Review

Ethnobotanical Perspectives on Natural Acetylcholinesterase Inhibitors: Towards Alternative Approaches to Alzheimer's Disease

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Abstract

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Ethnopharmacological relevance: Acetylcholinesterase (AChE) inhibitors are essential in managing neurodegenerative diseases, particularly Alzheimer's disease (AD), by preventing acetylcholine breakdown, enhancing memory, and cognition. Traditional medicinal and dietary plants, from Palestinian ethnopharmacology, hold promise due to their bioactive compounds with AChE inhibitory activity, offering alternative or complementary therapies with fewer side effects.
Aim of the study: This review aims to explore the potential of medicinal and dietary plants as natural sources of AChE inhibitors to aid in the management of AD, focusing on plants used in Traditional Arabic Palestinian Herbal Medicine (TAPHM).
Materials and Methods: A comprehensive literature review was conducted utilizing databases including Google Scholar, PubMed, Scopus, and Web of Science, spanning from 2014 to 2022. Keywords included "Acetylcholinesterase inhibition," "Alzheimer's disease," and "medicinal plants." The botanical identification of plants was verified using World Flora Online, and phytochemicals were analyzed for their AChE inhibitory and antioxidant activities.
Results: A total of 361 plant extracts from 180 species and 63 families were identified, with Lamiaceae, Asteraceae, and Polygonaceae showing significant AChE inhibition. Key phytochemicals, such as alkaloids, flavonoids, and terpenes, demonstrated multifaceted activities, including neuroprotection, antioxidant properties, and acetylcholinesterase inhibition.
Conclusion: Natural plant extracts, particularly from the Lamiaceae family, exhibit strong potential as AChE inhibitors and antioxidants, supporting their use in AD management. Future clinical trials are necessary to validate their therapeutic efficacy and safety, emphasizing the integration of traditional knowledge with modern pharmacological research

Introduction

Dementia (Overview)

Dementia is a broad term incorporating cognitive disorders related to memory, thinking, behavior, and ability to carry out daily activities. It is a leading cause of disfunction and reliance among olde people worldwide (WHO, 2023). While predominantly affecting older people, 2 to 10% of all cases are estimated to manifest before the age of 65, with the prevalence doubles approximately every five years thereafter (Alzheimer's Disease International (ADI), 2014). Dementia is associated with numerous brain pathologies, with alzheimer's disease (AD), vascular dementia (VaD), dementia with Lewy bodies, and frontotemporal dementia being the prevalent forms (2024 Alzheimer's disease facts and figures).

Dementia, including AD, represents one of the significant global public health issues facing our generation. In 2015, an estimated 46.8 million people worldwide were living with dementia, and epidemiological studies suggest that this number will increase at an alarming rate in the coming years. This number is expected to increase to an estimated 74.7 million in 2030, and 131.5 million in 2050 (Prince et al., 2015). A significant proportion of the increase will occur in developing countries, where 62% of the individuals with

dementia currently reside, this figure is expected to reach 71% by 2050. China, India, and neighboring South Asian and Western Pacific represents the regions with the most rapid growth in the elderly population (WHO, 2023).

Review methodology

For this review, the eligible studies published on medicinal plants used for treating AD, or possessing anticholinesterase activity, were searched in the following databases: Google Scholar, PubMed, Scopus, and Web of Science from 2014 to 2022. The following keywords were used: "medicinal plants" AND "Acetylcholine inhibition" AND "Alzheimer's disease" AND "neurodegenerative" AND "phytochemicals" AND "Ellman" AND "antioxidant" AND Acetylcholinesterase" AND "ACHE" AND "memory enhancer" AND "nervous system" AND "ethnobotany". Exclusion criteria included: summaries of incomplete studies, conference presentations, and duplicate articles. The scientific names of the plants have been validated with World Flora online (www.worldfloraonline.org).

Alzheimer's Disease

Alzheimer's disease (AD) is the most common form of dementia among neurodegenerative disorders, affecting more than 10 million people globally (Singhal et al., 2012). It is associated with substantial healthcare costs and familial burden. AD is characterized by a progressive decline in memory and cognitive function, primarily impacting individuals over the age of 65 through various biochemical pathways (Singhal et al., 2012). Approximately 5 % of people between ages 65-74 are affected by AD, with the risk increasing to 50 % in those over 85 years old (2024 Alzheimer's disease facts and figures).

AD was primarily described by the German psychiatrist, Alois Alzheimer, at the beginning of the 20th century (Su et al., 2014). AD as a progressive, complex, irreversible, chronic pathology has become a major issue, mostly in developed countries due to the increasing elderly population (over 65 years of age) with a high quality of life. AD is anticipated to account for 50 - 80 % of dementia cases in individuals over 65 years old. Cognitive dysfunction, behavioral disturbances, memory losses, and neurobehavioral symptoms such as apathy and anxiety, besides other deficits in daily life activities, are the main symptoms associated with this ailment (Kumar et al., 2024). Other features associated with the final stages of AD include depression, language deficits, and behavioral and mood problems including agitation and psychosis (Bassiony & Lyketsos, 2003; Iverson, 2005; Iverson et al., 2006).

Alzheimer's Disease Etiology

The extracellular accumulation of amyloid beta (Aβ) plaques and intracellular formation of neurofibrillary tangles (NFT) comprises the key pathological hallmarks of AD are. Moreover, the pathophysiological mechanisms which contribute to AD include glutamatergic and cholinergic dysfunction (Howes & Houghton, 2012), oxidative stress (Cheignon et al., 2018), prion proteins (Westergard et al., 2007), and inflammation (Latta et al., 2015).

The most currently available drug therapies for AD are based on the Cholinergic hypothesis, which highlights that AD is caused by the decrease in the synthesis of the neurotransmitter Acetylcholine (ACh) (Peera & Yellamma, 2015; Topcu & Kusman, 2014). ACh is extensively distributed across peripheral, autonomic, and enteric neurons, and is mainly prominent in the central nervous system (CNS). It is produced by the choline acetyl transferase enzyme, using acetyl coenzyme-A and choline as substrates to produce ACh within the cholinergic neurons (Marinova, et al., 2022). In the CNS, ACh ease many functions including motor control, memory, learning, and attention (Verma et al., 2014).

At the cholinergic synapses, two principal, closely related cholinesterase enzymes (ChE) are until now recognized, the Acetylcholinesterase (AChE) and Butyrylcholinesterase (BuChE) (Jamal et al., 2023). AChE and BuChE are available in the brain with various levels and sharing, in addition to the extracellular accumulation of neurofibrillary tangles and neuritic plaques. It was suggested that AChE predominates in the healthy brain (Zhao et al., 2013). However, BuChE corresponds to only 10% of total ChE in the normal brain, and is more abundant in liver, lung, heart tissues, and plasma.

Compared to AChE, there is limited information available about BuChE in the nervous system (Pinho et al., 2013). BuChE has historically been considered physiologically irrelevant because the absence of BuChE activity in humans does not result in any noticeable abnormalities. In contrast, AChE is a crucial enzyme for regulating ACh levels in the brain. The primary function of AChE is to terminate nerve impulse transmission at the cholinergic synapses through rapid hydrolysis of ACh (McHardy et al., 2017).

The inhibition of AChE leads to an increase in the levels of inhibiting the enzyme, which is responsible for its breakdown. Inhibition of AChE has been established as the most effective treatment strategy against AD, senile dementia, ataxia, myasthenia gravis and Parkinson's disease (PD) (Kumar et al., 2016).

Failure of cholinergic neurons in the brain is linked to cognitive decline, and reduction in these neurons in AD patients is directly linked to cognitive impairment and memory loss. Therefore, conserving acetylcholine levels is expected to mitigate the symptoms of AD (Kelley & Petersen, 2007). Currently, there is no actual cure for AD, and the attainable medications have limited effectiveness and can cause side effects (Chopra et al., 2011). However, therapeutic interventions are believed to delay the onset or progression of AD, which could significantly reduce the number of cases over the next 50 years (Rao et al., 2012). Existing medication for AD includes use of AChE inhibitor-approved drugs, namely tacrine, galanthamine, rivastigmine, and donepezil (Marucci et al,2021). However, some of these compounds are only efficient in the case of mild-to-moderate types of AD and were reported to have health adverse side effects including gastrointestinal disturbances, nausea, hepatotoxicity, bioavailability associated problems, dizziness, and pharmacokinetic disadvantages (Park et al., 2010). As a result, it is necessary to explore new alternatives to deal with AD, unaccompanied by secondary side effects.

Cholinesterase Inhibitors Mechanism of Action

Acetylcholine is hydrolyzed by cholinesterase resulting in the formation of its constituent components, acetate and choline. Cholinesterase inhibitors work by preventing cholinesterase activity, thereby prolonging the availability and action of acetylcholine at neuromuscular junctions. The AChE possesses two active sites: an anionic site derived from tryptophan and an esteractic site derived from serine. AChE inhibitors such as organophosphates bind to the serine esteratic site, thereby preventing the enzyme's ability to cleave acetylcholine. Consequently, acetylcholine will therefore continue to build up and activate related receptors (Oliveira et al., 2019).

AChE inhibitors are classified as reversible, irreversible, or pseudo-reversible. In general, reversible cholinesterase inhibitors are used for medical treatment. Pesticides and biological warfare (nerve agents) frequently employ irreversible and pseudo-reversible inhibitors (Wang et al., 2019; Bajgar et al., 2019).

