhare@gmail.com

Received: 08-05-2022 ;
Revised: 08-06-2022 ;
Accepted: 08-07-2022.

ALZHEIMER'S DISEASE

Alzheimer's disease (AD) is a most severe type of neurodegenerative disease affecting brain, the symptoms of this disease become more severe and worsens with time.[1] The disease is named after Alois Alzheimer, a German physician, who reported reported the first case of "Presenile Dementia".[2] He studied the brain of the patient and found the diffused cortical atrophy and particular changes in cortical cell clusters, plaques and tangles of nerve fibers which are identified as beta amyloid plaques and neuro-fibrillary tangles of tau in 1980.[3,4] In 1984 the clinical diagnostic criteria for AD was revised for mild-cognitive impairment and dementia stages of AD and established the role of biomarkers.[5-6]

The Alzheimer's patients are unable to notice the changes in the brain even for years till they experience noticeable symptoms like linguistic issues and memory loss. The AD remains undetected even after 20 years or more of actual start of condition. The symptoms are visible due to the significant damage to the neurons in brain associated with thinking, learning and memory beyond repair.[7] As the disease progresses, it starts affecting neurons in other parts of the brain thus affecting capability to carry out day to day functions like swallowing, walking and sitting straight to name some. Patients become bed ridden and depends on others for basic chore needing 24x7 attentions making him very week ultimately resulting in demise.[8] The differences in normal brain and brain of AD patients is given in Table 1.

Difference between Alzheimer's disease and Dementia

AD and dementia are erroneously considered same. AD is the most common cause/form of dementia. Dementia is characterized by difficulty with memory, speech/language, intellectual and thinking skills which affect patient's ability to do normal day-to-day activities due to changes in the brain of the person with AD.[9-10] The AD and dementia is differentiated in Table 2.

Epidemiology

As per WHO, worldwide, more than 55 million people worldwide are living with dementia and nearly 10 million new cases are

DOI: 10.5530/097515050344

reported every year.[11]It is reported that an estimated 0.7% of the global population (51.6 million people) has dementia and the number is projected to reach 152 million by mid-century. It is the seventh leading cause of death among all diseases.

Almost 30% increase in reported AD cases every five year is observed as per the report of the World Health Organization (WHO). Prevalence, incidence, mortality, and disability adjusted life a years (DALYs) due to AD has drastically increased worldwide.[5,12,13] Projections indicate that AD related deaths will increase from the current 2.4 million/year to 5.8 million/year by 2040.

The age is an important prevalence factor as AD has a progressive increase proportional to aging. [14] About 5% of individuals over 65 years and 20% of those over 80 years suffer from AD, indicating that the prevalence rate doubles every 5 years.[15] According to Javed *et al.* the high-income regions like Western Europe show higher prevalence than Asia and Africa.[16,17]

The available and reported data can be misleading as it is from health records. In many developing countries not all the health problems especially related to dementia in older people are reported. To get maximum correct data there is a need for improvement in the search and registration of the data for unregistered or under-diagnosed AD patients.[18]

Table 1: Differences in Normal and Alzheimer brain.

Normal Human brain	Alzheimer brain
The healthy human brain consists of billions of healthy neurons	The Alzheimer brain consists of injured and dead/dying neurons throughout the brain
Connections between neurons networks are strong	Connections between neurons networks are generally broken down
Continuous communication between neurons of different parts of the brain, and from the brain to the muscles and organs of the body takes place.	Communication process among neurons is disturbed with loss of function resulting in cell death.
Very good capacity to transmit information via electrical and chemical signals.	Capacity to transmit information via electrical and chemical signals is substantially lost.
In healthy aging though the brain shrinks to some extent but, neurons are not lost in large numbers.	In Alzheimer disease brain regions begin to shrink with loss of neurons
	At the microscopic level, the Alzheimer's brain shows amyloid plaques outside the neurons and neurofibrillary tangles inside the neurons.

The AD not only is a burden for quality of life and social issues but also a very big financial issue. According to the World Alzheimer Report 2015, the overall costs for the care of AD were 818 billion dollars, an increase of 35.4% compared to 2009. The trend suggests that the cost may be rising to 2 trillion in 2030. [19]

PATHOPHYSIOLOGY OF ALZHEIMER'S DISEASE

Alzheimer's disease is attributed to many aspects like the cholinergic dysfunction, amyloid/tau toxicity and oxidative stress/ mitochondrial dysfunctions.[20]Patients show loss of neurons and temporo-frontal cortex atrophy causing the deposits of amyloid plaques and inflammation. The prominent features of

Table 2: Difference between Alzheimer's and Dementia.

Alzheimer's Disease	Dementia
Alzheimer's disease is a most common type of dementia. But not every dementia is Alzheimer's.	Dementia describes difficulty in memory that affects, daily activities, and communication abilities.
Deposition of unusual proteins in the brain causes AD. Formation of protein plaques and tangle in the brain disturbs communication within brain. Slowly the cells damaged and no longer can function properly.	Dementia can be caused by many conditions and degenerative diseases Different set of brain cells or different part of brain is damaged in different type of dementia.
AD is a progressive disease of brain, slowly worsening with time, impairing memory and cognitive functions. Though many theories exist, the exact cause is unknown and cure is not available for AD.	It mostly affects people in the older age. Persons above 85 years generally have some kind of dementia. The cases are relatively low in young person
Early signs and symptoms of AD include: • Disorientation • Changes in mood and behavior • Difficulty with language • Difficulty in swallowing • Poor control on motor activities like walking • Confusion about times, places, and events	Early signs and symptoms of dementia include: • Symptoms of psychosis, depression, anxiety and distress • Showing detachment and disinterest • Asking the same questions, talking about same things and walking around for no reason • Disturbed Sleep pattern • Missing sense of appropriate behaviors
It is irreversible	It can be reversible

AD is presence of an irregular cluster of protein fragments and tangled fiber bundles. It increases the monocytes and macrophages in cerebral cortex and microglial cells in the parenchyma.[21]

AD causes neuronal losses in the entorhinal cortex, amygdala, and hippocampus. The cortical association of the frontal, temporal, parietal cortices and sub-cortical nuclei and the cholinergic basal nucleus also suffer neuronal loss. The deposited tangles show a specific pattern which starts from the trans-entorhinal cortex and continuing to the entorhinal cortex, the CA1 region of the hippocampus and then to cortical association area where frontal, parietal and temporal lobes join. The severity of dementia depends more on tangle formation than numbers of amyloid plaques.[22]The cognitive decline and brain atrophy, including hippocampal atrophy growthis linked with growth of hyper-phosphorylated tau proteins and amyloid β deposition. [23]AD patients also show high levels of redox transition metals in the brain [24] and reduced cholinergic receptor binding in specific brain regions which may be related to neuropsychiatric symptoms.[25]

Table 3: Different Symptoms of AD.

Cognitive Symptoms	Non-cognitive symptoms	Symptoms affecting normal living
Memory loss	Depression	Occasional muscle twitches.
Language difficulties	Hallucinations	Groaning, moaning, or grunting.
Executive dysfunction indicating loss of advanced planning and intellectual skills.	Delusions	Increased sleeping.
Repeating questions	Agitation	Loss of bowel and bladder control.
Getting lost	Aggression	Difficulties with performing daily activities.
Shortened attention span	Restlessness	Difficulty swallowing and eating unaided
Losing things often	Anxiety	Difficulty in dressing.
	Seizures	Difficulty in driving.
	Tearfulness	Difficulty in shopping, counting money and paying bills.
	Impulsive behavior	

SYMPTOMS OF ALZHEIMER'S DISEASE

Alzheimer's disease is basically identified by the symptoms before clinical diagnosis. The symptoms of Alzheimer's disease start showing very mild symptoms initially like partial memory loss and progress to very severe dementia and other behavioral changes. The symptomatic disease is being recognized and confirmed pathologically, clinically and epidemiologically. [26-29] The different symptoms of AD are summarized in Table 3.

CAUSES OF ALZHEIMER'S

There is still no confirmatory and confidant causes of AD. Studies have identified and linked some risk factors of AD which include progressive age, low physical and cognitive activity, head injury, depression, hypertension, family history, apolipoprotein (Apo) E4 status and other such comorbidities.[30]

The main histopathological features of Alzheimer's disease are neuritic/senile plaques indicated by phosphorylated TAU and neuro-fibrillary tangles showing deposits of amyloid. These features are associated with the severity of the dementia. Synaptic density in AD is a measure of neuronal loss.[31-36]Various risk factors for AD are given in Table 4.

Table 4: Risk factors of AD.

