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Review Article

Potential of Herbal Drugs for Application against Alzheimer's disease

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ABSTRACT

Alzheimer's disease (AD) is a neurological disease which progressively occurs in brain. Dementias are the most common form of Alzheimer's disease. Symptomatically used drugs which are used in treating AD include N-methyl D-aspartate (NMDA) receptor antagonist (memantine) and acetylcholinesterase inhibitors (AChEIs) (rivastigmine, galantamine, donepezil). Limited bioavailability of these drugs stresses continuity of search for novel therapeutics for this slow growing but complex disease. The memory related problems are treated by using the Herbal drugs, including Alzheimer's. The therapeutic potential of herbal drugs demonstrated both clinical and preclinical studies for the prevention of AD. Herbal drugs against Alzheimer's disease are possibly effective because of the multifaceted and pleiotropic action of the herbal drugs like neuroprotective, anti-inflammatory and antioxidants action. The current review aims to summarize the applications of herbs with anti-apoptotic and antioxidant properties in various *invivo* and *invitro* studies, different diagnostic tests for AD, mechanism of action associated with AD, stages and symptoms of AD, management of Alzheimer disease, therapeutic strategies of AD using herbal drugs, different herbal compounds altering BBB, herbs with AChE action and there plant parts used, alternative approaches used against AD, different herbal nanoparticles used in AD as well as limitations of using herbal drugs.

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1. INTRODUCTION

Alzheimer's disease (AD) is the progressive neurological disorder of brain. It was named by the Physician Aloes Alzheimer from German, and it was first described by him in the year 1906. Alzheimer's are the common form of dementia and 10 million peoples are affected worldwide. Advantages of using herbal drugs are having different beneficial actions than the synthetic drugs and possess less adverse effect, clinical efficacy potential, synergistic drug-drug interactions like improve in cholinergic and cognitive functions in treating AD (Anand R et al., 2014). The condition of AD includes disorientation, increased apathy, deterioration of virtually all intellectual functions, decrease in speech function, loss of memory progressively, and gait irregularities. Alzheimer diseases are also known as dementia or cognition disorders.

The beta-amyloid peptide (BAP), having amino acid residues of 39 to 42 (BAP), significantly develops AD. The availability of the herbal drugs is being used in the management of AD to some extent as because AD is not a curable disease. The scavenging of the free radicals which were generated during progression and initiation of AD are possible due to the natural antioxidants, like vitamin C, vitamin E, and beta-carotene. The nerve transmitter like acetylcholine shortage is considered to be the main cause of memory loss in the brain. By inhibiting the acetyl cholinesterase enzyme activity, which breaks down or splits the transmitter substance in the brain, as a result it can be possible in increasing the level of the transmitter like acetylcholine in brain. By breaking down the transmitter acetylcholine or messenger the development of AD can be inhibited (Jayaprakasam B et al., 2010).

There are different types of dementia, in Alzheimer's disease 50 to 70% cases are due to dementia. The symptoms or the disorders which are associated with dementia or causes confusion, memory loss includes: The second types of dementia are known as the vascular dementia, which are due to the impairment caused by decrease in the flowing of blood to different parts of the brain. One type of dementia is developed due to the major stroke which blocks the flowing of blood to the brain tissue. Other type of dementia also known as 'multi-infarct dementia, which are caused due to the small stroke in which the tiny arteries are clogged. In these types of dementia, causes of significant symptoms individually are having too minor strokes, but combined effects of dementia are noticeable. In vascular dementia symptoms are associated with Alzheimer's disease.

Different problems include difficulty in following instructions, memory loss, and confusion. Vascular dementia associated with impairment occurs in 'steps' usually observed in a steady decline and slow state in Alzheimer's. Mixed dementias are the condition which occurs together with Alzheimer's disease and vascular dementia. The control of movement which impairs speech, stiffness and tremor are affected by Parkinson's disease. At later stage dementia was developed by Parkinson's disease. Alertness and attention starts with the dementia associated with the Lewy bodies. Alzheimer's disease affected individual experience some illness like tremors, muscle rigidity as well as visual hallucinations which are similar with the Parkinson's disease. Automobile accident or trauma causes physical injury which result in destroying or damaging the brain cells causing dementia symptoms like, other cognitive difficulties, behavioral changes and memory loss.

Creutzfeldt-Jakob disease (CJD) is a disease associated with the memory coordination and impairment which leads to the behavioral changes. This 'variant Creutzfeldt-Jakob disease' (vCJD) is a rare and fatal disease which were known as the disorder of human and believed that it was caused by consuming the meat of the cattle affected by 'mad cow disease. Alzheimer's is also having a disorder which is difficult to distinguish known as Frontotemporal dementia or Pick's disease. Before the memory loss there is change in disorientation and personality. Building up extra brain fluid leads to a disorder called as Normal pressure hydrocephalus (NPH) which is also a brain disorder and the cause of this disease are not known in most of the cases, which causes symptoms like memory loss, loss of ability to urine control, walking difficulties. The excess brain fluid associated with NPH disorder can be treated with surgery, by which the excess brain fluid can be removed and the NPH disease can be cured (Singhal Ak et al., 2012). Alzheimer's disease can be caused due to the genetic and environmental factors. Different environmental factor includes exposer to aluminium and silicon for a long time can develop the Alzheimer's disease (Shin RW, 1997). And other factors like chronic exposure to traumatic head injury, free-radical damage, and exposer to different toxins can also lead to Alzheimer's disease (Rosler M et al, 1998).

