Review

Nature's Derivative(s) as Alternative Anti-Alzheimer's Disease Treatments

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Abstract. Alzheimer's disease (AD), the 'Plague of Twenty-First Century,' is a crippling neurodegenerative disease that affects a majority of the older population globally. By 2050, the incidence of AD is expected to rise to 135 million, while no treatment(s) that can reverse or control the progression of AD are currently available. The treatment(s) in use are limited in their ability to manage the symptoms or slow the progression of the disease and can lead to some severe side effects. The overall care is economically burdensome for the affected individuals as well as the caretakers or family members. Thus, there is a pressing need to identify and develop much safer alternative therapies that can better manage AD. This review discusses a multitude of such treatments borrowed from Ayurveda, traditional Chinese practices, meditation, and exercising for AD treatment. These therapies are in practice since ancient times and reported to be beneficial as anti-AD therapies. Ayurvedic drugs like turmeric, *Brahmi*, *Ashwagandha*, etc., management of stress by meditation, regular exercising, and acupuncture have been reported to be efficient in their anti-AD usage. Besides, a combination of vitamins and natural dietary intakes is likely to play a significant role in combating AD. We conclude that the use of such alternative strategies will be a stepping-stone in preventing, treating, curing, or managing the disease.

Keywords: Acupuncture, alternative treatments, Alzheimer's disease, Ayurveda, exercise, meditation

INTRODUCTION

Alzheimer's disease (AD) is a neurodegenerative disease that was first described by German psychiatrist and neuropathologist, Alois Alzheimer in 1906 [1]. It results in deterioration of cognition and memory, ultimately leading to the loss of a person's ability to carry out day to day activities independently. It is the most common form of dementia, contributing to 60–70% of the cases [2]. Generally observed in people around 65 years of age or more, the onset of

the disease is associated with aging and occasionally found in younger people [3]. Currently, no cure is available for AD, which is often referred to as the 'Plague of Twenty-First Century' due to the estimated sweeping escalation in the number of its cases from 48 million to 135 million by 2050 [4]. It calls for finding a cure or efficient methods of preventing the disease condition to manage and minimize its proliferation effectively.

What happens in AD?

Neuronal damage and death are widespread in the case of AD as critical processes like metabolism, communication among the neurons and with other brain cells, repair, remodeling, and regeneration gets disrupted. Generally, the disease progresses with the

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onset of aging. In the initial stages, neurons of the entorhinal cortex and hippocampus, responsible for memory, are destroyed. The disease then proceeds to the later stage to affect areas accountable for reasoning, language, and social behavior of the cerebral cortex. This fatal neurodegenerative disease then affects other areas of the brain, ultimately leading to the stage where the patient becomes incapable of functioning and living independently, before death.

The significant changes taking place in the brain at the molecular level are:

1. *Oxidative stress.* Reactive oxygen species (ROS) bring about the oxidative stress, especially in the case of age-related disorders like AD. Oxidative damage occurs early in the AD patient's brain. Its impact can be seen even before the plaque pathology is initiated as it precedes amyloid-β (Aβ) deposition as well as abnormal formation of intracellular neurofibrillary tau protein tangles. ROS also lead to neurodegenerative processes and neuronal death, at the cellular and tissue levels [5].
2. *Formation of Aβ plaques.* Formation of Aβ proteins occurs due to breakdown of the amyloid-β protein precursor (AβPP). These proteins begin to clump together to form plaques between neurons at abnormal levels. Ultimately, these clumps result in disruption of cellular function [6].
3. *Formation of neurofibrillary tangles.* Accumulation of abnormally high levels of hyperphosphorylated tau protein inside the neurons results in the generation of neurofibrillary tangles. Tau protein in healthy neurons is responsible for binding to and stabilizing microtubules [7]. However, after detaching from microtubules, tau sticks to other tau molecules in case of AD and forms threads that join together to form tangles that lead to blockage of synaptic communication between the neurons [8]. Due to the breakdown of a retrograde barrier at the axon initial segment, tau proteins present in the axonal region of neurons get missorted to the somatodendritic compartment [9].
4. *Chronic inflammation.* Microglial cells act as macrophages of the brain, clearing cell debris, including Aβ plaques, toxins, and dead neurons. Astrocytes also help in removing the plaques and cell debris from the brain. In the case of AD, these microglial cells of the brain assem-

ble around the neurons but are not successful in performing their function of clearing the debris. Thus, their build-up results in the release of chemicals that lead to chronic inflammation in the brain [10].

5. *Vascular attributions of AD.* AD may also cause Aβ accumulation in arteries of the brain, hardening of arteries, i.e., atherosclerosis, mini-strokes, etc. [11], and can reduce blood flow and oxygen supply to the brain. Ultimately, this leads to a degenerative and complicated cycle that is a cause as well as a consequence of AD [12].
6. *Brain atrophy.* Neuron cells are damaged and die in case of AD. Thus, the neural network may breakdown, and brain regions begin to shrink in volume [13].

The brain activity deterioration begins from the hippocampus in the medial temporal lobe, which is mainly related to memory and emotion. The deterioration then escalates, and the whole brain glucose metabolism is also affected, resulting in a reduction in neuronal processing of bilateral parietal and temporal lobes [14]. The parietal lobe is responsible for sensation, self-awareness, attention, memory retrieval, and theory of mind [15–17]. The temporal lobe is associated with episodic memory, emotions, and mood [18]. Thus, the regions affected by AD are responsible for the regulation of memory, emotions, and awareness.

Current treatments for AD

At present, there are a limited number of drugs available for the treatment of AD, and most of these can only treat the symptoms. These are inept at preventing the progression of the disease further or reversing its effects. The development of symptoms like memory loss is, however, slowed, prolonging life and alleviating the quality of life of the affected individuals. Some of the compounds used in case of mild to moderate AD are donepezil, rivastigmine, and galantamine. These are classified as cholinesterase inhibitors that prevent the breakdown of acetylcholine, necessary for memory and learning. For patients with moderate to severe AD, memantine, a N-methyl D-aspartate (NMDA) antagonist, is used [19]. A combination of memantine and donepezil is used for the same. Some other drugs are also used to treat depression, aggression, restlessness, and anxiety associated with AD. These include citalo-

pram, mirtazapine, sertraline, bupropion, duloxetine, and imipramine. However, the side effects of these drugs can be severe, often involving confusion, falls, dizziness, sleepiness, etc. and should be strictly taken as prescribed [20].