Social and demographic factors	Medical history and medicines	Family history and genetic factors	Lifestyle related factors
• Progressive age • Racialand ethnic profile • National profile	• Head injuries • Oestrogen replacement • Hypertension • Diabetes • Homocysteine and cholesterol level • Depression • Herpes simplex (mediatedby thepresence of ApoEe4.	Family history: AD in degree relative increases the risk. Conditions that mutate chromosomes 1, 14,and 21. Genotype ApoE Down's syndrome: Longer and higher education and intelligence are protective against AD.	• Heavy Drinking • Smoking • Diet • Occupational and recreation factors • Alcohol

MANAGEMENT OF AD

Currently a multi-factorial personalized management of AD is attempted consisting of following components:

Communication

A sincere and honest communication between patient, physician and caregiver generally results in identification and confirmation of symptoms, proper diagnosis and evaluation of AD and suitable strategy and treatment plan. Open communication amongst these three is a key to a successful treatment and management of AD.

Caregiver support

Care and support is very important in management of AD. Training and educating them for future risks and conditions arising from worsening of AD and how to deal with them can result in better management and control. Knowing beforehand

Table 5: Medicinal plants reported to have potential for treating Alzheimer's disease.

Sl.No	Plant name	Family	Part used	Chemical constituents	References
1.	*Melissa officinalis*	Lamiaceae or Labiatae	Leaf	Rhamnocitrin Luteolin, Flavonoids (quercitrin) Protocatechuic acid Triterpenes (ursolic and oleanolic acids) Polyphenolic compounds, Monoterpenoid aldehyde Rosmarinic acid Caffeic acid Monoterpene glycosides Rannins Sesquiterpenes Citral essential oils	54
2.	*Salvia officinalis*	Lamiaceae or Labiatae	Flowers, leaves, and stem	Alkaloids Flavonoids Tannins Glycosidic derivatives e.g., cardiac glycosides, flavonoid glycosides Saponins, Phenolic compounds e.g., coumarins Terpenes/terpenoids e.g., monoterpenoids, diterpenoids, triterpenoids Poly acetylenes Steroids Carbohydrate Fatty acids	55
3.	*Centella asiatica*	Apiceae	Fresh root	Aciaticosides (sapanonins)	56
4.	*Cantharantus roseus*	Apocynaceae	Dried root	Vincristine Vinblastine	57
5.	*Ginkgo biloba*	Gincoknaceae	Dried Leaves	Ginkolides A,B,C,J and M	58
6.	*Abutilon indicum* Linn.	Malvaceae	Whole	Alkaloid Saponins Flavonoids Glycosides steroids Amino acid.	59

Sl.No	Plant name	Family	Part used	Chemical constituents	References
7.	*Acanthus ebracteatus* Vahl.	Acanthaceae	Aerial Part	Alkaloids Flavonoids, Triterpenoids Steroids Saponins	60
8.	*Aegle marmelos* Linn.	Rutaceae	Fruit Pulp	Marmelosin, Luvangetin Aurapten Psoralen Marmelide Tannin.	59
9	*Albizia procera* (Roxb.) Benth	Fabaceae	Bark	Triterpenoids, Glycosides Phytosterols Saponins, Tannins Phenolic compounds, Flavonoids Carbohydrates.	61
10	*Bacopa monniera* Linn.	Scrophulariaceae	whole	Bacosides A and B Bacopasides III to V Bacosaponins A, B,and C, Bisdesmosides Bacopasaponins D, E, and F, Jujubogenin Betulic acid Sterols Alkaloids polyphenols Sulfhydryl compounds	61
11	*Buxus sempervirens* Linn.	Buxaceae	Wood ad leaves	Aalkaloids namely Buxine, Parabuxine, Parabuxonidine Butyraceous Volatile oil.	61
12	*Butea superba* Roxb.	Fabaceae,	Roots	Flavonoids Flavonoid glycosides Sterol compounds Bsitosterol Campesterol Stigmasterol.	62

Sl.No	Plant name	Family	Part used	Chemical constituents	References
13	*Carthamus tinctorius* Linn	Asteraceae.	Flower	Phenolics Flavonoids, Alkaloids Steroids Quinochalcone C-glycosides, Quinone-containing chalcones Oils Proteins Lignans, Minerals, Carboxylic acids Polysaccharides.	61
14	*Cassia fistula* Linn.	Legmues	Root	Anthraquinones derivatives, Tannins, Oxyanthra-quinones, Oxalic Acids.	61
15	*Nelumbo nucifera* Gaertn. Stamen	Nelumbonaceae	Stamen	Megastigmanes, Nelumnucifoside, Sesquiterpene, Nelumnucifoside B Alkaloids Flavonoids.	61
16	*Rhododendron luteum* Sweet	Ericaceae,	Whole	Luteum was found to be a-cadinol δ-cadinene A-terpineol Benzyl salicylate A-muurolene and 1,6-germacradien-5β-ol	62
17	*Withania somnifera* (L.)	solanaceae	Roots	Withasomidienone, Withanolides A to Y, Withaferin A, Withasomniferin A, Withasomniferols A to C, Dehydro withanolide R, Withanone, Alkaloids, Sitoindosides VII to X, Phytosterols Beta-sitosterol, Amino acids High amounts of iron.	63
18	*Aegle marmelo*	Rutaceae	Leaves and fruit	Coumarin, Xanthotoxol, Imperatorin Aegeline, and Marmeline	64

Sl.No	Plant name	Family	Part used	Chemical constituents	References
19	*Nigella sativa*	Ranunculaceae	Fruit	Fixed oil Proteins Alkaloid Saponin Essential oil	65
20	*Piper retrofractum* Vahl.	Piperaceae	Leaves	Amides Alkaloids phenylpropanoids, Alkyl glycosides, Lignans	66
21	*Acorus calamus*	Acoraceae	Root or rhizomes	α-Asarone β-asarone	67
22	*Blumea balsamifera* DC	Asteraceae	Leaves and whole plant	BlumpenesA, B, C, andD	68
23	*Cannabis sativa*	Cannabaceae	Flowers and fruits	Tetrahydrocannabinol	69
24	*Citrus grandis* Osbek	Rutaceae	Leaves,pulp and peel	3,5,6,7,8,3′,4′-Heptamethoxyflavone	63
25	*Clerodendrum infortunatum* L.	Verbenaceae	Aerial parts	Sterols, sugars Flavonoids Saponins Acteoside	63
26	*Lygodium flexuosum* (L.)Sws.	Lygodiaceae	Leaves, stem and root	Alkaloids Flavanoids, Saponins and Cumarins	70
27	*Rosmarinus officinalis*	(Lamiaceae)	Leaves	phenolic compounds, di- and triterpenes Essential oils	71
28	*Areca catechu* L.	Arecaceae	Fruit	Alkaloids, Flavonoids, Tannins, Triterpenes, Fatty acids,	71
29	*Ipomoea aquatica*	Convolvulace	Leaves	Alkaloids Steroids, Saponin, Phenols, Reducing sugar, Flavonoids, Tannins	70
30	*Caesalpinia crista* L.	Leguminosae	Fruit and seeds	Alkaloids Cassane-diterpenes, Flavonoids, nor-cassane diterpenes, Proteins Saponins Triterpenoids	70

Sl.No	Plant name	Family	Part used	Chemical constituents	References
31	*Senna tora* Roxb.	Leguminosae	Leaves	Alkaloids, Glycosides Tannins volatile oils Minerals Vitamins	70
32	*Phyllanthus reticulatus*	Phyllanthaceae	Root and leaves	Tannic acid, Terpenoids Flavonoids phenolic compounds Steroids as main chemical constituents	70
33	*Convolvulus pluricaulis*	Convolvulaceae	Whole plant, Leaves, stem and root	Alkaloids, Glycosides, Flavonoids, Carbohydrates Proteins Sterols Gum Mucilages compounds	58
34	*Smilax zeylanica* L.	Smilacceaae	Leaves and roots	Daucosterin Daucosterol Caffeic acid Catechin Engeletin Friedelin Epicatechin Heloniosides Hydroxyflavan Piceid Isoengeletin Naringenin Quercetin Flavonoids Resveratrol Resin Rutin Trihydroxystibene Scirpusin Saponin Stilbenes Smilacin Seiboldogenin Taxifoli Smilasides Tannin Vanillic acid	71

