THINK INDIA JOURNAL ISSN: 0971-1260

Vol-22-Issue-17-September-2019

Herbal Drugs Used in The Treatment of Alzheimer's Disease

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ABSTRACT

Till today many scientists are trying to find the cure of this neurodegenerative disorder known as Alzheimer's disease, which is the 4th root cause of death in most developed nations. It commonly occurs in elderly patients, in which dementia is the prevalent symptom. It is caused by neurodegeneration and amyloid beta tangles formation in the brain. While there are many treatment options available in the market, this review focuses on the natural herbal products showing good pharmacological response and is beneficial by improving memory and cognition, neurovascular function, and neuroprotection. In the recent years, discovery of herbal remedies has become more and more well-known, all around the globe and is showcasing very promising benefits in AD patients, with less adverse reaction.
Natural products continue to show more advantages over synthetic molecules day by day and the master objective of this review is to present the evidence of some of the herbal formulation already being used such as Galantamine from *Amaryllidaceae* family, *Melissa officinalis* and many more others which are explained later on in this writing, by inhibiting acetyl cholinesterase enzyme.
This review has subtopics in which everything has been explained from pathophysiology of disease to diagnosis and treatment and most importantly "why herbal drugs?"

Keywords: Dementia, Herbal, Elderly, Alzheimer's disease, Neurodegeneration, Amyloid, Acetyl cholinesterase.

INTRODUCTION

Alzheimer's disease is defined as CNS progressive neurodegenerative brain disorder that leads to dementia, personality change and unusual behavior. It is slow in onset but ultimately causes death. [1] The main behavioral change that occurs as the disease progresses, is the inability of the patients to do their own usual daily activities such as bathing, handling house

chores and having emotional disturbances, such as mood swings and this has been most commonly observed in the elder patients, The prevalence was found to rise exponentially with age, ranging from 3.1% patients from 65-74 years to most likely up to 47.3% in those with 85 years and above. [2] The patients tend to forget even family members. The brain is known to contain nerve cells which connect with each other to form a network for communication among them and it is recorded by brain specialist that an average brain has 100 billion of these cells. In which all groups of these nerve cells have their special duties, which are; learning, thinking, and remembering, etc. Others help us see which are found in the eyes, others in hearing and smelling. Characterization of AD can be seen physically by the loss of massive neurons, thus disturbance in transfer of signal is taken place in brain. Diagnosis can be done by postmortem, by which observation of tangles inside and senile plaques outside cells throughout the brain. The plaque is a small major component of 40/42-amino acid peptide amyloid-beta (Aβ). The first suggested amyloid hypothesis was Aβ, as the causative agent of A Dabout 15 years back and is now accepted widely among community of scientist. Amyloid-beta (Aβ) has been difficult to understand as it is an elusive entity with chemical and biological action. Crystallization is very difficult and because of this, its solubility is very low and has highly changeable structure in a solution.[3]

The studies have stipulated that as Alzheimer's disease advances, neurofibrillary tangles and also the plaques broaden in every part of the brain initiating in the neocortex. By the last stage, destruction widespread and brain tissue get narrow crucially. Studies have exhibited the participation of neurotransmitter acetylcholine in Alzheimer's disease springing into an out of proportional lack of acetylcholine. It has been set down in writing that producers for cholinergic neurons, acetylcholine transferase and acetylcholine esterase are in control for acetylcholine synthesis and its degradation drops low in the cortex and hippocampus area of

the brain associated with the cognition and memory.[4] The study has indicated that the resultant drop down in acetylcholine dependent neurotransmission is involved in progression of AD. [5]

The motive of cholinesterase inhibitors in the treatment of patient with Alzheimer disease has been found to be a great successful approach. [6] The tacrine, the acridine derivatives, was the introductory drug accepted by food and drug administration (FDA), USA for orthodox clinical use in AD. The additional four new choline esterase inhibitors approved by FDA, USA to treat it are Donepezil (Aricept), Galantamine (Reminyl) Rivastigmine (Exelon). [7]

In this review, a presentation of an all-inclusive analysis on use of ethnomedicine for the management of AD worldwide is portrayed. To boot it up, we also pin point 5 indigenous prominent plants traditionally used in the treatment of dementia and accentuate the constituents, responsible for plant's biological response. Presently, no such medicine is available which is specifically used to prevent the progression of dementia. [8] It is suggested that acquiring more knowledge on the active substances manufactured by these plants and their (MOA) mechanism of action may usher expansion of natural and novel therapies for the treatment of loss of memory. The compounds obtained from natural sources contributes towards the drug development process. [9] Regarding this, the current review could provide a useful information on the plant based formulations for the AD therapy.

Epidemiology

In the year 2016, roughly 47 million people lived with dementia from all parts of the world. Dementia is the single most common symptom of Alzheimer, encompassing about 70% of all cases. The majority of the patients with Alzheimer's have late-onset (around 65 years of age or later) and few have early-onset during 40's or 50's.

If we talk about Geographical distribution of Alzheimer's disease, Latin America has a relatively higher incidence of Alzheimer's compared to the western European countries. About 5.7 million, US population are suffering from AD. It's the 6th leading cause of death in the USA, and the number of deaths skyrocketed by 123% between 2000 and 2015 [10].