Need for alternative treatments

With the ever-increasing population and the growing life expectancy of individuals, AD incidences are also rising rapidly across the globe. As per the WHO factsheet on dementia, worldwide 50 million people are reported to have dementia, with 10 million new cases being added every year. It is also proposed that globally, one person develops dementia every 3 seconds [21]. This rapid increase necessitates the development of alternative treatment strategies to prevent and treat AD.

The currently available treatments have limited efficiency, a more significant number of side effects, and poor patient compliance. They are also burdensome for the patients and caregivers to bear as the socioeconomic costs of long-term attendance and hospital expenditure continue to rise annually [22]. This calls for the development of much safer alternative therapies that have been practiced since ancient times and have been reported to be beneficial in their use as anti-AD therapies. A multitude of such therapies can be borrowed from Ayurveda, traditional Chinese practices, meditation, and exercise. Many of the treatments aimed at fixing or preserving the functioning of synapses and cognition (the main attributes of AD) have proven to be useful for contributing in slowing the progression of AD and complementing the mainstream treatments currently in use.

Some of the alternative therapeutic and preventive strategies that can be adopted for long-term anti-AD beneficial effects are discussed in detail.

AYURVEDA

Ayu meaning longevity of life (*Chetananuvrutti*), *Ayurveda*, a Sanskrit word, is the 'scripture of longevity'; it is the science of life and wellbeing that encourages a holistic view of treatment to maintain the equilibrium of the body, mind, and soul. This traditional system of medication is based on the five basic elements of the universe: space, fire, water, air, and earth [23]. It finds its roots in India and the Indian subcontinent, dating back to the Indus Valley Civilization (about 3,000 BC). Ayurveda not only cures

but acts as an excellent preventive medication system that can delay the very onset of aging and ailments associated with it.

According to Ayurveda, disturbances in the *Tridosha* (Vata, Pitta, and Kapha) and *Triguna* (Sattva, Raja, and Tama) results in functional disorder of *Indriya* (cognitive and motor organs), *Mana* (psyche), and *Buddhi* (intellect). It leads to impaired memory or cognitive defects. Ayurvedic drugs help in maintaining and re-establishing the balance between *Tridosha* and *Triguna*. They also provide *Medhya* (intellect promoting) effect to improve the memory of the patients [24].

Recently, the world's first Ayurvedic drug against cancer has been launched, which is non-chemical, non-synthetic, and has no side-effects. 'Kudos CM9®' (CSIR-IICB) was developed by the Ministry of Science & Technology, CSIR-IICB (Council of Scientific & Industrial Research-Indian Institute of Chemical Biology), India. It helps in cure as well as control the progression of benign and malignant tumors. It can also be used to prevent cancer in high-risk individuals. Ayurvedic herbal medications often have a biosafety profile and generally, do not show significant side-effects. Thus, there is a surge in research interest of Ayurvedic drugs. Mechanistic studies being carried out have helped in elucidating the effect and efficacy of these drugs on central nervous system (CNS) disorders, like AD.

Some Ayurvedic herbal/traditional plant-based drugs that can treat disorders of the nervous system and improve cognitive function and memory are discussed.

Bacopa monniera (Brahmi)

In the traditional Indian system of medicine, *Brahmi* acts as *Medhyarasayana* (from the Sanskrit words; 'medhya,' meaning intellect or cognition, and 'rasayana,' meaning 'rejuvenation') plant-derived nerve tonics that enhance memory, intellect, and aid mental health [25]. *Brahmi* extracts, functioning as a nootropic, are used for disorders like epilepsy, insomnia, anxiety, etc. [26] since they have effects that can enhance memory, help in anti-inflammation, and act as an analgesic, antipyretic, sedative, and antiepileptic agents [24]. Steroidal saponins, Bacosides A and B, are the active constituents of *Brahmi* that scavenge free radicals and inhibit lipoxygenase activity, reducing lipid peroxidation, thus protecting neurons of the hippocampus, prefrontal cortex, and striatum

[27] against cytotoxicity and DNA damage related to AD [24]. Bacosides also chelate iron and increase glutathione peroxidase. The extracts show neuroprotective effects due to nitric oxide-mediated cerebral vasodilation [28].

A study by Le et al. on olfactory bulbectomized mice demonstrated that *Brahmi* protects the cholinergic neurons in the medial septal nucleus that projects into hippocampus [29]. A study on rat model of AD also shown the inhibition of degeneration of cholinergic neurons due to alcoholic *Brahmi* extracts suggesting the potential therapeutic use of the drug [30]. These studies suggest the cholinergic effect of *Brahmi* extracts are similar to the current treatments like donepezil, rivastigmine, and galantamine [29]. Studies also show that *Brahmi* extracts decrease Aβ deposition and stress-induced hippocampal damage as demonstrated by Mathew & Subramanian [31] and Holcomb et al. [32], indicating its potential therapeutic use in the case of AD. There are no proven side effects of the drug; however, excessive consumption of the same leads to conditions like diarrhea, stomach upset, and nausea. Limited intake of the drug for pregnant and breastfeeding women is recommended [19].

Centella asiatica (Mandukaparni)

Also known as *Gotu kola and Asiatic pennywort*, the extracts of this herb are useful in nerve regeneration [33], thereby helping in the recovery of their function. Enhancing memory retention [34] and promoting longevity, this neurodegenerative adaptogen also helps in preventing cognitive impairments and alleviating oxidative stress associated with AD due to its antioxidant properties [35]. It is an alternative for acetylcholinesterase inhibitors, which generally comprise the first-line of treatment for AD and can also help in lowering the phospholipase A_2 activity [36]. A natural process that plays a role in causing neurodegeneration, i.e., mitochondrial dysfunction, can be altered by the antioxidant activity of this herb [37]. It consists of saponins, asiaticoside derivatives at a molecular level as active compounds, which can significantly reduce cell death induced from hydrogen peroxide, lowering free radical levels and preventing Aβ-mediated neural cell death *in vitro*. Thus, its use can be significant in Aβ toxicity and AD prevention and treatment [38, 39]. A study conducted on 28 healthy elderly individuals also suggested the potential of *Gotu kola* extracts on alleviating mood disorders as well as the age-related cognitive decline

in them [40]. It is quite safe to use; however, higher doses of it can result in drowsiness [41].