Sl.No	Plant name	Family	Part used	Chemical constituents	References
35	*Abrus precatorius* L.	Fabaceae	Leaves	Abrusogenin, Saturated monoglyceride Unsaturated triglyceride	72
36	*Aframomum melegueta* K. Schum	Zingiberaceae	Seeds	Mrytenyl acetate Isolimonene γ-elemene	73
37	*Albizia adianthifolia* (Schumach.) W.F. Wigh	Fabaceae	Leaves	Apo-carotenoids, Dipeptide Steroids Elliptosides Flavonoids Histamines, Triterpenoids Imidazolyl carboxylic acids, Triterpene Saponins Essential oils Fatty acids	74
38	*Allium cepa* L.	Liliaceae	Bulb	Phenolic acids Thiosulfinates Flavonoids.	75
39	*Angraecum eichlerianus* Bory.	Orchidaceae	Leaves	Isovaleraldoxime	76
40	*Bacopa floribunda* (R.Br) Wettst.	Scrophuliaceae	Leaves	Bacosidesand bacopasaponins, are triterpene saponins of the dammarane class, which contain 2 or 3 sugars each.	77
41	*Baphia nitida* Lodd.	Papilinionaceae	Leaves and bark	Tannins, Flavonoids and saponin glycosides	78
42	*Bombax buonopozense* P. Beauv	Bombacaceae	Leaves	Tannin, Alkaloids, Saponin, Cyanogenic glycosides, Steroids, Flavonoids and Phenols.	79
43	*Digitaria horizontalis* Willd.	Poaceae	Whole plant	Avena fatua crabgrass (Digitaria sanguinalis	80
44	*Elaeis guineensis* Jacq.	Arecaceae	Leaves	Fatty acids Carotenes Vtamin E	81

Sl.No	Plant name	Family	Part used	Chemical constituents	References
45	*Flueggea virosa* (Roxb. ex Willd	Phyllantaceae	Leaves and root	Alkaloids Triterpenoids Resins Steroids Cardiac glycosides Bergenin Menisdaurin Anthraquinones.	82
46	*Jatropha curcas* L.	Euphorbiaceae	Fruits	Saponins Steroids Tannins Glycosides Alkaloids Flavonoids	83
47	*Justicia schimperi* (Hochst.) Dandy	Acanthaceae	Leave and root	Alkaloids Lignans Flavonoids Terpenoids Iridods Diterpenoids Triterpenoids	84
48	*Musa paradisiacal* L.	Musaceae	Leaves	Nor-epinephrine Serotonin Indole compounds Tryptophan Tannin Albuminoids Crystallisable and non-crystallisable sugars Vitamin C&B Fats Mineral salts	85
49	*Musa sapientum* L.	Musaceae	Fruits	Sitoindoside-I-IV Acyl steryl glycosides Steryl glycosides Sitosterol myo-inositylβ-D-glucoside Sitosterol gentiobioside	86
50	*Olax subscorpioidea* Oliv.	Olacaceae	Stem and bark	Alkaloids Saponins Tannins Cardiac glycosides Terpenoids Phenols	87
51	*Piper guineense* Schum. And Thonn	Piperaceae	Leaves and fruits	Alkaloid Cyanogenic glycosides Tannin Flavonoid Anthraquinones Saponin Phenol	88

Sl.No	Plant name	Family	Part used	Chemical constituents	References
52	*Rauvolfia vomitoria* Afze	Apocynaceae	Root	Deserpidine Ajmalicine Ajmaline	87
53	*Rinorea dentata* Kuntze	Violaceae	Leaves	Saponins Tannins Steroids Cardiac glycosides Flavonoids Alkaloids Terpenoids Phenols, Carbohydrates	89
54	*Spondias mombin* L.	Anacardiaceae	Leaves	Saponins Alkaloids Flavonoids Tannins Oxalates Phytates Cyanogenic glycosides	90
55	*Talinum triangulare* (Jacq.) Willd	Portulaceae	Leaves	Hydroxycinnamates Benzoic acid derivatives Alkaloids Flavonoids Carotenoids Phytosterols Glycosides Terpenes Saponins Allicins Lignans	91
56	*Piper* spp.	Piperaceae	Leaves	Phenolic glycosides Flavanol glycosides.	92
57	*Curcuma longa*	Zingiberaceae	Rhizomes	ar-turmerone, β-sesquiphellandrene Curcumenol	93
58	*Tinospora cordifolia* (Giloy)	Menispermaceae	Root	Diterpenoid lactones Glycosides Steroids Sesquiterpe-noid Phenolics Aliphatic compounds Essential oils Fattyacids Polysaccharide	94

Sl.No	Plant name	Family	Part used	Chemical constituents	References
59	*Magnolia officinalis*	Magnoliaceae	Bark	Magnoloside Ia,Ib Ic Magnoloside IIa , IIb Magnoloside IIIa Magnoloside IVa Magnoloside Va Crassifolioside Phenylethanoid glycosides	95
60	*Lepidium meyenii*	Brassicaceae	Root	Aromatic glucosinolates Benzyl glucosinolate(glucotropaeolin) M-methoxybenzyl glucosinolate(glucolimnanthin)	96
61	*Glycyrrhiza glabra*	Fabaceae	Root	Glycyrrhizin Rhamnoliquirilin Liquirtin Liquiritigenin Glucoliquiritin Apioside Licoarylcoumarin Licopyranocoumarin Flavonoids Prenyllicoflavone A 1-metho-Xyphaseolin Shinflavanone Shinpterocarpin Glisoflavone Coumarin-GU-12 Saponins	97
62	Huperzine A	Lycopodiaceae	Moss	Alkaloids Huperzine A	98

and being prepared for effects dementia related to AD on cognition, normal function and behavior, expectations. Understanding which situations can worsen the symptoms or pose dangers for safety and well-being may result in good care and management.[37]

Behavioral approaches

Strategies such as normal and cool interactions, easy language with simple words, engaging in pleasurable activities restricting only when situation may pose danger and safety is concerned[38] make them feel better and helps in management. Having consistent and normal simple surroundings, planned routines and prompt medical decisions can help immensely involving regular physical activity also has beneficial effects on symptoms and control of AD.[39]

Sleep

Disturbance in sleep is one major cause of AD. Sleep patterns directly or indirectly affect AD. Improper sleep accumulates Amyloid-β (Aβ) triggering the decline in memory and progressing to AD. Proper and sufficient sleep is as central for managing and treating AD, providing anticipatory and therapeutic benefits.

Other options for improving symptoms of AD include cognitive behavioral therapy, light therapy, music therapy exercise etc depending on patient situation and disease severity.[40]

Medical Approach

Along with behavioral and lifestyle changes treatment with prescription drugs under medical supervision is recommended and needed. FDA-approved AD medications like Acetyl choline esterase inhibitors (AChEI) e.g. donepezil, galantamine, rivastigmine, and the NMDA(N-methyl-D-aspartate) antagonist e.g. memantine are the only FDA-approved drugs for AD medications.[41] Only these four drugs are currently approved by USFDA and available for the treatment of AD-associated dementia. But as per the reports their utility is very limited.

Table 6: Phytochemicals and their mechanism of action reported to be effective in treating AD.

Sl. No.	Chemical Constituents	Application	References
1	Withanamides (*Withania somnifera*)	Enhanced dendrite and axon regeneration. Scavenges unobstructed radicals Obstructs activated neuronal cell death by amyloid plaques. Protects PC-12 cells from β-amyloid	99-100
2	Convolvine(*Convolvulus pluricaulis*)	Enhanced acetylcholinesterase activity in the hippocampal CA1 and CA3. Affecting memory and learning abilities	101
3	Celapanin, Celapagine and Celapanigine (*Celastrus paniculatus*)	Increased cholinergic activity contributing to improved memory	102
4	Bilobalide (*Gingko biloba*)	Averts neuro-degeneration and GABA inhibition by hippocampal corticosterone	103
5	Quercetin, and guggulsterones E and Z (*Commiphora whighitti*)	Reduced acetylcholinesterase in the hippocampus	104
6	Macamide (*Lepidium meyenii*)	Enhanced memory due to increased acetylcholine level	105
7	Rosmarinic acid and ellagic acid (*Salvia officinalis*)	Memory retention is increased due to interactions with muscarinic and cholinergic pathways.	106
8	Rutin, quercetin, rhamnetin, kaempferol, apigenin, and myricetin (*Moringa oleifera*)	Increased levels of monoamines (nor epinephrine, dopamine and serotonin)	107
9	Bebeerine (*Cissampelos pareira*)	Decreased activity of acetylcholinesterase Increased antioxidant and anti-inflammatory activities	108
10	Brahmine and bacosides (*Bacopa monnieri*)	Decreses activity of divalent metals, ROS, peroxides formation, and lipoxygenase movement.	109
11	Flavonols and phenolic compounds (*Ficus racemosa* and *Ficus carica*)	Increased levels of Acetylcholine in the hippocampus.	110
12	Baicalein (*Scutellaria baicalensis*)	Show powerful anti-BACE1 activity [IC_{50} =μM] Cause Aβ-oligomerization with fibrillation and inhibition of Aβ-induced toxicity in PC12 cells Disaggregation of preformed Aβ amyloid fibrils.	111
13	Myricetin (*Myrica rubra*) or hydroxyquercetin (*Oryza sativa*)	Enhance the crossing of BBB Neuro-protective against neuronal cell injury by Aβ.	112,113
14	Berberine (*Coptis chinensis*)	Regulate βAPP processing Decreases Aβ protein Mitigates lack of BACE1 protein levels.	114
15	Epiberberine and Groenlandicine (*Coptidis* Rhizoma)	Inhibit BACE1 activity	115
16	2,2,4-Trihydroxychalcone acid (TDC) (*Glycyrrhiza glabra*)	Decreases BACE1 activity Reduced Aβ40 and Aβ42 stages in the HEK293 Overcomes the BACE1 activity on the βAPP by reducing -APPswe cells.	116
17	Rutin (*Fagopyrum esculentum*) and Galangin (*Alpinia officinarum*)	βAPP selective BACE1 inhibitors. unstabilize BACE1 division.	117
18	Asperterpenes A and B meroterpenoids (*Aspergillus terreus*)	Prevents BACE1 Lowers Aβ42 development	118

