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Minireview

Therapeutic potentials of herbal drugs for Alzheimer's disease—An overview

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Alzheimer's disease (AD) is a well known progressive neurodegenerative disorder having complex pathophysiology. Currently, drugs that are used symptomatically in the treatment of AD include acetylcholinesterase inhibitors (AChEIs) (rivastigmine, galantamine, donepezil) and N-methyl D-aspartate (NMDA) receptor antagonist (memantine). Limited bioavailability of these drugs stresses continuity of search for novel therapeutics for this slow growing but complex disease. Herbal drugs are being used to treat memory related problems, including Alzheimer's from time immemorial. Both preclinical and clinical studies demonstrated the therapeutic potential of herbal drugs for the prevention of AD. Herbal drugs have been shown to be effective against Alzheimer's possibly due to their pleiotropic and multifaceted action that includes antioxidants, anti-inflammatory and neuroprotective action. This review highlights the therapeutic potential of herbal drugs for the treatment of AD.

Keywords: Acetylcholinesterase inhibitors; N-methyl D-aspartate receptor antagonist; amyloid beta; neurofibrillary tangles

Introduction

Alzheimer's disease (AD), is one of the most common neurodegenerative diseases worldwide, characterized by gradual memory loss and decline in cognitive performance[1]. The preponderance of this disease increases with age. Named after the German physician, Alois Alzheimer, who in 1906 first identified this disease, AD has two major hallmarks, amyloidal plaques and tangled fibers[2]. There are more than 36 million people worldwide suffering from AD[2].

Over the decade, researchers have tried to understand the various environmental, genetic, and other risk factors responsible for AD, and the pathophysiological events leading to formation of plaques and tangles in the brain[1]. Researchers have found that genetic factors as well as environmental factors believed to play an important role in the development of AD. Genetic factors include age, family history and heredity whereas environmental factors include long-term exposure to silicon or aluminum, chronic exposure to other toxins, free-radical damage and traumatic head injury[1,2]. Memory impairment is the major symptom of AD and usually involves behavioral changes that have been classified into three stages (Fig. 1)[2]. The diagnosis of AD is based on the presence of confirmed memory loss and the presence of one or more of the following cognitive deficits that is; apraxia (impaired ability for motor activities), aphasia (language impairment), agnosia (failure to recognize or identify objects) and impairment in executive functioning (the ability to plan, organize, sequence and abstract)[2].

Currently, the only available conventional treatment therapy approved by the United States Food and Drug Administration (USFDA), includes acetylcholinesterase inhibitors (AChEIs) (rivastigmine, galantamine, donepezil) and N-methyl D-aspartate (NMDA) receptor antagonist (memantine), to pharmacologically ameliorate the symptoms of AD[1-4]. Selegiline, normally used for the treatment of Parkinson's disease (PD) is sometimes used in AD also[1,4]. Previous studies have also shown the association between the use of estrogen replacement therapy in postmenopausal women and the decreased risk of developing AD[1,3]. Because of its antioxidant activity, estrogen therapy improves memory in AD[5]. Some non-steroids anti-inflammatory drugs (NSAIDS) such as ibuprofen also reduces the risk of developing AD. Long term use of NSAIDs such as aspirin, can decrease the inflammation in AD[1].

Complex pathophysiological mechanisms of AD provide a potential new insight that may help to identify new therapeutic lead compound for AD. Disease-modifying treatments that alter early pathogenic changes, prevent disease progression, and alter the natural course and outcome of AD are under

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various investigational phases of drug discovery program[6]. In the recent years, therapeutic potentials of complementary and alternative/herbal drugs has gained popularity and attract researchers' attention because of their market potential and currently assuming billion dollar worldwide market[7]. According to the World Health Organization (WHO), 80% of world populations rely on traditional remedies (mainly herbs) for the health care need. Besides, herbs/plants are best known as oldest friends of humanity. For centuries, herbs have been used as food and for medicinal purposes. Previous studies have shown that, herbs possess multifaceted action that includes antiamyloid, neuromodulatory, anti-inflammatory, antiapoptotic and antioxidant properties[7]. Recently, herbs have been tried for the treatment of neurodegenerative problems like AD. Mohan *et al.*[8], have shown that ethanolic extract of *Coriandrum sativum* L. protects against orofacial dyskinesia induced by tacrine, the anticholinesterase inhibitor used to improve memory in AD patients. Whole plant extract of *Bacopa monnieri* has significantly increased spontaneous locomotor activity and grip strength compared to *Mucuna pruriens* extract in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine induced Parkinsonian mice[9]. Further, *B. monnieri* extract showed improved the tyrosine hydroxylase activity, caspase-3 and expression of neurogenic gene in the substantia nigra region of the brain[9]. Similarly, dietary supplements and medicinal foods were also tested as memory enhancers and for the management of AD and related problems[10,11]. Table 1[12-16] shows various FDA-approved drugs that are obtained from herbal plant sources and which are currently in different phases of clinical trials and use for the treatment of AD targeting various pathological events.