Withania somenifera (Ashwagandha)

It very commonly is known as *Indian ginseng* and is known to possess multiple therapeutic properties, serving as a nerve tonic, memory enhancer, and a medicinal plant having anti-stress, immunomodulatory, and antioxidant properties [42]. These properties are due to its constituent compounds, Withaferin A and Withanolide A, which have comparable pharmacokinetic roles except for different oral bioavailability, with that of Withaferin A being greater than Withanolide A [43]. Its roots facilitate inhibition of the activation of the nuclear factor NF-κB, which controls the expression of genes responsible for inflammation and oxidative stress and prevents Aβ production, thus protecting from inflammation and oxidative stress. It also helps in the restoration of synaptic function, and reduction of apoptotic cell death. It aids in migration of nuclear factor related E2-related factor 2 (Nrf2) to the nucleus leading to a surge in the antioxidant enzyme expression and neuroprotective proteins like heme oxygenase-1, thus substantiating antioxidant effects beneficial in AD treatment and prevention [44, 45]. It also contributes to neurite outgrowth and neuroprotective effects *in vitro*, axonal regeneration, and synaptic reconstruction *in vitro* and *in vivo* [46]. Crossing the BBB, it can alleviate inflammation of the brain. It has no side effects, but some people report experiencing nausea or diarrhea after consuming its root [24].

Curcuma longa (turmeric)

The yellow curry, Indian spice consists of a hydrophobic compound known as curcumin or diferuloylmethane ($C_{21}H_{20}O_6$). This polyphenolic yellow pigment has anti-inflammatory and antioxidant characteristics [47]. The molecule can cross the BBB and bind to Aβ, thus preventing its aggregation and fibril formation *in vivo* as well as *in vitro* [48]. Turmeric acts as a therapeutic agent in case of AD as in addition to reducing amyloid deposition; it can also prevent tau phosphorylation, both of these events being significant implications of the neurodegenerative disorder [49].

Curcumin shows anti-inflammatory characteristics by suppressing pro-inflammatory pathways by

preventing the production of TNF-α, IL-1β, and other pro-inflammatory cytokines, like, IL-8, MIP-1β, and MCP-1, in astrocytes and microglia. It also inhibits phospholipase A_2 and cyclooxygenase (COX-2) enzymes associated with the metabolism of neural membrane phospholipids to prostaglandins, thus reducing neuroinflammation [50]. It reduces oxidative damage and enhances cognitive function, especially in the case of aging by modulating the Nrf2-Keap1 (Kelch-like ECH-associated protein 1) pathway [47]. Nrf2 bound to Keap1 and present in the cytoplasm get released upon binding of curcumin to Keap1. It then translocates to the nucleus and binds to antioxidant responsive elements in DNA as a heterodimer, thus, targeting the genes controlling the expression of antioxidant enzymes, DNA repair enzymes, molecular chaperones, and anti-inflammatory response proteins. These proteins lead to the lowering of ROS production and aid the cell's ability to fix any damage that follows [51].

A study also established that regular curry consumers performed better on the standard test (Mini-Mental State Examination, MMSE) of cognitive function than those who have never or rarely consumed it [52]. It also has the potential to lower cholesterol, inhibit acetylcholinesterase, mediate insulin signaling pathway, metal-chelation (binds copper) that prevents cerebral deregulation caused by bio-metal toxicity, and decrease microglia formation [53, 54]. It naturally has lower bioavailability, but when consumed with black pepper *(Piper nigrum)*, its bioavailability and absorption rate increases due to the active ingredient 'piperine' of black pepper [55]. The lower rates of AD in the Indian population has also been attributed to the extensive consumption of turmeric, hinting at the neuroprotective role of turmeric [55]. It can be used as a food additive and is safe to consume, with no significant side effects except diarrhea, nausea, dizziness, or stomach upset when consumed excessively.

Convolvulus pluricaulis (Shankhpushpi)

This plant commonly found in India is a nerve tonic that serves to improve memory and cognition. It has a calming effect, and it is used for neurological disorders, like anxiety, insomnia, stress, and mental fatigue [56]. Its ethanolic extracts induce antioxidant effects along with enhancing learning and memory in rats [57]. It comprises of glycosides, flavonoids, coumarins, anthocyanins, and alkaloids as its major bioactive components and has also shown to

contain sitosterol glycoside, octacosanol tetracosane, hydroxycinnamic acid, and glucose [58].

In an AD *Drosophila* model, its aqueous extracts extend the lifespan of the fly model by neutralizing human microtubule-associated protein tau-induced neurotoxicity, preventing early death. *Shankhpushpi* extracts significantly lower the tau protein in tauopathy. It also restores the declining acetylcholinesterase activity, boosts the antioxidant enzyme activities, and amends the tau-induced oxidative stress [59]. The increase in acetylcholine content caused by its extracts is also complemented by a substantial upsurge in the total dendritic intersections, number of branch points, and dendritic processes developing from the neurons' cell bodies, in comparison with age-matched saline controls. Thus, the increase in neurite outgrowth caused by ethanolic extracts of *Shankhpushpi* augments memory [60]. Addition of *C. pluricaulis* to regular standard food allows its action. The paste made from its small leaves along with its flowers and roots can be consumed regularly.

Guggulu

This pale yellow or brown oleo-gum resin is an exudate from cracks, fissures, or incisions on the bark of *Commiphora wightii, Commiphora mukul, Commiphora abyssinica, Commiphora molmol*, and *Commiphora Burseraceae* [61]. It is composed of phenols, ferulic acids, and other non-phenolic aromatic acids that have the potential to scavenge superoxide radicals, thus, making it significant in combating neurodegenerative diseases that have oxidative stress as a substantial implication [62].

