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Medicinal plants for Alzheimer's disease: An updated review

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Abstract
Alzheimer's disease is the major cause of dementia worldwide. The number of patients suffering from dementia continue to rise reaching pandemic levels. Alzheimer's disease is highly debilitating; starting from memory complains leading ultimately to complete dependence and inability to perform daily living tasks. Late initiation of Alzheimer's disease medications is argued to reduce their efficacy. The current treatment options provide symptomatic improvement without hindering the disease progression. The lack of disease-modifying drugs necessitates the development of newer therapeutic agents and different target-based strategies due to the complexity of underlying pathologies. Various plants and herbal preparations have been traditionally used for their memory and cognitive enhancing abilities; many of which were extensively studied in the last few years for therapeutic potential in Alzheimer's disease. This review will focus on recent research finding regarding the efficacy of various plants according to their; cognitive enhancing, neuroprotective, antioxidant, and anti-inflammatory properties in Alzheimer's disease.

Keywords: Alzheimer's disease, medicinal plants, Neuroprotection, antioxidants, anti-inflammatory, cognitive enhancers

Introduction
Alzheimer's disease (AD) is the major cause of dementia worldwide. The estimated number of individuals with dementia is 46.8 million and it is expected to reach 74.7 million by 2030 according to the 2015 world Alzheimer report [1]. AD is characterized by a progressive decline in cognitive functions starting with short-term memory deficits and ultimately leading to profound neuronal loss, brain atrophy, and massive deterioration in the patients' quality of life [2]. The major hallmark of AD is the accumulation and disposition of β-amyloid protein oligomers that have direct neurotoxic and pro-inflammatory effects [3]. AD puts a tremendous economic and social burden on the patients and their families. Furthermore, the growing number of patients reaching pandemic levels and the lack of medications to halt the disease progression necessitate the development of novel therapies to counteract AD desolation. The current "standard" treatments for AD, include; acetylcholinesterase inhibitors (e.g. donepezil, rivastigmine and galantamine) and the N-methyl-D-aspartate (NMDA) receptor antagonist memantine. However, their efficacy is limited with low response rates that only provide a symptomatic improvement [4]. Moreover, recent research findings revealed other mechanisms besides acetylcholinesterase inhibition and NMDA receptor blockade for cognitive enhancement. Hence, different target-based approaches should be followed in the development of other AD medications. The pathophysiology of AD is complex with various histological, cellular, and biochemical manifestations that are still unknown to be either causative or consequential. Despite the increased understanding of AD-associated; neuroinflammation, neurovascular disruption, neurotransmitter imbalance, neuronal excitotoxicity, metabolic dysfunction, reduced neuroprotective capacity, and homeostatic failure, the interplay between different processes is complex and long-term consequences of any alteration are unknown [5]. For centuries, plants have been used in the treatment of a wide range of conditions and diseases. Traditional herbal medicine including Chinese and Ayurvedic ones have been considered important sources in drug screening programs for the generation of lead structures in the drug discovery and development process. Multiple herbal preparations were traditionally used for their cognitive enhancing activity in the elderly. The lack of new therapeutic options and strategies for AD has directed researchers towards phytotherapy. Multiple clinical and *in vivo* studies have been conducted in order to; evaluate the extent and true potentials of certain medicinal plants that are believed to improve cognition, identify the biologically active

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constituents, and discover the underlying pathways. This review will focus on the most recent research findings regarding the potential of a number of medicinal plants in the management of AD.

Plants for Alzheimer's Disease
Ginkgo biloba
Ginkgo leaf extract has been traditionally used in the treatment of individuals with blood and memory issues, and is currently considered the most studied herbal preparation for AD. Ginkgo supplements are widely used for their effects on mood, energy, and memory [6]. Gingko beneficial effects on cognitive function of the young and elderly are well known and established. A study with a 20-year follow-up on non-demented patients above 65 years old, was conducted to evaluate the clinical effects of ginkgo supplementation (EGb-761) in comparison to non-receiving and piracetam-receiving groups. Using the mini-mental state examination (MMSE) score, ginkgo-supplemented group had the least decline while piracetam, which is believed to boost brain function, accelerated MMSE score decline [7]. In a 2015 study, evaluating the effects of ginkgo extract (EGb-761) and hyperbaric oxygen, an AD mouse model induced by the injection of β-amyloid aggregates was used [8]. The results showed a significant improvement in memory and cognitive abilities assessed by Morris water maze test; moreover, reduced hippocampal neuronal apoptosis was achieved through the activation of nuclear factor kappa-B pathway. The combined treatment of ginkgo extract and hyperbaric oxygen was more effective than monotherapy [8]. A study evaluating long-term administration effects of gingko EGb-671 extract using APP-transgenic TgCRND8 mice was conducted. Gingko extract was found to; promote autophagy, reduce synaptic impairment, minimize cognitive dysfunction, and inhibit neuronal inflammation through blocking β-amyloid activation of microglia [9]. Gingko leaf extract was clinically found to enhance cognitive functions in non-demented elderly, AD patients, and vascular dementia patients; via reducing mitochondrial dysfunction. Thus, supporting the dementia mitochondrial cascade hypothesis [10]. In various studies, EGb-761 was found to be efficacious in the treatment of mild cognitive impairment in patients with neuropsychiatric symptoms, which has improved their behavior, functionality, and cognition [11].