The pathogenesis of AD is due to the oxidative stress, homeostasis and biometal dysregulation like Fe, Zn, and Cu in cells of the brain (Kastenholz B, 2011). Aluminum plays a vital role in AD because long term exposure to the aluminum through the food sources like

antiperspirants, beverage cans, antacids, foil and cooking pots can be the leading cause to develop AD. Vascular diseases, including Alzheimer's and the dementia related to stroke are having risk factors like high blood pressure, diabetes and high cholesterol (Singhal Ak et al., 2012).

Different studies are having evidence that AD is caused due to the decrease in metabolic activity inside the brain. The recognized symptom of AD includes depression, anxiety, hallucinations, behavior disruption and insomnia. There are three stages in Alzheimer's disease which are having different symptoms;

Table 1: Different stages and symptoms associated with AD

Stages	Symptoms	Duration	Reference
Stage one	Changing of mood, recent loosing of memory; forgetfulness, confusion and disorientation.	The first stage of AD last upto two to four years.	(Kuller LH, 1996)
Stage two	Restlessness, hallucinations, muscle spasms, increased inability and irritability, decreased attention span, reduced memory; decrease in performing logic.	The second stage of AD lasts upto two to ten years.	(Kuller LH, 1996)
Stage three	Generally difficulty in swallowing, seizures, head injury, age, incontinence, skin infections.	The third stage of AD lasts upto one to three years.	(Kuller LH, 1996)

Table 2: Different types of diagnostic tests and their functions in AD

Diagnostic tests	Function
Mental Status Examination Diagnostic tests for Alzheimer's disease	For the diagnosis of dementia related disease like AD, Mental Status Examination (MSE) is the main diagnostic test.

The Mini-Cog test	These are the test which are administered within three minutes and are used in the Emergency Departments, for the Alzheimer's patients.
Urinalysis Urine test	It is also known as Routine analysis test of urine. These tests are carried out by the doctors in the suspected condition of AD or in any other type of dementia. Urinalysis (urine tests) is a method used for screening of abnormalities in case of AD patients. Urinalysis is the detection process in which the diseases having same symptoms or the condition associated with the dementia such as severe conditions associated with renal disease are detected.
Mild Cognitive Impairment (MCI)	Sometimes the disease onset like dementia may cause fear in peoples in which the people may experience mild impairment of the cognitive functions. MCI are the stage between the expected cognitive decline of aging and more serious decline of dementia. Based on history of cognitive examination the dementia conditions are diagnosed.
Visual Clues to Dementia Diagnosis	Indication of the strong visual clues can have a key role to identify the suffering of the people from dementia like AD. But only one aspect of presentation and human behavior are provided by the visual clues which are important in diagnosis of AD.
Lumbar Puncture test	Lumbar Puncture test is not a common test of dementia but it helps in revealing rare diseases which are used to mimic the signs of dementia.
The Mini Mental State Examination (MMSE)	MMSE are the most common and possible diagnostic procedure for dementia which is used to diagnose the memory related problems like dementia (Singhal Ak et al., 2012).
The electroencephalogram (EEG)	The EEG are the most commonly used diagnosis process in AD. In case of AD patients the brain waves diffuse and slows down symmetrically, which are registered in EEG. It is useful in diagnosing brain disorders, epilepsy and seizure disorders (Kuller LH, 1996).

Herbal Drugs or Plants Used Against Alzheimer`s Disease.

There are some herbs which act excellently to slow down the degeneration of the cells caused due to AD inside the brain. Therefore, by the use of these herbal drugs the ability of the brain to function is enhanced and also it provided the stability when used consistently like Guduchi, Amalaki, Musta Arjun, Kutaj, Pancha-Tikta-Ghruta, Gugguli, Vacha, Convolvulus pluricaulisj, Galo Satva, Ashwagandha, Padma (Nelumbo nucifera), Shankhpushpi, Yashtimadhuk.

There are some other medicinal herbs which are found effective in treating AD and there related symptoms are treated by some medicinal herbs like; Bacopa monniera, Clitoria ternatea L.(Leguminosae), Angelica archangelica L. (Umbelliferae), Codonopsis pilosula Franch (Campanulaceae), Curcuma longa L. (Zingeberaceae), Crocus sativus L. (Iridaceae), Acorus calamus L. (Araceae), Wettst. (Scrophulariaceae), Ginkgo biloba L. (Ginkgoaceae), Withania somnifera L (Solonaceae), Terminalia chebula L. (Combretaceae), Salvia officinalis L (Lamiaceae), Centella asiatica L (Umbelliferae), Celastrus paniculatus Willd. (Celastraceae), Piper methysticum Frost (Piperaceae), Rosmarinus officinalis (Lamiaceae), Melissa officinalis L (Lamiaceae), Glycyrrhiza glabra (Fabaceae), Galanthus nivalis L. (Amaryllidaceae), Huperzia serrata (Lycopodiaceae), Commiphora whighitti (Burseraceae), Lipidium Meyenii Walp (Brassicaceae), Serrate clubmoss, Acorus calamus L. (Araceae), Tinospora cordifolia (Menispermaceae), Angelica archangelica L.(umbelliferae)