High cholesterol is among one of the risk factors of AD. *Guggulu* is essential in modulating the activity of the cell membrane and regulating synaptic functions and neuronal plasticity. *Guggulu* helps in lowering cholesterol. Thus, this attribute of the drug contributes to reducing the frequency of AD development, since decreased neuronal cholesterol level leads to inhibition of Aβ-forming amyloidogenic pathway. It becomes possible due to the removal of precursor protein from cholesterol [63–65]. Studies have revealed that Z-guggulsterone pre-treatment of C57BL/6J mice models showing scopolamine (a muscarinic acetylcholine receptor antagonist)-induced memory impairments result in memory-improving effects due to the activation of the cAMP response element-binding protein (CREB)-brain-derived neurotrophic factor (BDNF)

signaling pathway [66]. Guggulipids also exhibit antioxidant effects, lower cholesterol, and show anti-acetylcholine esterase activities, thus improving the condition of streptozotocin-induced memory deficit mice model of dementia as demonstrated in a study by Saxena et al. It can lower serum LDL cholesterol as well as triglyceride levels [67]. Half-lives of *Guggulu* and its derivatives in circulation in body and brain are yet to be elucidated.

Ginkgo biloba (Ginkgo)

Extracts of *Ginkgo* consist of flavonoid glycosides (containing quercetin, kaempferol, isorhamnetin, etc.), terpenoids (containing Ginkgolides A, B, C, and J and bilobalide), and organic acids [68]. The flavonoids and terpenoids are constituting the pharmacological components, while organic acids contribute to the water solubility of the extract [69]. It shows antioxidant activity attributed to its free radical scavenging action as shown in a study by Wei et al. in which pre-treatment of a cerebellar granule with *Ginkgo* reduced the oxidative damage caused by $H_2O_2/FeSO^4$ [70]. It also upregulates the protein level and activity of antioxidant enzymes like superoxide dismutase and catalase, to stabilize the cellular redox state, in addition to direct weakening of ROS [71, 72].

In LPS-activated microglial cells, *Ginkgo* extracts have been used to inhibit the release of prostaglandin E_2 (PGE$_2$), a pro-inflammatory mediator and pro-inflammatory cytokines, thus, displaying anti-neuroinflammatory activity [73]. It also downregulates cytokines associated with inflammation, such as AGE- or LPS-induced nitric oxide (NO), TNFα, IL-6, and IL-1 [74]. The anti-inflammation effects may also be attributed to their platelet-activating factor (PAF)-antagonist activity. PAF is shown to have a role in regulating cytokines in inflammatory responses [68, 75].

Ginkgo also shows anti-apoptotic action and can act synergistically on multiple signaling apoptotic pathways, like maintaining the integrity of the mitochondrial membrane, blocking the apoptotic caspase cascade and apoptosome formation by preventing mitochondrial release of cytochrome c, enhancing the transcription of anti-apoptotic Bcl-2-like protein, attenuating the transcription of pro-apoptotic caspase-12, inactivating pro-apoptotic *c-Jun* N-terminal kinase (JNK), and inhibiting the cleavage of the vital effector protease caspase-3. Therefore,

it blocks apoptosis and also prevents nuclear DNA fragmentation, the molecular hallmark of apoptosis [76, 77]. It also plays a protective role in preventing neurotoxicity caused by Aβ aggregation by blocking Aβ-induced events, such as ROS accumulation, glucose uptake, mitochondrial dysfunction, activation of AKT, JNK, and ERK 1/2 pathways, and apoptosis [67, 78, 79].

Ginkgo also shows other protective effects such as ion homeostasis, modulation of phosphorylation of tau protein, and induction of growth factor synthesis [80]. *Ginkgo* extracts can also upregulate expressions of nerve growth factor in mouse [81] and glial-derived neurotrophic factor and vascular endothelial growth factor in cultured rat cortical astrocytes [82]. In a study by Ihl et al., treatment of 404 patients having AD or vascular dementia with standardized extracts of *Ginkgo*, popularly known as EGb 761, resulted in a considerable enhancement in cognitive function and neuropsychiatric symptoms [83]. Of late a study by Savaskan et al., involving 1,628 patients with dementia, also showed the improvement of behavioral and psychological symptoms of dementia (except psychotic-like features) and caregiver distress caused by such symptoms by the administration of 22–24 weeks' treatment with EGb 761 [84]. Recent studies have also shown the use of EGb761 in providing an appropriate environment to induce differentiation of stem cells into nerve cells, which opens new and fascinating avenues for stem cell treatment of neurodegenerative diseases [85]. *Ginkgo* extracts complexed with phosphatidylserine as a phytosome (Virtiva®) lead to an enhanced memory task performance due to increased bio-availability of active constituents of the extract when tested on 28 participants [86].

Cinnamon zeylanicum (Cinnamon)

Cinnamon is composed of a flavonoid, cinnamaldehyde, that gives it the characteristic flavor and aroma. Most commonly present are *E*-cinnamaldehyde and *o*-methoxycinnamaldehyde [87]. Its extracts are shown to inhibit tau aggregation and filament formation. It is not detrimental to normal tau functioning. This inhibitory effect is due to the proanthocyanidin trimer molecule as well as cinnamaldehyde [88]. Cinnamaldehyde and an oxidized form of epicatechin (EC) (ECox) of the extracts can also dissolve tau tangles by binding to the two cysteine residues in tau. ECox can also prevent oxidation

of tau by ROS and H_2O_2, preventing tau tangles. EC also has the potential to sequester toxic and reactive by-products of oxidation, like acrolein [89]. It showed that a diet rich in proanthocyanidin, catechin, and epicatechin in monomeric, oligomeric, and polymeric forms could promote learning and memory in AD [90]. It can also inhibit the TLR4/NOX4 signaling, which can then lessen the oxidative stress/nitrative stress in case of neuronal damage and apoptosis pathways [91]. It also shows its neuroprotective effects by reducing the intracellular ROS production as well as expression of pro-inflammatory cytokines, IL-1β, IL-6, TNFα, and NF-kB to reduce inflammation, as shown in case of LPS-stimulated rats in a study by Zhao et al. [92] and can also increase synaptic plasticity [93]. Its polyphenolic compounds can counter Aβ aggregation; it also inhibits β-secretase and production of Aβ_{40} in Chinese hamster ovary-APP CHO cells *in vitro* [94]. Thus, cinnamon extracts can target all three AD hallmarks: inhibition of acetylcholinesterase activity, Aβ formation/aggregation, and tau phosphorylation as summarized by S. Momtaz et al. [95].