Sl. No.	Chemical Constituents	Application	References
19	Ferulic acid (*Oryza sativa* and *Triticum aestivum*)	Reduce the Aβ groups and BACE1 enzymatic action and affects BACE1 stability. It also affects mRNA expression level.	119
20	Cardamonin (*Boesenbergia rotunda*)	Shows potent inhibition and does not alter the TACE (α-secretase).	120
21	Salvianolic acid (*Salvia miltiorrhiza*)	Disaggregate Aβ fibril formation. Modulates BACE1 activity and decreases Aβ production.	121
22	Medium-chain fatty acids (MCFAs) with medium-chain triglycerides. (Coconut oil)	Inhibits Aβ by Suppressing ADP-ribosylation factor 1	122,123

Most commonly used acetyl cholinesterase inhibitors (AChEI0drugs acts on central nervous systems (CNS) cholinergic pathways. Galantamine, a natural alkaloid, acts as an allosteric modulator at nicotinic acetylcholine receptors thus benefiting in alleviating symptoms of AD. These drugs are approved for mild to severe dementia and are often used to treat patients in earlier pre-dementia stages showing progressive memory impairment established on cognitive testing results.[42]

Recently excessive glutamate saturation at excitatory synapses caused by decreased glutamate reuptake from microglia has been identified as one of the patho-physiological mechanism of AD. To target this Memantine is the first approved AD acting on N-methyl-d-aspartate (NMDA) receptor and glutaminergic pathways. Memantine is prescribed in combination with stable ChEI therapy for improved safety profile in patients with AD.[43]

Challenges in Alzheimer Therapy

The progression of AD spans from asymptomatic to severely impaired conditions. Identifying these conditions is challenging as the separation between symptoms of normal aging and preclinical AD is not clearly defined. The reasons for relatively higher incidence of AD in women are also not yet properly understood.[44] Future research may be able answer many questions about AD in future.

Use of NSAIDs reduce the risk of developing AD indicating inflammation can be a relevant target in AD. But conclusive outcomes have not yet been generated.[45] It may be due to action of anti-inflammatory drugs on generic targets and not on specific neuro-inflammatory components of AD. Control and treatment of inflammation at early stages of AD is necessary to study the effectiveness of targeting inflammation in neuro-degeneration.[46]

Greater knowledge of the complex features of AD such as behavioral, mood, metabolic disturbances and inflammation may develop successful innovative therapies.[47] Promising new therapies with immune-globulins and monoclonal antibodies are currently under evaluation. Earlier Intervention with re-purposed drugs, combination therapy, anti-inflammatory agents or drugs that can modify underlying conditions could prove beneficial in successful outcomes in AD therapy.[48]

Herbal Approach for Alzheimer's Disease

There is a pressing need for the alternative treatments for AD with minimal or no side effects as current AD therapies are inadequate and have many adverse effects. Herbal medicines are considered as very safe and affordable, having potential clinical efficacy, and drug-drug synergistic interactions.[49] In Ayurveda and Chinese traditional medicines several drugs are given for treatments of various diseases. Numerous scientific studies have reported the important role of medicinal plants in the treatment of nervous disorders, enhancement of the memory and improvement of nervous system in general. Herbal therapy for AD promises to have more advantages as compared to existing drug therapies having unavoidable side effects thus improving the patients' quality of life.[50]

Herbal medicines are of interest in many diseases, especially in psychiatric and neurological disorders as dissatisfaction of patients with current treatment, to have control over their healthcare decision, and herbal medicine is in accordance with their beliefs and values. Several studies and documents indicate an exceptional role of herbal medicines in the treatment of AD.[51]

The phyto-chemical analysis of herbal drugs used for treating AD reveals the presence of compounds like tannins, lignans, poly-phenols, flavonoids, sterols, triterpenes and alkaloids indicating anti-amyloidogenic, anti-inflammatory, anti-cholinesterase, hypo-lipidemic, and antioxidant effects as possible mechanisms of action.[52]

Limitations of Herbal Drugs

For AD, the herbal drugs should target multiple mechanisms like Aβ production, fibrillation, Aβ-mediated oxidative stress, and neuro-inflammation. There are some limitations of herbal drugs like hepatic and other toxicity if used in higher concentration, lack of statistically significant clinical efficacy poor ability to cross BBB. Processing limitations like difficulty in obtaining the active compounds in large quantities, effect of irregular environmental conditions on the activity of herbal drugs and preparations without stringent adherence to GMP guidelines.[51]

Herbal Drugs for the Treatment of AD

Herbal plants according to many researchers have been proved effective on Alzheimer disease and dementia. The herbal drugs mainly decrease the symptoms and progress of disease without or with very few side effects. Table 5 give information of medicinal plants that are used or have potential for the treatment of AD.[53,54]

Phytochemicals for treating AD

Many researchers not only reported the herbal plants but also evaluated active constituents from these plants for their effectiveness against AD. Table 6 depicts information related to phyto-constituents isolated and identified for their effectiveness for treating AD with proposed mechanism of actions for each constituent.

Clinical trial on Alzheimer diseases based on herbal drugs

Phase II and III clinical trials of *Ginkgo biloba* extract (GBE) to investigate its efficacy in the treatment of AD were conducted in 2016. The studies showed promising results indicating changes in the MMSE, ADAS-cog electroencephalography P300, and 1.5 T MRI. GBE also improved daily activities, renal function, liver function, neuropsychiatric state and reduced depression.[124,125]

Phase III clinical trials were conducted to find out the effectiveness of coconut oil in AD with mild to moderate symptoms. It was reported that coconut oil due to presence of medium-chain fatty acids and medium-chain triglycerides shows remarkable improvement in AD.[126,127]

A double blind, randomized and placebo-controlled trial to evaluate efficacy of *Salvia officinalis* extract was carried out in 2003. Outcome was measured by ADAS-cog CDR-SB (Alzheimer's disease assessment scale).[128] Similar study for *Melissa officinalis* extract was also reported. The results show significant therapeutic effects in treating AD in both drugs and remarkable decrease in episodes of agitation in AD patients in case of *Melissa officinalis* was observed.[129]

The traditional Chinese medicine Yi-Gan San was evaluated in randomized, controlled trial for treating behavioral and psychological symptoms along with effects on quality of life of patients suffering from dementia. The outcomes were measured by NPI Barthel Index MMSE (mini-mental state examination scale; NPI, neuropsychiatric).[130] Also a randomized, double-blind, placebo-controlled study for 'Ba Wei Huang Wan', a Chinese herbal medicine has been conducted. Both the studies indicated improvements in patients with more than 12 months of AD diagnosis.[131]

CONCLUSION

The review discusses basic pathophysiology and epidemiology of AD including risk factors and management. There are very few options of medical intervention and need for the search of new drugs for treating AD. This can be achieved by exploring herbal options. Herbal medicines are generally considered as safe with fewer side effects. A large number of plants show neuronal activities and can be exploited for treating AD. The plants and their phytoconstituents mentioned in this review can be used not only for improvement of Alzheimer memory loss but also treating various other disorders. The scientific community should be actively involved in identifying the plants, along with their mechanism of action so that it can be used for safe and better treatment for AD. Research on these herbal and other Ayurvedic medicine may provide new functional leads and effective alternatives for treating AD.

ACKNOWLEDGEMENT

Authors are thankful to Datta Meghe College of Pharmacy, DMIMS (DU), Wardha and Institute of Pharmacy, GITAM University, Hyderabad for providing facility for completion of this work.

