

Essential Oils as Treatment Strategy for Alzheimer's Disease: Current and Future Perspectives

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ABSTRACT

Alzheimer's disease is a multifarious neurodegenerative disease that causes cognitive impairment and gradual memory loss. Several hypotheses have been put forward to postulate its pathophysiology. Currently, few drugs are available for the management of Alzheimer's disease and the treatment provides only symptomatic relief. Our aim is to review the relevant *in vitro*, *in vivo*, and clinical studies focused toward the potential uses of essential oils in the treatment of Alzheimer's disease. Scientific databases such as PubMed, ScienceDirect, Scopus, and Google Scholar from April 1998 to June 2018 were explored to collect data. We have conducted wide search on various essential oils used in different models of Alzheimer's disease. Out of 55 essential oils identified for Alzheimer's intervention, 28 have been included in the present review. A short description of *in vivo* studies of 13 essential oils together with clinical trial data of *Salvia officinalis*, *Salvia lavandulifolia*, *Melissa officinalis*, *Lavandula angustifolia*, and *Rosmarinus officinalis* have been highlighted. *In vitro* studies of remaining essential oils that possess antioxidant and anticholinesterase potential are also mentioned. Our literary survey revealed encouraging results regarding the various essential oils being studied in preclinical and clinical studies of Alzheimer's disease with significant effects in modulating the pathology through anti-amyloid, antioxidants, anticholinesterase, and memory-enhancement activity.

Introduction

Alzheimer's disease (AD) is a multifarious neurodegenerative disease that causes cognitive impairment and gradual memory loss. Senile plaques and neurofibrillary tangles (NFTs) comprised of amyloid β ($A\beta$) peptides and hyper-phosphorylated tau proteins, respectively, are the classic pathological hallmarks of AD [1]. Several hypotheses have been put forward to reveal the pathobiology of the disorder including cholinergic hypothesis, inflammation hypothesis, oxidative stress, mitochondrial cascade hypothesis, and metabolic hypothesis [2,3]. According to the World Health Organization, AD is the most common form of dementia and accounts for about 60–70% of all dementia cases [4]. There is more prevalence for people aged over 65 y [5]. Epigenetic variations on the genetic material of neurons can result in neurodegenerative disorders and these variations in AD genes change from region

to region [6]. Familial Alzheimer's disease (FAD) and sporadic Alzheimer's disease are the 2 specific types of AD [7]. The combined action of environmental and genetic factors might be culpable for the SAD and FAD types [8]. Depending on the age of onset, AD can be further grouped into early onset (EOAD) and late onset (LOAD) [9]. Mutations in some specific genes like amyloid precursor protein (APP), presenilin I, and presenilin II are responsible for EOAD whereas apolipoprotein E is the only gene identified that causes LOAD [10]. Approximately 5% of the AD cases is familial early onset type and it develops before 65 y of age, and the remaining 95% accounts for sporadic late onset type and it develops after 65 y of age [11, 12].

The neuropathophysiology of the neurodegeneration in AD is triggered by anomalous deposition of amyloid plaques and NFTs in varied regions of the brain involved in cognition and memory [13]. Amyloid plaques are protein fragments composed of $A\beta$

ABBREVIATIONS

ABTS	2,2-azinobis(3-ethylbenzthiazoline-6-sulfonic acid)
ACh	acetylcholine
AChE	acetylcholinesterase
AD	Alzheimer's disease
A β	amyloid β
APP	amyloid precursor protein
BChE	butyrylcholinesterase
DPPH	1,1-diphenyl 2-picrylhydrazyl
EOAD	early onset Alzheimer's disease
EO	essential oil
FAD	familial Alzheimer's disease
ICV	intracerebroventricular
LD ₅₀	lethal dose 50%
LOAD	late onset Alzheimer's disease
MCFA	medium-chain fatty acid
MWM	Morris water maze
NFTs	neurofibrillary tangles
SAD	sporadic Alzheimer's disease
SHXW	SuHeXiang Wan
ZM	<i>Zataria multiflora</i> Boiss

peptides originated from APP by the synergistic action of enzymes β -secretase and γ -secretase [14]. Polymerization of these A β peptides results into insoluble filaments that build up in the walls of cerebral blood vessels and configure senile plaques. Microglial activation, reactive astrocytosis, cytokine release, and neuro-inflammation also occur in accordance with the formation of amyloid plaques [15]. NFTs are made up of tau protein found inside the neurons as a bunch of insoluble fibers. Hyperphosphorylation of these tau proteins results in the formation of paired helical filaments and finally forms microscopic tangles that cause cell death [16].

Out of all above pathogenetic pathways, the mechanisms of essential oils (EOs) are associated with cholinergic hypothesis and oxidative stress hypothesis. As stated by cholinergic hypothesis, loss of cholinergic neurotransmission in the cerebral cortex and the destruction of cholinergic neurons in the basal forebrain disturb cognitive function [17]. Depletion of acetylcholine (ACh) level is usually noticed in dementia patients and exploratory studies in animals and humans have also confirmed the role of ACh in learning and memory [18]. Oxidative stress is inevitably linked with various primary AD pathogenesis such as A β -induced neuronal loss, mitochondria dysfunction, tau protein pathology, and disturbance in metal homeostasis [19]. Senile plaques mediated oxidative imbalance can elevate the levels of lipid peroxidation by-products, DNA/RNA oxidation, and protein oxidation in several regions of the brain. In addition, oxidative stress causes depletion of brain antioxidants level like uric acid, vitamin C and E and antioxidant enzymes such as catalase, glutathione reductase, superoxide dismutase, etc. [20].