Panax ginseng (Ginseng)

Ginsenosides, a type of terpenoid dammarane glycoside, constitute the major bioactive component of the plant extracts. Ginseng root has been observed to contain over and about 60 different ginsenosides, like Rb1, Rb2, Rb3, Rc, Rd, Re, Rg1, Rg2, and Rg3 [96]. It shows anti-inflammatory effects due to inhibition of phosphorylation of p38MAPK and STAT1 in BV2 microglial cells, thus reducing LPS-induced mediators that are pro-inflammation such as COX-2, TNFα, and inducible nitric oxide synthase (iNOS) [97].

Studies show the use of its extracts to improve thinking as well as working memory in case of AD patients [98]. Ginseng treatment improved Alzheimer's Disease Assessment Scale cognitive subscale (ADAS-cog) and MMSE scores in AD patients [99].

A study also reported the potential of GP-17, a novel phytoestrogen isolated from ginseng, in the clearing of Aβ *in vivo* and *in vitro* in the AD mouse models, Swedish mutant of APP695 (APP695swe) and APP/PS1. The neuroprotective effect was due to the autophagy-based elimination of Aβ due to the activation of transcription factor EB responsible for lysosome biogenesis [100]. It is useful in the inhibition of formation of Aβ, stimulation of soluble AβPPα formation, anti-inflammation, anti-

apoptosis, decreasing oxidation stress, and enhancing CNS cholinergic function to counter impairments and implications associated with AD [101,102]. Its combination with *Ginkgo* is expected to give better results [103].

Cannabis sativa (cannabidiol)

The main constituent of phytocannabinoids, cannabidiol (CBD), is present in *Cannabis sativa*. It is less toxic and lipophilic, making it easier to cross the BBB [104]. It can show anti-inflammation effects and inhibit the neuroinflammation caused by Aβ aggregation. CBD inhibits glial fibrillary acidic protein (GFAP) mRNA and protein expression, impairing iNOS and IL-1β protein expression, and their related release in Aβ-injected animals as shown by Esposito et al. [105].

CBD also prevents tau hyperphosphorylation in Aβ-stimulated PC12 neuronal cells due to reduction in phosphorylated glycogen synthase kinase 3β (p-GSK3β) which is the active form of GSK3β. GSK3β, called tau protein kinase, is associated with tau protein hyperphosphorylation, which then leads to the formation of tau tangles [106]. CBD treatment has shown to enhance memory and learning, along with decreasing IL-6 levels in AD mice models [107]. Chronic CBD treatment administered following the inception of AD-like symptoms, cognitive insufficiencies and formation of Aβ plaques, has shown to reverse social recognition memory and object recognition deficits in double transgenic APPswe/PS1E9 mice. The study also suggested the modulation of cytokine TNFα levels by CBD [108].

Sativex® is a combination of CBD and Δ^9-tetrahydrocannabinol (THC) in the ratio of 1 : 1. It has shown to reduce neuroinflammation and iNOS levels in the cerebral cortex and alleviate the stress-related behaviors in parkin-null, human tau overexpressing (PK$^{-/-}$/Tau^{VLW}) mice. It also stimulated autophagy and reduced cortical and hippocampal Aβ, plaques, and phosphorylated tau [109]. THC/CBD treatment increased fear-associated learning and preserved object recognition memory. It also reduces cortical soluble Aβ_{42} levels and changes plaque composition. Also, it effectively lowers inflammation and alters neuroinflammatory processes in APPxPS1 transgenic mice [110]. CBD shows anti-AD effects; antioxidant activity, anti-inflammation effects, and neuroprotective properties, and reduces Aβ generation and tau hyperphosphorylation *in vitro* [111].

Table 1
Summary of *Ayurveda* drugs, their active components, and their significant anti-AD effects

S.No.	Ayurveda drug	Active compounds	Major impacts
1.	*Brahmi*	Bacosides A and B	Nootropic effects Anti-inflammatory effects Scavenge free radicals Decrease Aβ deposition
2.	*Mandukaparni*	Asiaticoside derivatives	Enhances memory retention Prevents cognitive impairments Anti-oxidant effects Lowers Aβ toxicity Alters mitochondrial dysfunction Alleviates mood
3.	*Ashwagandha*	Withaferin A and Withanolide A	Enhances memory Anti-stress effects Immunomodulatory and anti-oxidant properties Prevents Aβ production Neurite outgrowth and neuroprotective effects Regenerates axons Reconstructs synapses
4.	*Turmeric*	Curcumin or diferuloylmethane	Inhibits Aβ aggregation Anti-oxidant effects Anti-AChE effects Modifies insulin signaling pathways Lowers cholesterol Binds copper/metal-chelation Modulates microglia Prevents tau phosphorylation
5.	*Shankhpushpi*	Glycosides, flavonoids, coumarins, anthocyanins, and alkaloids	Ameliorates memory and cognition Anti-oxidant effects Neutralizes tau induced neurotoxicity Increases acetylcholine content Neurite outgrowth and dendritic development
6.	*Guggulu*	Phenols, ferulic acids, and other nonphenolic aromatic acids	Lowers cholesterol (a risk factor for AD) Regulates synaptic functions and neuronal plasticity Anti-oxidant effects Anti-AChE activities
7.	*Ginkgo*	Flavonoid glycosides and terpenoids	Anti-apoptotic effects Anti-oxidant effects Anti-inflammatory effects Protection against Aβ aggregation
8.	*Cinnamon*	Cinnamaldehyde	Inhibits tau aggregation and filament formation Counters Aβ aggregation Inhibits AChE activity Promotes learning and memory Reduces oxidative stress /nitrative stress in neuronal damage and apoptosis pathways Anti-inflammatory effects Immunomodulatory functions
9.	*Ginseng*	Ginsenosides	Improve thinking and working memory Anti-inflammatory effects Enhancement of CNS cholinergic function Anti-apoptotic effects
10.	*Cannabis*	Cannabidiol	Inhibits neuro-inflammation caused by Aβ aggregation Prevents tau hyperphosphorylation Enhances memory and learning Antioxidant effects

AChE, acetylcholinesterase, AD, Alzheimer's disease, Aβ, amyloid-β.