REFERENCES

1. Quiroz YT, Zetterberg H, Reiman EM, Chen Y, Su Y, Fox-Fuller JT, *et al*. Plasma neurofilament light chain in the presenilin 1 E280A autosomal dominant Alzheimer's disease kindred: A cross-sectional and longitudinal cohort study. Lancet Neurol. 2020;19(6):513-21. doi: 10.1016/S1474-4422(20)30137-X.
2. Mohamed T, Shakeri A, Rao PPN. Amyloid cascade in Alzheimer's disease: recent advances in medicinal chemistry. Eur J Med Chem. 2016;113:258-72. doi: 10.1016/j.ejmech.2016.02.049.
3. Chase TN, Farlow MR, Clarence-Smith K. Donepezil plus solifenacin (CPC–201) treatment for Alzheimer's disease. Neurotherapeutics. 2017;14(2):405-16. doi: 10.1007/s13311-016-0511-x.
4. Kim DH, Lee SB, Young LD. VYang HD. Hist Alzheimers Dis Dem Neurocognitive Disord. 2016;15(4):115-21. doi: 10.3390/geriatrics6010005.
5. Soria Lopez JA, Gonzalez HM, Leger GC. Chapter 13. Alzheimer's disease. In: Handbook of clinical neurology. 2019; 167:231-55. doi: 10.1016/B978-0-12-804766-8.00013-3.
6. Glenner GG, Wong CW. Alzheimer's disease: initial report of the purification and characterization of a novel cerebrovascular amyloid protein. Biochem Biophys Res Commun. 1984;120(3):885-90. doi: 10.1016/s0006-291x(84)80190-4.
7. Barthelemy N, Joseph-Mathurin N, Gordon BA, Hassenstab J, Benzinger TLS, *et al*. A soluble phosphorylated tau signature links tau, amyloid and the evolution of stages of dominantly inherited Alzheimer's disease. Nat Med. 2020;26:398-407. doi: 10.1038/s41591-020-0781-z.
8. Available from: https://www.verywellhealth.com/the-alzheimers-brain-97675 [cited 22.11.2022].
9. Brahma D. The persistence of memory: the burden of Alzheimer's disease in India. (Online article) [cited Jul 1, 2021]. Available from: https://www.brookings.edu/blog/upfront/2019/09/20/the-persistence-of-memory-theburden-of-alzheimers-disease-in-india/.
10. Available from: https://www.tapgenes.com/blog/the-difference-between-alzheimers-and-dementia.
11. WHOhttps:. Available from: http://www.who.int/news-room/fact-sheets/detail/dementia.
12. Bondi MW, Edmonds EC, Salmon DP. Alzheimer's disease: Past, present, and future. J Int Neuropsychol Soc. 2017;23(9-10):81831https:. doi: 10.1017/S135561771700100X.
13. Alzheimer report 2015. Available from: http://alz.co.uk/research/worldreport-2015 (World Accessed May 02, 2016).
14. Wimo A, Guerchet M, Ali G, Wu Y, Prina AM, Winblad B *et al*. World alzheimer report. Alzheimer's and Dementia. 2017;13(1):1-7. doi: 10.1016/j.jalz.2016.07.150.
15. Manual diagnostico e Estatistico de transtornos mentais-DMS-5. 5rd Artmed, editor. Porto Alegre, 2014.