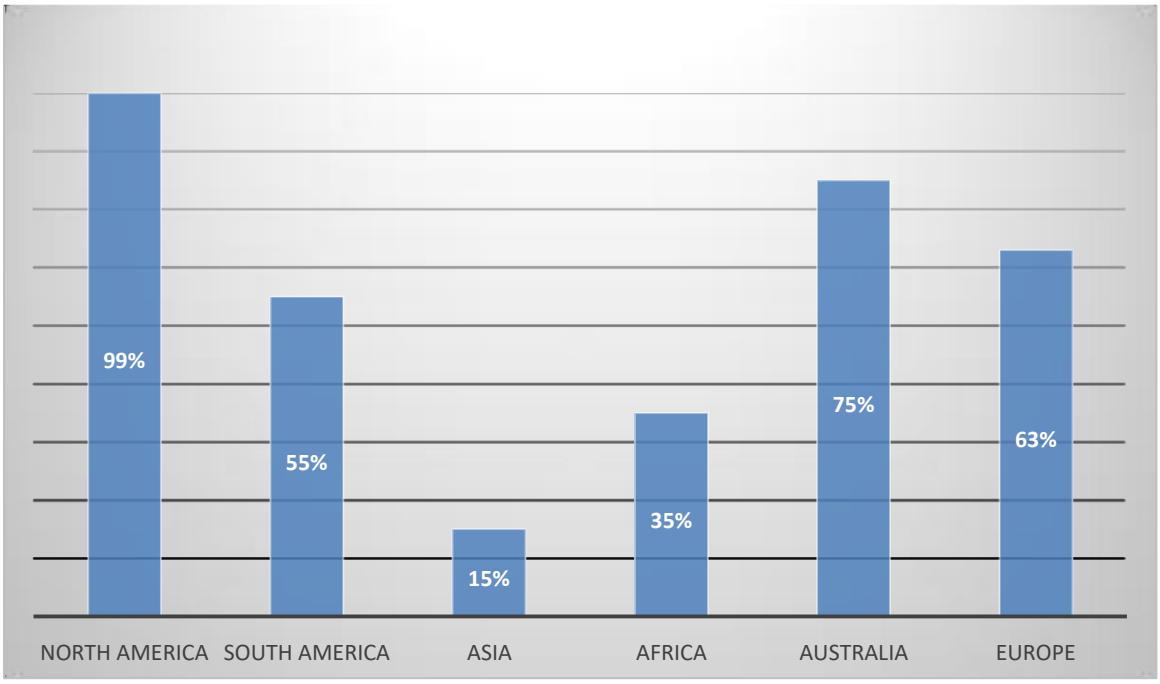


FIG 1: 2018 Epidemiology of AD, Reported by WHO.

Pathophysiology

There are several components involving interrelated systems which play a part in the developing stages of AD which include alterations during protein processing, lipid transport, nerve cell signaling, apoptosis, inflammation, oxidative damage and stress responses, neurodegeneration and energy metabolism affecting brain homeostasis and last tau pathology.[11] These manifest as clinical premature symptoms of deficit in memory, directing to decline in cognition and in due course dementia. The lead of neuronal cell loss and damage to the vascular system is due to the neurofibrillary tangles and the amyloid plaques characteristic of AD, causing reduced flow of blood to the brain and consequential

cognitive impairment. [3] To form smaller peptides Amyloid-β protein precursor (AβPP), found in high concentrations in neuron synapses is broken down by secretases soluble amyloid precursor protein and amyloid beta peptide (AβP.) [12] Upon interaction with the parent protein forms oligomers; AβP dissociates and diffuse into synaptic clefts from the nerve cell. The cause of neurofibrillary tangle (NFT) formation and neuronal cell death is due to the build-up of AβP which is neurotoxic (sensitizing neurons to excitotoxic damage). NFTs are comprised of tau with hyperphosphorlyation; a protein associated microtubule, phosphorylated by Glycogen synthase kinase-3 (GSK3) and balanced by the calcium-dependent protease Calpain. AβP also disrupts intracellular regulation of calcium directing to a rise in cytosolic calcium concentrations; a proposed cause of NFTs. The main pathways thought to be involved include aggregation of amyloid, phosphorylation of Tau, calcium homeostasis and stress oxidation [11].

Summary of AD pathways

- reduced methylation
- protagonist demethylation
- Amyloid processing
- Presenilin expression/activity
- β secretase expression/activity
- Phosphorylation of Tau
- PP2A
- Calcium homeostasis
- Oxidative stress
- Species with reactive oxygen
- Choline

- Phosphatidyl choline

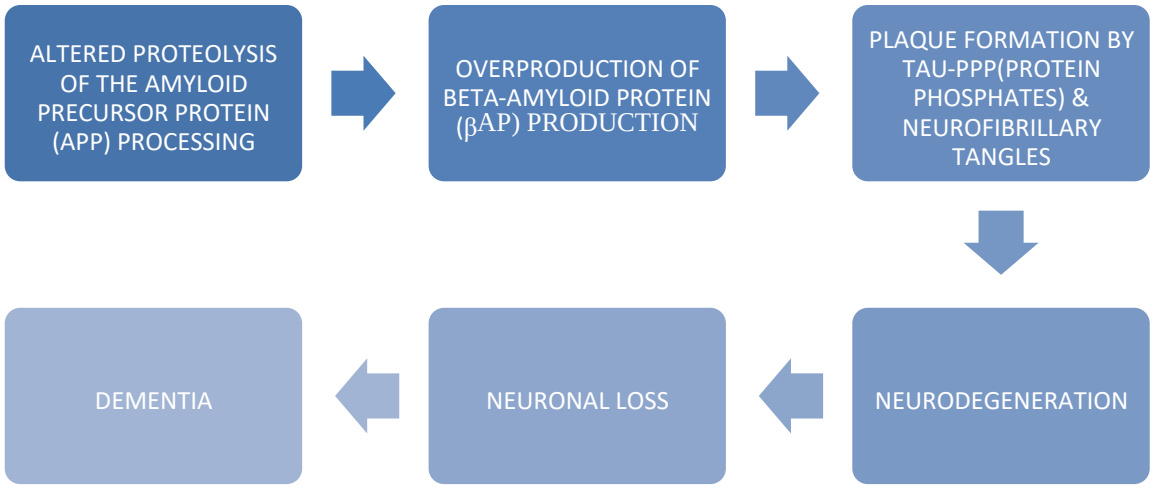


FIG 2: PATHOPHYSIOLOGY of AD

Etiology

The study of AD is complex. It is a result of the interrelation of neurobiological processes and genetics. The following are the leading hypothesis of AD:

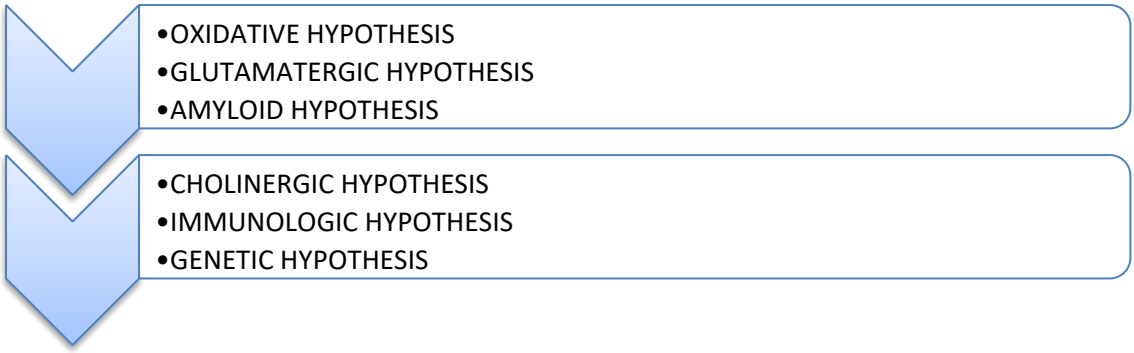


FIG. 3: ETIOLOGY OF AD

Signs and Symptoms

Scientists till today are still pursuing to clear up the multiplex changes in the brain, which are associated with the onset and development of AD. The early symptoms of Alzheimer's vary from person to person. Memory problems are generally one of the most predominantly signs

of Alzheimer's disease. Decrease memory characteristic such as cognition, for example; difficulty in finding words, blunt reasoning or judgment, vision disability may also indicate the first levels of AD.

Mild Alzheimer's disease	Moderate Alzheimer's disease	Severe Alzheimer's disease
➢ Loss of memory ➢ Decrease in Sharpness is ruling to poor decisiveness ➢ Delay in completing normal daily chores ➢ Replicating questions, even the unnecessary ➢ Difficulty in ➢ managing his own ➢ pocket and ➢ anything financially ➢ Forgetting where ➢ one is presently like place e.g. one goes to shop and forget where they are ➢ Mood swings where	➢ Worse loss of memory and sceptic. ➢ Hard to learn something different from their daily routines ➢ Speaking problems, ➢ Can't read, write, and work with numbers ➢ Very hard to arrange thoughts and difficult to think straight ➢ Less concentration ➢ One tends to forget his /her relatives or find it hard to recall who they are. ➢ Daydreaming gets common, imaginations become unrealistic	➢ Communication Inability ➢ Loss of weight ➢ Seizures ➢ Skin infections ➢ Swallowing difficulties ➢ Weeping/crying unnecessarily ➢ Sleeping time reduced ➢ Bladder control ➢ gets loose including bowel

one has multiple ➢ characters ➢ Uneasiness and belligerence	➢ Sudden behavior changes at awkward times such as one takes off his clothing in public place easily angered at any time or over excitement edginess, jitteriness, impatient saying something over and over again or moving around the house continuously	

Tab. 1: Sighs and symptoms of Different Types of AD.

Diagnosis

Diagnosis of AD is performed by exclusion due to the fact that there are no accurate diagnostic methods other than post-mortem. The early diagnosis of AD is done by what is known as (MCI) which is mild cognitive impairment such as memory complaints and other symptoms mentioned in the above table. Neuropsychological examination tests aid with diagnosis, such as mini mental state, ADAS (AD assessment scale), Dementia Questionnaire, Neurological examination, Has chinsky scale. Brain computed axial tomography (CAT) gives data about the subcortical atrophy of brain and brain cortical [13]. Functional studies allow us to detect alterations in the neuronal metabolism such as the positron emission tomography (PET), the single photon emission computed tomography (SPECT)[14]. Recent development has emerged in which Omics technologies has been introduced e.g. Genomics, Epigenomics, Transcriptomics, Proteomics and Metabolomics.

Treatment and Therapy

Quality of life of the patient is the most valuable principle and therefore, the early treatment improves one's health. Presently, the medicines used for AD is tended to treat only its symptoms and with limited effectiveness. There is no cure for AD leading to decreased mortality rate of generic patients. Recently many research scientists have been looking for better drug from various system of medicinal practice like allopathic, siddha, Ayurveda, Homeopathy etc. Siddha and Ayurveda are similar way of treatment with natural source of drug substance [15-19]. The following diagram shows the various treatment methodologies followed:

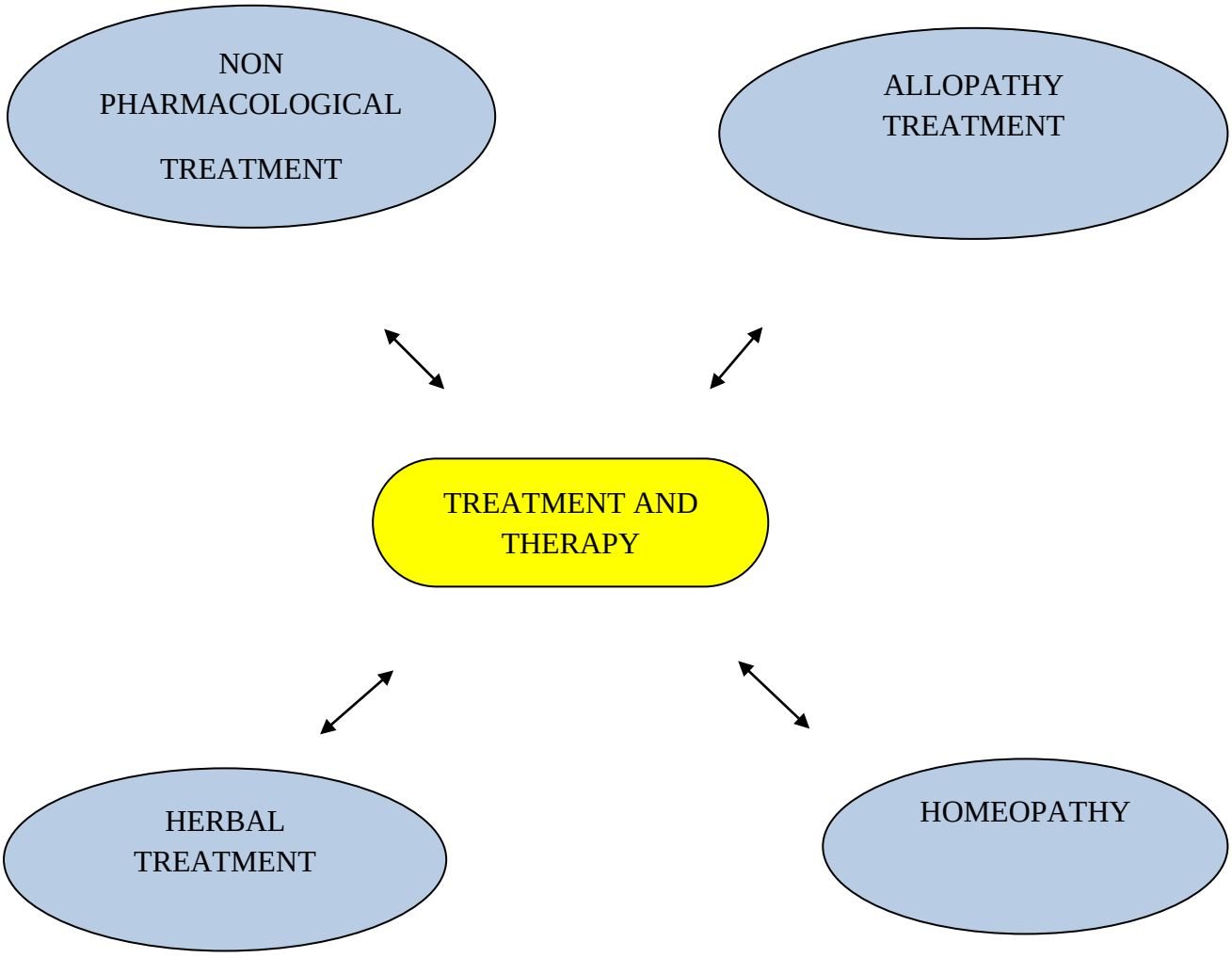


FIG.4 TREATMENT AND THERAPY DIAGRAM

A. NON PHARMACOLOGICAL TREATMENT

In this category, main focus is on care giving and implementation of psychotherapeutic and stimulation talking sessions. The care giver must be willing to be with patient at all cost because it is a very sensitive involment, adaptation of context, the work with the family members, and make sure that patient is always calm and in good situation. Psychoeducation is very important as to avoid problems such as isolation of patient. All family members must be ready to accept and support the patient at all times.

B. ALLOPATHY TREATMENT

Abundant evidence has been produced by the scientists that there is a relationship between the cholinergic neurotransmitter system with cognitive performance and memory function. Acetyl cholinesterase (AChE) has shown good results in being a reliable therapeutic target for Alzheimer's indicative development. Pharmacologic techniques have been concentrated on neurotransmitters alterations which are inter-related on AD diseases conditions to manipulate and provide a good normal life. The available treatment strategies can be characterized as symptomatic or neuroprotective. At present practicable pharmacologic therapies, including (a) cholinesterase inhibitors (ChEIs) and (b) N-methyl-D-aspartate (NMDA) receptor antagonists and these are considered symptomatic treatments based on their ability to slow down the clinical enhancement of cognitive, behavioral and functional domains [20-24]. Centrally active Choline esterase

inhibitors (ChEIs), which directly target acetyl choline esterase alone or affecting both AChE and butyl choline esterase were the first class of drugs approved by the US Food and Drug Administration (FDA) for the treatment of Alzheimer's disease. The following therapeutic drugs are known choline esterase inhibitors; Donepezil hydrochloride (Donepezil), Galantamine hydrochloride (Galantamine), Rivastigmine tartrate (Rivastigmine), and Tacrine hydrochloride (Tacrine). Currently, memantine hydrochloride (memantine) is the only available drug for targeting cognitive symptoms via a putative glutamatergic mechanism. [25-28]