At present, very few drugs are available for the medical care of AD and are directed toward symptomatic relief. The currently

available U.S. Food and Drug Administration approved drugs in the market for AD include cholinesterase inhibitors (rivastigmine, galantamine, and donepezil) and N-methyl-D-aspartate receptor antagonist (memantine) [21]. Tacrine has been the first approved drug (1993) as a reversible inhibitor of AChE later on abandoned in 2013 due to its hepatotoxicity, short half-life, and cholinergic side effects [22]. Huperzin A obtained from *Huperzia serrata* (Thunb.) Trevis (Lycopodiaceae) is a naturally derived AChE inhibitor used in the treatment of memory ailments in China [23].

EOs constitute a blend of enormously complex, volatile, naturally derived compounds that are obtained as secondary metabolites from plants. They are found to be copious in leaves, seeds, flowers, barks, and rhizomes and are commonly obtained through cold pressing, hydro-distillation methods [24]. Its major constituents include monoterpenes hydrocarbon, sesquiterpenes hydrocarbon, oxygenated sesquiterpenes, oxygenated monoterpenes, and esters [25]. A review on therapeutic and pharmaceutical use of EOs related to cardiovascular disease, cancer, antidiabetic, penetration enhancer, antimicrobial, massage therapy, neuroprotective, aromatherapy, and anti-aging effects revealed the immense medicinal benefits of EOs [26]. Dobetsberger and Buchbauer [27] pointed out the analgesic, anxiolytic, anticonvulsive, and anti-AD effects. Recently, the anti-aging and neuroprotective effects of numerous EOs and their involvement in various brain disorders have been outlined [24]. Studies revealed that EOs are classic naturally derived antioxidants and most of them exhibits cholinesterase inhibitory potential and are relevant in AD pathogenesis [28]. ► **Table 1** shows the list of EOs with respect to their anti-Alzheimer's intervention.

Methods and Results

Scientific databases such as PubMed, ScienceDirect, Scopus, and Google Scholar from April 1998 to June 2018 were explored to collect data. The keywords searched were Alzheimer's disease, EOs, amyloid hypothesis, NTFs, antioxidants, acetylcholinesterase, and dementia. We have conducted wide search on various EOs used in different models of AD. A total of 540 papers were obtained by scientific search, and 89 papers found to be relevant to the review. Studies of about 55 EOs were identified for Alzheimer's intervention. Twenty-eight EOs were finally included based on the quality of the study of which short descriptions of *in vivo* studies of 13 EOs together with clinical trial data of *Salvia officinalis* L., *S. officinalis* L. ssp. *lavandulifolia* (vahl) Gams, *Melissa officinalis* L., *Lavandula angustifolia* Mill., and *Rosmarinus officinalis* L. were highlighted. Chemical constituents and medicinal benefits of the EOs, animal models, doses and time of administration, study duration, behavioral parameters, and biochemical and histological assessments were also summarized. *In vitro* studies of 15 EOs that possess antioxidant and anticholinesterase potential are also mentioned.

Coriandrum sativum

Coriandrum sativum L. (coriander) of Umbelliferae/Apiaceae family has been reported to have anti-anxiety, anticonvulsive, antioxidative, antispillage, hypoglycemic, anti-inflammatory, antimutagenic, diuretic, antihypertensive, carminative, hypolipidemic,

► **Table 1** List of EOs with respect to their anti-Alzheimer's intervention.