Oxidative stress

Oxidative stress (OS) arises from a significant variation between the body's production of free radicals or their byproducts and antioxidant defenses (Rekatsina et al., 2020). OS plays a crucial role in neurodegeneration by altering the composition and functionality of biomolecules, leading to the degeneration of neuron cells. Neurons are particularly vulnerable to the effects of OS because they have a high oxygen demand, low glutathione (GSH) levels, a high concentration of polyunsaturated fatty acids, and an abundance of redox-active metals, which are essential to produce OS (Singh et al., 2019). The excessive production of reactive oxygen species (ROS) and reactive species (RNS) can lead to various damaging outcomes, including DNA/RNA molecules oxidation, interfering in lipid-protein interactions, inhibition of some enzyme activities, and peroxidation of lipids in the neuronal membrane. These factors can also inhibit Ca^{2+} uptake and induce glutamate release, which can raise intracellular Ca^{2+} levels, trigger neuroinflammation, and promotes apoptosis, ultimately resulting in neuronal damage, necrosis, or apoptosis. This indicates that OS is crucial to the etiology and progression of certain neurodegenerative disorders (Lee et al., 2020).

The role of OS in neurodegeneration has been investigated by several research studies, and the existence of aberrant protein deposits has been documented. The following deposits are markers of brain injury in AD (*Aβ* and hyperphosphorylated tau), PD (alpha-synuclein (*α*-Syn), Huntington's disease (HD) (huntingtin (Htt)), and amyotrophic lateral sclerosis (ALS) (superoxide dismutase 1 (SOD1)) or trans-activation response (TAR) DNA binding protein-43 (TDP-43)], cause the brain to go into an inflammatory state, which leads to a substantial production of ROS and, eventually, oxidative stress (Xiao et al., 2008). Elevated levels of OS biomarkers have been detected in AD patients. Similarly, PD patients show higher levels of most of these markers, except for iso- and neuroprostanes (Schmidt et al., 2021). In ALS, elevated concentrations of malondialdehyde (MDA), 4 hydroxynonenal (HNE), thiobarbituric acid reactive substances (TBARs), 3-nitrotyrosine (3-NT), and DNA/RNA oxidation products 8-hydroxy-2-deoxyguanosine (8-OHdG) has been recorded, while HD patients exhibited increased levels of isoprostane, TBARs, 3-NT, 8-OHdG, and neuron-specific enolase (Kumar & Ratan, 2016).

Plants used traditionally for central nervous system and cognitive disorders in Palestine

The term "traditional plants for neuro-protection nootropic" refers to pharmaceuticals or dietary supplements that enhance brain function. Various pharmacological substances on the market work by altering the balance of specific neurotransmitters to achieve neuroprotective effects. Many drugs derived from medicinal plants contain active phytochemicals that have been found to enhance memory. A commonly proposed cause of AD is the decline in cholinergic activity in the brain. Consequently, cholinergic medicines of plant origin, such as cholinesterase inhibitors like Huperzine, can be used to improve memory. The elevated rise in neurological disorders recently and the realization of the significant adverse effects associated with pro long consumption of manufactured medications have brought researchers to focus on natural resources (Kumar et al., 2015).

An ethnopharmacological approach might help in the identification identifying plant species and potential new drugs relevant to the healing of cognitive illnesses, including AD. Traditional medical practices have long used plants to improve cognitive function and to alleviate other symptoms related to AD (Tewari et al., 2018).

Ethnobotanical knowledge provides valuable potential for guiding new directions in therapeutic research methodologies. In addition to cooperating with other phytochemicals from the same plant, phytochemical constituents may also increase the activity of other compounds or mitigate the adverse effects of other plant species' compounds (Sudha et al., 2016). This strategy has been employed in several traditional medical procedures, including Ayurveda, where a plant combination is routinely suggested. Research studies on the use of traditional medicines, such as plant medicinal substances in AD therapy, have been conducted during the past ten years. The understanding of these significant sources may be useful for allopathic science. With the help of this knowledge, some alkaloidal compounds from plant sources have been researched for their viability in AD therapy and are currently being used in clinical settings. For instance, galantamine from *Galanthus nivalis* L. has been discovered to be a potential AChE inhibitor, which is currently one therapeutic option in the treatment of AD (Adhami et al., 2011).

In Palestine traditional medicine plays a vital role in primary healthcare (Ali-Shtayeh & Jamous, 2006; Ali-Shtayeh et al., 2014). Particularly, medicinal plants are broadly used in Traditional Arabic Palestinian Herbal Medicine (TAPHM) for health maintenance and for the treatment of various ailments including chronic diseases (Ali-Shtayeh et al., 2000; 2011; 2012; 2013).

In Palestine, numerous plants have been documented to treat ailments related to CNS and as memory enhancers. The number of plants documented in TAPHM to be used by the Palestinian communities for the treatment of various ailments exceeds 360 plant species (Ali-Shtayeh et al., 2014), of these, 55 plant species have been reported to be used for the treatment of CNS ailments and as memory enhancers (Table 1) (Ali-Shtayeh & Jamous, 2008).

Seven of the plants reported to be used in TAPHM as memory enhancers belong to the Lamiaceae family (*Lavandula officinalis, Mellisa officinalis, Mentha spicata, Salvia fruticosa, Micromeria fruticosa, Origanum syriacum,* and *Rosmarinus officinalis)* (Table 1). A total of 44 plants mentioned in TAPHM for CNS and cognitive disorders are edible plants, consumed by the Palestinian people either fresh or cooked (Table 1); these plants and their oils hold potential as valuable new flavoring agents for functional foods and nutraceutical products, particularly in supplements targeted at the elderly population. (Table 1).

Table 1. Plants used in Traditional Arabic Palestinian herbal medicine (TAPHM) for the treatment of central nervous system diseases and as a memory enhancer.

Scientific name, Family (Common name)	**Uses in TAPHM**	**Uses**	**References**
Allium cepa L, Liliaceae (Onions)	Memory enhancer	The administration of onions powder to experimental mice mitigated behavioral deficits induced by immobilization stress, and increased memory performance in stressed mice pre-treated with AC in Morris water maze test. The results suggested that supplementation of Allium cepa may be beneficial in managing anxiety and depression, as well as enhancing memory function.	Samad & Saleem, 2017
Allium sativum L, *Liliaceae* (Garlic)	Relaxant	Garlic has some bioactive compounds, such as allicin and sulfur compound, that have the potential to inhibit the production of free radicals in the brain and improve short-term memory in rats.	Sarkaki et al., 2013
Boswellia carterii Birdw, Burseraceae (Olibanum, Incense)	Relaxation	The gum resin extract, volatile oil fraction, and oil fraction of Boswellia, along with their components, have demonstrated utility in enhancing mental condition and improving brain functions, including cognition, memory, learning, communication, and overall brain health. These fractions are also effective in treating memory impairments and in preventing or managing disorders related to memory and cognitive function.	Gokaraju, et al., 2013
Camellia thea Lin, Theaceae (Tea)	Stimulant, Memory enhancer	The plant contains caffeine, theanine, and theophylline, which function as central nervous system stimulants, while also alleviating stress and anxiety. Additionally, it enhances concentration and promots generation of ideas.	Kapoor et al., 2013
Carum carvi L, Apiaceae (Caraway)	Relaxant	Fruit extract of Carum carvi effectively inhibited AChE and BuChE, demonstrating a beneficial therapeutic role in the management of AD by restoring cognitive function and enhancing memory. R-carvone and D-limonene, found in C. carvi have shown to possess AChE inhibitory activity.	Agrahari & Singh, 2014; Abdelgaleil et al., 2009; Lopez et al., 2009
Cerastium glomeratum Thuill, *Caryophyllaceae* (Mouse- ear, Chickweed)	Relaxant	-	-
Chrysanthemum coronarium L., Asteraceae (Common Chrysanthemum)	Relaxant	*C. coronarium* essential oil was reported to possess AChE inhibitory activity	Bardaweel, et al., 2015
Cinnamomum zeylanicum Blume., Lauraceae (Cinnamon Tree)	Relaxant	*C. zeylanicum* has been traditionally utilized for alleviating stress, serving as a nervine tonic, and acting as a stimulant. The lyophilized AQU extract of the bark significantly attenuated streptozotocin (STZ)-induced cognitive deficit. Additionally, this extract restored STZ-induced alterations in AChE activity and OS levels. The memory-enhancing effects of the lyophilized aqueous extract may be related to the synergistic interplay between its anti-AChE and antioxidant properties.	Malik et al., 2015
Citrus aurantium L., Rutaceae (Bitter Citrus)	Insomnia	The flower extract of the plant exhibits reparative effects on memory and behavioral disorders urged by scopolamine, suggesting potential benefits for the treatment of AD.	Rahnama et al., 2015
Citrus sinensis (L.) Osbec, Rutaceae (Sweet Orange – Tree)	Stimulant	The fruits juice has memory enhancing potentials, by reducing AChE activity in mice.	Milind & Dev, 2012
Coffea arabica L., Rubiaceae (Coffee)	Stimulant	Caffeine from *Coffea arabica* possesses high AChE inhibitory activity	Yilmaz et al., 2014
Corchorus olitorius L., Tiliaceae (Jews Mallow)	Memory Enhancer	The plant ethanolic extract has been proposed for use as a natural antioxidant and antimicrobial agent in functional foods.	Ben Yakoub et al., 2018
Coriandrum sativum L., Apiaceae (Coriander)	Memory Enhancer	The plant leaves might be useful in managing AD, given their diverse effects, which include memory enhancement, cholesterol-lowering property and anticholinesterase activity in experimental mice fed orally for 45 days on the plant.	Mani et al., 2010a
Crataegus aronia (L.) Bosc. ex DC., Rosaceae (Hawthorn)	Relaxant	*Crataegus* may enhance impaired memory by improving cerebral circulation, which increases oxygen delivery to the brain, particularly when combined with *Ginkgo biloba*.	Haughton, 2013
Crocus sativus L., Iridaceae (Saffron)	Memory Enhancer, Relaxant, Epilepsy	Administration of saffron (60 mg/kg body weight, intraperitoneally) to both normal and aged mice over one week, significantly enhanced learning and memory capabilities. It was shown that saffron and its active compound crocin, can prevent OS in the hippocampus, thereby mitigating deficits in spatial learning and memory. Additionally, saffron extract was found to reduce memory impairment induced by morphine.	Ghadrdoost et al., 2011; Naghibi et al., 2012; Haghighizad et al., 2008