Table 3: Herbal Drugs used against AD

Sl.No.	Herbs	Function	References
1	*Curcuma longa L. (Zingiberaceae)*	It is responsible in suppressing IL-1ß which decreases the Aß plaque burden and oxidative damage. This herb is also having neuroprotective action on apoptic gene expression and inflammatory action in AD. *Curcumin* helps in reducing the amyloid pathology and oxidative injury associated with AD.	(Singhal Ak et al., 2012; Elias EJ et al., 2010).
2	*Bacopa monniera Wettst. (Scrophulariaceae)*	It is found effective in treating the cognitive functions in case of patients with Alzheimer's disease, and it was concluded that the herb could be	(Goswami S et al., 2011).

		effective in AD patients	
3	*Centella asiatica L. (Umbelliferae)*	Its leaf extract are used for the improvement of memory, as an alternative medicine for the treatment of AD.	(Singhal Ak et al., 2012).
4	*Ginkgo biloba L. (Ginkgoaceae)*	It is having cholinergic and neuroprotective action as well as helps in protecting against the damage caused due to the Aß protein-induced oxidative damage as a result the oxygen species are trapped, prevents lipid oxidation and hydrogen peroxide are degraded. It is having vasorelaxing property which inhibits the aggregation of platelet, lowers the blood pressure and enhances the circulation in the body.	(Singhal AK et al., 2012).
5	*Adhatoda vasica*	*Adhatoda vasica* extract is having acetylcholinesterase inhibition activity and possess reversible enzyme effect against AD.	(Kumar S et al., 2011).
6	*Withania somnifera (Solanaceae)*	*Withania somnifera* consists of glycowithanolides which increase glutathione peroxidase, catalase and superoxide dismutase. *Ashwagandha* possess Nervine tonic and boosts as well as improve energy. It inhibits AChE in concentration-dependent manner	(Kumar S et al., 2011).
7	*Urtica dioica L. (Clusiaceae)*	It helps in decreasing inflammation and consists of mineral boron which are used to increase the levels of estrogen hormone inside the body. It is found effective in case of short-term memory and the mood is elevated in patients with AD. It is also known as Stinging Nettle and are used in hayfever which is an allergic disorder.	Yalla Reddy K et al., 2010).
8	*Bertholettia excelsa (Lecythidaceae)*	It contains lecithin in major concentration containing choline as the acetylcholine building block as a result improves the acetylcholine concentration in patients with AD	(Keyvan D et al., 2007).
9	*Collinsonia canadensis*	The breaking down of acetylcholine is stopped by Horsebalm (*Monarda*) and having thymol and	Yalla Reddy K et al.,

	(Lamiaceae)	carvacol as the chemical constituent which are used in case of AD. The blood-brain barrier did not allow the harmful compounds to reach to the brain tissue, so this herb helps in preventing harmful medicines to the brain.	2010).
10	*Salvia officinalis (Lamiaceae)*	These herbs are also known as sage and are commonly used medicinal herb in assisting the brain to fight against AD. Sage consists of different antioxidants like rosmarinic and carnosic acid which are responsible for protecting the oxidative stress in brain hence, they are used in treating AD.	(Singhal AK et al., 2012).
11	*Rosmarinus officinalis (Lamiaceae)*	*Rosemary (Satapatrika)* has both anti-inflammatory as well as antioxidant activity and consists of natural COX-2 inhibitors like; thymol, ursolic acid, carvacrol, eugenol, Apigenin, oleanolic acid which are used in case of AD. The substances with strongest antioxidant property are ferulic and carnosic acids present in this herb are used to treat AD.	(Singhal AK et al., 2012).
12	*Melissa officinalis L (Lamiaceae)*	It acts by inhibiting acetyl cholinesterase and having antioxidant activity. It helps in memory sharpening, improving the cognitive decline temporarily and in the improvement of mood in case of Alzheimer's patients.	(Ahn JY et al., 2010).
13	*Matricaria recutita (Asteraceae)*	It is also known as German Chamomile which helps in stimulating the brain, calming the nerves, insomnia counteracting, and digestion aid, and break down the mucus in lungs and throat. Chamomile used in relieving anxiety, higher dose of Chamomile causes drowsiness.	Yalla Reddy K et al., 2010).
14	*Glycyrrhiza glabra (Fabaceae)*	Alzheimer's disease are caused due to memory loss, and senile plaques having amyloid-ß peptide (Aß). It is having a protective effect against the brain cell	(Sener B and Orhan I, 2005).

		death caused due to Aβ fragments. Brain cell death is prevented by the root extract of licorice in case of AD.	
15	*Galanthus nivalis L. (Amaryllidaceae)*	The chemical constituent present in Galanthus nivalis is Galanthamine, which are the Acetyl cholinesterase (AChE) inhibitor and isoquinoline alkaloid which are involved in treating AD. It is an AChE enzyme inhibitor and a long-acting herb which is a nicotinic acetylcholine receptor modulator as a result can be used in treatment and prevention of AD.	(Bores et al., 1996).
16	*Huperzia serrata (Lycopodiaceae)*	It is used to enhance the memory which contains a group of alkaloid known as 'Lycopodium alkaloids' which is a potent, reversible and selective AChE inhibitor. Huperzine-A is used in the treatment of AD as a therapeutic agent and also used in improving the learning capacity, concentration and memory in AD. In the brain of AD patient's blood, the reduced abnormal high radical activity were reduced by Huperzine-A.	(Ranjan N and Kumari M, 2017; Yalla Reddy K et al., 2010).
17	*Tinospora cordifolia (Menispermaceae)*	*Tinospora Cordifolia* (*Guduchi*) acts by improving memory and learning in normal as well as memory defective animals. *Tinospora Cordifolia* enhances cognitive function by synthesizing acetylcholine and immunostimulation.	(Lannert H and Hoyer S, 1998).
18	*Collinsonia canadensis (Lamiaceae)*	The breaking down of acetylcholine is stopped by Horsebalm (*Monarda*) and having thymol and carvacol as the chemical constituent which are used in case of AD. The blood-brain barrier did not allow the harmful compounds to reach to the brain tissue, so this herb helps in preventing harmful medicines to the brain.	Yalla Reddy K et al., 2010).
19	*Magnolia officinalis*	*Magnolia Officinalis* (*talauma*) barks are used	(Singhal AK