Plant/source	Study design	Results	Reference
<i>C. sativum</i>	ICV A β (1–42)-induced AD in rats	Reduced oxidative stress induced by A β (1–42) and confer neuroprotective effects	[31]
<i>S. aromaticum</i>	ICV colchicine-induced AD in rats	Reversed memory impairment, restored the levels of ACh and antioxidants, reduced neuroinflammation and mitochondrial dysfunction in colchicine treated rats.	[33]
<i>Z. multiflora</i>	ICV A β (25–35)-induced AD in rats	Reversed A β -induced learning deficits, exhibited antioxidant, anti-inflammatory and anti-cholinesterase activities.	[35]
SuHeXiang Wan	<i>Drosophila</i> model of AD	Neuroprotective effects	[39]
	ICV A β (1–42)-induced AD in ICR mice	Reversed A β (1–42)-mediated memory deficit Suppressed A β (1–42)-mediated JNK, tau phosphorylation, and p38 in the mice hippocampus.	[40]
<i>A. nemorosa</i>	Scopolamine-induced spatial memory impairment in rats	Prevented cognitive defects.	[42]
<i>S. officinalis</i>	Single blind trial in healthy volunteers	Enhanced mood and cognitive performance	[45]
<i>S. officinalis</i> ssp. <i>lavandulifolia</i> (vahl) Gams	Single blind trial in healthy volunteers	No significant effects.	[45]
	Clinical study in healthy volunteers for mood and cognition.	Enhanced mood and cognition	[50]
	Clinical trial in mild/moderate AD patients	Improved memory and cognition	[51]
<i>M. officinalis</i>	Double-blind placebo-controlled trial in AD patients	Improved agitation and quality of life indices	[54]
	Clinical trial in AD patients	No significant effects	[55]
	Anti-agitation studies	Anti-agitation effects	[56, 57]
<i>J. communis</i>	ICV A β (1–42)-induced AD in rats	Reduced memory impairment, antioxidant and anti-cholinesterase potential	[59, 60]
<i>C. nucifera</i>	Prospective study in AD patients	Improved memory status in AD patients.	[62]
	<i>In vitro</i> neurotoxicity study in rat cortical neurons	Neuroprotective effects	[63]
<i>P. peregrina</i>	Scopolamine-induced memory deficits, depression, and anxiety in a rat model of AD	Hindered depression, anxiety, and memory deficits.	[65]
<i>L. angustifolia</i>	Scopolamine-induced amnesia model in rats	Hindered depression, anxiety, and memory deficits.	[69]
	Clinical trials	Improved mood and cognitive performance.	[70, 71]
<i>R. officinalis</i>	Scopolamine-induced dementia model in mice	Reduced memory impairment.	[75]
	Memory performances in aged and young mice.	Improved memory performances	[76]
	Clinical trials	Improved mood and cognitive performances	[70, 71, 76–78]

AD: Alzheimer's disease, ICV: intra-cerebroventricular, A β : amyloid β

antispasmodic, and antidepressant effects [29]. The major constituents of its EO include linalool (60–80%), terpinen-4-ol (3%), r-cymene (3.5%), γ -terpinene (1–8%), α -pinene (0.2–8.5%), linalyl acetate (0–2.7%), α -terpineol (0.5%), camphor (0.9–4.9%), camphene (1.4%), myrcene (0.2–2.0%), geranyl acetate (0.1–4.7%), and geraniol (1.2–4.6%) [30]. The effects of EO from dried fruits of *C. sativum* in AD has been studied in an *in vivo* study by Cioanco et al. [31] AD model was developed in rats by ICV A β (1–42) injection and the animals of the test group were made inhale *C. sativum* EO (1% and 3%) daily for 21 d. Cognitive performances were evaluated using radial arm maze and Y-maze tests. A β (1–42)-treated rats showed notable cognitive dysfunction, which was significantly reversed by EO inhalation. Coriander oil inhalation significantly decreased levels of SOD, LDH, and MDA and increased

glutathione peroxidase levels in rat hippocampus. Presence of amyloid deposits were abundant in rats brain induced with ICV A β (1–42) and the deposits were less in rats treated with both doses of *C. sativum* EO. Authors concluded that exposure of *C. sativum* EO in A β (1–42)-induced rats could capably rebuild brain antioxidant status and confer neuroprotective effect possibly due to suppression of oxidative stress caused by A β (1–42).

Syzygium aromaticum

Syzygium aromaticum (L.) Merr. & L. M. Perry. (clove) is an aromatic flower bud of Myrtaceae family. Clove oil is a mind stimulant used for medical care in anxiety, insomnia, and depression. The active constituents of its EO are eugenol (87.34%) and smaller amounts of eugenol acetate (5.18%) and β -caryophyllene (2.01%) [32]. The

neuroprotective potential of clove oil in ICV colchicine-induced memory impairment in rats has been reported in a study by Kumar et al. [33]. Male SD rats were subjected to intraperitoneal injection of minocycline (25 and 50 mg/kg), clove oil (0.05 mL/kg and 0.1 mL/kg), and their combinations for 21 d. ICV colchicine-treated rats showed significant cognitive impairment in Morris water maze (MWM) test and showed an increase in AChE activity, oxidative stress, neuro-inflammation, and mitochondrial dysfunction as compared to control group. Treatment with clove oil was found to reverse the memory impairment, restored the levels of ACh and antioxidants, and reduced neuroinflammation and mitochondrial dysfunction in colchicine-treated rats. Authors highlighted that the favorable potential of clove oil in reversing memory impairment and cognitive dysfunction is due to its antioxidative, mitochondrial-restoring, and microglial inhibitory mechanisms.

Zataria multiflora

Zataria multiflora Boiss (ZM), belonging to Lamiaceae family, is a traditional Iranian herb with anti-inflammatory, antibacterial, antifungal, spasmolytic, antinociceptive, antiprotozoal, antioxidative, and immune stimulant properties. The main constituents of its EO include thymol (40.94%), carvacrol (22.23%), p-cymene (7.73%), linalool (7.92%), caryophyllene (3.95%), and γ -terpinene [34]. Majlessi et al. [35] mentioned the beneficial effects of EO from the leaves of ZM in ICV $A\beta(25-35)$ -induced AD model in rats. Seven days after induction of disease, EO was administered in a dose of 50, 100, and 200 μ g/mL (i. p.) 30 min prior to MWM task. $A\beta$ injection in the rat brain remarkably impaired the ability of rats to locate the hidden platform in MWM task. Administration of ZM EO significantly reversed $A\beta$ -induced learning deficits. Also, LD₅₀ of EO was determined in male NMRI mice and was found to be 1264.9 μ L/kg. Authors concluded that EO administration remarkably reversed $A\beta(25-35)$ -induced cognitive dysfunction in rats due to its antioxidant, anti-inflammatory, and anticholinesterase activities. Further studies are needed to detect the presence of amyloid peptides and neurological alterations and more significant results can be obtained.