Salvia officinalis
Sage is one of the most used plants in folk medicine. It has been used in the management of multiple conditions; for instance, rheumatism, ulcers, inflammation, gout, tremor, and dizziness [12]. In addition, it is found to exhibit anti-inflammatory, antioxidant, antinociceptive, and anti-dementia properties [12]. Previously, due to its reported mood/cognitive enhancing abilities and proposed cholinergic effects; sage extract was clinically tested in mild to moderate cases of AD. Using the clinical dementia rating (CDR) and Alzheimer's disease assessment scale (ADAS-cog), the oral administration of Salvia extract over a period of four months has illustrated a significant improvement in the cognitive state with lesser reports on agitation occurrences compared to placebo [13]. A systematic review of 16 clinical trials of two Salvia species; S.officinalis and S.lavandulaefolia, has assessed their memory and cognitive enhancing abilities in healthy individuals, mildly-demented and AD patients. In all of the enrolled groups, different sage preparations were found to be effective in improving memory and cognitive functions [14]. Various

active constituents of S.officinalis have been isolated and analyzed, in which phenolic diterpenes were found to be responsible for the majority of the observed biological effects and were suspected to have an acetylcholinesterase inhibition activity [15]. Using Ellman's method and molecular docking for affinity determination, two of the seven isolated diterpenes; isorosmanol and 7α-methoxyrosmanol, have potently inhibited acetylcholinesterase by 65% and 50% respectively, concluding a possible therapeutic potential of these compounds in the management of dementia-related disorders [15]. Despite the lack of a standardized extract, research findings show a promising potential of sage in AD. Nevertheless, further analytical testing together with better understanding of S.officinalis properties will aid in identifying the mechanisms mediating its effects.

Melissa officinalis
M. officinalis (also known as lemon balm) belongs to the plant family Lamiaceae/Labiatae. Lemon balm is well known for its central effects, using either the leaves tea extract or its essential oil. It was widely used as a herbal remedy to reduce stress, improve sleep, elevate mood, and enhance concentration [16]. A double-blind randomized placebo-controlled trial using M.officinalis extract was conducted to evaluate its therapeutic potential in mild to moderate AD patients. The extract's beneficial effects on cognitive functions were statistically significant at 4-months of treatment, as measured through CDR and ADAS-cog scale [13]. In addition to its suggested muscarinic and nicotinic binding properties, M.officinalis is also found to exhibit antioxidant, anti-inflammatory, anxiolytic, antidepressant, and neuroprotective effects, all of which are key elements in AD management [17]. Central antioxidant effects of lemon balm extract were assessed against manganese (Mn)-induced oxidative damage in mice, in which mice were exposed to Mn for 3 months, followed by a concomitant Mn and extract treatment for additional 3 months. The study results showed a significant attenuation of superoxide dismutase as well as catalase enzymes, reduced oxidative damage, and lowered total thiol markers compared to placebo [18]. Moreover, M.officinalis acidic-fraction extract was found to display potent neuroprotective effects against toxic oxidative damage of β-amyloid. Terpenoic acids and polyphenolic compounds were responsible for the mediated effects while cholinesterase inhibition role was insignificant [19]. Furthermore, lemon balm extract was shown to significantly enhance learning/memory in naïve rats and ameliorate scopolamine-induced impairment in the scopolamine treated group. Nevertheless, the effects were not dose-dependent and higher doses (above 200 mg/kg) were not effective [20]. In an in vitro study conducted to evaluate the effects of ethyl acetate extract fraction of M.officinalis, which was found to contain the most active flavonoids (e.g. gallic acid), the extract had an anticholinesterase activity and potent antioxidant properties with promising potential in AD treatment [21].

Rosmarinus officinalis
Rosemary leaf extract has been suggested to enhance cognition, relieve migraine headache, and treat insomnia [22]. A study on a rat model was conducted to investigate the possible mechanisms mediating rosemary's cognitive effects and its ability to inhibit butyryl-/acetyl-cholinesterase enzymes. Short-term (4-weeks) administration of the leaf extract has resulted in improved cognition, long-term memory, acetylcholinesterase inhibition, and hippocampal

increase of butyryl-cholinesterase activity and expression in the scopolamine-treated rats [23]. The flavonoid o-glycoside nepitrin, which is found in high levels in rosemary, has been tested for its memory-enhancing properties *in vivo*. Using scopolamine-induced amnesia model in rats, nepitrin reversed memory impairments as evident through the novel object recognition and Y-maze tests. In addition, nepitrin inhibited the activity of both acetyl- and butyryl-cholinesterases; moreover, nepitrin binding site was found to be the same as donepezil [24]. Rosemary also contains high levels of diterpenes that are suggested to have antioxidant, anxiolytic, antidepressant, anti-inflammatory and neuroprotective effects [25].