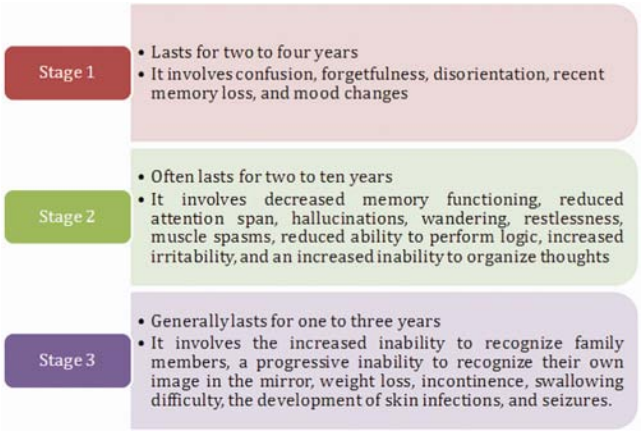

Fig. 1—Different stage of behavioral changes in Alzheimer's disease

This review discusses different herbal drugs that have interesting pharmacological efficacy with special reference to anti-Alzheimer activity of herbal drugs and their extracts.

Neuropathophysiology of AD

AD is pathophysiologically characterized by the presence of extracellular deposits of amyloid beta (Aβ) plaques (senile plaques) and intracellular accumulation of neurofibrillary tangles (NFTs) composed of hyperphosphorylated tau, leads to neuronal and synaptic loss and neurotransmitter dysfunction[5,17].

Aβ plaques majorly constitute toxic Aβ peptide surrounded by dystrophic neurites and activated microglia[1]. Aβ accumulation happens due to the altered proteolytic processing of amyloid precursor protein (APP) by β-secretase and γ-secretase which further leads the formation of soluble monomeric form of Aβ 42 that self-aggregates to form Aβ oligomers. These oligomers are known to be highly toxic in nature and responsible for the cause of synaptic dysfunction, oxidative stress and inflammation[3,18] (Fig. 2).

Table 1—List of herbs-derived compounds that are FDA-approved and in clinical trials against AD

Herbal Drugs	Brand name	Plant source	FDA-approved	Clinical trials	MOA
Rivastigmine	Exelon	*Physostigma venensosum (Leguminosae)*	2000	-	Inhibits AChE in the cortexand hippocampal region[12]
Galantamine	Razadyne	*Lycoris radiata (L'Hér.) Herb (Amaryllidaceae)*	2001	-	Reversible inhibition of AChEand allosteric potentiation ofnicotinic ACh receptors[13]
Huperzine A	-	*Huperzia serrata (Lycopodiaceae)*	-	Phase III	Restores cognitive deficits by reversibly inhibiting AChE[14]
Curcumin	Longvida	*Curcuma longa L. (Zingiberaceae)*	-	Phase II	Anti-amyloidogenic, anti-inflammatory, anti-ChE, anti-β-secretase[15]
Resveratrol	-	*Vitis vinifera L. (Vitaceae)*	-	Phase III	Prevents cognitive impairments and associated oxidative stress by reducing plaque formation[16]

Therapeutic strategies using herbal drugs with anti-Alzheimer's activities

The herbal drugs for symptomatic treatment of AD have gained considerable attention over the years. Besides, Chinese traditional herbal therapy for the treatment and prevention of AD is not uncommon (accounts for 40%)[19]. Based on the mechanisms of action and therapeutic targets of various herbal drugs the therapeutic stratagies of AD (Fig. 3) are classified as given below.

Antiamyloid effect

In AD pathology, therapeutic strategies targeting Aβ oligomers level are one of the major areas of research. Various therapeutic approaches have been adopted such as decreasing Aβ oligomers level by inhibiting Aβ generation[5], and reducing soluble Aβ levels and clearance of Aβ from the brain[20]. It has been well documented that AD results into progression of various cellular changes like inflammatory responses, mitochondrial dysfunction, oxidative damage, synaptic failure and tau hyperphosphorylation. These cellular changes directly results into the production of Aβ[17]. Several herbs have been found to exhibit antiamyloidogenic activities (Table 2)[21-30]. In particular, they exhibit specific effects on aggregation and destabilization of preformed Aβ fibrillar structures in the brain[31,32]. Since the formation of fibrillar aggregates remains the most important pathophysiological event, the herbs with potential anti-amyloidogenic activity will be highly beneficial in developing novel drug leads against AD[11,20,33].