Scientific name, Family (Common name)	Uses in TAPHM	Uses	References
Cucurbita pepo L., Cucurbitaceae (Pumpkin)	Memory enhancer	-	-
Daucus carota L., Apiaceae (Carrot)	Memory enhancer, relaxant	*Daucus carota* extract might be effective in managing cognitive dysfunctions due to its memory-enhancing and cholesterol-lowering properties.	Vasudevan & Parle, 2006; Mani et al. 2010b
Dianthus strictus Banks & Sol, Caryophyllaceae (Wild Pink)	Relaxant	-	-
Dittrichia viscosa (L.) W. Greuter *(Inula viscosa* (L.) Ait., Asteraceae (Inula)	Relaxant	Flowers and roots extracts showed strong antioxidants and AChE inhibitory activity.	Trimech et al., 2014
Elaeagnus angustifolia L., Elaeagnaceae (Narrow-Leaved Oleaster)	Epilepsy	Plant water extract enhances spatial learning and memory induced by scopolamine in rats.	Tamtaji et al., 2014
Eucalyptus camaldulensis Dehn., Myrtaceae (Red River Gum)	Relaxant	Plant essential oil exhibited a potent AChE inhibition activity.	Kiendrebeogo et al., 2011
Ficus carica L., Moraceae (Fig Tree)	Epilepsy, Memory enhancer	The n-hexane and acetone extracts showed a notable AChE and BuChE inhibitory activity.	Orhan et al., 2011
Foeniculum vulgare Miller, Apiaceae (Fennel)	Relaxant	The plant extract possesses memory-enhancing effect and has the potential to alleviate stress. The whole plants extract showed memory-enhancing properties in scopolamine-induced amnesic rats.	Koppula & Kumar, 2013.
Hibiscus sabdariffa L., Malvaceae (Roselle)	Relaxant	Aqueous extract of calyces of *H. sabdariffa* significantly reduced AChE activity in mice, suggesting that the extract might serve as a beneficial memory restorative agent.	Joshi and Parle, 2006.
Hordeum vulgare L., Poaceae (Barley)	Nerve strengthens	-	-
Juglans regia L., Juglandaceae (Walnut)	Memory enhancer	Walnuts exhibited strong AChE inhibition activity.	Kulisic-Biluisic et al., 2008, Ali-Shtayeh et al.,2014
Lactuca sativa L., Asteraceae (Lettuce)	Relaxant, Nerve strengthen	-	-
Lavandula officinalis Chaix & Kitt, Lamiaceae (Lavender)	Nerve strengthens	Luteolin flavonoids from the plant may enhance its calming effects on the central nervous system by modulating GABA receptors. Additionally, lavender extract has been shown to inhibit AChE in cell line studies.	Jivad & Rabiei, 2014; Hosseinzadeh & Nassin, 2003
Matricaria aurea (L.) Sch. Bip. Asteraceae (Golden Cotula)	Relaxation	-	-
Mellisa officinalis L. Lamiaceae (Balm)	Relaxant	The plant leaves contain monoterpenes, such as citral with mild AChE inhibitory activity, and phenol carboxylic acids like rosmarinic acid, which exhibited anti-oxidative, anti-amyloidogenic and anti-apoptotic properties. In patients with mild to moderate AD, the plant extract significantly improved cognition after 16 weeks. Additionally, the plant modulates ACh receptors in CNS, enhancing mood and cognitive performance with acute administration.	Jivad & Rabiei, 2014; Wake et al., 2000; Kennedy et al., 2002. Akhondzadeh et al., 2014.
Mentha spicata L., Lamiaceae (Peppermint)	Memory enhancer	The plant possesses memory-enhancing properties. The plant possesses strong AChE inhibition activity.	Adsersen et al., 2006; Ali-Shtayeh et al., 2014
Micromeria fruticosa (L.) Druce, Lamiaceae, (Thyme)	Memory Enhancer		
Musa sapientum L., Musaceae (Banana)	Memory enhancer	The stems and leaves of the plants were reported to be used traditionally as memory enhancers. The fruit pulp was reported to possess AChE inhibitor activity	Elufioye et al., 2012
Myristica fragrans Houtt., Myristicaceae (Mace Nutmeg)	relaxant	*Myristica fragrans* seeds have demonstrated potent AChE inhibitory activity. The seeds extract improved significantly learning and memory in both young and aged mice, and reversed scopolamine- and diazepam-induced cognitive impairments in young mice. Furthermore, the extract enhanced learning and retention capacities across both age groups.	Cuong et al., 2014; Parle et al., 2004
Myrtus communis L., Myrtaceae (Common Myrtle)	Relaxant, Epilepsy	*M. communis* exhibits neuroprotective effects on brain tissue, primarily due to its antioxidant, anti-inflammatory, and anti-lipid peroxidative activities.	Aslan et al., 2024.
Nigella sativa L., Ranunculaceae (Nigella, Black Cumin)	Memory enhancer, relaxant	The plant was reported to enhance memory, attention, and cognition. Thymoquinone, a key bioactive component of its essential oil, has demonstrated beneficial effects in various CNS disorders.	Bin Sayeed et al., 2013; Khazdair, 2015
Origanum syriacum (Majorana syriaca (L.) Rafin., Lamiaceae (Wild Thyme)	Memory Enhancer, Relaxant	The plant is used traditionally to stimulate memory, Leaves and essential oil possess high AChE inhibitory activity.	Ali-Shtayeh et al., 2014; Loizzo et al., 2009
Phoenix dactylifera L., Palmae (Date Palm)	Memory enhancer	The plant extract exhibits nootropic activity even in the absence of cognitive deficits and effectively prevents chemically induced memory impairments in experimental mice	Hussain et al., 2015

Scientific name, Family (Common name)	Uses in TAPHM	Uses	References
Pistacia paleastina Boiss., Anacardiaceae (Palestinian pistachio)	Neuropathic pain	-	-
Prunus domestica L., Rosaceae (Plums, Common Plum)	Memory enhancer	Fruits consumption is associated with improved cognitive function	Igwe & Charlton, 2016.
Prunus mahaleb L. (*Cerasus mahaleb*), Rosaceae (Mahaleb Cherry)	Relaxant	Extracts of P. mahaleb seeds possess moderate antioxidant potential, and anticholinesterase activities.	Oskoueian et al., 2012
Prunus dulcis (Mill.) D.A.Webb (*Amygdalus communis* L., Rosaceae (Almond)	Relaxant, Memory Enhancer	Almond consumption has been shown to reduce activity in rats, while also demonstrating significant cholesterol and triglyceride-lowering properties. almond-derived compounds, particularly phenolic acids (PA), could serve as potential memory-restorative agents. This might be relevant in the context of AD.	Kulkarni et al., 2010
Pyrus malus L., Rosaceae (Apple)	Insomnia	-	-
Rosmarinus officinalis L., Lamiaceae (Rosemary)	Memory enhancer, Relaxant, Epilepsy	*Rosmary has been* traditionally used for AD, dementia, and symptoms of aging, debility, and fatigue. It also aids neuralgia, indigestion, neuropathic pain, circulatory disorders, and hypertension. *R. officinalis* protects neuronal cells from hydrogen peroxide damage, indicating its potential to prevent neurodegenerative diseases linked to oxidative stress and apoptosis.	Park et al., 2010
Ruta chalepensis L. , Rutaceae (Rue)	Relaxant	Rutin increased significantly learning abilities, improved spatial memory, and reduced secondary latency in rats.	Asgharian et al., 2020
Salix acmophylla Boiss., Salicaceae (Willow)	Relaxant	-	-
Salvia fruticosa Mill., Lamiaceae (White Sage, Common Sage)	Relaxant	Methanolic plant extracts of S. fruticose possess strong AChE and BuChE inhibitory activity and strong antioxidant activity.	Topcu et al., 2013
Santalum album L., Santalaceae (Sandalwood Tree)	Relaxant	α -santalol possesses a strong AChE inhibitory activity.	Misra & Dey, 2013
Sesamum indicum L., Pedaliaceae (Sesame)	Memory Enhancer, Relaxant	Seeds exhibited noticeable AchE inhibition activity.	Sharififar et al., 2013
Sinapis arvensis L. , Brassicaceae (Wild Mustard)	Nerve strengthens, Brain clot, Memory enhancer	The phenolic acid compound sinapic acid, found in natural herbs like *Sinapis species* has demonstrated neuroprotective effects against ICV-STZ-induced OS, neuro-inflammation, cholinergic dysfunction, and neuronal loss, suggesting its potential to enhance learning and memory in AD patients.	Verma et al., 2020.
Theobroma cacao L., Sterculiaceae (Cacao Tree)	Memory Enhancer	Polyphenols derived from cacao dietary supplements might counteract or slow the cognitive progression related to ageing and neurological disorders.	Fernández-Fernández et al., 2012
Trigonella berythea Boiss. & Blanche (*T. foenum-graecum* L.), Fabaceae (Fenugreek Seed)	Nerve inflammation, Memory enhancer, Relaxant	Seeds powder possesses anticholinesterase and antioxidant properties.	Ali-Shtayeh et al., 2014; Sharififar et al., 2013
Urtica pilulifera L., Urticaceae (Roman Nettle)	Memory Enhancer	Leaves of the plants possess strong AChE inhibitor activity	Ali-Shtayeh et al., 2014
Vitis vinifera L., Vitaceae (Grape)	Relaxant	Raisins of *Vitis vinifera* contain bioactive compounds that possess distinguished memory enhancer activity.	Kakad et al., 2008; Aslam & Sultana, 2015.
Zingiber officinale Rose., Zingiberaceae (Ginger)	Memory Enhancer, Relaxant	Ginger improves cognitive function for middle-aged women and may serve as potential restorative agent in the treatment of dementia in the elderly due to its antioxidant and AChE inhibitory property, which are key mechanisms underlying its action.	Saenghong et al., 2011