C. HOMEOPATHY TREATMENT

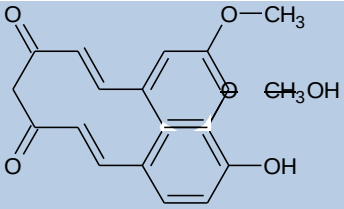
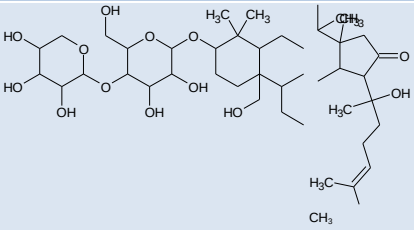
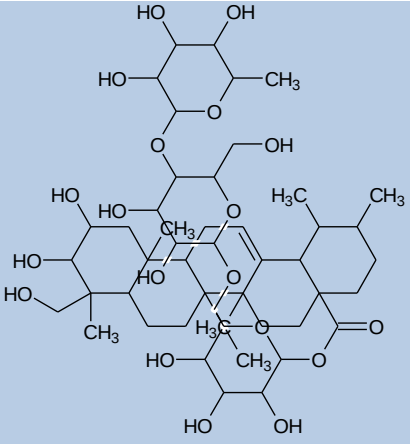
Homeopathy is known as a branch of medical sciences & therapeutics, practiced globally, which confides in curing the disease and not entirely infected portion of the patients. The traditional aims of the homeopathy treatment are to find the simillimum or the therapy that conceals the most dominant features of the case. Homeopathy can slow the development of the disease and ease symptoms, as shown by the Heel studies. Homeopathy take an effective therapy for treating multiple, chronic and deep-seated diseases, including Alzheimer's. The potency of multi- drug formulations of homeopathic medicines is proved to be effective in relieving symptoms of Alzheimer's disease. [29-30] The role of homeopathic drugs for various disorders is probably do not talk of the 'cure' in real sense, but more of 'control' and 'relief'‟. Homeopathy system of medicines gives positive treatment if not cure, where homeopathy system of medicine had a major role on the progression of disease. List of Homeopathic medicines utilized in the treatment of Alzheimer's disease; Baryta Carb, Natrum Sulf, Nux Vomica, Alumina, Mercurius, Ignatia, Calcarea Carb, Lycopodium, Staphisagria, Chamomilla, Terentula and Conium. [31-34]

D. HERBAL TREATMENT

The Herbal medicine treatment for AD has begun to be very well-known now a days due to their effectiveness against AD and advancement in slowing it down .Plenty of research on herbal drugs has been worked on and the advantages which were got from the use of natural entities in the treatment of AD and dementias seems promising with big time success. Neither the less, these natural herbs are affordably cheap and are easily present in all seasons. The observed results from this treatment using herbal medicines can be promising in future also with very fewer adverse effects. Instead of using synthetic drugs with more side effects, herbals supplements can be used as their substitutes. In this review article, we will try our best to present some of herbal drugs which are being used nowadays for the treatment of AD. Also, some current research work going on them to prove their mechanism for slowing down the progression of AD. Following herbal plants or their parts are used for treatment for AD.

Summary table of commonly used Herbal Drugs

SN.	SCIENTIFIC NAME& FAMILY	COMMON NAME	CHEMICAL STRUTURE	STRUCTURE	MECHANISM OF ACTION

1.	*Curcuma longa.l* *Zingiberaceae*	turmeric,haridra	-curcuminoids -curcumin		-acetylcholinesterase inhibition -amyloid-b inhibition [33]
2.	*Bacopa monnieri. l* *scrophulariaceae*	weltst (nirabrahmi)	-bacosides a&b		-decreases whole brain ache activity [34]
3.	*Centella asiatica apiaceae*	mandookparni/brahmi	-Triterpenoidssaponins(asiaticosides)		-alteration of amyloid-b pathology in the brains of psapp [35]