SuHeXiang Wan

SuHeXiang Wan (SHXW) is a conventional Chinese medicinal mixture of about 15 crude herbs including *Cyperus rotundus* L., *Atractylodes macrocephala* Koidz., *Boswellia sacra* Flueck., *Bubalus bubalis* Linnaeus L. horn powder concentrate, artificial moschus, *Santalum album* L., *Aquilaria sinensis* (Lour.) Spreng, *Borneolum*, *Syzygium aromaticum* (L.) Merr. & L.M. Perry, *Aucklandia lappa* DC., *Piper longum* L., *Terminalia chebula* Retz., *Liquidambar orientalis* Mill., and *Styrax tonkinensis* Craib ex Hartwich and *Cinnabaris* [36]. Traditionally, it has been used for seizures, infantile convulsion, CNS depression, and stroke. Analgesic, anticonvulsant, antioxidative, and sedative effects of its EO has been reported [37]. Modified SHXW exhibited neuroprotective effects in drosophila model of AD [38, 39]. Jeon et al. demonstrated the memory enhancement effect of SHXW EO in an ICR mice model of AD. ICV $A\beta(1-42)$ - or $A\beta(42-1)$ -induced mice were subjected to inhalation of 2 g EO twice daily for 21 d. Behavioral parameters were assessed by step-through passive avoidance and Y-maze tests. The

signaling mechanism was examined by measuring the phosphorylation status of the stress stimulated JNK, protein kinases, and p38 in the mice brain. SHXW treatment significantly reversed the $A\beta(1-42)$ -mediated memory deficit by suppressing $A\beta(1-42)$ -mediated JNK, tau phosphorylation, and p38 in the mice hippocampus. In addition, an *in vitro* investigation was also performed to examine the inhibitory potential of SHXW EO in $A\beta(1-42)$ -induced neurotoxicity in SH-SY5Y cells. Not reported were any toxic effects on cell viability assays. EO suppressed $A\beta$ -induced apoptosis and exhibited antioxidant effect through an upregulation of Nrf2 and HO-1 expression in SH-SY5Y cells [40].

Anthriscus nemorosa

Anthriscus nemorosa (M. Beib.) Spreng. (chervil) is a common plant genus belonging to the family Apiaceae. Its EO contains caryophyllene (23.6%), germacrene D (5.6%), α -terpineol (2.7%), β -elemene (4.2%), and trans-pinocarveol (9.8%) as major constituents. The antimicrobial property of its EO has been reported [41]. The EO obtained from the aerial parts of *A. nemorosa* has been studied by Bagci et al. [42] for its beneficial effects on anxiety, depression, and cognition in scopolamine-induced amnesia model in rats. The rats were exposed to inhalation of *A. nemorosa* EO for 21 d and behavioral parameters were analyzed by Y-maze and radial arm-maze tasks. Scopolamine (0.7 mg/kg i. p.) was administered 30 min prior the behavior testing. Also, anxiety- and depression-like behaviors were tested in elevated plus-maze and forced swimming tests, respectively. Positive results were obtained for EO-treated groups in all behavioral tests, suggesting the benefits of *A. nemorosa* EO against cognitive defects, anxiety, and depression. Even though there was some behavioral evidence for memory improvement, more findings are required to elaborate the benefits of *A. nemorosa* in cognitive dysfunction.

Salvia species

The *Salvia* genus include around 900 species, of which *Salvia officinalis* L. (common sage/sage) and *Salvia officinalis* L. ssp. *lavandulifolia* (Vahl) Gams (Spanish sage) of Lamiaceae family have prominent medicinal benefits [43]. The active constituents of *S. officinalis* EO are camphor (95.5%), 1,8-cineole (59.0%), cis-thujone (65.5%), trans-thujone (40.1%), α -humulene (33.7%), and linalool (35.0%). *S. lavandulifolia* EO contains 1,8 cineole (34.5%), α -pinene (23.2%), β -pinene (19.2%), limonene (16.6%), camphor (15.4%), and β -caryophyllene (8.1%) as main constituents [44]. In a single-blind randomized controlled trial led by Moss et al. [45], the reputed effects of these EOs on mood and cognition in healthy volunteers have been evaluated. *S. officinalis* EO-treated group showed better positive performance compared to control group. Results confirmed an enhancement in mood and cognitive performance deliberated through Bond-Lader mood scales and cognitive drug research system, respectively. EO of *S. lavandulifolia* does not exhibit any significant effects. EO of *S. lavandulifolia* and its constituents reported antioxidant [46], anti-inflammatory, oestrogenic [47], CNS depressant, and AChE inhibitory potential in bovine erythrocyte and human brain tissue [48] and in rat brain [49]. In a clinical trial conducted in healthy volunteers, EO treatment reported successive results on mood and cognition [50]. Oral administration of *S. lavandulifolia* EO in patients with mild/