Medicinal plants as a source of acetylcholinesterase inhibitors

Medicinal plants contain a diverse range of bioactive compounds that have been widely utilized for the treatment of various ailments by most of the global population. Approximately 80% of people worldwide primarily rely on traditional medicines for their health care needs, and at least 25% of modern pharmacopeia drugs are plant-derived, with others being synthetic analogues modeled after plant-isolated prototype compounds (Kim, 2005; Tugume & Nyakoojo, 2019). Renewed interest in medicinal plants has also been driven by the rising costs of prescription drugs, making them an increasingly attractive option for

maintaining personal health and well-being (Harvey et al., 2015).

For over 3,000 years, plants have been utilized for treating and preventing diseases, promoting health, and improving both the longevity and quality of life (Dhivya et al., 2014). Plant species are viable sources of bioactive chemicals with the potential to synthesize AChE inhibitors (Di Giovanni et al., 2008). Biologically active natural compounds are pivotal in mitigating the progression of various pathogenic and neurodegenerative disorders, including AD (Wszelaki et al., 2010). Regular consumption of fresh vegetables has associated with a delayin cognitive decline in elderly (Jiang et al., 2017). Additionally, extracts from several medicinal plants have been demonstrated AChE inhibitory activity, suggesting their potential as lead compounds in the development of noval therapeutic drugs (Dhivya et al., 2014; Ali-Shtayeh et al., 2014; de Torre et al., 2022). The history of drug discovery has demonstrated that plants serve as significant sources for identifying newbioactive compounds, presenting challenge for modern pharmaceutical industries in harnessing their potential (Newman & Cragg, 2012). Although artificial drugs are available for the symptomatic treatment of AD, the discovery of new molecules from natural product resources has gained much attention from researchers. The structural biodiversity present within the plant kingdom provides a vast array of natural bioactive compounds (Rahman & Choudhary, 2001). Among plant products, are essential oils, polyphenols, flavonoids, terpenes, and alkaloids (Siddiqui et al., 2009). Although acetylcholinesterase inhibitory therapy may be considered a simple symptomatic short-term intervention, recent data from long-term interventions demonstrates that the persistence of the clinical effect can be lengthened to up to 36 months (Mukherjee et al. 2007).

Extracts of different medicinal plants have been reported to exhibit AchEI activity. This review provides a summary of plants which were investigated for their AchEI, and antioxidant activities, along with their family name, scientific names, plant parts, and solvents used for extraction during the period 2014-2022. AchEI activity and antioxidant activity were reported consistently with the authors' methodology, and IC50 values were selected instead of inhibition percentages when both metrics were available (Supplementary Table 1).

In this review, 361 plant extracts belonging to 180 plant species and 63 families were reported to possess varying degrees of AchEI and antioxidant activities (Supplementary Table 1). Three families Lamiaceae, Asteraceae, and Polygonaceae were represented by 43, 15, and 8 species, respectively. The reported effectiveness of a plant as AchEI and antioxidants varies between different plants or in the case of the same plant, this might be attributed to the extraction method, plant parts tested, and the method used for the evaluation of AChEI activity. From the 361 plant extracts retrieved from the included studies, 73 plant extracts belonging to 48 plant species were considered to possess strong AchEI activity with IC50 < 50 µg/mL of this group, the Amaryllidaceae and Lamiaceae families were represented by 4 and 8 plants, respectively.

The Amaryllidaceae family

Alkaloids from the Amaryllidaceae family are among the most extensively studied secondary metabolites in relation to AD. On a chemical basis, these alkaloids form a significant group of isoquinoline compounds, synthesized entirely by plants of the family, and are considered as a distinct category (Cahlíková et al., 2021). Phenylalanine and tyrosine, aromatic amino acids, serve as a key precursor, supplying critical intermediates for the biosynthesis of the Amaryllidaceae alkaloid 4-O-methylnorbelladine (Kilgore & Kutchan, 2016). Following various intramolecular oxidative couplings, this molecule forms fundamental structural kinds of alkaloids including galanthamine, lycorine, haemanthamine, crinine, homolycorine, tazettine, and montanine (Cahlíková et al., 2021). The biological activity of Amaryllidaceae plants is linked to the presence of alkaloids. These compounds exhibit various biological activities, such as inhibitory effects on acetylcholinesterase and butyrylcholinesterase, as well as antitumor, antimicrobial, antioxidant, anti-inflammatory, and insect-feeding effects (Nair et al., 2017; Al Mamun et al., 2020).

The most well-known alkaloid of the amaryllaceae is galanthamine, a reversible, competitive AchEI

that was first isolated from the bulbs of *Galanthus woronowii* Losinsk (Fulton & Benfield, 1996). Furthermore, galanthamine alters the conformation of nicotine by binding to their allosteric regions (Raskind et al., 2000). Acetylcholine triggers a greater response from the nicotinic receptor due to this allosteric modulation. Acetylcholine is released more readily when presynaptic nicotinic receptors are activated, which lead to the increase of its availability) Kotra & Park, 2017). In 2001, the FDA (Food and Drug Administration) certified galanthamine for the management of mild to moderate Alzheimer's disease. According to reports in the early 21st century (López et al., 2002), the galanthamine and lycorine structural types of AAs are mostly linked to their acetylcholinesterase activity. However, in the past ten years, novel structural kinds of AAs have been discovered that are intriguing cholinesterase inhibitors.

The Lamiaceae Family

Lamiaceae family (the mint family) is the one of the largest plant families, approximately 236 genera and more than 7000 species have been identified (Monteiro, et al., 2018). Certain plants belonging to this family, particularly *Rosmarinus, Salvia, Melissa officinalis,* and *Lavandula,* are rich in rosmarinic acid and other phenolic compounds, which exhibit potent antioxidant, anti-inflammatory, and neuroprotective properties. These bioactive compounds are particularly beneficial in the treatment of neurological disorders, including AD (Topcu & Kusman, 2014). Rosmarinic acid (RA) is one of the most active phytochemical products from the Lamiaceae, RA has drawn attention for its potential therapeutic effects, particularly in neurodegenerative diseases like dementia (Topcu & Kusman, 2014). RA exerts multiple neuroprotective mechanisms relevant to dementia prevention and treatment. Its strong anti-inflammatory and antioxidant properties help mitigate the neuroinflammation and oxidative stress that contribute to cognitive decline in conditions such as Alzheimer's disease. RA reduces inflammation in the brain through inhibiting the production of pro-inflammatory cytokines and modulating pathways like NF-κB and MAPK,while its antioxidant activity protects neuronal membranes from lipid peroxidation and enhances endogenous antioxidant enzymes like superoxide dismutase (SOD) (Al-Harbi and Imam, 2014; Arafe, 2005). Furthermore, RA possesses AChE inhibitory activity, which helps to elevate ACh levels, and thus improve cognitive function (Alagawany et al., 2017).

Additionally, RA exhibits different important mechanisms, such as inhibition of Aβ aggregation (Ono et al., 2005). It also protects neurons from excessive programmed cell death by modulating apoptotic pathways and enhances the expression of brain-derived neurotrophic factor (BDNF), which support neuronal plasticity and synaptic health (Braidy and Guillemin, 2012). Furthermore, RA protects against glutamate-induced excitotoxicity by modulating calcium homeostasis and helps maintain the integrity of the blood-brain barrier, preventing neurotoxic substances from entering the brain. The various mechanisms of RA positioned the compound as an enthralling target for more investigations in the development of therapeutic strategies to delay or prevent cognitive decline in patients with dementia.