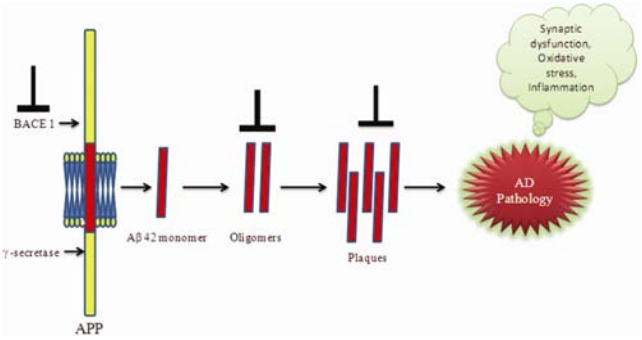

Fig. 2—Neuropathophysiological mechanism of generation of toxic Aβ 42 oligomers and AD related pathologies

Apart from the mentioned herbal drugs, researchers have also evaluated several edible food constituents for their antiamyloidogenic activities which include ellagic acid, garlic acid, dry ginger (*Zingiber officinale* Roscoe) extract, mulberry leaf extract and aqueous extract of caper (*Capparis spinosa*) buds[11,33-35]. Another study on APP/PS1 transgenic mouse model of AD shows that oral administration of extract of *Withania somnifera* root having withanolides and withanosides as main active constituents reversed behavioral deficits, plaque pathology, accumulation of β-amyloid peptides (Aβ) and oligomers in the brain[36].

β- and γ-secretase inhibitors

As Aβ accumulation results in altered proteolytic processing of APP by β- and γ-secretase leading to Aβ oligomers formation, targeting β- [also known as β-site APP cleaving enzyme 1 (BACE-1)] or