moderate AD reported significant improvement in memory and cognition in a pilot open-label study [51]. Even though *S. lavandulifolia* EO possesses antioxidant, anti-inflammatory, anti-AChE, and memory enhancement potential, it fails in a clinical study [45] and that might be due to lack of standardization and pharmacokinetics studies of this EO. The concentration of bioactive components varies in plants based on its region, climate, etc., and this variation remains a major drawback concerning the properties of EO and is likely to remain so.

Melissa officinalis

Melissa officinalis L. (lemon balm) of Labiatae has been used traditionally in nervous system diseases, cognitive dysfunction, and sedation [52]. Geranial (65.4%), geranyl acetate (7.4), neral (24.7%), (Z)-carveol (0.1%), linalool (0.8%), myrtenol (0.1%), farnesene (0.1%), 2,3-dehydro-1,8-cineole (0.1%), and caryophyllene (0.8%) are the active components that have been isolated from the leaves of *M. officinalis* EO [53]. Agitation is one of the main symptoms of AD. Aromatherapy of *M. officinalis* EO or placebo (sunflower oil) in a double-blind placebo-controlled trial in 72 Alzheimer's patients (agitation with severe dementia) has been reported by Ballard et al. [54] Patients were advised to apply oil combined with base lotion in faces and arms twice daily for 4 wk. Treatment analysis like Cohen-Mansfield Agitation Inventory score and quality of life indices were assessed and the results reflected 35% and 11% improvement in agitation in EO and placebo-treated groups, respectively. Later in 2011, a clinical trial report revealed that massaging EO in hands and upper arms of dementia patients with agitation does not produce any significant results compared to standard drug donepezil or placebo oil [55]. However, positive results of *M. officinalis* oil for its anti-agitation potential have also been reported [56, 57]. While all these trials comprised comparatively short duration and small sample sizes, the significant improvement in agitation with *M. officinalis* oil appear to explain the importance for further long-term clinical studies, assessment of adverse effects, appropriate doses, and efficacy compared to standard drugs for AD.

Juniperus communis

Juniperus communis L. (juniper) belongs to the family Cupressaceae. The chemical compositions of its EO are α -pinene (41.13%), α -thujene (3.78%), myrcene (10.16%), sabinene (11.73%), γ -terpinene (1.57%), and limonene (8.63%) followed by lower quantities of β -elemene (1.1%), terpinen-4-ol (3.42%), β -caryophyllene (1.03%), eremophyllene (1.17%), and germacrene D (1.51%). The EO obtained from needles and berries of *J. communis* has been reported to have carminative, diuretic, anti-anxiety, astringent, rubefacient, antispasmodic, stimulating, stomachic, blood purifier, antirheumatic, antiseptic, and tonic effects. [58, 59] Cioanco et al. [59] reported about the multiple exposure of juniper oil inhalation boosted memory defects in an $A\beta$ -induced rat model of AD. In this study, rats were split up into 4 groups, of which control group received saline treatment (0.9% NaCl), disease group was subjected to ICV $A\beta(1-42)$ injection, and the other 2 treatment groups were subjected to inhalation of juniper volatile oil 1% and 3% for 20 d after ICV $A\beta(1-42)$ injection. Y-maze and radial arm maze tests were used for the evalua-

tion of memory status. Juniper oil treated groups showed significantly less memory impairment in both behavioral tests as compared to $A\beta(1-42)$ alone treated group. Later Cioanco et al. [60] demonstrated that antioxidant and anti-AChE potential of juniper volatile oil ameliorates cognitive dysfunction in $A\beta(1-42)$ -induced rat model of AD.

Cocos nucifera

Cocos nucifera L. (coconut) belonging to Arecaceae family, consists of saturated fatty acids (SFA) 92% and medium-chain fatty acids (MCFA) 62–70% as major constituents. MCFA can be transformed into ketone bodies, which are alternative energy source in the brain in conditions wherein disturbance in brain glucose level and can be favorable to humans progressing or earlier with cognitive dysfunction [61]. Hu Yang et al. [62] conducted a prospective study in Alzheimer's patients in which the test group was provided with coconut oil (40 mL/day) for 3 wk. The memory test such as lobo cognitive test and mini test scores pre- and post-involvement were performed in test and control groups. A statistically appreciable elevation in test score was noticed in patients taking the oil and therefore a positive improvement in memory status was noted. An *in vitro* study conducted by Nafer et al. [63] highlighted the neuron protecting effects of coconut oil in $A\beta$ -induced neurotoxicity in rat cortical neurons. Cells were initially induced with $A\beta$ for 1, 6, or 24 h and then treated with coconut oil further for 24 h. Survival of neurons and various cellular parameters (synaptophysin labeling, cleaved caspase 3, and reactive oxygen species) were assessed. Reports unveiled that coconut oil protects against $A\beta$ -induced neurotoxicity, inhibits $A\beta$ -induced elevation of cellular stress markers, and in addition provides neuron protecting effects by activating Akt and ERK signaling pathways