NATURAL DIETARY INTAKES

An insightful review article by Islam et al. (2017) sheds light on the importance and use of natural dietary products, like fruits (berries: blueberries, mulberries, and strawberries, apple, fig, mangosteen, papaya, dates, grapes, pomegranate, walnut, etc.), vegetables (broccoli, etc.), spices (cinnamon, black pepper, saffron, turmeric, garlic, ginger, etc.), drinks (tea, coffee, wine, fruit juice, etc.), marine products, and Mediterranean diet, in showing positive effects for AD prevention and treatment. These, thus, have the potential for being developed into therapeutic anti-AD drugs [112].

A recent study by Jabir et al. (2018) shows that polyphenols have a high therapeutic value and are present in plants. Quercetin derived from fruits and vegetables, such as onions, apples, berries, peanuts, soybeans, potatoes, etc.; resveratrol from grapes' skin and seeds; curcumin from turmeric; cinnamic acid and its derivatives from cinnamon, citrus fruits, tea, cocoa, etc.; caffeine from *Coffea arabica* and caffeic acid abundantly found in all plants and dietary products, are some of the critical polyphenolic compounds that have been discussed. They inhibit cholinesterase activity, thus, qualifying as potential drugs for AD treatment. However, their exact mechanism of action has not been elucidated [113].

N-acetylcysteine (NAC), abundantly present in onions, is a glutathione (GSH) precursor which is an antioxidant [114]. It is included in the World Health Organization's List of 40 Essential Medicines, being a well-established drug since the 1960 s [115]. GSH levels are depleted in the hippocampal regions in AD, implying that NAC supplementation can be beneficial for cognitive enhancement [116]. A study by Moreira et al. provides evidence that NAC is efficient in enhancing the mitochondrial related oxidative stress in case of AD. It also showed that the combination of lipoic acid and NAC was more potent to use [117].

VITAMINS

Lower levels of vitamin B are often associated with decreasing cognitive ability, commonly due to the increased level of homocysteine [118]. Vitamin B6, B9 (folate), and B12 (cyanocobalamin) are involved in homocysteine metabolism, which can thus be boosted with the help of vitamin B supplementation, resulting in reduced risk of dementia [119].

Vitamin A and C have antioxidant activity, thus their use in enhancing cognition and preventing dementia. Vitamin A (retinol) is essential for memory, learning, and cognition. Its levels in the brain decline with age and are very low in AD patients [120]. Performed retinoids or provitamin carotenoids provide vitamin A, with β-carotene most commonly found in food. In Physicians' Health Study II (PHSII), a randomized trial of β-carotene supplementation, it was found that long-term use conferred cognitive benefits [121]. Retinoic acid was also reported to protect neurons of the hippocampus by preventing Aβ-induced cell death [122].

A study demonstrated that low vitamin D dietary intake was associated with the poor cognitive performance [123]. Similar results were obtained from another study from the Third National Health and Nutrition Examination Survey (NHANES III).

Vitamin E is a potent antioxidant and anti-inflammatory agent. It also has neuroprotective roles. Lower levels of vitamin E have been reported in AD patients [124,125]. It has shown positive results on cognition. However, further research is required to support the use of vitamin E as a therapeutic agent for AD [126].

Medical food cocktail

According to a study by Parachikova et al., administration of a cocktail that comprised of curcumin, piperine, epigallocatechin gallate, α-lipoic acid, N-acetylcysteine, vitamin B and C, and folate for six months in transgenic mice model of AD resulted in improvement in memory and learning. It also helped in reducing the soluble Aβ concentrations, including Aβ oligomers [127]. Thus, combinations of different medicinal compounds must be extensively studied to derive different formulations that show greater efficacy in their preventive and therapeutic anti-AD usage.

STRESS, MEDITATION, AND AD

Stress, an effect of a threat to homeostasis, is a situation wherein individuals encounter aversive stimuli leading to a negative physiological change [128]. Stress and cortisone (a hormone released by the adrenal gland in response to stress) can activate glucocorticoid receptors, leading to a reduction of hippocampal plasticity. It affects memory (especially spatial memory) and learning, potentially leading to cognitive deterioration and age-linked neurodegener-

ative diseases [129,130]. Excess cortisol production also leads to a decreased volume of right hippocampi and orbitofrontal cortex [131]. It showed that stress diminishes telomerase levels, thus affecting the telomere length and the genetic health of an individual. The accelerated shortening of telomeres is associated with faster aging, inflammation, and AD [132,133]. Managing stress allows alleviating the progression and implications of AD since stress is considered to be a factor that accelerates AD pathology [134,135].

A review by Jesse Russell-Williams et al. analyzed ten different studies, comprising of six studies on mindfulness (mindfulness-based stress reduction, MBSR), three studies on Kirtan Kriya (KK) meditation, and one study on mindfulness-based Alzheimer's stimulation (MBAS) [136]. The analysis highlights that the investigation by Quintana-Hernandez et al., spanning over two years, shows that mindfulness can be used as a non-pharmacological method to delay cognitive deterioration in case of mild to moderate AD patients, a study based on MBSR and KK [137]. Newberg et al. reported that practicing KK for eight weeks in case of subjective memory loss due to AD or mild cognitive impairment resulted in a significant increase in cerebral blood flow (CBF) within the frontal lobe and right superior parietal lobe [138]. A study by Paller et al. also showed that mindfulness augments attention as assessed by P3-related activity. The pre and post-analysis following eight weeks of MBSR also showed benefits like better subjective sleep quality, improved ratings of quality-of-life, and fewer depressive symptoms [139]. Studies also showed that eight weeks of KK or mindfulness sessions helped in alleviating worry [135] and soaring positive mood and energy [140]. A majority of patients found the experience to have positive impacts since the sessions were relaxing, calming, peaceful, and uplifting [141]. Thus, mindfulness can act as an efficient disease management method, and different kinds of meditation (KK, MBAS, and MBSR) can work as suitable complementary treatments.