	(Magnoliaceae)	traditionally in enhancement of memory as well as treating stroke, neurosis, dementia and anxiety. *Magnolia Officinalis* helps in inhibiting AChE and scopolamine induced memory loss. In *in-vitro* and *in-vivo* models *M. officinalis*, *honokiol* and *magnolol* possess antioxidant activity in methanol extract.	et al., 2012).
20	*Ginseng (Araliaceae)*	Panaxi ginseng's consists of panaxsaponin, oleanolic acid, protopantriol, and protopanaxadiol which can improve cognitive, scopolamine induced memory improving property and psychomotor activity. These herbs are also used in increasing cholinergic function in the brain, decreasing the Aβ level, and in neuronal damage repairing.	(Ahn JY et al., 2010; Singhal AK et al., 2012).
21	*Serrate clubmoss*	*Serrate clubmoss* are the herb which is a reversible, potent and selective acetyl-cholinesterase inhibitor. *Serrate clubmoss* is a medicinal herb which is having Huperzine-A extracted from the herb. Huperzine A is having different advantages like it improves the disturbance caused due to behavior, functional activities, and cognitive functions, without any side effect for AD patients.	(Ahn JY et al., 2010).
22	*Acorus calamus L. (Araceae)*	*Acorus calamus* also known as sweet flag, which are used in enhancing the memory, treating loss of memory and modifying the behavior. *Acorus Calamus* acts by inhibiting the acetyl cholinesterase (AChE) enzyme activity and having major amount of α-and ß-asarone. It possess pharmacological activities like antioxidant, antispasmodic, anti-inflammatory, immunosuppressive, cardiovascular hypolipidemic, cytoprotective, antimicrobial, anthelmintic, and antidiarrheal activity.	(Lannert H and Hoyer S, 1998).
23	*Angelica archangelica*	*Angelica archangelica* (Laghu Coraka) is having other name called as Dudhachoraa do not have any	(Singhal AK et al., 2012).

	L.(umbelliferae)	side effects as compared with drugs like insomnia, nausea, stomach pain etc. *Angelica archangelica* are having different compounds having same action like the AD drugs. The phytochemical present in *Angelica archangelica* increases flowing of blood to the brain and in an *in-vitro* study it was observed that methanolic extract of chloromethane sub-fraction inhibited the enzyme activity of AChE.	
24	*Lipidium Meyenii Walp (Brassicaceae)*	*Lipidium Meyenii* also called as Maca and having learning and memory enhancing property. Black maca are used in improving memory impairment which are caused due to ovariectomy in experimental studies as well as its antioxidant and inhibitory AChE activities. Black maca are also having memory and learning enhancing properties in OVX (ovariectomized) mice and having reducing properties like reduction of AChE and LPO (Lipid peroxidation) level in OVX mice.	**(**Fu LM and Li JT, 2009).
25	*Commiphora whighitti (Burseraceae)*	*Commiphora whighitti* are the medicinal herb which is having main constituent of guggulipid called as guggulsterone. The guggulipid possess enhancing property which helps in memory enhancing and leads to improve memory in deficits like scopolamine-induced memory disorder. *Commiphora whighitti* helps in decreasing the level of acetylcholine transferase in hippocampus part of the brain and impairs the learning and memory. *Commiphora whighitti* herbs is higher effective in functioning of memory and have maximum potential in treating disorders related to dementia.	(Rubio J et al., 2011).

Therapeutic strategies of AD using herbal drugs

The uses of herbal drugs are having more attention than that of synthetic drugs. Herbal drugs are having fewer side effects so considered as the safest drug and used symptomatically in treating different diseases including AD. Based on the therapeutic action targets and the mechanism of drug action different herbal medications are used in the prevention and treatment of AD (Skolnick AA, 1997). **Antiamyloid effects**

In the pathology of AD, oligomer levels of Aβ targeting are the main area for research (Ono K et al., 2006). Different therapeutic strategies are followed to decrease the oligomer levels of Aβ by clearing Aβ level, Aβ generation inhibition and by reduction of soluble Aβ level in the brain (Huang Y and Mucke L, 2012).

In case of AD different alteration are observed in cellular action such as mitochondrial dysfunction, inflammatory action, tau hyperphosphorylation, synaptic failure, and damage in oxidative stress which results in Aβ production (Maccioni RB et al., 2010). In the brain the herbal drugs perform destabilization and aggregation of structured Aβ fibrillar actions (Agrawal R et al., 2010) (Goel A et al., 2016). The herbal drugs which possess anti-amyloidogenic action will be effective in treating AD (Syad AN and Devi KP, 2014) (Ono K et al., 2006) (Perry EK et al., 1998).