ISSN: 0971-1260

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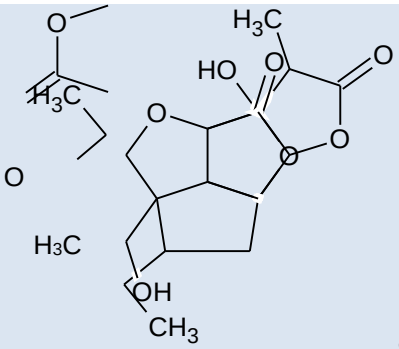
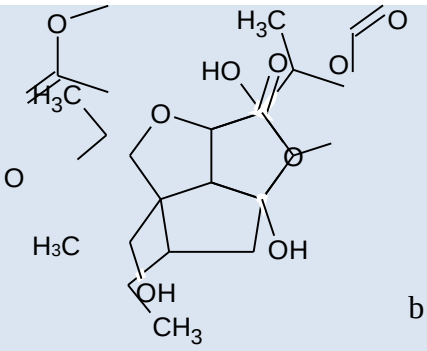
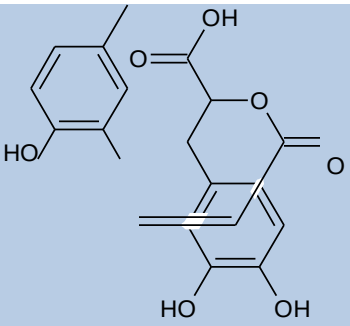
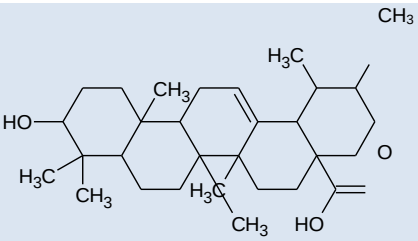
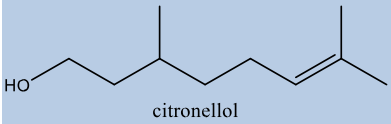
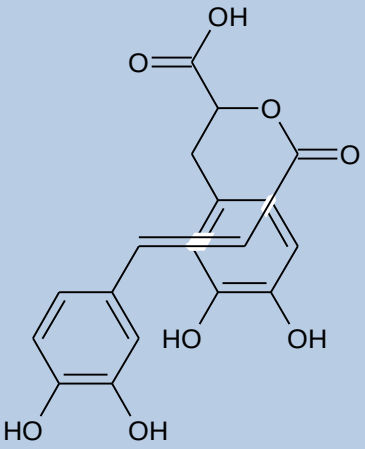
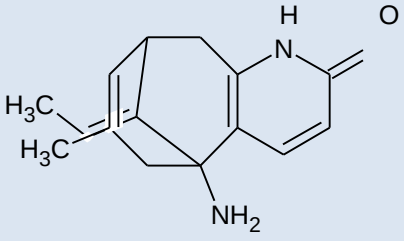
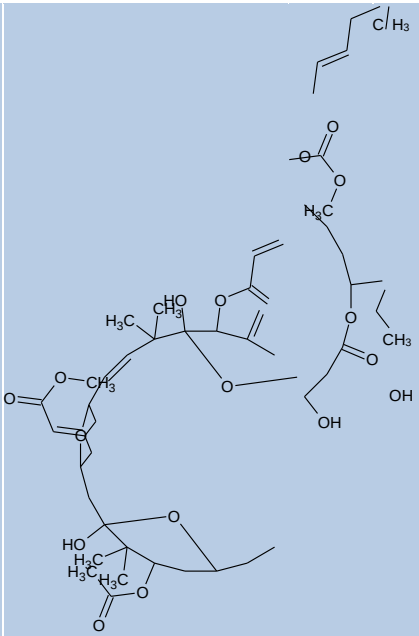
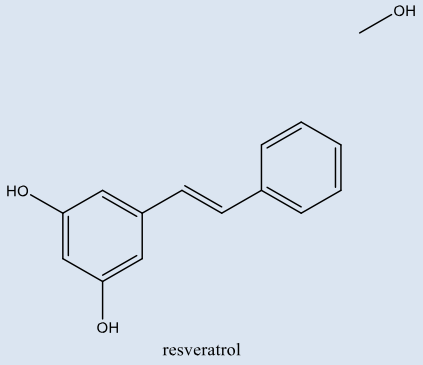
4.	*Ginko biloba ginkgoaceae*	maiden hair tree	-bilobalides ginkgolides -flavonoid glycosides	 a	-decreases ab proteininduced oxidative damages -inhibits platelet activating factor(paf) -protects nerve cells & regenerates motor nerve cells
				 b	-indirectly improves atp production -improved alpha2-adrenoreceptor activity possible inhition of catecholo-methyl transferase(comt). [36-39]

5.	*Salvia officinalis lamiaceae*	sage	-carnosia acid - rosmarinic acid	 OH	-antioxidant by reducing fress radicals -inhibition of acertylcholinesterases [40]
6.	*Rosmarinus officinalis lamiaceae*	satapatrika	-apigenin -carvacrol -eugenol - oleanolic acid -thymol - ursonlic acid - carsonic acid		-inhibition of ache -b-amyloid alteration -anti-buche (butyrylcholinesterase -reduces free radicals [41]
			-ferolic acid	 ursolic acid	

7.	*Melissa officinalis* *Lamiaceae*	lemon balm	-rosmarinic acid -citronellal -flavanoids -monotrepene glycoside -citronellol	 citronellol  rosmarinic acid	-inhibition of ache -reduces free radicals [42]
8.	*Huperzia serrate licopodiaceae*	firmosses thumb	-huperzin a		-inhibit the enzyme acetylcholinesttrasere vesibly& selectively -reduces free radicals [43]

9.	*Bugula neritina Bugulidae*	pink seaweed	bryostatin-1		-increases alpha-secretase activation in human fibroblast cells -decreases ab levels and decreases transgenic ad [44]
10	*Vitis vinifera vitaceae*	grape	resveratrol		-antioxident by reducing free radicals -activator of srrtuin 1(sirti) [45]

TAB. 2 SUMMARY OF SOME HERBAL PLANTS USED FOR AD

1. CURCUMA LONGA (CURCUMIN)

Curcumin is a popular polyphenolic compound obtained from the turmeric plant *Curcuma longa* L. (Zingiberaceae). It is under investigation in the area of dementia. According to Yang F *et al*. curcumin has antioxidant properties and various other beneficial actions such as antiinflammatory and anticancer [46-47]. Recent details have suggested pharmacological

potency of curcumin in AD. Hamaguchi T *et al.* reported *in-vitro* studies on curcumin and its potential to stop amyloid-β(Aβ) protein aggregation and Aβ induced inflammation as well as the activities of β-secretase and acetylcholinesterase. Chiam P.C.*et al.* conducted *in-vivo* studies and stated that upon administration of curcumin through oral route shown the inhibition of Aβ deposition, Aβ oligimerization and phosphorylation of tau in the brains of AD animal models and improvements in behavioral impairment in animal models. Currently, Longvida, a curcumin preparation formula has been developed and evaluation test is being carried out in phase II AD clinical trial. [48]

2. BACOPA MONNIERI (Linn.)

Traditionally, it has been used as a brain tonic to enhance memory development, learning, and concentration [49]. In literature, it is reported that Bacopa is known as medhya drug (Noo-tropicagent). Chopra RN *et al*. have discovered that this herb is used for the treatment of neurological and mental disorders. [50-54] Kapoor LD *et al*. outlined that the constituents which are responsible for Bacopa's cognitive effects are bacosides A and B [55], the triterpenoid saponins and their bacosides are responsible for Bacopa's ability to enhance nerve impulse transmission. Joshi H *et al*. have also added on saying that the bacosides aid in repair of damaged neurons by enhancing kinase activity, neuronal synthesis and restoration of synaptic activity and ultimately nerve impulse transmission.