Pimpinella peregrina

Pimpinella peregrina L. is an aromatic herb belonging to Apiaceae family. The major constituents of its EO are trans-pinocarveol (35.1%), α -cubebene (12.4%), pregeijerene (15.1%), (+)-epi-bicyclosesquiphellandrene (7.5%), and α -terpineol (6.7%) [64, 65]. EO is widely used in flavored drinks like raki, ouzo, pastis, arak etc. Adyn et al. [65] reported the effects of inhalation of EO from aerial parts of *P. peregrina* in scopolamine-induced memory deficits, depression, and anxiety in a rat model of AD. Rats were exposed to inhalation of EO (1% and 3%) continuously for 21 d. Scopolamine was injected (i. p.) 30 min before the behavioral tests. Memory impairments were observed through radial arm-maze and Y-maze tests. Also, elevated plus-maze and forced swimming tests were used for checking anxiety and depressive behavior, respectively. Successive results were obtained in EO-treated groups as compared to respective scopolamine-treated groups, suggesting the neuroprotective effects of *P. peregrina* EO in the treatment of anxiety, depression, and memory deficits. In conclusion, more biochemical and histological findings are needed to prove the effect of *P. peregrina* EO on AD.

Lavandula angustifolia

Lavandula angustifolia Mill. (lavender) belongs to the family Lamiales. The dominant components of its EO are caryophyllene (24.12%), terpinen-4-ol (9.57%), β -phellandrene (16%), and euca-

lyptol (15.69%) [66]. It has been used in the treatment of anxiety, migraines, stress, irritability, exhaustion, depression, headaches, digestion, colds, flatulence, insomnia, loss of appetite, stomach upset, liver diseases, nervousness, and aromatherapy [67,68]. Hritcu et al. [69] reported the effects of 2 distinct EOs from *Lavandula hybrida* Rev. and *L. angustifolia* subsp. *angustifolia* on neurological capability in scopolamine (0.7 mg/kg)-induced amnesia model in rats. Lavender EO inhalation for 7 consecutive days notably hindered depression, anxiety and memory impairment in scopolamine treated rats as observed through various behavioural tests. A human study led by Moss et al. [70] unveiled that exposure of EOs of *Rosmarinus officinalis* L. and *L. angustifolia* significantly affects the mood and cognitive performances of sound volunteers. Aromatherapy of 4 different EOs from *R. officinalis*, *Citrus limon* (L.), *Citrus sinensis* (L.) Osbeck, and *L. angustifolia* reported significant improvement in cognitive function in a clinical trial led in 28 elderly people [71].

R. officinalis

Rosmarinis officinalis L. (rosemary) belongs to the family Lamiales. The EO of *R. officinalis* consist of α -pinene (21.3%), 1,8 cineole (28.5%), camphor (27.7%), camphene (8.7%), β -pinene (4.7%), and borneol (2.5%) as major constituents. [72] Antioxidant, antiproliferative, antibacterial, antimutagenic, antiphlogistic, and chemopreventive, and ANS stimulant potentials of its EO has been reported [73,74]. Satiou et al. [75] have recently studied the beneficial effects of EO from leaves and flowers of *R. officinalis* on scopolamine-induced Alzheimer's-type dementia model in mice. The results showed that inhalation of *R. officinalis* EO (4 μ L/L or 8 μ L/L air) have shown a positive result in spontaneous alternation behavior in Y-maze test, and 1,8 cineole, α -pinene, and β -pinene were found in dominant concentration in the mice brain. Asadi et al. [76] have tested the potential of EO from leaf and aerial part of *R. officinalis* on memory in aged and young mice. The test group were administered EO (200,400,600 and 800 mg/kg i.p.) daily for 7 d and improvement in memory performances were found in all test groups. Filiptsora et al. [77] reported the effects of *R. officinalis* EO on the short-term and numerical memory in a study conducted in 79 school students (aged 13–17 y). The result showed positive results as evidenced by increased image and number memory compared to control groups. The positive correlation of 1,8 cineole on mood and cognitive performances following inhalation of rosemary oil has been described in a clinical study conducted in healthy volunteers [78]. As mentioned above, *R. officinalis* EO reported memory enhancement potential in many clinical studies [70,71]. Further studies are essential for this oil to verify possibility for drug interactions and adverse effects in long duration trials and to determine appropriate dose that can mediate relevant neuroprotective effects.