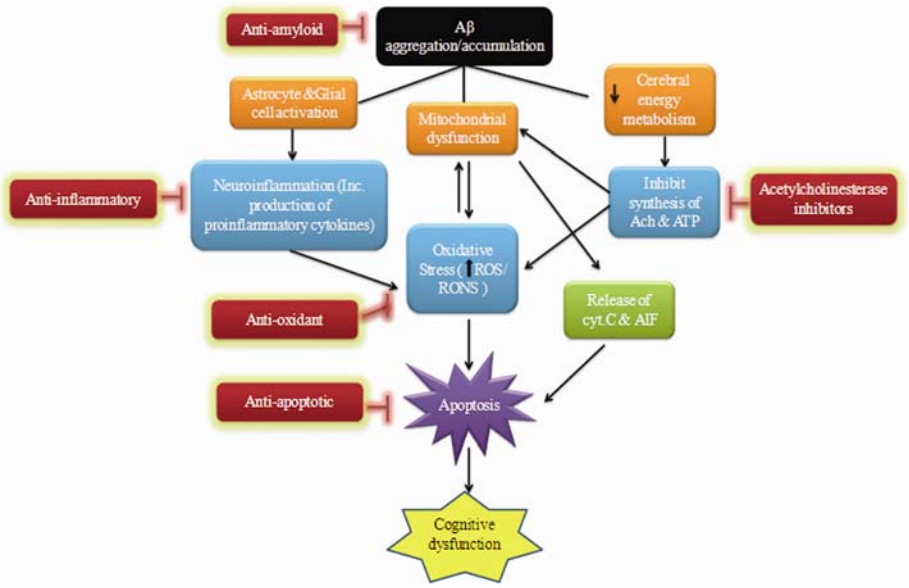

Fig. 3—Various mechanisms of action and therapeutic targets of herbal drugs

Table 2—Various herbal drugs with anti-amyloid properties

Herbal drug	Mechanism of action
Uncaria rhynchophylla Miq. (Rubiaceae)	Traditional Chinese medicinal herb, exhibits excellent inhibitory activity against aggregation of both Aβ 1-40, Aβ 1-42 peptide and Aβ fibrils[21]
Paeonia suffruticosa Andrews (Paeoniaceae) (methanolic, ethanolic and water extracts)	Showed inhibitory effect on Aβ fibril formation and promote defibrillation of preformed Aβ fibrils[22].
Crocus sativus L. (Iridaceae)	It is an extract, significantly inhibited the formation of amyloid fibrils[23]
Salvianolic acid B, (Salvia miltiorrhiza Bunge.) (Lamiaceae)	Chinese herbal medicine commonly used for the treatment of cardiovascular and cerebrovascular disorders, has been found that salvianolic acid B inhibits fibril aggregation and destabilizes the Aβ fibril[24].
Butanolic extract of *Ecklonia cava Kjellman* (Lessoniaceae)	Reduces the production of toxic Aβ peptide from APP with Swedish mutation and also inhibited the formation of Aβ oligomers from the soluble monomers[25]
Curcumin from *Curcuma longa Linn* (family Zingiberaceae)	Showed excellent antioxidant and anti-inflammatory activities in various *in vivo* and *in vitro* model systems and also promotes the disaggregation of preformed fibrils[26,27].
Huperzine A from Lycopodium alkaloid isolated from *Chinese herb Huperzia serrata* (Qian Ceng Ta)	Previously it was used as analgesic and anti-inflammatory. It is widely used as a potent, selective and well tolerated inhibitor of AChEs. It is approved by FDA of China for AD therapy in 1994. Clinical study has showed that it significantly improves the memory, cognitive skills, and daily life activities associated with AD. It is also known to be used for memory impairment associated with vascular dementia, schizophrenia, and sleep disorder in insomniacs[28].
Ginkgo biloba (*maidenhair tree*) living fossil	Oldest tree on earth, which is native to China its standardized extract EGb761 (extract *Ginkgo biloba* 761) prepared from its leaves widely used for peripheral vascular disorders and memory impairment (both vascular and neurodegenerative dementia). It exerts multiple cellular and molecular neuroprotective mechanisms, including the attenuation of apoptosis, the inhibition of membrane lipid peroxidation, anti-inflammatory effects and the direct inhibition of Aβ aggregation[29].
Lemon balm (*Melissa officinalis*)	A very old medicinal plant used for >2000 years and has been well known for promoting long life and restoring memory The leaves of this plant contain: (i) monoterpenes (e.g. citral) with weak anti-AChEs activity; and (ii) phenol carboxylic acids including rosmarinic acid, which exerts a combination of antioxidative, anti-amyloidogenic and antiapoptotic effects[30].

γ-secretase has become the most promising therapeutic approach for AD[11,37,38] Various herbs and their extracts have been found that influence Aβ production, by interacting with β-secretases[38]. Ellagic acid and punicalagin obtained from the husk of pomegranate, *Punica granatum* L. (Lythraceae), were found to inhibit β-secretase[11]. Another herbal compound lipophilic alkylated flavanones from *S. flavescens* Aiton. (Fabaceae) possess an excellent BACE-1 inhibiting activity noncompetitively[11]. Another study showed that the dried rhizomes of *Smilax china* L. (Smilacaceae) and green and black tea polyphenols known to be as potent inhibitor of BACE-1, thereby reducing the progression of AD[38].

Similarly, inhibitors of γ-secretase (that cleaves β-APP in the transmembrane domain and generates the toxic Aβ peptides) [11,39] may also provide a therapeutic strategy against AD. It has also been reported that green tea polyphenol epigallocatechin-3-gallate inhibits LPS-induced elevation of Aβ levels through the attenuation of LPS-induced β- and γ-secretase activities[11,39,] and in another study a novel triterpene isolated from the extract of *Actaea racemosa* reduces Aβ-induced toxicity through the modulation of γ-secretase activity[11,38].

Targeting Tau hyperphosphorylation

Normally, tau protein stabilizes microtubules in neurons[39]. However, abnormal hyperphosphorylation of tau leads to aggregation of tau as observed in AD like condition. Diseases associated with these aggregates are termed tauopathies including AD[39]. Targeting the tau protein in AD may perhaps be the most effective strategy for treating post-symptomatic AD, which includes inhibiting the formation of tau aggregates, regulating tau using kinases, controlling tau degradation via chaperones and stabilizing tau microtubules[39]. Herbal drugs and extracts have been proved useful for their anti-tau properties. Curcumin, a linear diarylheptanoid, present in turmeric (*Curcuma longa*) extract is an antioxidant reported to significantly increase production of anti-inflammatory cytokine IL-4, and reduce Aβ and tau levels in Aβ-overexpressing mice[39]. Another study on a potent macrocyclic diarylheptanoid obtained from bayberry root bark (*Myrica cerifera*) extract, (+)-aR, 11S-myricanol has been reported to reduce tau levels[11,38].

Table 3—Various herbal drugs with anti-oxidant or anti-apoptotic properties

Herbs	Models	Mechanism of action
(A) *In vivo* models		
Centella asiatica extract	Male Wistar rats; ICV-STZ model of SAD	Increased cognitive behavior and prevented oxidative stress[44].
EGb 761(Ginkgo biloba)	Wistar rats deficient in vitamin E	Increased the proportion of small-sized synapses and mitochondrial density[45].
Vitamin E, Pycnogenol, Ascorbyl palmitate	ApoE-deficient mice	Increased the life span and reduced periodic acid Schiff positive inclusion bodies and apoptotic cells[46].
Kaempferol, Quercetin	Mutant C. elegans worm	Attenuated age-related accumulation of ROS[47].
Resveratrol, S-allylcysteine derived from the bulbs of garlic (*Allium Sativum*)	Male Wistar rats; ICV-STZ model of SAD	Prevented ICV STZ-induced cognitive impairment and oxidative stress[48].
(B) *In vitro* models		
Curcuma longa extract	Rat PC12 cells; Pyrogallol, H_2O_2	Rescued cells from cell death and increased anti-oxidant enzyme activity[49].
Aged garlic extract and S-allylcysteine	Rat PC12 cells; Aβ25– 35	Suppressed ROS, caspase-3, and DNA fragmentation; protected cells from apoptosis[48].
Ginsenoside Rg1 (*Vitis vinifera*)	Cortical cells from SD rats	Reduced apoptosis[50].
Bacopa monniera extract	Astrocytes from Wistar albino rat brains; S-nitroso-N-penicillamine	Inhibited DNA fragmentation and ROS formation[51].
Epigallocatechin gallate (*Camellia sinensis*)	Hippocampal neurons from Sprague–Dawley rats; Aβ25–35	Protected cells against apoptosis[52].