Curcuma longa
Zingiberaceae family plants, especially turmeric (*C.longa*), are the major source of curcumin which has been extensively investigated for its therapeutic efficacy in various disorders. Curcumin has been found to exhibit potent antioxidant, anti-inflammatory, and cognitive enhancing properties; in addition to, its ability to break down β-amyloid plaques [26]. Due to solubility issues, curcumin has been integrated with nanoparticles in order to enhance its oral bioavailability and central nervous system penetration. In a study on TG2576 AD mice evaluating oral nano-curcumin treatment (3-months) effects compared to unformulated curcumin, the nano-curcumin had 6-times higher area under the curve and significantly enhanced working memory [27]. In another formulation, PLGA-encapsulated curcumin nanoparticles, the treatment displayed potent antioxidant and β-amyloid aggregate destruction abilities [26]. Furthermore, long-term turmeric capsule treatment was found to improve behavioral and psychological symptoms of dementia (BPSD) and prevent associated exacerbations [28]. Surprisingly, curcumin PLGA-encapsulated nanoparticles have been found to modulate gene expression in the hippocampus and activate Wnt/β-catenin pathway resulting in neurogenesis, enhanced neuronal differentiation, and reversal of cognitive and memory defects in AD mouse model of acute β-amyloid exposure [29]. It is also found that curcumin and its analogs (i.e. curcuminoids) display potent and highly selective binding to amyloid plaques observed via postmortem studies, a property of essential need in the development of AD-associated plaque imaging techniques and radioligands [30]. The results of several *in vivo* and *in vitro* studies illustrate the ability of curcumin to modulate β-amyloid aggregation, regulate its production, interfere with its neurotoxic effects, and aid in its clearance together with improvements in cognition, memory, behavioral and psychiatric symptoms; therefore, curcumin has a high potential in the treatment of AD [31].

Panax ginseng
Ginseng is one of the most cultivated and consumed plants that can be found in various supplemental products. Ginseng tea has been used to increase physical/mental capacity, improve stress tolerance, and enhance memory/cognitive functions [32]. Red Korean Ginseng (RKG) is a steam-dried product of *P.ginseng* with an altered ginsenosides content. In a study conducted on AD patients, treatment with RKG (24 weeks) has significantly improved cognitive functions, and its long-term activity sustained up to 96 weeks [33]. A lysophosphatidic acid receptor agonist called gintonin was isolated from *P. ginseng* [34]. Gintonin was found to activate a non-amyloidogenic pathway resulting in the formation of a soluble neuroprotective amyloid precursor variant. Gintonin

treatment reduced the production, attenuated the toxicity, and reversed cognitive defects of β-amyloid in AD transgenic mice [34]. The administration of fermented ginseng to scopolamine-treated (2-weeks) and transgenic mice (4-months) AD models resulted in significant reduction of soluble β-amyloid level and recovery of memory functions [35]. At last, ginseng protein administration to galactose/AlCl3-induced AD mice reduced the levels of soluble β-amyloid and tau-protein. In addition, increased the expression and activation of PI3K/Akt pathway in the hippocampus [36].

Centella asiatica
Centella has gained the attention of researchers in the last few years due to its wide range of biological effects, including; antidiabetic, antibacterial, cardioprotective, anticonvulsant, sedative, antioxidant, anti-inflammatory, and neuroprotective properties [37]. *In vitro,* centella ethanol extract was found to improve neuronal viability, reduce neurotoxicity, and lower oxidative damage of β-amyloid aggregates exposure [38]. Centella water extract (CAW) treatment was found to improve learning, memory, and cognitive functions in aged mice; in addition, enhanced mitochondrial and antioxidant pathways' gene expression [39]. Moreover, CAW treatment in TG2576 APP-overproducing mice improved synaptic differentiation, neuronal arborization, and prevented dendritic growth restriction of β-amyloid in the spinal cord. Triterpenes and caffeoylquinic acids were found to differentially mediate most of the observed neuroprotective effects [40]. Centella treatment was able to attenuate all AD pathologies related to AlCl3 exposure, in AlCl3-induced AD model in mice. As centella reversed the elevations in; amyloid precursor protein (APP) expression, ϒ-secretase activity, β-amyloid production, and inflammatory markers such as interleukins; IL-1β, IL-2, IL-4, IL-6, and TNF-α [41].

Conclusion
The wide range of therapeutic targets, biological effects, and structural variations of medicinal plants' active constituents, have made phytomedicine and plant-derived lead structures of a significant value in the development of AD treatments. Different species of traditional plants were found to display multiple mechanisms in mediating the observed cognitive improvements. Thereby, creating a multi-target potential in the management of AD via its combined properties of; anti-inflammatory, antioxidant, and neuroprotective effects, that counteract β-amyloid disposition and neurotoxicity. Moreover, clinically studied preparations have been found to be relatively safe with no reports of serious adverse events. Further research is required for a complete understanding of the involved pathways from the level of gene expression and molecular basis up to the reflection on the clinical state. Research findings have revealed the futuristic potential of a number of medicinal plants in AD; nonetheless, robust long-term drug-controlled clinical trials are needed in order to confirm their efficacy.

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