In vitro studies

Ayaz et al. [79] reported the cholinesterase inhibitory activities and reactive oxygen species scavenging potential of EOs from the flowers and leaves of *Persicaria hydropiper* (L.) Delarbre. In AChE inhibition assay, EO of leaf exhibited IC₅₀ of 120 μ g/mL and flower of 220 μ g/mL, whereas flower and leaf EOs reported IC₅₀ of 225 and 130 μ g/mL, respectively, in butyrylcholinesterase (BChE)

inhibitory assay. In 1,1-diphenyl 2-picrylhydrazyl (DPPH) antiradicals assay, these EOs showed remarkable radical scavenging potentials. Also, IC₅₀ of 50 and 45 μ g/mL for flower oil and 60 and 180 μ g/mL for leaf oil was obtained in hydrogen peroxide and 2,2-azinobis(3-ethylbenzthiazoline-6-sulfonic acid) (ABTS) scavenging assays, respectively. Ahmed et al. [80] reported the antioxidant and anticholinesterase activities of EO from *Rumex hastatus* D. Don. It exhibited significant BChE and AChE inhibitory activities with IC₅₀ of 97.38 and 32.54 μ g/mL, respectively. Also, IC₅₀ values of 6.29 and 3.71 μ g/mL were obtained for ABTS and DPPH assays, respectively. *Salvia chionantha* Boiss EO was analyzed for its antioxidant activity and reported 77.4 \pm 0.5% inhibition in ABTS assay. The anti-AChE and BChE activities were found to be 56.7 \pm 1.9% and 41.7 \pm 2.9%, respectively [81]. *In vitro* anti-AChE activity of EO from *Acorus calamus* L. rhizomes has been studied and exhibited significant AChE inhibitory potential (IC₅₀ = 10.61 μ g/mL) [82]. Ertas et al. [83] reported the anticholinesterase activities of EOs from *Anchusa arvensis* subsp. *Orientalis* (L.) Nordh. and *Tragopogon latifolius* Boiss. Both of them betrayed moderate AChE and BChE inhibitory activities.

EO isolated from leaf and stem of *Gynura bicolor* (Roxb.ex Willd.) DC. has been screened for anti-AChE activity. These oils have been evaluated and compared with standard AChE inhibitor pulegone. The leaf and stem oil inhibited AChE (53%) at a concentration of 0.50 μ g/mL with ID₅₀ values of 85 and 92 μ g/mL, respectively. Both oils showed better results than pulegone [84]. EO obtained from fresh *Chaerophyllum aromaticum* L. root and aerial parts exhibited significant anticholinesterase and antioxidant activities [85]. Bonesi et al. [86] reported the cholinesterase inhibitory activities of EOs from *Pinus nigra* J.F. Arnold and *Pinus heldreichii* Christ. *P. heldreichii* was more active with IC₅₀ of 80.6 and 51.1 μ g/mL toward BChE and AChE inhibitory assays, respectively. EOs from *Cistus libanotis* L., *Cistus salvifolius* L., *Cistus creticus* L., *Cistus villosus* L., and *Cistus monspeliensis* L. were evaluated for antiradicals and anti-AChE activities. In ferric reducing antioxidant assay, *C. libanotis* exhibited most potent value of 19.2 l MFe (II)/g. In AChE inhibitory assay *C. salvifolius* revealed IC₅₀ of 58.1 μ g/mL. Meanwhile, *C. creticus*, *C. libanotis*, and *C. salvifolius* exhibited significant anti-BChE effects with IC₅₀ values of 29.1, 23.7, and 34.2 μ g/mL, respectively. In β -carotene bleaching test, *C. monspeliensis* EO exhibited better results with IC₅₀ of 54.7 μ g/mL [87]. Eminent results of all this data suggest the anticholinesterase and antioxidant potential of EOs for the development of therapeutic remedies targeting AD pathogenesis. ► **Table 2** shows the list of *in vitro* studies of EOs that possess antioxidant and anticholinesterase activities.

Discussion

This literature review displayed promising evidence that supports the use of EOs for reversing cognitive and memory impairment of AD. EOs obtained from numerous medicinal plants are reported to possess anti-AD potential. EOs of *S. officinalis*, *S. officinalis* ssp. *lavandulifolia* (vahl), *M. officinalis*, *L. angustifolia*, and *R. officinalis* have proven their putative effects in clinical studies. EOs are rich in various bioactive markers in different concentrations and it changes from place to place. Linalool, thymol, β -caryophyllene,

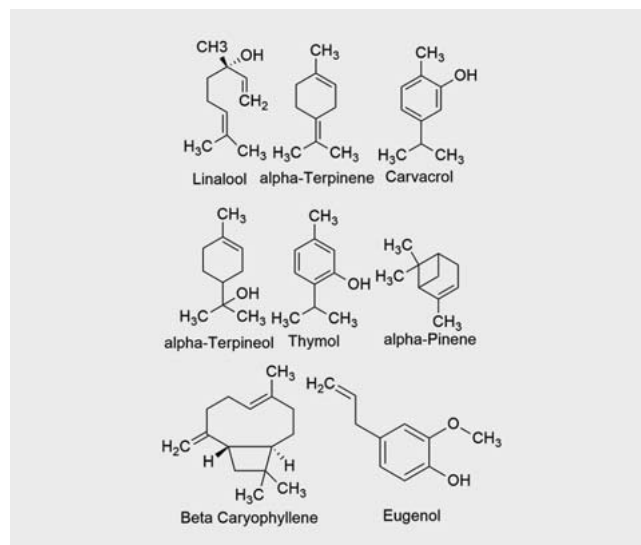
► **Table 2** List of *in vitro* studies of essential oils that possess antioxidant and anti-cholinesterase activities.