The cinnamon (*Cinnamonium zeylanicum*) extract also demonstrated inhibition of tau aggregation; and the inhibitory activity attributable to both compounds cinnamaldehyde and procyanidin oligomers of the catechins/epicatechin[39]. Another herbal drug paclitaxel from the Pacific Yew, *Taxus brevifolia*, showed curative effects in neurodegenerative tauopathy by counteracting 'loss-of-function' effects of tau pathology in a transgenic mouse model[39].

Antioxidant and Antiapoptotic effect

In AD, oxidative stress causes generation of free radicals (RONS/ROS) via microglial activation by Aβ oligomers[40]. The expected antioxidant effects decrease in ROS-induced p53, Bax, and caspase-3 activity, reduced apoptosis, prevented a reduction in cytochrome c levels, attenuated DNA fragmentation, restored mitochondrial function, reduced the formation of toxic cyclooxygenase (COX), and protected cells against lipid peroxidation[41]. Some endogenous antioxidants, both enzymatic (e.g., superoxide dismutase, glutathione peroxidase and catalase) and non-enzymatic (e.g., ascorbic acid (vitamin C), α-tocopherol (vitamin E), glutathione, carotenoids, and flavonoids), are insufficient to combat this disease[42]. Some studies have shown that antioxidant combination treatment strategy including *Ginkgo biloba*, vitamin E, pycnogenol, and ascorbyl palmitate reduce apoptotic cells in the hippocampus of ApoE-deficient mice (C57B1/6J hybrid)[41-43] Table 3[44-52] shows various herbal drugs with antioxidant and antiapoptotic potential in different *in-vitro* and *in-vivo* models of AD. Apart from the mentioned herbal drugs, in table 3, another drug that gained attention was sage obtained from *Salvia officinalis*, known to possess antioxidant activity, anti-inflammatory effects and weak AChEs inhibition[53]. Rosmarinic acid (the active ingredient of sage) reduces several deleterious events induced by Aβ oligomers including the ROS formation, lipid peroxidation, DNA fragmentation, caspase-3 activation and tau protein hyperphosphorylation[53]. *Panchagavya Ghrita*, an Ayurvedic formulation has been reported to attenuate seizures, cognitive impairment and oxidative stress in pentylenetetrazole induced seizures in rats[34]. Curcumin also increased latency to myoclonic jerks, clonic seizures significantly and generalized tonic-clonic seizures, improved the seizure score and decreased the number of myoclonic jerks. Pretreatment with curcumin reversed PTZ kindling induced apoptosis oxidative stress and neuronal injury significantly. Over all, Saha *et al*.[54], demonstrated antiepileptogenic potential of curcumin on kindling-induced epileptogenesis.

Anti-inflammatory effect

As discussed earlier, in AD, Aβ accumulation and aggregation of tau occur in various neuronal