Synaptic changes contribute to AD pathogenesis, affecting cognition. Practicing KK has shown to stabilize brain synapses by increasing neurotransmitter levels, including acetylcholine, norepinephrine, glutamate, and possibly GABA [142–144]. KK also activates the posterior cingulate gyrus (PCG) [145] which is a metabolically active region and is vital for memory and emotional functions. Reduced cerebral blood flow and hypometabolism in PCG are considered to be early signs of AD [146]. Thus, regular activation of PCG by KK can significantly contribute to decreasing AD risks [147]. A study analyzed the effects of KK on caregivers and reported that practicing KK for eight weeks helps in lowering depressive symptoms, boosting mental health, memory, and well-being. It improved the telomerase activity as well, suggesting an alleviation of stress-induced cellular aging [148]. Practicing KK also enhances sleep, poor sleep being a risk factor in the case of AD [149]. KK is thus proved to be an effective, safe, and free of side-effects. It is a self-directed program that is easy to learn and is affordable. It can be used to complement pharmacological treatments for increased preventive or therapeutic results [147].

A study by Luders et al. highlights that the brain age of people who have regularly been meditating for an extended period is found to be is 7.5 years lesser than that of the non-practitioners. The brain age was calculated using a machine learning algorithm, and scores obtained in years as BrainAGE index. Not just were the brains of practitioners of meditation found to be younger, but with every passing year, meditators' age reduced by one month and 22 days than their chronical age. Thus, there was a positive impact of meditation on the preservation of the brain and its activity. Therefore, by reducing the age-related atrophy, meditation slows the rate of brain aging [150].

EXERCISE AND AD

Higher levels of daily physical activity and exercise, complemented by bright light and proper nutrients [151], aid in lowering the chances of AD development [152]. Regular walking shows improvement in cognition [153]. In people aged 60 years or more, regular aerobic exercises enhance the production of gray and white matters in the cortical regions [154]. Physical activities, such as treadmill, ergo cycle, stair-climbing, etc., done for 40 min over 12 weeks consecutively, contribute to neuroprotective mechanisms of reduction of Aβ plaques, and increase blood flow to the cerebral region that improves neurogenesis and synaptogenesis, that will enhance memory and cognitive functions. The increased blood flow results in developing vascular reserve and maintenance of neuronal plasticity due to the activation of NO/endothelial NO synthase, thus lowered cerebrovascular and endothelial dysfunction pathophysiology is seen [155]. Exercise upregulates the

production of neurotrophins which are responsible for neurogenesis, improved memory, and brain plasticity [156].

Regular physical exercising helps in reducing the rate of production of ROS, which is associated with the onset and progression of AD. Exercising helps escalate the activity and the level of antioxidant enzymes in different regions of the brain. Thus, reducing oxidative stress [157]. Regular exercising causes a reduction in the levels of lipid peroxidation and protein oxidation. It can also limit ROS production by decreasing the ROS generating source itself or attenuating ROS generating capacity [158]. Therefore, it acts as a preventive tool to combat AD. Physical activity not only thwarts the effects of oxidative stress but also helps in lowering cholesterol and insulin resistance, subsequently leading to increased vascularization and improved energy metabolism, such as glucose metabolism [159].

A study by Nagarah et al. has shown that BDNF is critical for the upkeep of adult cortical neurons of the entorhinal cortex, whose early dysfunction furthers the initial short-term memory loss in AD. Thus, administration of BDNF helps in reversal of synapse deterioration, normalization of aberrant gene expression as well as the restoration of memory and learning [160]. Moderate to high-intensity physical exercise intensifies BDNF production, thus, bringing about its positive impacts [161].

In older healthy subjects and AD patients following one year of moderately intense aerobic exercise, i.e., 40-min session, three days per week, showed an increase of more than 2% in hippocampal volume and plasma concentration of BDNF [162]. The environmental conditions also play a crucial role in BDNF enhancement as mice trained in enriched environment showed more significant environment-related cognitive improvement in BDNF, hippocampal neurotrophin, and activation of hippocampal neurogenesis. By enriching environmental conditions, BDNF production can thus be enhanced [157]. Decrease of neurofibrillary degeneration and neuroinflammation attributed to physical training, along with prevention of loss of choline acetyltransferase expression [163,164].

Neurotrophins are proteins that mediate neuronal survival and differentiation during development, maintain neuronal viability in adults by protecting and restoring neurons in case of injury or aging. They also function as activity-dependent modulators of synaptic plasticity [165] in which BDNF is known to be an essential mediator in memory

centers of the brain [166]. Neurotrophins also have the potential to regulate genes coding for structural proteins, enzymes, or neurotransmitters, thus, modifying neuronal morphology and function. With the right standardization and universal protocols, this can be used to prescribe appropriate levels of physical exercises for brain health and to alleviate AD conditions [167].

As per a recent finding, the beneficial effects of exercising on AD models are mediated by irisin, a hormone initially discovered as an exercise-induced myokine that leads to thermogenesis and adipocyte browning, and is cleaved from a transmembrane precursor protein, fibronectin type III domain-containing protein 5 (FNDC5). Under the control of peroxisome proliferator-activated receptor-γ coactivator 1α, FNDC5 is expressed in muscle [168]. FNDC5/irisin stimulates the expression of BDNF in the hippocampus. In the case of AD, FNDC5/irisin levels are lowered in the hippocampi and cerebrospinal fluid, thus leading to impairment of cognition and novel object recognition memory. Regular physical exercise boosts the molecular levels of FNDC5/irisin, which thus mediates protection and repair of synapse function and memory impairment, and prevents cognitive decline in AD [169].