Plant/source	Study design	Results	References
<i>P. hydropiper</i>	AChE, BChE inhibition DPPH, ABTS, H ₂ O ₂ assay	↓ AChE, BChE, DPPH, ABTS, H ₂ O ₂ activity	[79]
<i>R. hastatus</i>	AChE, BChE inhibition DPPH, ABTS, H ₂ O ₂ assays	↓ AChE, BChE, DPPH, ABTS activity	[80]
<i>S. chionantha</i>	AChE, BChE inhibition ABTS assays	↓ AChE, BChE, ABTS activity	[81]
<i>A. calamus</i>	AChE inhibition	↓ AChE activity	[82]
<i>A. arvensis</i> subsp. <i>Orientalis</i> <i>T. latifolius</i>	AChE, BChE inhibition	↓ AChE, BChE activity	[83]
<i>G. bicolor</i>	AChE inhibition	↓ AChE activity	[84]
<i>C. aromaticum</i>	AChE inhibition Antioxidant assay	↓ AChE activity Significant antioxidant activity	[85]
<i>P. nigra</i> <i>P. heldreichii</i>	AChE, BChE inhibition	↓ AChE, BChE activity	[86]
<i>C. creticus</i> <i>C. libanotis</i> <i>C. salvifolius</i> <i>C. monspeliensis</i> <i>C. villosus</i>	AChE, BChE inhibition FRAP assay, β-carotene bleaching assay	↓ AChE, BChE activity Significant antioxidant activity	[87]

AChE: acetylcholinesterase, BChE: butyrylcholinesterase, H₂O₂: hydrogen peroxide, ABTS: 2,2-azinobis(3-ethylbenzthiazoline-6-sulfonic acid), DPPH: 1,1-diphenyl 2-picrylhydrazyl, FRAP: ferric-reducing antioxidant power, ↓ : decreasing/inhibiting.

carvacrol, α-pinene, α-terpineol, α-terpinene, and eugenol are some of the components that are common in above-mentioned oils. ► **Fig. 1** depicts the chemical structure of some of the main constituents of EOs. Some are present in higher amount like linalool (60–70%) in *C. sativum*, caryophyllene (23.6%) in *A. nemorosa*, and 1,8 cineole (46.0%) in *R. officinalis* while others are in minor amounts. Monoterpenes like pinene, limonene, sabinene, etc., are found to be responsible for the antioxidant and anticholinesterase properties [88]. Therefore, it seems to be important to screen the main constituents of EOs based upon the strength of the biologic potential and more findings are needed to establish the required dose and proportions that are necessary to protect the brain from degenerative diseases.

Majority of the clinical as well as animal studies prefer inhalation as the route of administration of EO for AD therapy. Aromatherapy for AD are used since long back and found to be very effective. The aroma of EO acquired through inhaling or massaging directly affects mood and cognition. These oils are supposed to enter the blood stream through lung mucosa, nasal, or even diffuse directly into the olfactory nerve and reach limbic system in the brain [89]. The EOs mentioned in this review is mostly non-toxic at the recommended doses. Most of the EOs possess anti-cholinesterase property. *In vitro* studies of 15 EOs that displayed both AChE and BChE inhibitory potentials are mentioned. ACh is the brain neurotransmitter involved in regulating memory and cognition and cholinesterase inhibitors prevent degradation of ACh and maintain its synaptic concentration. Hence, assessment of the potential shown by EOs on cholinesterase adds up a useful approach for developing new drugs for AChE/BChE inhibitor with fewer cholinergic side effects. Oxidative stress plays a major role in the pathophysiology of AD. Imbalance in oxidants/antioxidants defense generates free radical that causes cell/neuron damage.



► **Fig. 1** Some of the main bioactive constituents of EOs.

Antioxidant-rich EOs can hence counteract the free radical mediated oxidative stress and thereby protects brain from neuronal damage. The ability of EOs to cross blood brain barrier remains as a main reason for activity in brain regions

However, it is important to initiate further studies on pharmacokinetics and toxicities of EOs and their bioactive markers responsible for anti-Alzheimer's action. More cell culture and *in vivo* studies are essential. All these findings result in the establishment of good interventions and subsequent development of safer and more effective anti-Alzheimer's drug.

There are numerous natural resources with reputed ethnobotanical uses shown to ameliorate memory impairment in different Alzheimer's studies. However, comparatively only few are explored to determine any therapeutic support for their putative effects. Our literary survey revealed encouraging results regarding various EOs being studied in preclinical and clinical studies of AD with significant effects in modulating the pathology through anti-amyloid, antioxidants, anti-AChE, and memory enhancement activity. The literature studies disclosed many drugs that showed positive results in animal studies but failed in clinical trial. This demands more studies focused on human physiology, pharmacokinetics, dose, and route of administration. Thus, the establishment of potential targets and optimization of safety and efficacy of EOs in AD remain as a promising area for future research.

Conflict of Interest

There are no conflicts of interest among the authors.

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