There are different food constituents which are edible and also possess anti-amyloidogenic actions like extract of dry ginger (*Zingiber officinale)*, extracts of mulberry leafs, caper bud extracts *(Capparis spinosa),* ellagic and garlic acid (Syad AN and Devi KP, 2014) (Perry EK et al., 1998) (Mathew M and Subramanian S, 2014).

In a study on APP/PS1 mouse model in AD, it was observed that the root extract of the herb *Withania somnifera* with withanoside and withanolides as the chief constituent having different actions in brain such as deficits in behavior or behavioral changes, reversed oligomers reversed pathology of plaque, reverse ß-amyloid peptide (Aβ) accumulation, when the herb was administered orally (Sehgal N et al., 2012).

β- and γ-secretase inhibitors.

APP processing are altered due to the accumulation of Aβ by γ- and β-secretase which results in formation of Aβ oligomers and γ- and β- (BACE-1) secretase targeting is having therapeutic effect in AD (Descamps O et al., 2013). (Anekonda TS and Reddy PH, 2005).

From the husk of pomegranate Punicalagin and Ellagic acid are obtained. Granatum Punica L. (Lythraceae) is the β-secretase inhibitor. Alkylated lipophilic flavanone compound obtained from the herb S.flavescens Aiton (Fabaceae) noncompetitively inhibit BACE-1 activity.

Smilax china (Smilacaceae) consists of dried rhizomes which help in BACE-1 inhibition activity as a result reduce the AD progression. Polyphenol black and green tea help in BACE-1 inhibition activity as a result reduce the AD progression (Anekonda TS and Reddy PH, 2005).

In a study it was reported that Epigallocatechin-3-gallate green tea polyphenol inhibit level of Aβ through γ- and ß-secretase induced LPS elevation activity (Calcul L et al., 2012). In another study Actaea racemosa extract have isolated triterpene which helps in decreasing toxicity induced by Aβ by modulating γ-secretase activity (Anekonda TS and Reddy PH, 2005).

Tau hyperphosphorylation Targeting

The microtubules present in neurons are normally stabilized by the tau proteins (Calcul L et al., 2012). The tau aggregation was observed in AD, those are related to the AD conditions that occur because of the hyperphosphorylation of the tau abnormally. Tauopathies are the diseases those are associated with the aggregates including AD. Post-symptomatic AD can be treated by using tau protein targeting that may be effective, includes inhibition of tau aggregates formation, regulation of tau by kinases, tau microtubule stabilization, by using chaperones controlling the degradation of tau (Calcul L et al., 2012). Hence, for the anti-tau properties, extracts of herbal drugs are found to be useful in case of AD. The extracts of turmeric (Curcuma longa) consist of linear diarylheptanoid and possess antioxidant properties which reduces the tau and Aβ level as well as increases the anti-inflammatory cytokine IL-4 significantly in case of Aβ- overexpressing mice (Calcul L et al., 2012).

In a study root bark extract of bayberry consists of macrocyclic diarylheptanoid and (+)-aR, 11S-myricanol are found effective in decreasing the level of tau (Anekonda TS and Reddy PH, 2005).

The herbal extract of Cinnamon (Cinnamonium zeylanicum) acts by inhibiting the aggregation of tau and also possesses attributing inhibitory action for both the compounds like procyanidin and cinnamaldehyde oligomers of epicatechin/catechins (Calcul L et al., 2012).

The paclitaxel are the herbal drugs obtained from the herb Pacific Yew, Taxus brevifolia are found to be effective in preventing or curing neurodegenerative tauopathy in case of transgenic mouse model by counteracting the ‘loss-of-function’ effects related to pathology of tau (Calcul L et al., 2012).

Antiapoptotic and Antioxidant effect

The free radical (ROS/RONS) generations in AD by activation of microglial cells via the oligomer Aβ which are caused due to the oxidative stress (Veerendra Kumar MH and Gupta YK, 2003).

The decrease in antioxidant activity like p53 induced ROS activity, reduction in apoptosis, reduction of cytochrome c level are prevented, caspase-3 and bax activity, DNA fragmentation attenuated, reduction in toxic cyclooxygenase COX) formation, cells were protected against the lipid peroxidation, and mitochondrial function restored (Rahman K, 2007). The antioxidants which are endogenous have both activities like enzymatic (e.g., catalase, glutathione peroxidase, and superoxide dismutase) and non-enzymatic (e.g., flavonoids, carotenoids, ascorbic acid or vitamin C, α-tocopherol or vitamin E, and glutathione), are not enough in treating AD (Lobo V et al., 2010). In some studies it was observed that in the treatment of AD, combination of antioxidants like vitamin E, Ginkgo biloba, ascorbyl palmitate and pycnogenol acts by decreasing the apoptotic cells present in hippocampus part of the brain in ApoE-deficient mice (Iuvone T et al., 2006) (Rahman K, 2007).

The most well known drug known to possess weak AChEs inhibition activity, anti inflammatory effects and antioxidant activity are sage obtained from the herb Salvia officinalis (Iuvone T et al., 2006). The rosmarinic acid reduces deleterious activities that are induced by Aβ oligomers are caspase-3 activation, DNA fragmentation, tau protein hyperphosphorylation, lipid peroxidation and ROS formation (Iuvone T et al., 2006)

An Ayurvedic drug like Panchagavya Ghrita, has been proved to attenuate seizures, cognitive impairment, and oxidative stress in seizures induced by pentylenetetrazole in rats (Joshi R et al., 2015).