ACUPUNCTURE

Acupuncture is a traditional Chinese practice that is said to be more than 3,000 years old. It is gaining global recognition as a complementary medicine system for a variety of conditions [170]. It involves the application of heat or pressure or insertion of sharp, thin needles into the specific points on the body to stimulate nerve receptors via the connective tissue surrounding the site of application. It is aided by mechanical, electrical, or other physical manipulations [171]. Acupuncture with deeper needling is shown to induce stronger, wider-ranging *de qi* sensations and enhance nodal centrality, chiefly in the abnormal brain regions in case of mild cognitive impairment. It was reported by a small-scale functional magnetic resonance imaging study that examined the effect of *de qi* sensations induced by different needling depths on the reorganizations of whole-brain networks [172].

Some studies support the benefits of acupuncture in case of AD [173]. Eighty-seven patients with mild-to-moderate AD were involved in a clinical

trial in which acupuncture treatment, when used as a monotherapy for 12 weeks, resulted in substantial lowering in ADAS-cog scores from baseline compared with the use of donepezil. The study emphasized that acupuncture is safe and effective in improving cognitive function [174]. Ding et al. showed that manual acupuncture could significantly improve spatial learning, relearning, and memory abilities in SAMP8 mice models of AD. It could be due to the increase in CBF in prefrontal lobe and hippocampus due to the acupuncture treatment since a reduction in CBF considered a sensitive biomarker to early perfusion deficiencies in AD [175].

RHEUMATOID ARTHRITIS AND AD

Rheumatoid arthritis (RA), an autoimmune disease, is marked by synovial inflammation, cartilage and bone destruction, and autoantibody production, causing progressive disability. RA has also been linked to cardiovascular disease, diabetes mellitus, and depression. RA also causes inflammation of the heart, lungs, and blood vessels [176]. Thus, inflammation is a common implication observed in case of both RA and AD. Common inflammatory biomarkers found in the two provide evidence for the same. These include IL-6 [177,178], pentraxin 3 [179,180], resistin [179,181], etc. There is epidemiological evidence for reduced AD incidence in the case of RA due to the use of nonsteroidal anti-inflammatory drugs (NSAIDs) [182].

A study by Judge et al., based on observational studies and experimental data, highlights the inverse relationship between the manifestation of RA and AD. It shows that the use of classical disease-modifying antirheumatic drugs (cDMARDs) decreased AD risk, with methotrexate (MTX) being the most effective cDMARDs in the study. Thus, the protective effect of cDMARDs was independent of that of NSAIDs. This study brings forth the potential therapeutic use of cDMARDs in treatment of AD [183]. MTX shows limited penetrance potential of the BBB. However, even moderate penetrance shows therapeutic effects. At higher doses, it is used to treat brain tumors [184]. According to a study, administration of GM-CSF, which gets upregulated in RA, helped in reducing Aβ load and alleviating cognitive impairments in mice models of AD. The study highlighted the use of the recombinant human form of GM-CSF (Leukine®), approved by the FDA, as a therapeutic agent for AD [185].

DIABETES AND AD

Insulin signaling is damaged in the brain in the case of AD [186]. A review article by Kamal et al. highlights the similarities between AD and type 2 diabetes mellitus (T2DM) including impaired brain insulin signaling, abnormal brain glucose metabolism, amyloidogenesis, mitochondrial dysfunction, inflammation, and oxidative stress. It emphasizes that the interrelation between the two is complex and that with T2DM, AD incidences also increase. Thus, the mechanisms and factors that are common can be potential therapeutic targets [187].

The neuroprotective effect of an antidiabetic drug, triple receptor agonist (TA), that can activate glucagon-like peptide-1, glucose-dependent insulinotropic polypeptide, and glucagon receptors, was tested in the APPSWE/PS1dE9 mouse model of AD. TA treatment leads to memory and learning enhancement and reduction of amyloid plaques in the brain. It did not just ease the chronic inflammation by activating microglia and astrocytes but also reduced oxidative stress in hippocampus and cortex. TA also helped in reducing the levels of the mitochondrial pro-apoptotic signaling molecule BAX, increasing the anti-apoptotic signaling molecule Bcl-2, and enhancing the levels of BDNF, growth factor that protects synaptic function. The synaptic loss got prevented, indicated by a rise in levels of synaptophysin. It also enhanced the neurogenesis in the dentate gyrus. Thus, TA is a potential drug for AD [188].

CONCLUSION

As the global population continues to increase, the number of people affected by age-related disorders such as AD is going to increase manifold. It is predicted among the aging population, that the number of AD cases will escalate to 135 million by 2050. Thus, alternative preventive and therapeutic strategies are attracting mounting attention for advanced research and development of appropriate medicine systems. It is attributed to their efficacy and safe usage as they are shown to have little or no side effects and potential to provide overall wellbeing.

AD is not just crippling for the health of the patient but also imposes an economic burden on the patients and caregivers as it demands long-term medication, healthcare, and caregiving services, thus, necessitating the need to promptly formulate and adapt economically viable long-term medication and

assistance systems to address the concerning rise of AD incidences in the coming future.

Ayurveda drugs including turmeric, *Brahmi*, etc., natural dietary products, vitamins, meditation and management of stress, regular exercising, and traditional Chinese practices are significant in contributing toward the development of such alternative strategies. The anti-AD treatment systems discussed to provide an economical alternative to strive to combat the disease, derived from nature or naturally existing resources. Besides, various drugs in use for RA as well as diabetes also have therapeutic potential for anti-AD treatment. To efficiently establish the effectiveness of the alternative therapeutic and preventive strategies suggested, research studies with more extensive sampling size and appropriate control groups are required.

It would be correct to conclude that the alternative strategies discussed have proven to be efficient in preventing, treating, curing, or managing AD. They have also proven to be useful for the wellbeing of the caregivers. The drugs and treatment options currently available do not fully cure or reverse the effects of the disease. These strategies can thus be used in combinations to complement the mainstream AD treatments presently being used for better management of the disease condition and increased cognition and memory of the patients.

CONFLICT OF INTEREST

The authors have no conflict of interest to report.

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