Phytochemicals with acetylcholinesterase inhibitory activity

Phytochemical compounds are occurring naturally in plants and are classified based on their role in plant metabolism into primary and secondary constituents. Primary constituents are essential for plant growth, these include amino acids, proteins, common sugars, pyrimidines of nucleic acids, and chlorophylls. While, secondary metabolites, which are referred to as phytochemicals, encompass a wide range of compounds including alkaloids, terpenes, phenolics, saponins, tannins, anthraquinones, cardiac glycosides, and cyanogenic glycosides. The use of plants in traditional medicine is likely to be associated with the presence of secondary metabolites (Thatoi & Patra, 2011).

A significant number of phytochemical compounds possess AChE inhibitory activity (Ali-Shtayeh et al., 2014; Murray et al., 2013). Huperzine A and galanthamine are potent AchE inhibitors derived from natural sources used in the treatment of AD. Galanthamine is the first alkaloid approved as a prescription drug for AD treatment

mainly during the mild to moderate stages of the disease, while huperzine A is commercially available as a dietary supplement. This limitation drives the ongoing search for new AchE inhibitors from plant sources (Cortes et al., 2015).

Plants' phytochemicals have been widely utilized as enzyme inhibitors, with several thousand plant extracts screened for AchE inhibition across different regions of the world (Ashraf et al., 2011). Scientific research into medicinal plants or herbs for dementia began approximately 30 years ago, although empirical exploration of plant-based treatments dates back centuries. Ethnopharmacology, the study of traditional medicine practices, has long documented the use of plants for various conditions, with knowledge on species, preparation, and dosages passed down through generations. The continued use of these plant-based medicines suggests a degree of safety and tolerability when used appropriately.

The influence of phytochemicals on the complex cerebral functions, such as memory, is likely associated with their role to deter predators or attract pollinators or disseminators by affecting the nervous system; the same action has been exploited for developing natural insecticides such as the pyrethrins, derived from *Chrysanthemum* species, which target sodium channels in insects leading to the disruption the function of their nervous system (Shafer et al., 2005).

Plants have been the sole most fruitful source of leads for drugs development. Indeed, several scientific research have documented the use of medicinal plants and their natural compounds for the treatment of AD. despite the fact that mechanism of their action is still not clear, phytochemical studies of the various plants have reported the presence of many valuable chemical compounds, such as alkaloids, flavonoids, polyphenols, lignans, tannins, triterpenes, and sterols (Bordoloi et al., 2024)., that show a wide spectrum of pharmacological activities, including anticholinesterase, antioxidant, and anti-inflammatory, effects (Table 2). Historically, plant medicines were discovered by trial and error.

Table 2 provides a detailed overview of the mechanisms of action of various plant chemical compounds in the treatment of AD. Mechanisms of action of these compounds include target cholinergic dysfunction by increasing acetylcholine (ACh) levels and inhibiting AChE and BuChE, reducing amyloid plaque formation, combating oxidative stress, targeting neuroinflammation, and protein aggregation.

Table 2. Mechanisms of action of phytochemicals in alzheimer's disease: a comprehensive overview of key bioactive compounds and their therapeutic targets

Category	Specific Compounds	Plant Sources	Target Mechanisms in Alzheimer's Disease	Mechanisms of Action	References
Alkaloids	Galantamine	Galanthus woronowii	Cholinergic Dysfunction	Increases Ach levels; Inhibits AChE & BuChE	Vaibhav, 2021
Flavonoids	Apigenin	Various fruits and vegetables	Cholinergic Dysfunction	Increases ACh levels	Olasehinde & Olaokun, 2024
	Baicalein	Scutellaria baicalensis	Protein Aggregation Oxidative Stress	Reduces amyloid plaque formation reduce oxidative stress	Jadhav & Kulkarni, 2023
	Catechin	Camellia sinensis	Oxidative Stress	Enhances antioxidant enzymes	Bawono et al., 2023
	Epicatechin	Camellia sinensis	Cholinergic Dysfunction	Increases ACh levels	Baranowska-Wójcik et al., 2020
	Fisetin	Various fruits and vegetables	Protein Aggregation	Inhibits β-amyloid peptide aggregation	Xiao et al., 2021
	Luteolin	Various fruits and vegetables	Neuroinflammation	Reduces neuroinflammation	Burton et al., 2016
	Myricetin	Various fruits and vegetables	Cholinergic Dysfunction	Inhibits AChE and BuChE	Katalinić et al., 2010
Lignans	Arctigenin	Arctium lappa	Neuroinflammation	Reduces neuroinflammation Reduces pro-inflammatory cytokines	Zhang et al., 2018
	Matairesinol	Various plants	Neuroinflammation Oxidative Stress	Inhibits microglia activation Enhances antioxidant enzymes	Wu et al., 2021
	Pinoresinol	Olea europaea	Oxidative Stress Protein Aggregation	Inhibits ROS formation Reduces amyloid plaque formation	Pal et al., 2020
	Secoisolariciresinol diglucoside (SDG)	Linum Usitatissimum (Flaxseed)	Oxidative Stress Protein Aggregation	Reduces oxidative stress Inhibits β-amyloid peptide aggregation	Rom et al., 2018
	Sesamin	Sesamum indicum (Sesame seeds)	Cholinergic Dysfunction	Increases ACh levels	Kim et al., 2023

Category	Specific Compounds	Plant Sources	Target Mechanisms in Alzheimer's Disease	Mechanisms of Action	References
Polyphenols	Chrysin	Passiflora caerulea	Neuroinflammation	Inhibits microglia activation	Mishra et al., 2021
	Curcumin	Curcuma longa	Oxidative Stress	Reduces oxidative stress	Selvi et al., 2014
			Protein Aggregation	Inhibits β-amyloid peptide aggregation	Doytchinova et al., 2020
	Tyrosol	Olea europaea	Neuroinflammation	Reduces neuroinflammation	Grubić Kezele & Ćurko-Cofek, 2022
	Quercetin	Various fruits and vegetables	Neuroinflammation	Inhibits microglia activation	Han et al., 2021
				Reduces pro-inflammatory cytokines	Han et al., 2021
	Resveratrol	Vitis vinifera	Oxidative Stress	Inhibits ROS formation	Leonard et al., 2023
	Epigallocatechin gallate (EGCG)	Camellia sinensis	Protein Aggregation	Reduces amyloid plaque formation	Fernandes et al., 2021
Sterols	Campesterol	Various plants	Oxidative Stress	Reduces cholesterol levels	Wang et al., 2017
	Stigmasterol	Soybeans	Oxidative Stress	Modulates membrane fluidity	Hodzic et al., 2008
	β-Sitosterol	Various plants	Oxidative Stress	Reduces cholesterol levels	Lomenick et al., 2015
Tannins	Ellagic Acid	Punica granatum	Oxidative Stress	Reduces oxidative stress	Xiao et al., 2022
			Protein Aggregation	Inhibits β-amyloid peptide aggregation	
	Gallic Acid	Various plants	Neuroinflammation	Reduces neuroinflammation	Dong et al., 2022
			Neuroinflammation	Reduces pro-inflammatory cytokines	
	Proanthocyanidins	Vitis vinifera	Oxidative Stress	Inhibits ROS formation	Nallathambi et al., 2020
			Protein Aggregation	Reduces amyloid plaque formation	
	Schisandrin	Schisandra chinensis	Cholinergic Dysfunction	Inhibits AChE	Hung et al., 2007
	Tannic Acid	Various plants	Neuroinflammation	Inhibits microglia activation	Azimullah et al., 2023
			Oxidative Stress	Enhances antioxidant enzymes	
Triterpenes	Asiatic Acid	Centella asiatica	Neuroinflammation	Reduces neuroinflammation	Wong et al., 2021
			Neuroinflammation	Reduces pro-inflammatory cytokines	
	Betulinic Acid	Betula papyrifera (Birch bark)	Oxidative Stress	Inhibits ROS formation	Adepoju et al., 2023
			Protein Aggregation	Reduces amyloid plaque formation	
	Glycyrrhizic Acid	Glycyrrhiza glabra	Cholinergic Dysfunction	Increases ACh levels	Zulfugarova et al., 2023
			Cholinergic Dysfunction	Inhibits AChE and BuChE	
	Oleanolic Acid	Olea europaea	Neuroinflammation	Inhibits microglia activation	Castellano et al., 2019
			Oxidative Stress	Enhances antioxidant enzymes	
	Ursolic Acid	Malus pumila	Oxidative Stress	Reduces oxidative stress	Fu et al., 2023
			Protein Aggregation	Inhibits β-amyloid peptide aggregation	Liang et al., 2017

Conclusion

AD remains an intimidating challenge in neurodegenerative diseases, notably influencing cognitive functions and daily activities of the elderly. The pathogenesis of AD is multifactorial process including age, sex, oxidative stress, and other biochemical pathways. AChE inhibitors have been considered as one of the most effective therapeutic strategies for managing AD by enhancing ACh signal release from neurons, thus relieving symptoms related to AD. Ethnobotanical studies underscore the potential of plant chemical compounds in providing neuroprotection and improving cognitive functions, suggesting an alternative or complementary approach to synthetic drugs. However, the curative efficacy of these phytochemicals needs further investigation and verification through precise scientific research.