Curcumin decreases the myoclonic jerks number, increases the latency to myoclonic jerks, generalized and significantly tonic-clonic seizures, clonic seizure, and also improve the score of the seizure. Significantly, pretreatment by curcumin results in reversible changes like neuronal injury, oxidative stress and apoptosis induced by kindling of PTZ (Saha L et al., 2016).

Anti-inflammatory effect

The accumulations of Aß and tau aggregation are found in compartments with neurons inside the brain which causes inflammation in neurons, dysfunction in synapse, and loss in neurons.

In many studies activation of microglial cells, the inflammatory process execution by increase in production of cytokine, increase in interleukins (IL)-1β and enhanced tumor necrosis factor (TNF)-α release are caused by accumulation of Aβ (Izzo AA and Capasso F, 2007). There are some herbal drugs that are having anti-inflammatory potential which are found effective in treating ROS-mediated inflammatory disease such as AD. The traditionally used Chinese drug Dipsacus

asper Wall (Dipsacaceae) which are the perennial medicinal herb and are used in treating different diseases like fractures in bone, rheumatic arthritis, threatening abortion, and traumatic hematoma. A bioactive saponin triterpenoid obtained from *D. asper* rhizomes are having different inhibitory actions in the brain of the rats like inhibiting the cyclooxygenase 2 (COX-2), IL-1ß, and TNF-α expressions (Jung KY et al., 1993).

In different studies in vivo there are THP-1 monocytic cells which stated that curcumin are having inhibitory action which inhibits Aß-induced protein Erg-1 activity and DNA-binding activity of Erg-1 helps in reducing monocyte inflammation by inhibiting Erg-1 activity.

Phosphodiestrase inhibitors (PDEIs)

PDEIs are having different pharmacological activities like anti-depressant, relaxation of the smooth muscle, vasodilator, anti-inflammatory, and enhancing the cognitive functions. There are some herbal compounds which possess PDEIs activity are saponins, flavonoids and alkaloids (Rahimi R et al., 2010).

Flavonoids

Favonoids are having different pharmacological effects like antiallergic, anti-cancer, anti-hepatotoxic, anti-mutagenic, antispasmodic, anti-inflammatory, anti-oxidant, antiviral activity, antiulcer and provides protection in case of cardiovascular mortality. These are used to inhibit, protein kinase C, PDE, and xanthine oxidase. Herbs like *Rheeoia* spp, *Sophora* spp., and *Euchresta japonica,* and *Scutellaria* spp have cAMP PDE inhibition activity in its aqueous extract. Natural flavonoids like Naringenin are having PDEI, 4 and 5 inhibitory actions which are obtained from the citrus fruits. Flavonoid like Isoliquiritigenin present in *Glycyrrhiza glabra* are having PDEIs effects. *Caesalpinia sappan, Ventilago denticulate, Bauhinia winitii, Berchemia floribunda, Betula alnoids, Plantago asiatica, Senna surattensi, Hiptage benghalensis, Butea monosperma, Matricaria recutita, Crataegu oxyacantha, Butea superba, Ginkgo biloba,* and *Leea indica* are the herbal drugs possess PDEIs activities (Temkitthawon P et al., 2008).

Alkaloids

Alkaloid content of *Ailanthus altissima* and *Picrasma quassiodes* are having cAMP PDEs inhibitory activity. Viscolin which are obtained from *Viscum coloratum* also have PDEIs activity. Neferin obtained from *Nelumbo nucifera* cAMP concentration are enhanced in cavernosum tissue present in rabbit by PDE inhibitory action (Hwang TL et al., 2006).

Saponins

These are the surface active compounds or non-volatile group of glycosides which possess properties like, antiviral, antileishmanial, antimutagenic, anti-

inflammatory, hepatoprotective, and hemolytic activities. *Lilium henryi, Lilium regale,* ethanol extract of *Periandra dulcis,* and *Allium chinense* herbs had saponin content which possesses PDEIs activity (Mimaki Y et al., 1993).

Essential Oils

Essential oils have pharmacological properties like carminative, antispasmodic and antimicrobial activities. The Resins and essential oils present in *Senecio eriophyton, Satureja parviflora* and *Haplopappus rigidus,* possess PDEIs activity (Andersen OM and Markham KR, 2005).

Anticholinesterase activity

The acetylcholines are breaking down by the enzyme acetyl cholinesterase (AChEs) and AChE inhibitions are used in the neurological diseases like AD (Das A et al., 2002). The herbs like *Salvia miltiorhiza* root extracts, and the *Ginkgo biloba* whole plant extracts, are having cholinergic activity and are used in AD.

Herbal compounds that alter BBB.

BBB alterations are caused due to accumulation in Aß. Breakdown of BBB and neuronal dysfunction are caused due to neuroinflammation. Generations of ROS are caused due to accumulation in Aß. Herbal compound like Curcumin helps in protecting the integrity of BBB. Different flavonoid protects against neuronal dysfunction and ROS. The herbal drug *Withania somnifera* root extract inhibit NO mediated inflammatory apoptotic pathway and improves cognitive functions and convulsive disorders (Baitharu I et al., 2013).

Table 4: FDA-approved herb-derived compounds which are used against AD and their mechanism of action

Herbal compounds	Mechanism of action
Curcumin	Anti-ß-secretase, anti-inflammatory, anti-amyloidogenic, anti-cholinesterase activity (Rajakrishnan V et al., 1999).
Rivastigmine	In the hippocampal cortexand region it inhibits AChE (Polinsky RJ, 1998).
Huperzine A	Inhibit AChE reversibly and helps in cognitive deficits restoring (Ha GT et al., 2011).
Resveratrol	Plaque formation are reduced by impairment of cognitive function and oxidative stress (Karuppagounder SS et al., 2009).
Galantamine	Ach nicotinic receptor potentiation and inhibits AChE reversibly (Maelicke A et al., 2010).