Loss of cholinergic neuronal activity in the hippocampus is the primary feature of Alzheimer's disease. Bacopa has been shown to decrease whole brain AChE activity which reflects that Bacopa might prove to be a useful memory restorative agent in the treatment of Alzheimer's and dementia [56]. A clinical study on human subjects demonstrated the potential of Bacopa monnieri in the treatment of neuritis by Bhalla M *et al*. [57]. Kapoor

L.D.*et al*. calculated that dosage of powdered drug is 5-10 g and infusion 8-16 ml will show maximum potency.[58]

3. CENTELLA ASIATICA

In this drug neuro protective property has been demonstrated to show this possession. [59] Alternative medicine for memory improvement is the extract from the leaves of *centella asiatica* in the Indian ayurvedic system of medicine. [60] From the study conducted by Dhanasekaran M *et al*. recently on transgenic animal model in the management of AD for evaluating the efficacy of *Centella asiatica* extract (CaE), the result was that CaE can neurodegenerative changes occurring in AD. [61]

4. GINKO BILOBA

A herbal medicine *Ginko biloba* has been used in traditional chinese medicine for thousands of years until then for treatment of variety of ailments. DeKosky S.T.*et al*. observed it to reduce memory loss, to slow down the degenerative effects of Alzheimer's disease and enhance the brain activity [62, 63]. To explain the broad therapeutic spectrum of Ginkgo was from the fact that it influences two fundamental aspects of human physiology: 1) it improves blood flow to the brain and other tissues and 2) it enhances cellular metabolism. Because these functions are essential for good health, it is not unreasonable to consider the possibility that Ginkgo might have a broad spectrum of clinical applications. According to Perry E.K.*et al*. an extract ginkgolide is found to have less side effects as compared to synthetic drug molecules found in the market such as Donepezil.[64] Sandrine A *et al*. informed that Ginkgo biloba acts as a protective agent against Aβ protein-induced oxidation by reducing formation of hydrogen peroxide, lipid oxidation, and removing free radical oxygen species. [65] Sophie

G *et al*. observed the following as the various constituents present in this leaf extract; flavonoid glycosides, terpenoids which have bilobalides and ginkgolides. The flavones components are known to lessen the tenderness of capillaries and also protects the body from loss of blood when capillaries are damaged, especially the center of brain. In the case of ginkgolides, there exist two types A & B. The active one used in AD is B, as it prevents activating factor of platelets, making blood more less viscous causing better circulation around and making it an anticerebral thrombosis agent and reducing incidences of stroke. [66] In conclusion, Kanowski S *et al.* and Le Bars PL *et al.* informed that it has been found that this natural product when used to treat AD for months 3-6 at 120-250 mg, it gave amazing results like no or less side effects as that of synthetic medicines. [67-70]

5. SALVIA OFFICINALIS

The extract of a common plant known as sage produces an extraordinary improvement in cognition to those suffering from mild to moderate AD. Akhondzadeh S *et al.* stipulated that within only 16weeks*S. Officinalis* shows its 100% potency and efficacy [71]. Duke JA *et al. informed* that it is an antioxidant as it contain scarnosic acid and rosmarinic acid which help in reducing free radical species and protects the brain against oxidative damage [72].Wake G *et al.* also stated that in this case the side effects are as same as that of cholinesterase inhibitor [73].Therefore, there was a lot of agitation in placebo group which is an added advantage to the property of this plant.

6. ROSMARINUS OFFICINALIS

In this plant, Duckett P *et al.* accounted for the following constituents; ursolic acid, Apigenin, oleanolic acid, eugenol, thymol and carvacrol which all areCOX-2 inhibitors. Apart from this, this plant's extract acts as antioxidants (reducing free radical) and also anti-

inflammatory agent. Carsonic acid and ferulic acid are the strongest present antioxidants as compared to the synthetic ones e.g. (BHA) Butylated hydroxyanisole and (BHT) Butylated hydroxytoluene. [74] Moss M *et al.* reported that the oil of this herb plant is found to be amazingly effective for the improvement in the cognition of AD patient and also improved one's mood changes. [75] Ożarowski M *et al.* informed that under pharmcological clinical trials, they had carried out *in vitro* and *in vivo* ideal models which resulted in the proof that this oil indeed has its own potency on brain. Kujawski R *et al.* observed during *in vitro* studies that it showed an added advantage apart from inhibiting AchE or β- amyloid it also has anti BuChE activity. In this lamiaceae plant, apart from antioxidant and anti-inflammatory properties, it has also reported to possess cytoprotective and anti-apoptotic. [76]

7. MELISSA OFFICINALIS (Lemon Balm)

Melissa officinalis was believed to sharpen memory. It has tremendously displayed its activity of improving cognition and decreasing agitation in AD patients. When administered orally, its showed maximum efficacy by increase in Ach receptor activity in the CNS. Perry E.K. *et al.* informed that it also possesses the properties of the muscarinic and nicotinic receptor interaction. [77-78] According to Kennedy DO *et al,* during testing trials, it was tried on healthy young volunteers and it was observed that it normalized moods and cognition of the mindset improved [79]. Therefore, it was summarized that *Melissa officinalis* is amongst the many herbal plant which can be used to improve the condition of AD patients due to its ablility to inhibit acetylcholinesterase and also reduce oxidative stress.