compartments of the brain and it is associated with neuronal loss, synaptic dysfunction and neuroinflammation[1,11]. Studies have shown that Aβ accumulation causes microglial activation, execution of the inflammatory process through enhanced cytokine production and increased release of tumor necrosis factor (TNF)-α and interleukins (IL)-1β[10,11]. Various herbs have been identified as possessing anti-inflammatory properties, which are currently being used to treat various neuroinflammatory disorders. The potential anti-inflammatory mechanisms of some commonly used herbs that may be effective in treating ROS-mediated inflammatory disorders like AD are explained below. *Dipsacus asper* Wall (Dipsacaceae) is a perennial herb, used traditionally in China for the treatment of rheumatic arthritis, traumatic hematoma, and bone fractures, and threaten abortion[38,55]. *Akebia* saponin D (ASD), a typical bioactive triterpenoid saponin isolated from the rhizome of *D. asper*, inhibited the expression of TNF-α, IL-1β, and cyclooxygenase 2 (COX-2) in rat brain, suggesting that ASD possesses potential anti-inflammatory activity[11,55]. *In vivo* studies involving THP-1 monocytic cells have shown that curcumin isolated from *Curcuma longa* inhibit Aβ-induced expression of Egr-1 protein and Egr-1 DNA-binding activity and reduce inflammation in monocytes through inhibition of Erg-1[10,11,31]. Ginger extracts isolated from *Zingiber officinale* is known to inhibit lipopolysaccharide (LPS), cytokine, and amyloid Aβ-peptide-induced proinflammatory genes TNF-α, IL-1β, COX-2, macrophage inflammatory protein α and monocyte chemotactic protein-1[11,19,35]. They have shown that ginger can inhibit the activation of human monocytic THP-1 cells and reduce the inflammation-related genes[35]. Certain phenolic compounds, like curcuminoids, also downregulate the expression of inflammatory enzymes[31]. Other medicinal herbs viz., *Eclipta alba* L. (Asteraceae), *Hybanthus ipecacuanha* L., Baill (Violaceae Batsch), *Justicia pectoralis* Jacq. (Acanthaceae), *Kalanchoe pinnata* (Lam.) Pers. (Crassulaceae), *Pterodon polygaliflorus* Benth. (Pteranodontidae), *Sarcostemma secamone* L. Bennet (Asclepiadaceae), and *Torresea cearensis Allemão* (Fabaceae), have also been reported to possess anti-inflammatory activity[10,11,33].

Anticholinesterase activity

The key enzyme, acetylcholinesterase (AChEs) is required for the breakdown of acetylecholine. Its inhibition is a promising strategy against neurological disorders such as AD[56]. Majority of the potential source of AChEs inhibitors is provided by herbal compounds abundantly available in nature[1,10,57-63]. At present, AChEIs are the first group of drugs approved by the US FDA to treat mild to moderate AD[57]. Studies have shown that there are varieties of herbal compounds that possess anticholinesterase activities against AD[11,38]. Drugs like huperzine A and galanthamine were of herbal origin[11,14]. Chinese herbal drugs like the root of *Salvia miltiorhiza*, the whole plant of *Ginkgo biloba*, have been reported to have cholinergic activities against AD[58-60]. A variety of herbal drugs have been reported to show AChEIs activity against age related neurodegenerative disorders such as AD (Table 4)[58-61].

Phosphodiestrase inhibitors (PDEIs)

PDEIs are known for their pharmacological properties including vasodilator, antidepressant, smooth muscle relaxant, anti-inflammatory and enhancer of cognitive functions[62]. Herbal compounds that possess PDEIs include alkaloids, flavonoids and saponins.

Flavonoids

The flavonoids are a group of polyphenolic compounds widely distributed in plants[63]. They possess various pharmacological effects such as antioxidant, anti-inflammatory, antihepatotoxic, antiulcer, anticancer, antimutagenic, antispasmodic, antiallergic, antiviral activities and protection against cardiovascular mortality[63]. Flavonoids have also been reported to show inhibitory action on xanthine oxidase, protein kinase C and PDE[63]. Medicinal herbs containing flavonoids such as *Sophora* spp.,

Table 4—Herbal drugs with AChEs inhibitory activity

Herbal drug	Parts used
Abutilon indicum Linn.	Whole[58]
Acanthus ebracteatus Vahl.	Aerial part[58]
Aegle marmelos Linn.	Fruit pulp[58]
Albizia procera (Roxb.) Benth.	Bark[58]
Bacopa monniera Linn.	Whole[58]
Butea superba Roxb.	Root barks[58]
Buxus sempervirens Linn.	Whole[59]
Carthamus tinctorius Linn.	Flower [59]
Cassia fistula Linn.	Roots[58]
Ginkgo biloba Linn.	Whole[57]
Melissa officinalis Linn.	Aerial part[58]
Nelumbo nucifera Gaertn.	Stamen[58]
Rhododendron luteum Sweet.	Whole[59]
Salvia officinalis Linn.	Whole[60,61]

Scutellaria spp., *Rheeoia* sp. and *Euchresta japonica* demonstrated that flavanones present in their aqueous extracts have cAMP PDE inhibitors[64]. Naringenin a natural flavonoid isolated from citrus fruits has been reported to show PDE1, 4, and 5 inhibitory activities[65]. Isoliquiritigenin, a flavonoid in *Glycyrrhiza glabra*, has PDEIs effect[63]. Other herbal drugs with PDEIs activity because of their flavonoid contents are *Berchemia floribunda*, *Betula alnoids*, *Caesalpinia sappan*, *Hiptage benghalensis*, *Leea indica*, *Ventilago denticulate*, *Bauhinia winitii*, *Butea monosperma*, *Senna surattensi*, *Matricaria recutita*, *Crataegu oxyacantha*, *Butea superba*, *Plantago asiatica* and *Ginkgo biloba*[64,65].