Table 5: Herbal drugs with anti-amyloid properties

Herbal drugs	Mechanism of action
Uncaria rhynchophylla Miq. (Rubiaceae)	It possesses inhibitory action against peptides like Aß 1-42, Aß 1-40 and Aß fibrils (Fujiwara H et al., 2006).
Paeonia suffruticosa Andrews (Paeoniaceae)	It inhibits formation of Aß fibril and helps in promoting performed Aß fibril defibrillation (Tabuchi M et al., 2009).
Crocus sativus L. (Iridaceae)	It inhibits amyloid fibril formation (Papandreou MA et al., 2006).
Ecklonia cava Kjellman (Lessoniaceae)	It inhibits the Aß oligomer formation obtained from soluble monomers as well as helps in reducing Aß peptide production from APP (Kang IJ et al., 2011).
Curcumin from *Curcuma longa* (Lessoniaceae)	It possesses antioxidant and anti-inflammatory actions in different *in vitro* and *in vivo* animal models and also promotes preformed fibril disaggregation (Kumar A et al., 2007).
Huperzine A from *Huperzia serrata*	It helps in AChEs inhibitory action and are used in anti-inflammatory and analgesic activity. It is a FDA of China approved therapy in 1994 for treatment in AD. In different clinical studies it was observed that it helps in memory improvement like activities involved in our day to day life and also cognitive improvement in AD. It is also used in impairing the memory associated with the disorder in sleeping in insomniacs, vascular dementia, and schizophrenia (Zhang HY, 2012).
Ginkgo biloba	Its leaves are used for the impairment of memory and vascular peripheral disorders. It also exerts mechanisms associated with neuroprotective like Aß aggregation inhibition, lipid peroxidation inhibition, apoptosis attenuation and anti-inflammatory effects (Luo Y, 2006).
Lemon balm (*Melissa officinalis)*	It helps in memory restoring and long life. The leaf of the herb contains a) monoterpenes which contain weak anti-AChEs action. b) phenil carboxylic acid contains rosmarinic acid which has combined effect like antiapoptic, anti-oxidative, anti-amyloidogenic activities (Houghton PJ and Howes MJ, 2005).

Table 6: Herbal Drugs with AChE action and there plant parts used

Herbal drugs	Plant parts used
Abutilon indicum Linn.	Whole plant parts are used (Orhan I et al., 2004).
Acanthus ebracteatus Vahl.	Aerial parts of these plants are used (Orhan I et al., 2004).
Aegle marmelos Linn.	The pulps of the fruits are used (Orhan I et al., 2004).
Albizia procera (Roxb.) Benth.	Barks are used (Orhan I et al., 2004).
Bacopa monniera Linn.	Whole parts of the plant are used (Orhan I et al., 2004).
Butea superba Roxb.	Root barks are used (Orhan I et al., 2004).
Buxus sempervirens Linn.	Whole plant parts are used (Perry N et al., 1996).
Cassia fistula Linn.	Roots are used (Orhan I et al., 2004).
Carthamus tinctorius Linn.	Flowers are used (Perry N et al., 1996).
Ginkgo biloba Linn.	Whole plant parts are used (Ingkaninan K et al., 2003).
Melissa officinalis Linn.	Aerial parts of these plants are used (Orhan I et al., 2004).
Nelumbo nucifera Gaertin.	Stamens of the plant are used (Orhan I et al., 2004).
Rhododendron luteum Sweet.	Whole plant parts are used (Perry N et al., 1996).
Salvia officinalis Linn.	Whole plant parts are used (Kurz A and Van Baelen B, 2004).
Adhatoda Vasica.	Leafs of the plant are used (Perry NS et al., 2000).

Table 7: Herbs with anti-apoptotic and antioxidant properties

(A) *In vitro* studies

Herbal Drugs	Models	Mechanism of action
Extract of *Curcuma longa*	Rat PC12 cells; H_2O_2, Pyrogallol.	The cells were protected from apoptosis and the enzymes anti-oxidant activity were increased (Koo BS et al., 2004).
Ginsenoside Rg1 (*vitis vinifera)*	Cortical cells obtained from SD rats.	Helps in reducing cell death or apoptosis (Wang B et al., 2014).

Epigallocatechin gallate (*Camellia sinensis*)	Hippocampal neurons from Sprague-Dawley rats; Aß25-35.	It protects the cells from cell death or apoptosis (Choi YT et al., 2001).
Extract of Bacopa monniera	Astrocytes from Wistar albino rat brains; S-nitroso-N-penicillamine.	Formation of ROS and fragmentation of DNA are inhibited (Bhattacharya S et al., 2000).
Extract of Aged garlic and S-allylcysteine	Rat PC12 cells; Aß25-35.	Fragmentation of DNA, caspase-3 and ROS activity are suppressed; cells are protected from apoptosis (Colín-González AL et al., 2012).