16. Javed SF, Giebel C, Khan MA, Hashim MJ. Epidemiology of Alzhemiers disease and other dementia:rising global burden and forecasted trends F1000Research; 2021.10.25. doi: 10.12688/f1000research.50786.1.
17. Weiner MW, Friedl KE, Pacifico A, Chapman JC, Jaffee MS, Little DM *et al*., McK, *et al*. Psychological stress-induced immune response and risk of Alzheimer's disease in veterans from Operation Enduring Freedom and operation Iraqi freedom. Clin Ther. 2020;42(6):974-82. doi: 10.1016/j.clinthera.2020.02.018.
18. Langlois JA, Rutland-Brown W, Wald MM. The epidemiology and impact of traumatic brain injury: A brief overview. J Head Trauma Rehabil. 2006;21(5):375-8. doi: 10.1097/00001199-200609000-00001.
19. Thunnan DJ, Branche CM, Sniezek JE. The Epidemiology of Sports-Related Traumatic Brain Injuries in the United States: Recent Developments. J Head Trauma Rehabil. 1998;13(2):1-8. doi: 10.1097/00001199-199804000-00003.
20. Alzheimer [cited May 02, 2016]. Available from: http://alzheimermed.com.br/conceitos/epidemiologia.
21. Available from: https://www.researchgate.net/figure/Pathophysiology-of-Alzheimers-disease [cited 22.11.2022].
22. Herrera Jr E, Caramelli P, Silveira ASB, Nitrini R. Epidemiologic Survey of Dementia in a Community-Dwelling Brazilian Population. Alzheimer Dis Assoc Disord. 2002;16(2):103-8. doi: 10.1097/00002093-200204000-00007.
23. Blennow K. Biomarkers in Alzheimer's disease drug development. Nat Med. 2010;16(11):1218-22. doi: 10.1038/nm.2221.
24. Prakash A, Dhaliwal GK, Kumar P, Majeed ABA. Brain biometals and Alzheimer's disease – boon or bane? Int J Neurosci. 2017;127(2):99-108. doi: 10.3109/00207454.2016.1174118.
25. Feldman H, Woodward M. The staging and assessment of moderate to severe Alzheimer disease. Neurology. 2005;65:10-7. doi: 10.2147/CIA.S39959.
26. Brayne C. Elephant in the room—healthy brains in later life, epidemiology and public health. Nat Rev Neurosci. 2007;8:233-9. doi: 10.1038/nrn2091.
27. Nestor PJ, Scheltens P, Hodges JR. Advances in the earlydetection of Alzheimer's disease. Nat Rev Neurosci. 2004;5:34-41. doi: 10.1038/nrn1433.
28. Chong MS, Sahadevan S. An evidence-based clinical approach to the diagnosis of dementia. Ann Acad Med Singapore. 2003;32:740-8. doi: 10.11622/smedj.2018026.
29. Spaan PE, Raaijmakers JG, Jonker C. Alzheimers's disease versus normal ageing: a review of the efficiency of clinical and experimental memory measures. J Clin Exp Neuropsychol. 2003;25:216-33. doi: 10.1076/jcen.25.2.216.13638.
30. McGirr S, Venegas C, Swaminathan A. Alzheimer's disease: A brief review. J Exp Neurol. 2020;1(3):89-98. doi: 10.33696/Neurol.1.015.
31. Leroi I, Lyketsos C. Neuropsychiatric aspects ofdementia BurnsA. 3rd ed Dementia. 2005:55-64. doi: 10.1136/bmj.b158.
32. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group* under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology. 1984;34(7):939-44. doi: 10.1212/wnl.34.7.939, PMID 6610841.
33. Burns A, Byrne J, Ballard C, Holmes C. Sensory stimulation in dementia: an effective option for managing behavioural problems. BMJ (compact Ed.). 2002;325(7376):1312-3. doi: 10.1136/bmj.325.7376.1312.
34. Román GC, Tatemichi TK, Erkinjuntti T, Cummings JL, Masdeu JC, Garcia JH, *et al*. Vascular dementia: Diagnostic criteria for research studies: report of the NINDS-AIREN International Workshop. Neurology. 1993;43(2):250-60. doi: 10.1212/wnl.43.2.250, PMID 8094895.
35. Atri A. Current and future treatments in Alzheimer's disease. Semin Neurol. 2019;39(2):227-40. doi: 10.1055/s-0039-1678581.
36. Kishita N, Backhouse T, Mioshi E. Nonpharmacological interventions to improve depression, anxiety, and quality of life (QoL) in people with dementia: an overview of systematic reviews. J Geriatr Psychiatry Neurol. 2020;33(1):28-41. doi: 10.1177/0891988719856690.
37. Heinrich M, Lee Teoh H. Galanthamine from snowdrop–the development of a modern drug against Alzheimer's disease from local Caucasian knowledge. J Ethnopharmacol. 2004;92(2-3):147-62. doi: 10.1016/j.jep.2004.02.012, PMID 15137996.
38. Olazarán J, Reisberg B, Clare L, Cruz I, Peña-Casanova J, Del Ser T, *et al*. Nonpharmacological therapies in Alzheimer's disease: a systematic review of efficacy. Dement Geriatr Cogn Disord. 2010;30(2):161-78. doi: 10.1159/000316119, PMID 20838046.
39. Ballard C, Khan Z, Clack H, Corbett A. Nonpharmacological treatment of Alzheimer disease. Can J Psychiatry. 2011;56(10):589-95. doi: 10.1177/070674371105601004, PMID 22014691.
40. van Someren EJW, Mirmiran M, Swaab DF. Non–pharmacological treatment of sleep and wake disturbances in aging and Alzheimer's disease:chronobiological perspectives. Behav Brain Res. 1993;57(2):235-53. doi: 10.1016/0166-4328(93)90140-l, PMID 8117428.
41. Christensen A, Pike CJ. Menopause, obesity and inflammation: Interactive risk factors for Alzheimer's disease. Front Aging Neurosci. 2015;7:130. doi: 10.3389/fnagi.2015.00130, PMID 26217222.
42. Mosconi L, Berti V, Quinn C, McHugh P, Petrongolo G, Osorio RS *et al*. Perimenopause and emergence of an Alzheimer's bioenergetic phenotype in brain and periphery. PLOS ONE. 2017a;12(10):e0185926. doi: 10.1371/journal.pone.0185926, PMID 29016679.
43. Liu F, Day M, Muñiz LC, Bitran D, Arias R, Revilla-Sanchez R *et al*. Activation of estrogen receptor-b regulates hippocampal synaptic plasticity and improves memory. Nat Neurosci. 2008;11(3):334-43. doi: 10.1038/nn2057, PMID 18297067.
44. Howes MJR, Perry NS, Houghton PJ. Plants with traditional uses and activities, relevant to the management of Alzheimer's disease and other cognitive disorders. Phytother Res. 2003;17(1):1-18. doi: 10.1002/ptr.1280, PMID 12557240.
45. Akhondzadeh S, Noroozian M. Alzheimer's disease: Pathophysiology and pharmacotherapy. IDrugs. 2002;4:1167-72.
46. Anand R, Gill KD, Mahdi AA. Therapeutics of Alzheimer's disease: past, present and future. Neuropharmacology. 2014;76:27. doi: 10.1016/j.neuropharm.2013.07.004.
47. Huang Y, Mucke L, Kelley BJ, Knopman DS. Alzheimer mechanisms and therapeutic strategies. Cell. Alternative medicine and Alzheimer's disease Neurologist.2012;299. doi: 10.1016/j.cell.2012.02.040.
48. Anekonda TS, Reddy PH. Can herbs provide a new generation of drugs for treating Alzheimer's disease? Brain Res Brain Res Rev. 2005;50(2):361-76. doi: 10.1016/j.brainresrev.2005.09.001, PMID 16263176.
49. Izzo AA, Capasso F. Herbal medicines to treat Alzheimer's disease. Trends Pharmacol Sci. 2007;28(2):47-8. doi: 10.1016/j.tips.2006.12.001, PMID 17218017.
50. Howes MJR, Perry NS, Houghton PJ. Plants with traditional uses and activities, relevant to the management of Alzheimer's disease and other cognitive disorders. Phytother Res. 2003;17(1):1-18. doi: 10.1002/ptr.1280, PMID 12557240.
51. Onofrio D G, Sancarlo D, Ruan Q, Yu Z, Panza F, Daniele A, *et al*. Phytochemicals in the treatment of Alzheimer's disease: a systematic review. Curr Drug Targets .2016;17. doi: 10.2174/138945 0117666161102121553.
52. Ansari N, Khodagholi F. Natural products as promising drug candidates for the treatment of Alzheimer's disease: molecular mechanism aspect. Curr Neuropharmacol. 2013;11(4):414-29. doi: 10.2174/1570159X11311040005, PMID 24381531.
53. Perry EK, Pikering AT, Wang WW, *et al*. Medicinal plants and Alzheimer's disease: from etnobotany to phytotherapy. J Pharm Pharmacol. 1999;51:527-34. doi: 10.1211/0022357991772808.
54. Ghorbani A, Esmaeilizadeh M. Pharmacological properties of *Salvia officinalis* and its components. J Trad Complement Med. 2017;7(4):433-40. doi: 10.1016/j.jtcme.2016.12.014, PMID 29034191.
55. Speers AB, García-Jaramillo M, Feryn A, Matthews DG, Lichtenberg T, Caruso M *et al*. *Centella asiatica* Alters metabolic pathways associated with Alzheimer's disease in the 5xFAD mouse model of ß-amyloid accumulation. Front Pharmacol. 2021;12:788312. doi: 10.3389/fphar.2021.788312, PMID 34975484.
56. Uddin MJ, Zidorn C. Traditional herbal medicines against CNS disorders from Bangladesh. Nat Prod Bioprospect. 2020;10(6):377-410. doi: 10.1007/s13659-020-00269-7, PMID 33057963.
57. J. Nataraj, T. Manivasam, A.J. Thenmozhi, M.M. Essa, Neurochem. Res. Traditional Herbal Medicines Against CNS Disorders from Bangladesh.Natural Products and Bioprospecting. 2020 ;10:377–410 https://doi.org/10.1007/s13659-020-00269-7.
58. Uddin SN. Traditional uses of Ethnomedicinal plants of the Chittagong Hill Tracts. Dhaka: Published by Bangladesh National Herbarium; 2006. p. 992. doi: 10.9734/jpri/2021/v33i30B31642.
59. Khan NA, Rashid RM. Afr J Tradit Complement Altern Med. 2006;3(105):37-47.
60. Azam FMS, Biswas A, Mannan A, Afsana NA, Jahan R, Rahmatullah M. J Evid Based Complement Altern Med. 2014:1-28. doi: 10.1007/s13659-020-00269-7.
61. Perry N, Court G, Bidet N, Court J, Perry E. European herbs with cholinergic activities: Potential in dementia therapy. Int J Geriatr Psychiatr. 1996;11:1063. doi: 10.1002/(SICI)1099-1166(199612)11:12<1063::AID-GPS532>3.0.CO;2-1.
62. Orhan I, Sener B, Choudhary MI, Khalid A. Acetylcholinesterase and butyrylcholinesterase inhibitory activity of some Turkish medicinal plants. J Ethnopharmacol. 2004;91(1):57-60. doi: 10.1016/j.jep.2003.11.016, PMID 15036468.
63. Matsuda H, Murakami T, Kishi A, *et al*. Structures of withanosides I, II, III, IV, V, VI, and VII, new withanolide glycosides, from the roots of Indian *Withania somnifera* DUNAL and inhibitory activity for tachyphylaxis to clonidine in isolated guinea-pig ileum. Bioorg Med Chem. 2001;9(6):1499-507. doi: 10.1016/s0968-0896(01)00024-4.
64. Laphookhieo S, Phungpanya C, Tantapakul C, Techa S, Tha-in S, Narmdorkmai S. Chemical constituents from Aegle marmelos. J Braz Chem Soc. 2011;22(1):176-8. doi: 10.1590/S0103-50532011000100024.
65. Islam MH, Ahmad IZ, Salman MT. Neuroprotective effects of *Nigella sativa* extracts during germination on central nervous system. Pharmacogn Mag. 2015;11(Suppl 1):S182-9. doi: 10.4103/0973-1296.157729, PMID 26109765.
66. Jamal Y, Irawati P, Fathoni A, Agusta A. Chemical constituents and antibacterial effect of essential oil of javaneese pepper leaves (*Piper retrofractum* vahl). Media Litbangkes. 2013;23(2):65-72. doi: 10.22435/mpk.v23i2.3128.65-72.
67. Ingkaninan K, Temkitthawon P, Chuenchom K, Yuyaem T, Thongnoi W. Screening for acetylcholinesterase inhibitory activity in plants used in Thai traditional rejuvenating and neurotonic remedies. J Ethnopharmacol. 2003;89(2-3):261-4. doi: 10.1016/j.jep.2003.08.008, PMID 14611889.
68. Pang Y, Wang D, Fan Z, chen X, Yu F, Hu X, *et al*. *Blumea balsamifera*—A phytochemical and pharmacological review. Molecules. 2014;19(7):9453-77. doi: 10.3390/molecules19079453, PMID 24995927.