Alkaloids

Alkaloids are natural nitrogen-containing secondary metabolites mostly derived from amino acids. A number of plant alkaloids show inhibitory effect on PDE. Previous studies have shown that *Picrasma quassiodes* and *Ailanthus altissima* have inhibitory effect on cAMP PDEs because of their alkaloids content. On another hand, Neferin, a bis-benzyl isoquinoline alkaloid, from *Nelumbo nucifera* known to enhance the concentration of cAMP in rabbit cavernosum tissue probably by inhibiting PDE activity[66]. Viscolin from *Viscum coloratum* also known to possess PDEIs activity[66].

Saponins

They are group of glycosides also known as non-volatile, surface active compounds including steroids, steroidal alkaloids, and triterpenoids as aglycones that are widely distributed in nature, occurring primarily in the plant kingdom[67]. Saponins have a diverse range of properties, including hemolytic properties[67], as well as hepatoprotective, antimutagenic, antiviral, antileishmanial and anti-inflammatory activities. Some herbs have also been demonstrated to possess PDEIs activity related to their saponin content for e.g. *Lilium regale*, *Lilium henryi*, ethanol extract of *Allium chinense* and *Periandra dulcis*[68].

Lignans

Lignans are phenylpropene derivative and are dimeric in nature. Lignans in *Eucommia ulmoides* have PDEIs effect. PDEIs activity from norlignans of various herbs include *Amomum costatum*, *Aralia elata*, *Areca catechu*, *Bupleurum facatum*, *Cassia obtusifolia*, *Carthamus tinctorius*, *Citrus reticulate*, *Daphne genkwa*, *Forsythia suspense*, *Fraxinus bungeann*, *Glycyrrhiza glabra var. glandulifera*, *Inula britannica*, *Iris florentina*, *Nepeta japonica*, *Nuphar japonicum*, *Perilla frutescens*, *Phyllostachys nagra*, *Caesalpinia sappan* and *Polygala tenuifolia*[63].

Coumarins

These are benzopyrone derivative compounds with various pharmacological and biochemical properties and therapeutic applications includes reduction of lymphoedema, hypolipidaemic, antioxidant, hypotensive, inhibition of platelet aggregation, antispasmodic properties anti-tumoural, anti-HIV and as CNS-active compounds. The potent antispasmodic properties of glycocoumarins in the root of *Glycyrrhiza ularensis* is mediated by PDE3 inhibitory activity[63]. Osthole, a coumarin isolated from *Crindium monnier* and *Angelica pubescens* has shown PDEIs activity.

Essential oils

Essential oils are volatile in nature and are found in herbs belonging to different families especially Lamiaceae. Different pharmacological properties have been reported from essential oils mainly antimicrobial, carminative, and antispasmodic activities Essential oils and resins in *Haplopappus rigidus*, *Satureja parviflora* and *Senecio eriophyton* have PDEIs activity[63].

Herbal compounds that alter BBB

As mentioned earlier Aβ accumulation results in ROS generation and causes neuroinflammation which further causes BBB breakdown and related neuronal dysfunction[11]. It has been found that alteration in BBB due to Aβ accumulation provides a new approach to the researcher for the development of herbal compounds that target these irregularities[10]. In addition, Aβ accumulation degenerate the perforating arterial vessels and cerebral capillaries of the BBB[10,11]. It has been reported curcumin, a phenolic compound obtained from the rhizome of *Curcuma longa* Linn. (Zingiberaceae), protects BBB integrity[49]. Some studies have also shown that several flavonoids, like fisetin, apigenin, and luteolin, known to protect against ROS and inflammation mediated BBB breakdown and related neuronal dysfunction[10,11]

With the growing advancement in the field of herbal drugs, herbal extracts with multiple active principles have emerged as preferred prophylactics because of their broad spectrum activity against the disease and minimum side effects as compared to the synthetic drugs. For eg; *Withania somnifera*, the root extract of this herbal drugs has been reported to

improve cognitive functions and convulsive disorders via inhibition of NO mediated inflammatory apoptotic pathway[69]. Potential screening of these anti-inflammatory herbs may prove to be helpful in identification of new agents for the prevention of Aβ-peptide-induced neuroinflammation in AD.

Alternative approaches against AD

The use of alternative approaches as preventive aids for AD is of great interest to many researchers[7]. With increasing lifestyle, including a diet rich in anti-inflammatory, antioxidant and neuroprotective agents may reduce the risk of development of AD. The Alzheimer's Prevention Foundation International (APFI) discusses the guidelines of four pillars for the prevention of Alzheimer's disease. The first pillar involves a regimen of diet and vitamins[5]. The second pillar involves the proper management of stress. The third and fourth pillar involves the use of physical exercise, brain aerobics, mind/body exercises, and meditation exercises using yoga[7]. Other alternative approaches may include diet therapy and nutritional therapy (Table 5)[70-83].