(B) *In vivo* studies

Herbal Drugs	**Models**	**Mechanism of action**
Extract of *Centella asiatica*	Male Wistar rats; ICV-STZ model of SAD.	Oxidative stress is prevented and cognitive behavior are increased (Kumar A et al., 2011).
Pycnogenol, Ascorbyl palmitate, Vitamin E	ApoE-deficient mice.	Apoptotic cells and periodic acid Schiff positive inclusion bodies are reduced and the life spans are increased (Veurink G et al., 2003).
EGb 761(*Ginkgo biloba)*	Vitamin E deficient Wistar rats.	Small-sized synapse proportion and mitochondrial density is increased (Beritoni-Freddari C et al., 2002).
Quercetin, Kaempferol	Mutant C. elegans worm.	Attenuated age-related accumulation of ROS (Smith JV and Luo Y, 2003).
Resveratrol, S-allylcysteine derived from the bulb of garlic (*Allium Sativum*)	Male Wistar rats; ICV-STZ model of SAD.	Oxidative stress and ICV STZ-induced cognitive impairment are prevented (Colín-González AL et al., 2012).

Table 8: Herbal Nanoparticles used against AD

SL.No.	Herbs	Function	References
1	*Magnolia officinalis*	The Magnolol or honokiol that are derived from the *Magnolia officinalis possesses* choline acetyltransferase enhancing effect as well as helps in inhibiting the acetylcholine cleavage.	(Lee et al., 2010; Liou et al., 2003).
2	*Lepidium meyenii*	It helps in enhancing the memory function in case of patients with AD.	(Rubio et al., 2007; Rubio et al., 2011).
3	*Tinospora cordifolia* (Giloy)	It acts by enhancing the memory in case of memory loss as well as normal patients or animals.	(Adams and Gmünder, 2007).
4	*Convolvulus pluricaulis* (Shankhpushpi)	Administration of these herbs was observed to have nerve calmness activity which helps in regulating the synthesis of stress hormones.	(Bihaqi et al., 2011; Nahata et al., 2008)
5	*Curcuma longa* (Turmeric)	It is having anti-inflammatory activities which are correlated in reducing the risk of AD.	(Aggarwal and Harikumar, 2009; Breitner et al., 1995).
6	*Glycyrrhiza glabra*	In case of dementia induced by scopolamine, these plants proved to have memory enhancing properties.	(Parle et al., 2004; Dhingra et al., 2004).
7	*Centella asiatica* (Gotu Kola)	Its extracts acts by reversing β-amyloid pathology and also modulates the components of oxidative stress response as well as enhancing the longevity, memory and intellect.	(Cervenka and Jahodar, 2006; Shinomol and Bharath, 2011).

Alternative approaches used against AD

The alternative measures and the management of AD are the main interest for the researchers. The diet which consists of antioxidant, anti-inflammatory and different neuroprotective agents can help in decreasing the risk of AD development. There are four pillar guidelines which were discussed by Alzheimer's Prevention Foundation International (APFI) were used in management and treatment of AD. The vitamins and diet are included in the first pillar, proper stress management were included in the second pillar, the third and fourth pillar includes yoga, exercise of brain and body, brain aerobics, physical and mental exercise (Kelley BJ and Knopman DS, 2008)

Prevention of AD				
Reduced smoking	Minimizing alcohol	Consumption of balanced diet like fruits, leafy vegetables, nuts, berries, beans etc.	Exercising at least 150 minutes every week and maintaining healthy weight.	Controlling blood pressure at healthy level, brain or mental exercise, dietary and nutritional therapy.

Limitations of using herbal drugs

The herbal drugs are more effective than the synthetic drugs. The use of herbal drugs in high dose can produce severe adverse effects like hepatic failure and can also lead to toxicity (Kelley BJ and Knopman DS, 2008). Herbal drugs are not having statistically significant efficacy of the clinical trials (Izzo AA and Capasso F, 2007).

Herbal drugs should possess high range of targets like production of Aß, neuroinflammation, Aß-mediated oxidative stress, fibrillation and the other limitation of herbal drugs are less ability to cross BBB (Kelley BJ and Knopman DS, 2008). The main challenge in the development of therapeutic agents obtained from the herbal products should possess active compounds in more amounts.s

Conclusion

Herbal drugs play a vital role in treatment of different memory related diseases like Alzheimer's disease or dementia. Herbal drugs possess fewer side effects or adverse effects as compared to synthetic drugs so they have a beneficial pharmacological action in treating different diseases. Many studies reported that different herbal plants are used in treating Alzheimer's disease like Ginkgo biloba, Glycyrrhiza glabra, Melissa officinalis, Centella asiatica, Tinospora cordifolia, Withania somnifera, Salvia officinalis, Bacopa monnieri, etc. There are some studies including active principle identification which helps in improving clinical trial validation. There are two long-term remedies for the patients with loss of memory, Alzheimer's disease and Dementia which includes Ginkgo/acorus therapy (with gingko and salvia) and Huperzine A extract with Vinpurazine. The current review provided evidence on the use of herbal drugs (included in European Medicine System, Chinese Medicine System, Indian Medicine System, etc.) and their effectiveness in treating different diseases like dementia, memory related diseases and AD moreover applications of herbs with anti-apoptotic and antioxidant properties in various *invivo* and

invitro studies, different diagnostic tests for AD, mechanism of action associated with AD, stages and symptoms of AD, management of Alzheimer disease, therapeutic strategies of AD using herbal drugs, different herbal compounds altering BBB, herbs with AChE action and there plant parts used, alternative approaches used against AD, different herbal nanoparticles used in AD as well as limitations of using herbal drugs. Future multicenter and large-scale studies are required for the determination of advantages of herbal drugs in treating cognitive deterioration of AD.

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