69. Eubanks LM, Rogers CJ, Beuscher AE, Koob GF, Olson AJ, Dickerson TJ, *et al*. Traditional herbal medicines against CNS disorders from Bangladesh. Mol Pharm. 2006;3:773-7. doi: 10.1007/s13659-020-00269-7.
70. Yadav E, Mani M, Chandra P, Sachan N, Ghosh AK. A review on therapeutic Potential of *Lygodium flexuosum* Linn. Pharmacogn Rev. 2012;6(12):107-14. doi: 10.4103/0973-7847.99944, PMID 23055636.
71. Ragasa YC, Lorena GS, Mandia EH, Raga DD, Shen CC. Chemical constituents of Abrus precatorius. Am J Essent Oils Nat Prod. 2013;1(2):7-10.
72. Owokotomo IA, Ekundayo O, Oguntuase BJ. Chemical constituents of the Leaf, stem, Root and seed essential oils of *Aframomum melegueta* (K. Schum) from south West Nigeria. IRJPAC. 2014;4(4):395-401. doi: 10.9734/IRJPAC/2014/7397.
73. Maroy AAA. Botany, medicinal uses, phytochemistry, and pharmacological properties. Sci World J;2018:18:Article ID 7463584. doi: 10.1155/2018/7463584.
74. Sampath Kumar KP, Bhowmik D, Chiranji B. Biswajit and Tiwari P. Allium cepa: A traditional medicinal herb and its health benefits. J Chem Pharm Res. 2010; 2(1);7384:283-291ISSN : 0975.
75. Mubo AS, Ibukun OA. Medicinal plants used in the treatment of neurodegenerative disorders in some parts of Southwest Nigeria. Afr J Pharm Pharmacol. 2015;9(38):956-65. doi: 10.5897/AJPP2014.4164.
76. Goswami S, Saoji A, Kumar N, Thawani V, Tiwari M, Thawani M. Effect of Bacopa monnieri on Cognitive functions in Alzheimer's disease patients. Int J Collab Res Intern Med Public Health. 2011;3(285):93. doi: 10.18805/ijare.v50i1.8582.
77. Agyare C, Oguejiofor S, Bekoe OE, Amoah LA, Boakye YD. Anti-inflammatory and anti-infective Properties of ethanol Leaf and Root Extracts of *Baphia nitida* gyare *et al*. BMRJ. 2016;11(4):1-7:Article no.BMRJ.22459. doi: 10.9734/ajob/2020/v10i230101.
78. Abdullahi M, Buhari F, Abdulrauf S. Antimicrobial activity of *Bombax buonopozense* P. Beauv. (Bombacaceae) Edible Floral Extracts. Eur J Sci Res. 2011;627-630 ISSN 1450-216X;48(4).
79. Kumar KM, Sharma A, Dhiman A. Medicinal potential of Digitaria: An overview. J Pharmacogn Phytochem. 2021;10(1):1717-9.
80. Victor OB, Owolabi GO. Traditional oil palm (*Elaeis guineensis* jacq.) and its medicinal uses. A review. 2014;4(3):16. doi: 10.5667/tang.2014.0004.
81. Satya R, Narain SR, Rawat A, Kaur J, Kumar S, Fatima N. Taxonomy, phytochemistry, pharmacology and traditional uses of *Flueggea virosa* (Roxb. ex Willd.) Royle. A Review. Int J Life Sci. 2018;6(2):579-85. doi: 10.11648/j.jdmp.20210704.14.
82. Abobatta WF. Jatropha curcas: an overview Journal of Advances in Agriculture. 2019;2349-0837. doi: 10.24297/jaa.v10i0.8145.
83. Corrêa GM, De AF, Alcântara C. Chemical constituents and biological activities of species of Justicia – a review. Rev BrasFarmacognosia Braz J Pharmacogn. 2012;22(1):220-38.
84. Cocchia N TS ,Carotenuto D , Vassetti A , Staropoli A, Mastellone V ,Peretti V, et.al .Musa. Paradisiaca L. and Musa sapientum L.: A Phytochemical and Pharmacological Review. J Appl Pharm Sci. 2011:14-20.
85. Ahmad MH, Jatau A, Alshargi AY, Julde SM, Mohammed M, Muhammad S, *et al*. Ethnopharmacological uses, phytochemistry, pharmacology, and toxicology of *Olax subscorpioidea* Oliv. (Olacaceae): A review.Ahmad *et al*. Future J Pharm Sci. 2021;7:11.
86. Isikhuemen EM, Ogbomwan BO, Efenudu IU. Evaluation of phytochemical and mineral constituents of *Piper guineense* Schum. and Thonn. and *Piper umbellatum* Linn: implications for ethnomedicine. Eur J Med Plants. 2020;31(1):84-97.Article no EJMP 54232.
87. Amoateng P, Quansah E, Karikari TK, *et al*. Medicinal plants used in the treatment of mental and neurological disorders in Ghana evidence-based complementary and alternative medicine volume .2018; 14. Vol. 0381:Article ID 8590381.https://doi.org/10.1155/2018/859.
88. Mahdy K, Shaker O, Wafay H, Nassar Y, Hassan H, Hussein A. Effect of some medicinal plant extracts on the oxidative stress status in Alzheimer's disease induced in rats. Eur Rev Med Pharmacol Sci. 2012;16;Suppl 3:31-42. PMID 22957416.
89. Attah AF, Hellinger R, Sonibare MA, Moody JO, Arrowsmith S, Wray S, *et al*. Ethnobotanical survey of *Rinorea dentata* (Violaceae) used in South-Western Nigerian ethnomedicine and detection of cyclotides. J Ethnopharmacol. 2016;179:83-91. doi: 10.1016/j.jep.2015.12.038. PMID 26721222.
90. Elufioye TO, Obuotor EM, Agbedahunsi JM, Adesanya SA. Anticholinesterase constituents from the leaves of *Spondias mombin* L. (Anacardiaceae). Biologics. 2017;11:107-14. doi: 10.2147/BTT.S136011, PMID 28814827.
91. Swarna J and ravindhran R. Parmacognostical and phytochemical evaluation of *Talinum triangulare* (jacq.) willed. Int J Pharm Pharm Sci. 2013;5(2):249-56.
92. Zaveri M, Khandhar A, Patel. S, Patel. A chemistry and pharmacology of *Piper longum*. Int J Pharm Sci Rev Res. 2010;5:Article-010.
93. Aggarwal BB, Harikumar KB. Potential therapeutic effects of curcumin, the anti–inflammatory agent, against neurodegenerative, cardiovascular, pulmonary, metabolic, autoimmune and neoplastic diseases. Int J Biochem Cell Biol. 2009;41(1):40-59. doi: 10.1016/j.biocel.2008.06.010, PMID 18662800.
94. Sharma P. Bharat P. Dwivedee D, Bisht AK. Dash D and Kumar. The chemical constituents and diverse pharmacological importance of *Tinospora cordifolia*. Heliyon. 2019:e024373. doi: 10.1016/j.heliyon.2019.e02437.
95. Jae L, Kyung L, Beom J, *et al*. Inhibitory effect of ethanol extract of *Magnolia officinalis* and 4-O–methylhonokiol on memory impairment and neuronal toxicity induced by beta-amyloid. Pharmacol Biochem Behav. 2009;95(1):31-40. doi: 10.1007/s11418-009-0330-z.
96. Tafuri S, Cocchia N, Carotenuto D, Vassetti A, Staropoli A, Mastellone V *et al*. Chemical Analysis of *Lepidium meyenii* (Maca) and its Effects on Redox Status and on Reproductive Biology in Stallions †. Molecules. 2019;24(10):1981. doi: 10.3390/molecules24101981, PMID 31126050.
97. El-Saber Batiha G, Magdy Beshbishy A, El-Mleeh A, Abdel-Daim MM, Prasad Devkota H1A. Traditional uses, bioactive chemical constituents, and pharmacological and toxicological activities of *Glycyrrhiza glabra* L. (Fabaceae). Biomolecules. 2020;10(3):352. doi: 10.3390/biom10030352, PMID 32106571.
98. Zhang Z, Wang X, Chen Q, Shu L, Wang J, Shan G. Clinical efficacy and safety of huperzine alpha in treatment of mild to moderate Alzheimer disease. A placebo-controlled, double-blind, randomized trial. Zhonghua Yi Xue Za Zhi. 2002;82(14):941-4. PMID 12181083.
99. Tomoharu K, Chihiro T, Katsuko K. Neuritic regeneration and synaptic reconstruction induced by withanolide A. B J Pharmacol. 2005;144:961-71.
100. Jayaprakasam B, Padmanabhan K, Nair MG. Withanamides in *Withania somnifera* fruit protect PC-12 cells from β-amyloid responsible for Alzheimer's disease. Phytother Res. 2010;24(6):859-63. doi: 10.1002/ptr.3033, PMID 19957250.
101. Dubey GP, Pathak SR, Gupta BS. Combined effect of Brahmi (*Bacopa monniera*) and Shankhpushpi (*Convolvulus pluricaulis*) on cognitive functions. Pharmacopsychoecol.1994;7:249-51.
102. Bhanumathy M, Harish MS, Shivaprasad HN, Sushma G. Nootropic activity of Celastrus paniculatus seed. Pharm Biol. 2010;48(3):324-7. doi: 10.3109/13880200903127391, PMID 20645820.
103. Walesiuk A, Braszko JJ. Preventive action of Ginkgo biloba in stress- and corticosterone-induced impairment of spatial memory in rats. Phytomedicine. 2009;16(1):40-6. doi: 10.1016/j.phymed.2007.04.012, PMID 17482446.
104. Lannert H, Hoyer S. Intracerebroventricular administration of streptozotocin causes long-term diminutions in learning and memory abilities and in cerebral energy metabolism in adult rats. Behav Neurosci. 1998;112(5):1199-208. doi: 10.1037//0735-7044.112.5.1199, PMID 9829797.
105. Wang R, Yan H, Tang XC. Progress in studies of huperzine A, a natural cholinesterase inhibitor from Chinese herbal medicine. Acta Pharmacol Sin. 2006;27(1):1-26. doi: 10.1111/j.1745-7254.2006.00255.x, PMID 16364207.
106. Eidi M, Eidi A, Bahar M. Effects of *Salvia officinalis* L. (sage) leaves on memory retention and its interaction with the cholinergic system in rats. Nutrition. 2006;22(3):321-6. doi: 10.1016/j.nut.2005.06.010. PMID 16500558.
107. Obulesu M, Rao DM. Effect of plant extracts on Alzheimer's disease: An insight into therapeutic avenues. J Neurosci Rural Pract. 2011;2(1):56-61. (PMC Free article). doi: 10.4103/0976-3147.80102, PMID 21716802.
108. Pramodinee D, Mahesh M, Niranjan D, Sankpala S. Memory enhancing activity of *Cissampelos papiera* in mice. Int J Pharm Sci. 2011;3:206-11.
109. Dhanasekaran M, Tharakan B, Holcomb LA, Hitt AR, Young KA, Manyam BV. Neuroprotective mechanisms of ayurvedic antidementia botanical *Bacopa monniera*. Phytother Res. 2007;21(10):965-9. doi: 10.1002/ptr.2195, PMID 17604373.
110. Saxena V, Ahmad H, Gupta R. Memory enhancing effects of *Ficus carica* leaves in hexane extract on interoceptive behavioral models. Asian J Pharm Clin Res. 2013;6:109-13.
111. Lu JH, Ardah MT, Durairajan SSK, Liu LF, Xie LX, Fong WF *et al*. Baicalein inhibits formation of α-synuclein oligomers within living cells and prevents Aβ peptide fibrillation and oligomerisation. Chem Bio Chem. 2011;12(4):615-24. doi: 10.1002/cbic.201000604, PMID 21271629.
112. Shimmyo Y, Kihara T, Akaike A, Niidome T, Sugimoto H. Multifunction of myricetin on A beta: Neuroprotection via a conformational change of A beta and reduction of A beta via the interference of secretases. J Neurosci Res. 2008;86(2):368-77. doi: 10.1002/jnr.21476, PMID 17722071.
113. Ramezani M, Darbandi N, Khodagholi F, Hashemi A. Myricetin protects hippocampal CA3 pyramidal neurons and improves learning and memory impairments in rats with Alzheimer's disease. Neural Regen Res. 2016;11(12):1976-80. doi: 10.4103/1673-5374.197141, PMID 28197195.
114. Asai M, Iwata N, Yoshikawa A, Aizaki Y, Ishiura S, Saido TC *et al*. A berberine alters the processing of Alzheimer's amyloid precursor protein to decrease Aβ secretion. Biochem Biophys Res Commun. 2007;352(2):498-502. doi: 10.1016/j.bbrc.2006.11.043, PMID 17125739.
115. Jung HA, Min BS, Yokozawa T, Lee JH, Kim YS, Choi JS. Anti-alzheimer and antioxidant activities of Coptidis rhizoma alkaloids. Biol Pharm Bull. 2009;32(8):1433-8. doi: 10.1248/bpb.32.1433, PMID 19652386.
116. Descamps O, Spilman P, Zhang Q, Libeu CP, Poksay K, Gorostiza O, *et al*. AβPP-selective BACE inhibitors (ASBI): novel class of therapeutic agents for Alzheimer's disease. J Alzheimers Dis. 2013;37(2):343-55. doi: 10.3233/JAD-130578, PMID 23948888.
117. Qi C, Bao J, Wang J, Zhu H, Xue Y, Wang X *et al*. Asperterpenes A and B, two unprecedented meroterpenoids from *Aspergillus terreus* with BACE1 inhibitory activities. Chem Sci. 2016;7(10):6563-72. doi: 10.1039/c6sc02464e, PMID 28042460.
118. Mori T, Koyama N, Guillot-Sestier MV, Tan J, Town T. Ferulic acid is a nutraceutical β-secretase modulator that improves behavioral impairment and alzheimer-like pathology in transgenic mice. PLOS ONE. 2013;8(2):Article ID e55774. doi: 10.1371/journal.pone.0055774, PMID 23409038.