Advantage of using herbal drugs for AD

Herbal drugs, apart from safety, have basic advantages in AD treating *viz.* no side/adverse drug effects, potential clinical efficacy, and drug-drug synergistic interactions. Herbal drugs exert multiple synergistic effects, including improved cognitive and cholinergic functions[1].

Limitations of using herbal drugs

Use of herbal drugs as an alternative approach, has been growing these days because of inefficiency of conventional medicines and side effects of synthetic drugs[7]. But there are some limitations while using herbal drugs like, herbals drugs may produce serious side effects like hepatic failure[38]. Another problem that arises from the use of highly concentrated doses of herbal drugs is toxicity. Further, herbal drugs lack statistically significant clinical efficacy[1,10]. For AD, the herbal drugs should have wider range of targets like Aβ production, fibrillation, Aβ-mediated oxidative stress, and neuroinflammation[1,7]. Another important limitation is poor ability to cross BBB. It must that herbal drugs must reach the brain in the biologically active form to exert their beneficial

Table 5—Various alternative approaches towards prevention of AD

Approach	Examples	Mechanism
Diet Therapy	High carbohydrate rich diet	Possibly scavenging reactive oxygen species, strengthening the ability of neurons to protect themselves, and down regulating factors in the immune system called cytokines[70]
	Rich in omega-3 fatty acid	Decreases the ability of the body to produce the amyloid protein, which is the key process in the development of AD[71]
	Mediterranean diet	Involves the high intake of monounsaturated fats, cereals, and wine[72]
Nutritional therapy	Vitamin E	Antioxidant[73]
	Thiamine	It mimics acetylcholine which is the primary chemical involved in normal memory function and the lack of which is key in the development of AD[74]
	Vitamin B12	Vitamin B12 supplementation has led to improved mental function in patients with AD[75]
	Folic acid	Folic acid deficiencies have been associated with the development of depression. Depression is one of the most common symptoms of AD[76]
	DHEA (Dehydroepiandrosterone)	DHEA can improve memory and enhance cognitive function in elderly persons with cognitive problems[77]
	L-Acetylcarnitine	LAC has been found to be an effective treatment for memory problems and depression[78]
	Phosphatidylcholine	Researchers have found that phosphatidylcholine, a key substance found in lecithin, supplementation can lead to increased levels of acetylcholine in the brain[79]
	Phosphatidylserine	Phosphatidylserine is a compound in the brain that is involved in the creation and protection of the integrity and fluidity of the membranes of cells[80]
	Antioxidants	vitamin A, vitamin D, lycopene, beta-carotene , selenium, glutamine, taurine, coenzyme Q10, pantethine, and magnesium were all significantly lower oxidative stress in AD[73]
	Music therapy	Study has been reported to demonstrate that music therapy provides beneficial effects to AD[81]
	Therapeutic touch & massage	The researchers found improvement in the patients on a variety of measures including increased physical relaxation, improved communication, increased sleepiness, and a decrease in abnormal behaviors[82].
	Exercise therapy	Exercise therapy reduces the risk of developing vascular dementia and AD[83].

effects. One of the most important challenges in developing therapeutic agents from natural products is obtaining the active compounds in large quantities[38]. It has been evidenced that many herbal drugs and its preparations are marketed without any stringent adherence to GMP guidelines[1]. External factors like irregular environmental conditions may also affect the activity of herbal drugs[10]. Hence, the use of herbal drugs by the physicians and regulators should remain cautious[38]. Appropriate scientific evidence for the claimed clinical benefits should be mandatory worldwide, and the standards for production and safety monitoring should abide with established standards for chemically defined products[1].

Conclusion

AD is a multifactorial slow growing neurodegenerative disease. Various therapeutic approaches have been under diverse phases of investigations as a possible drug treatment strategies in order to treat and manage AD effectively targeting anti-inflammatory, antiamyloid, antioxidant and pro-cholinergic pathways, etc. Presently, anti-Alzheimer drugs which has been approved by FDA provide symptomatic relief and have their own limitations in terms of adverse effects[1]. Therefore, there is a need to explore new alternative therapeutic approaches employing herbal drugs to treat AD effectively. Herbal drugs have gained significant attention among scientific community due to their pleiotropic and multifaceted actions that includes antioxidant, anti-inflammatory, and antiapoptotic action[7,10,11,38]. Thus, herbal drugs can be a promising alternative medicine for the treatment of AD. The therapeutic potential of herbal drugs raised new hope in the field of neurodegenerative diseases including AD.

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Author Contribution

Anil Kumar designed and analyzed the manuscript, Arti Singh wrote the paper and Archi Aggarwal contributed in the preparation of the manuscript.

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