Recommendations

The collaboration between physicians, ethnobotanists, and pharmacologists is encouraged to investigate the therapeutic potential of chemical compounds derived from medicinal plants. The integration of traditional knowledge with modern scientific methods would lead to the identification of novel AChE inhibitors. Given the higher incidence of AD in women, it is imperative to investigate the sex-specific effects of AChE inhibitors and other therapeutic agents. Understanding the role of estrogenic compounds in protecting against amyloid-beta toxicity can guide the development of targeted interventions. Investigate the potential of combining AChE inhibitors with other neuroprotective agents, including antioxidants and anti-inflammatory compounds, to achieve a synergistic effect and enhance therapeutic outcomes. Advocate for regulatory frameworks that support the integration of ethnomedicine into mainstream healthcare. Ensuring the standardization and quality control of plant-based AChE inhibitors is crucial for their acceptance and widespread use. Increase awareness about the potential benefits of plant-based therapies

among healthcare providers and the general public. Educational initiatives can help in promoting the acceptance of these alternative therapies.

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Table S1. List of plants with AChE inhibitory and antioxidant activity retrieved from the literature during the period from 2014-2022.

Family Plant species	AChE inhibition (%)/ IC50	Antioxidant activity (IC50)	Method of extraction (Part tested)	Reference
Acoraceae				
Acorus calamus L.	17.0 µg/mL	615.0 µg/mL	MOH extract (R)	Mathew & Subramanian, 2014
Amaranthaceae				
Atriplex laciniata L.	267 µg/mL	210 µg/mL	AQU fraction (WP)	Kamal et al., 2015
	270 µg/mL	382 µg/mL	EAC fraction (WP)	
	280 µg/mL	82 µg/mL	MOH extract (WP)	
	310 µg/mL	270 µg/mL	Hexanic fraction (WP)	
	390 µg/mL	210 µg/mL	CHLfraction (WP)	
Amaryllidaceae				
Allium neapolitanum Cirillo	74.25 mg/mL	> 100 mg/mL	60% ETOH extract (L)	Ali-Shtayeh et al., 2014
	99.4 mg/mL	6.16 mg/mL	60% ETOH extract (Fl)	
Crinum bulbispermum (Burm.f.) Milne-Redh. & Schweick.	107.90 µg/mL		ALK fraction (B)	Cortes et al., 2015
Crinum jagus (J. Thomps.) Dandy	18.3 µg/mL		ALK fraction (B)	
Hippeastrum puniceum (Lam.) Voss.	28.1 µg/mL		ALK fraction (B)	
Zephyranthes carinata Herb.	18.0 µg/mL		ALK fraction (B)	
Anacardiaceae				
Buchanania axillaris (Desr.) T.P.Ramamoorthy in C.J.Saldanha & Nicolson	136.2 µg/mL		AQU fraction (AP)	Penumala et al., 2018
	67.5 µg/mL		Buthanolic fraction (AP)	
	4.9 µg/mL		MOH extract (AP)	
	12.3 µg/mL	5.97 mg AAE/g	Chloroform fraction (AP)	
Pistacia vera L.	204.1 µg/mL		50% MOH (H)	Jazayeri et al. 2014
Searsia mysorensis (G. Don) Moffett.	41.3 µg/mL	16.4 mg AAE/g	Chloroform fraction (AP)	Penumala et al., 2018
	83.5 µg/mL		Buthanolic fraction (AP)	
	93.7 µg/mL		AQU fraction (AP)	
Apiaceae				
Angelica decursiva (Miq.) Franch. & Sav.	16.6 µg/mL		MOH extract (WP)	Ali et al., 2015
	2.6 µg/mL		AQU fraction (WP)	
	6.0 µg/mL		Buthanolic fraction (WP)	
	9.7 µg/mL		EACfraction (WP)	
	13.7 µg/mL		Chloroform fraction (WP)	
Centella asiatica (L.) Urb.	0.0152 mg/mL	0.0192 mg/mL	ETOH extract (L)	Azhari et al., 2014
Coriandrum sativum Linn.	>1000 µg/mL	>1000 µg/mL	MOH extract (L)	Mathew & Subramanian, 2014
Ferula assa-foe`tida L.	281.3 µg/mL		50% MOH(G)	Jazayeri et al. 2014
Foeniculum vulgare Mill.	3.5 mg/mL	27.54 mg/mL	60% ETOH extract (L)	Ali-Shtayeh et al., 2014
Apocynaceae				
Hemidesmus indicus (L.) R. Br. Ex Schult.	28.1 µg/mL	5.50 mg AAE/g	Chloroform fraction (AP)	Penumala et al., 2018
	48.6 µg/mL		MOH extract (AP)	
	113.5 µg/mL		Buthaolic fraction (AP)	
	129.4 µg/mL		AQU fraction (AP)	
Rauvolfia serpentina Linn.	22.0 µg/mL	96.0 µg/mL	MOH extract (RT)	Mathew & Subramanian, 2014
Rhazya stricta Decne.	191.44 µg/mL	12.80 µg/mL	MOH extracts	Shahat et al., 2015
Asparagaceae				
Bellevalia flexuosa Boiss.	97.30 mg/mL	> 100 mg/mL	60% ETOH extract (S)	Ali-Shtayeh et al., 2014
	73.50 mg/mL	> 100 mg/mL	60% ETOH extract (FL)	
	31.75 mg/mL	12.76 mg/mL	60% ETOH extract (L)	
	97.9 mg/mL	2.14 mg/mL	60% ETOH extract (Fruit)	
Ornithogalum narbonense L.	92.50 mg/mL	> 100 mg/mL	60% ETOH extract (FL)	Ali-Shtayeh et al., 2014
	25.9 mg/mL	21.81 mg/mL	60% ETOH extract (L)	
	78.63 mg/mL	86.32 mg/mL	60% ETOH extract (S)	
Asphodelaceae				
Asphodeline lutea (L.) Rchb.	17.75 mg/mL	> 100 mg/mL	60% ETOH extract (L)	Ali-Shtayeh et al., 2014
Asteraceae				
Achillea millefolium L.	190.80 µg/mL		ETOH extract (L)	de Torre et al., 2022
.	128.87 µg/mL		ETOH extract (I)	
	>250 µg/mL		AQU Extract (S)	
	>250 µg/mL		AQU Extract (I)	
Anthemis arvensis L.	234.76 µg/mL		ETOH extract (AP)	de Torre et al., 2022
	158.84 µg/mL		AQU Extract (AP)	
Anthemis cotula L.	156.84 µg/mL		ETOH extract (AP)	de Torre et al., 2022
Cichorium intybus L.	55.92µg/mL		ETOH extract (F)	de Torre et al., 2022
	189.81 µg/mL		AQU Extract (F)	
Conyza bonariensis Cronquist.	2.89 mg/mL	2.74 mg/mL	60% ETOH extract (L)	Ali-Shtayeh et al., 2014