8. HUPERZIA SERRATA (FIRMOSSES)

It is one of the most leading herbal plant used in AD and scientist are paying much attention on one of its phytoconstituent known as lycopodium which is an alkaloids. Commonly termed as Huperzia A is popularly known to act as potent and selective AChE inhibitor which is also reversible. According to Ha G.T.*et al,*. this helps in improving memory and other mental dysfunctionalities in patient with AD and remaining severe conditions that can be addressed. [80] Li C *et al.* informed that it is an active antioxidant and protects the neuro structure of brain. [81]

9. BUGULA NERITINA (BRYOSTATIN-1)

   It was George Pettit from the bryozoans who isolated bryostatin for the first time, he found it to be a very large lactone. At this very moment, it is being investigated for anticancer properties. It was then found to have very good memory enhancement in average adult. According to Hale K.J.*et al.* mechanism of action of Bryostatin-1 was to enhance α-secretase secretion in human fibroblast cells then to reduce Aβ level sand finally to reduce the death of transgenic AD mice [47]. This showed the researcher that it had a broad future in memory enhancement. [82]. Mackay HJ *et al.* informed that in addition to improved memory in rats, it also showed increased concentration and quick learning. It was also reported that this molecule could repair damaged brain tissue [83,84].

10. VITIS VINIFERA (RESVERATROL)

Resveratrol is presently available in plants belonging to family Vitaceae family such as grapes and we eat them once in while without realizing that is a very good source of antioxidants which can help in the AD treatment. Feng Y *et al*. informed that resveratrol enhanced proteosomal degradation of Aβ and this polyphenol enables Aβ aggregates to

decompose and clear out. Proteosome activity was found to be the main target in reducing aggregates in AD brain. [85] Jang JH *et al*. stipulated that prevention of fibril formation was due to disruption of Aβ hydrogen bonding by destabilization of preformed Aβ *in vitro* except Oligomerization. [86] Rossignol E *et al*. informed that to be specific, it hunts down all free radicals of active oxygen species and destroys them leading to reduced oxidation stress. [87] According to De Almeida L.M.V *et al*. this agent acts as a protectant on astrocytes in brain by reducing hydrogen peroxide caused by oxidative stress with the help of glutathione (antioxidant). [88] Karuppagounder S.S. *et al*. informed that apart from this, it is known to improve cognition disabilities and prevents plaque synthesis in patient of AD. [89] According to Pall M *et al*, Williams P *et al*. and Anekonda T.S. *et al*. recent proof has shown resveratrol as an active modulator in AD pathology because of its ideal properties. [90-92] As we speak resveratrol is under in the 3rd phase in clinical trials.

Other natural plants that aid in the treatment of AD [93]:

1) *Acorus calamus*
2) *Albizzia julibrissin*
3) *Albizzia lebbeck*
4) *Anemarrhenaasphodeloides*
5) *Artemisia absinthium*
6) *Bacopa monnieriVallarai / Brahmi*
7) *CelastrusPaniculatus*
8) *Clitoriaternatea*
9) *Commiphorawhighitii*
10) *Cornus officinalis*

11) Eclipta alba

12) Evolvulusalsinoides

13) Foeniculum vulgare

14) Ficusreligiosa

15) Glycyrrhiza glabra

16) Hypericum perforatum

17) Leontopodiumalpinum

18) Panax ginseng

19) Passiflora actinia

20) Polygala tenuifolia

21) Prunusamygdalus

22) Ptychopetalumolacoides

23) Pueraria tuberosa

24) Rubiacordifolia

25) Tabernaemontanadivaricata

26) Thespesia populnea

27) Vitis vinifera

28) Withaniasomnifera

WHY HERBAL TREATMENT?

Herbs have a little to no toxicity compared to allopathic medicines approved by FDA, USA and plays a major role in the early stages of the disease and also conditions in AD involving bad memory and dementia. The herbal drugs can be used with other drugs side by side as supplementary. For the patients having the history of AD in the family, may start taking these

supplements to delay or to reduce the further progression of the condition. This review is to pin-point the possible role of many herbs which have shown their effectiveness in Alzheimer's or any other memory related disorders. The plants mentioned in this article are very much helpful in treating and managing the disease due to their anti-oxidant, anti-inflammatory, neuroprotective, pro-cholinergic and anti-acetylcholinesterase qualities. Further, large scale studies are required to determine effectiveness of these herbs in the treatment and management of AD. Until then, this review will render some facts regarding the benefit of the herbs mentioned in the article.

Conclusion

Finally, we can say that in the treatment for AD, a large group of natural plants are being used all around the globe. Anti-inflammatory, antiapoptotic, antioxidative, are the mechanisms of action of the reviewed ten prominent representative plants, and generally activity that are mainly dealing with the protection of neuro cells. All of these indigenous plants show a bright future in not only improving the AD condition but also curing it. Best example where in curcumin which showed tremendous synergetic effects on cognition and oxidative stress, as well as good BBB permeability. Medicinal herbs are plentifully available worldwide and can have a great deal in formulation of effective new drugs for the disease. The main objective of this review is to highlighting the obvious role of many herbs, which have displayed the possibility of their effectiveness in Alzheimer's or memory related disorders in experimental models and human studies. This review gives sum herbal drug data from which scientists can get lead to work extensively to find out the technique and will further establish the authenticity to carry out advance research work in this field to yield the new molecule for future prevention and treatment of Alzheimer's & memory deficient CNS disorders.

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