119. Srinivasan M, Sudheer AR, Menon VP. Ferulic acid: therapeutic potential through its antioxidant property. J Clin Biochem Nutr. 2007;40(2):92-100. doi: 10.3164/jcbn.40.92, PMID 18188410.
120. Youn K, Jun M. Biological evaluation and docking analysis of potent BACE1 inhibitors from *Boesenbergia rotunda*. Nutrients. 2019;11(3):662. doi: 10.3390/nu11030662, PMID 30893825.
121. James S, Aparna JS, Paul AM, Lankadasari MB, Mohammed S, Binu VS, *et al*. Cardamonin inhibits colonic neoplasia through modulation of microRNA expression. Sci Rep. 2017;7(1):13945. doi: 10.1038/s41598-017-14253-8, PMID 29066742.
122. Chen W, Chen G. Danshen (*Salvia miltiorrhiza* Bunge): A Prospective Healing Sage for Cardiovascular Diseases. Curr Pharm Des. 2017;23(34):5125-35. doi: 10.2174/1381612823666170822101112, PMID 28828985.
123. Tang Y, Huang D, Zhang MH, Zhang WS, Tang YX, Shi ZX, *et al*. Salvianolic acid B inhibits Aβ generation by modulating BACE1 activity in SHSY5Y- APPsw cells. Nutrients. 2016;8(6):333. doi: 10.3390/nu8060333, PMID 27258307.
124. Tian J, Liu Y, Chen K. *Ginkgo biloba* extract in vascular protection: Molecular mechanisms and clinical applications. Curr Vasc Pharmacol. 2017;15(6):532-48. doi: 10.2174/1570161115666170713095545, PMID 28707602.
125. Khoury R, Grysman N, Gold J, Patel K, Grossberg GT. The role of 5 HT6-receptor antagonists in Alzheimer's disease: An update. Expert Opin Investig Drugs. 2018;27(6):523-33. doi: 10.1080/13543784.2018.1483334, PMID 29848076.
126. Pinto A, Bonucci A, Maggi E, Corsi M, Businaro R. Anti-Oxidant and Anti-Inflammatory Activity of Ketogenic Diet: New Perspectives for Neuroprotection in Alzheimer's Disease. Antioxidants (Basel). 2018;7(5):63. doi: 10.3390/antiox7050063, PMID 29710809.
127. Yuan Q, Wang CW, Shi J, Lin ZX. Effects of *Ginkgo biloba* on dementia: An overview of systematic reviews. J Ethnopharmacol. 2017;195:1-9. doi: 10.1016/j.jep.2016.12.005, PMID 27940086.
128. 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. doi: 10.1046/j.1365-2710.2003.00463.x. PMID 12605619.
129. Akhondzadeh S, Noroozian M, Mohammadi M, Ohadinia S, Jamshidi AH, Khani M. *Melissa officinalis* extract in the treatment of patients with mild to moderate Alzheimer's disease: A double blind, randomised, placebo controlled trial. J Neurol Neurosurg Psychiatry. 2003;74(7):863-6. doi: 10.1136/jnnp.74.7.863, PMID 12810768.
130. Iwasaki K, Satoh-Nakagawa T, Maruyama M, Monma Y, Nemoto M, Tomita N *et al*. A randomized, observer-blind, controlled trial of the traditional Chinese medicine Yi-Gan San for improvement of behavioral and psychological symptoms and activities of daily living in dementia patients. J Clin Psychiatry. 2005;66(2):248-52. doi: 10.4088/jcp.v66n0214, PMID 15705012.
131. Iwasaki K, Kobayashi S, Chimura Y, Taguchi M, Inoue K, Cho S *et al*. A randomized, double-blind, placebo-controlled clinical trial of the Chinese herbal medicine "ba wei di huang wan" in the treatment of dementia. J Am Geriatr Soc. 2004 September;52(9):1518-21. doi: 10.1111/j.1532-5415.2004.52415.x, PMID 15341554.

Cite this article: Potbhare MS, Barik R, Khobragade DS. Management of Alzheimer's disease: A Review of Herbal Drugs Having Potential Pharmacological and Therapeutic Activity. J Young Pharm. 2023;15(1):13-30.