Family Plant species	AChE inhibition (%)/ IC50	Antioxidant activity (IC50)	Method of extraction (Part tested)	Reference
	3.45 mg/mL	2.74mg/mL	60% ETOH extract (FL)	
Helichrysum sanguineum (L.) Kostel.	6.35 mg/mL	44.5 mg/mL	60% ETOH extract (L)	Ali-Shtayeh et al., 2014
	35.5 mg/mL	53.5 mg/mL	60% ETOH extract (FL)	
Helichrysum stoechas (L.) Moench	>250 µg/mL		AQU Extract (AP)	de Torre et al., 2022
Jasonia glutinosa (L.) DC.	239.76 µg/mL		ETOH extract (I)	de Torre et al., 2022
	60.83 µg/mL		AQU Extract (I)	
Jasonia tuberosa (L.) DC.	219.10 µg/mL		AQU Extract (AP)	de Torre et al., 2022
Phagnalon rupestre (L.) DC.	6.25 mg/mL	0.93 mg/mL	60% ETOH extract (FL)	Ali-Shtayeh et al., 2014
	10.2 mg/mL	1.9 mg/mL	60% ETOH extract (L)	
Santolina chamaecyparesus L. ssp. Squarrosa Nyman	100.90 µg/mL		ETOH extract (I)	de Torre et al., 2022
Saussurea lappa C.B.Clarke.	>1000 µg/mL	510 µg/mL	MOH extract (R)	Mathew & Subramanian, 2014
Sylibum marianum (L.) Gaertner	>250 µg/mL		ETOH extract (I)	de Torre et al., 2022
Tanacetum parthenium (L.) Schultz	>300 µg/mL		ETOH extract (S)	de Torre et al., 2022
	92.80 µg/mL		ETOH extract (L)	
	116.95 µg/mL		ETOH extract (I)	
	193.80 µg/mL		AQU Extract (S)	
	>250 µg/mL		AQU Extract (L)	
	178.92 µg/mL		AQU Extract (I)	
Tussilago farfara L.	160.83 µg/mL		ETOH extract (L)	de Torre et al., 2022
	178.92 µg/mL		AQU Extract (Le)	
Brassicaceae				
Brassica alba (L.) Boiss.	84.30 µg/mL		50% MOH(SD)	Jazayeri et al. 2014
Brassica nigra W.D.J.Koch	135.0 µg/mL		50% MOH(SD)	Jazayeri et al. 2014
Diplotaxis harra (Forssk.) Boiss.	0.76 mg/mL	0.86 mg/mL	AQU extract (FL)	Bahloul et al., 2016
	4.36 mg/mL	1.36 mg/mL	AQU extract	
	3.13 mg/mL	2.16 mg/mL	AQU extract (SD)	
	2.28 mg/mL	5.47 mg/mL	AQU extract (L)	
Diplotaxis simplex Asch. ex Rohlfs	2.33 mg/mL	0.31 mg/mL	AQU extract (SD)	Bahloul et al., 2016
	0.42 mg/mL	0.41mg/mL	AQU extract (FL)	
	5.44 mg/mL	15.91 mg/mL	AQU extract (S)	
	3.04 mg/mL	3.67 mg/mL	AQU extract (L)	
	3.16 mg/mL	3.88 mg/mL	AQU extract	
	4.01 mg/mL	5.03 mg/mL	AQU extract (RT)	
Cannabaceae				
Humulus lupulus L.	369.6 µg/mL		50% MOH(FL)	Jazayeri et al. 2014
Caprifoliaceae				
Nardostachys jatamansi (D. Don.) DC.	40.5 µg/ml	295.0 µg/ml	MOH extrac (AP)	Mathew & Subramanian ,2014
Celastraceae				
Celastrus paniculatus Willd.	>1000 µg/mL	943 µg/mL	MOH extract (SD)	Mathew & Subramanian ,2014
Combretaceae				
Terminalia chebula Retz.	180.0 µg/mL	8.5 µg/mL	MOH extract (F)	Mathew & Subramanian ,2014
Convolvulaceae				
Convolvulus pluricaulis Choisy.	234.0 µg/mL	275.0 µg/mL	MOH extract (WP)	Mathew & Subramanian ,2014
Evolvulus alsinoides Linn.	245.0 µg/mL	280.0 µg/mL	MOH extract (WP)	Mathew & Subramanian ,2014
Ipomoea aquatica Forssk.	49.03 µg/ml	19.64 µg/mL	Hydro-alcoholic extract (L)	Dhanasekaran et al., 2015
	165.0 µg/ml	42.6 µg/mL	ETOH extract (L)	
Mimosa pudica L.	0.0114 mg/mL	0.014 mg/mL	ETOH extract (L)	Azhari et al., 2014
Crassulaceae				
Hylotelephium maximum (L.) Holub	238.76 µg/mL		AQU Extract (AP)	de Torre et al., 2022
Cucurbitaceae				
Citrullus colocynthis (L.) Schrad.	131.02 µg/mL	12.83 µg/mL	MOH extracts	Shahat et al., 2015
Cupressaceae				
Cupressus sempervirens L.	54.84% 100 µg/mL	18.14 % 1 g/mL	ACE (N)	Senol et al., 2015
	32.67 % 100 µg/mL	76.68 % 1 mg/ml	ACE (SH)	
Juniperus communis L.	32.34 % a100 µg/mL	64.69 % 1mg/ml	ACE (SH)	Senol et al., 2015
	54.84 % 100 µg/mL	25.38 % 1mg/ml	ACE (N)	
Juniperus sabina L.	379.9 µg/mL		50% MOH(FR)	Jazayeri et al. 2014
Equisetaceae				
Equisetum arvense L.	62.16 µg/mL		ETOH extract (S)	de Torre et al., 2022
	155.61 µg/mL		AQU Extract (S)	
Equisetum telmateia L	63.93 µg/mL		ETOH extract (S)	de Torre et al., 2022
	>300 µg/mL		AQU Extract (S)	
Euphorbiaceae				
Acalypha alnifolia Klein ex Willd.	32.9 µg/mL	127.18 µmol AAE/g	ChL fraction (AP)	Penumala et al., 2018
	59.2 µg/mL		MOH extract (AP)	Penumala et al., 2018
	64.8 µg/mL		AQU fraction (AP)	Penumala et al., 2018
	257.5 µg/mL		BUT fraction (AP)	Penumala et al., 2018
Emblica officinalis Gaertn.	53.5 µg/mL	7.0 µg/mL	MOH extract (F)	Mathew & Subramanian, 2014

Family Plant species	AChE inhibition (%)/ IC50	Antioxidant activity (IC50)	Method of extraction (Part tested)	Reference
Euphorbia characias L.	>300 µg/mL		AQU Extract (AP)	de Torre et al., 2022
Euphorbia helioscopia L.	41.95 µg/mL		AQU Extract (AP)	de Torre et al., 2022
Jatropha gossypifolia L.	95.7 µg/mL		EAC fraction (L)	Saleem et al., 2016
	176 µg/mL		Dichloromethane extract (RT)	
	222 µg/mL		MOH extract (RT)	
	289 µg/mL		Dichloromethane extract (L)	
Fabaceae				
Leucaena leucocephala (Lam.) de Wit	118.23 µg/mL	9.86 µg/mL	ACE (L)	Dzoyem, & Eloff,2015
Securidaca longipendunculata Oliv.	108.02 mg/mL		AQU extract (RT)	Saliu & Olabiyi, 2016
Trifolium angustifolium L.	89.06 % at 200µg/ml		AQU extract (WP)	Ertaş et al., 2015
	54.14 % 200µg/ml	56.71 % 100 µg/ mL	ACE (WP)	
	72.89% 200 µg/ml	65.82% a100 µg/ mL	MOH extract (WP)	
Trigonella foenum-graceum Linn.	>1000 µg/mL	830 µg/mL	MOH extract (SD)	Mathew & Subramanian ,2014
Fumariaceae				
Fumaria capreolata L.	0.921 mg/mL	> 100 mg/mL	60% ETOH extract (FL)	Ali-Shtayeh et al., 2014
	0.025 mg/mL	0.69mg/mL	60% ETOH extract (F)	
	0.035 mg/mL	1.34 mg/mL	60% ETOH extract (L)	
Fumaria densiflora DC.	0.62 mg/mL	0.51 mg/mL	60% ETOH extract (L)	Ali-Shtayeh et al., 2014
	10.50 mg/mL	0.68mg/mL	60% ETOH extract (FL)	
Fumaria vaillantii loisel	10.50 mg/mL	1.4 mg/mL	60% ETOH extract (L)	Ali-Shtayeh et al., 2014
Geraniaceae				
Pelargonium graveolens L'Hér.	196.9 µg/ml		50% MOH(AP)	Jazayeri et al. 2014
Juglandaceae				
Juglans regia L.	8.52 mg/mL	43.86 mg/mL	60% ETOH extract (F)	Ali-Shtayeh et al., 2014
	647.5 µg/mL		50% MOH (F)	Jazayeri et al. 2014
Lamiaceae				
Acinos arvensis (Lam.) Dandy	<50% 1 mg/mL)	17.50 µg/mL	ETOH extract (AP)	Vladimir-Knežević, 2014
Calamintha officinalis Moench	50.5%–68.1% 1 mg/mL)	16.45 µg/mL	ETOH extract (AP)	Vladimir-Knežević, 2014
	(50.5%–68.1% 1 mg/mL)	10.75 µg/mL	ETOH extract (AP)	
	67.90 µg/mL		ETOH extract (AP)	de Torre et al., 2022
	157.84 µg/mL		AQU Extract (AP)	
	<50% 1 mg/mL	18.61 µg/mL	ETOH extract (AP)	Vladimir-Knežević, 2014
Clinopodium serpyllifolium (M.Bieb.) Kuntze	13.10 mg/mL		EO (AP)	Ali-Shtayeh et al., 2018
	2.36 mg/mL	0.14 mg/mL	AQU extract (AP)	
	3.03 mg/mL	0.45 mg/mL	MOH extract (AP)	
Clinopodium vulgare L.	<50% 1 mg/mL	17.39 µg/mL	AQU extract (AP)	Vladimir-Knežević, 2014
Isodon rugosus (Wall.) Codd	83.73 % 50 µg/ml	162 µg/ml	MOH extract (AP)	Zeb et al 2014
Lavandula angustifolia Moench (Synonym of *Lavandula latifolia* Medik.)	50.5%–68.1% 1 mg/mL	31.62 µg/mL	ETOH extract (FL)	Vladimir-Knežević, 2014
Lavandula intermedia Emeric ex Loisel.	50.5%–68.1% 1 mg/mL	43.97 µg/mL	ETOH extract (FL)	Vladimir-Knežević, 2014
Lavandula latifolia Medicus	47.95 µg/mL		ETOH extract (I)	de Torre et al., 2022
	70.92 µg/mL		ETOH extract (S, L)	
	19.98 µg/mL		AQU Extract (I)	
	71.92 /mL		AQU Extract (S, L)	
Lavandula pubescens Decne (LP)	0.90 µl/mL	0.160 µl/mL	EO (AP)	Ali-Shtayeh et al., 2020
Majorana syriaca (L.) Rafin.	2.90 mg/mL	0.21 mg/mL	60% ETOH extract (L)	Ali-Shtayeh et al., 2014
Marrubium incanum Desr.	(<50% inhibition 1 mg/mL)	11.82 µg/mL	ETOH extract (AP)	Vladimir-Knežević, 2014
Melissa officinalis L	84.91 µg/mL		ETOH extract (AP)	de Torre et al., 2022
	171.82 µg/mL		AQU Extract (AP)	
	(50.5%–68.1% 1 mg/mL)	7.74 µg/mL	ETOH extract (L)	Vladimir-Knežević, 2014
Mentha aquatica L.	118.87 µg/mL		AQU Extract (AP)	de Torre et al., 2022
Mentha longifolia (L.) Hudson	>75% 1 mg/mL	8.43 µg/mL	ETOH extract (AP)	Vladimir-Knežević, 2014
	130.86 µg/mL		ETOH extract (AP)	de Torre et al., 2022
	62.93 µg/mL		AQU Extract (AP)	
Mentha piperita L.	>75% 1 mg/mL	8.88 µg/mL	ETOH extract (L)	Vladimir-Knežević, 2014
Mentha pulegium L.	226.7 µg/mL		AQU Extract (AP)	de Torre et al., 2022
	<50% 1 mg/mL	24.27 µg/mL	ETOH extract (AP)	Vladimir-Knežević, 2014
Mentha spicata L.	23.1 µl/mL		Essential Oil (AP)	Ali-Shtayeh et al., 2019
	6.30 mg/mL	0.56 mg/mL	60% ETOH extract (L)	Ali-Shtayeh et al., 2014
Mentha suaveolens Ehrh.	217.78 µg/mL		ETOH extract (AP)	de Torre et al., 2022
	113.88 µg/mL		AQU Extract (AP)	

Family Plant species	AChE inhibition (%)/ IC50	Antioxidant activity (IC50)	Method of extraction (Part tested)	Reference
Micromeria croatica (Pers.) Schott	(<50% inhibition 1 mg/mL)	29.48 µg/mL	ETOH extract (AP)	Vladimir-Knežević, 2014
Micromeria graeca (L.) Benth. ex Reich.	(50.5%–68.1% 1 mg/mL)	8.79 µg/mL	ETOH extract (AP)	Vladimir-Knežević, 2014
Micromeria juliana (L.) Benth. Ex Rchb	(<50% inhibition 1 mg/mL)	17.52 µg/mL	ETOH extract (AP)	Vladimir-Knežević, 2014
Micromeria thymifolia (Scop.) Fritsch	50.5%–68.11 mg/mL	6.53 µg/mL	ETOH extract (AP)	Vladimir-Knežević, 2014
Origanum vulgare L.	<50% 1 mg/mL	4.19 µg/mL	ETOH extract (AP)	Vladimir-Knežević, 2014
Origanum vulgare L. spp. *virens*	56.55 µg/mL		ETOH extract (I)	de Torre et al., 2022
Bonnier and Layens	4.62 µg/mL		ETOH extract (AP)	
	120.85 µg/mL		AQU Extract (I)	
	>250 µg/mL		AQU Extract (AP)	
	2.59 µg/mL		ETOH extract (AP)	
	175.82 µg/mL	3.22 µg/mL	AQU Extract (AP)	
Phlomis herba-venti L.	189.10 µg/mL		ETOH extract (AP)	de Torre et al., 2022
	190.90 µg/mL		AQU Extract (AP)	
Phlomis lychnitis L.	248.73 µg/mL		ETOH extract (I)	de Torre et al., 2022
	247.75 µg/mL		ETOH extract (S and L)	
Prunella vulgaris L.	24.97 µg/mL		ETOH extract (AP)	de Torre et al., 2022
Rosmarinus officinalis L.	2.40 mg/mL	0.38 mg/mL	60% ETOH extract (L)	Ali-Shtayeh et al., 2014
	50.5%–68.1% 1 mg/mL	5.06 µg/mL	ETOH extract (L)	Vladimir-Knežević, 2014
Salvia fruticosa (L.) Mill.	4.45 mg/mL	33.08 mg/mL	60% ETOH extract (L)	Ali-Shtayeh et al., 2014
Salvia pratensis L.	>300 µg/mL		ETOH extract (AP)	de Torre et al., 2022
Satureja montana L	>75% 1 mg/mL	9.95 µg/mL	AQU extract (AP)	Vladimir-Knežević, 2014
Satureja subspicata Bartl. ex Vis.	50.5%–68.1% 1 mg/mL	3.08 µg/mL	AQU extract (AP)	Vladimir-Knežević, 2014
Sideritis hirsuta L.	31.96 µg/mL		AQU Extract (AP)	de Torre et al., 2022
Sideritis hyssopifolia L.	>250 µg/mL		AQU Extract (AP)	de Torre et al., 2022
Teucrium arduinii L.	>75% 1 mg/mL	18.06 µg/mL	ETOH extract (AP)	Vladimir-Knežević, 2014
Teucrium chamaedrys L.	33.96 µg/mL		ETOH extract (AP)	de Torre et al., 2022
	97.90 µg/mL		AQU Extract (AP)	
	>75% 1 mg/mL	5.97 µg/mL	ETOH extract (AP)	Vladimir-Knežević, 2014
Teucrium polium L.	>75% 1 mg/mL	5.90 µg/mL	ETOH extract (AP)	Vladimir-Knežević, 2014
Teucrium montanum L.	>75% 1 mg/mL	7.78 µg/mL	ETOH extract (AP)	Vladimir-Knežević, 2014
Thymus praecox subsp.	71.92 µg/mL		ETOH extract (AP)	de Torre et al., 2022
*polytrichus (*A.Kern. ex Borbás) Jalas	>250 µg/mL		AQU Extract (AP)	
Thymus vulgaris L.	(>75% 1 mg/mL)	12.27 µg/mL	ETOH extract (AP)	Vladimir-Knežević, 2014
Thymus vulgaris L. ssp. *vulgaris*	79.92 µg/mL		ETOH extract (AP)	de Torre et al., 2022
Leguminosae				
Glycyrrhiza glabra Linn.	418.0 µg/mL	145.0 µg/mL	MOH extract (RT)	Mathew & Subramanian ,2014
Senna obtusifolia (L.) H.S. Irwin & Barneby.	9.4 µg/mL		EAC fraction (L)	Jung et al., 2016
	14.5 µg/mL		AQU fraction (L)	
	29.2 µg/mL		MOH fraction (L)	
	9.9 µg/mL		BUT fraction (L)	
	12.7 µg/mL		CHL fraction (L)	
Liliaceae				
Tulipa sharonensis Dinsm.	44.5 mg/mL	> 100 mg/mL	60% ETOH extract (L)	Ali-Shtayeh et al., 2014
	37.5 mg/mL	24.62 mg/mL	60% ETOH extract (FL)	
Lycopodiaceae				
Huperzia brevifolia (Grev. & Hook.) Holub	39.6 µg/mL		ALK fraction (AP)	Armijos et al., 2016
Huperzia compacta (Hook.) Trevis.	62.4 µg/mL		ALK fraction (AP)	Armijos et al., 2016
Huperzia serrata (Thunb.) Trevis.	6.0 µg/mL		ALK fraction (WP)	Ohba et al., 2015
Huperzia squarrosa (G. Forst.) Trevis.	23.4 µg/mL	9.35 µg/mL	EACfraction (AP)	Tung et al., 2017
Huperzia squarrosa (G. Forst.)	50.1 µg/mL	16.21µg/mL	BUT fraction (AP)	Tung et al., 2017
Trevis.	112.2 µg/mL	26.91 µg/mL	ETOH extract (AP)	Tung et al., 2017
	257 µg/mL	83.70 µg/mL	Hexanic fraction (AP)	Tung et al., 2017
Phlegmariurus tetragonus (Hook. & Grev	0.9 µg/mL		ALK fraction (AP)	Armijos et al., 2016
Lythraceae				
Lythrum salicaria L.	69.93 µg/mL		AQU Extract (AP)	de Torre et al., 2022
Punica granatum L.	408.2 µg/mL		50% MOH(F)	Jazayeri et al. 2014
Menispermaceae				
Tinospora cordifolia (Thunb.) Miers	230.0 µg/mL	410.0 µg/mL	MOH extract (S)	Mathew & Subramanian ,2014
Moraceae				
Morus alba L.	2.5 µg/mL		EACfraction (RT, BR)	Kuk et al., 2017
	13.4 µg/mL		Chloroform fraction (RT,BR)	
	36.6 µg/mL		BUT fraction (RT, BR)	

Family Plant species	AChE inhibition (%)/ IC50	Antioxidant activity (IC50)	Method of extraction (Part tested)	Reference
	43 µg/mL		AQU fraction (RT,BR)	
Myrtaceae				
Myrtus communis L.	3.6 mg/mL	> 100 mg/mL	60% ETOH extract (L)	Ali-Shtayeh et al., 2014
Nelumbonaceae				
Nelumbo nucifera Gaertn.	33.2 µg/mL		BUT fraction (L)	Jung et al., 2015
	61.1 µg/mL		Ethylacetate fraction (L)	
	67.3 µg/mL		Chloroform fraction (L)	
	119.6 µg/mL		AQU fraction (L)	
	184.5 µg/mL		MOH fraction (L)	
	76.0 µg/mL	45.0 µg/mL	MOH extract (FL)	Mathew & Subramanian ,2014
Nitrariaceae				
Peganum harmala L.	5.81 mg/mL	3.1 mg/mL	60% ETOH extract (SDs)	Ali-Shtayeh et al., 2014
Ochnaceae				
Ochna obtusata DC.	25.7 µg/mL	183.96 µmol AAE/g	Chloroform fraction (AP)	Penumala et al., 2018
	82.2 µg/mL		MOH extrac (AP)	
	174.4 µg/mL		BUT fraction (AP)	
	369.1 µg/mL		AQU fraction (AP)	
Olacaceae				
Olax nana Wall. ex Benth.	33.2 µg/mL	71.46 µg/mL	MOH extract (L)	Ovais et al., 2018
Olax subscropioidea Oliv.	110.35 mg/mL		AQU extract (L)	Saliu & Olabiyi, 2016
Orchidaceae				
Ophrys dinsmore Schltr	12.1 mg/mL	22.22 mg/mL	60% ETOH extract (L)	Ali-Shtayeh et al., 2014
	89.5 mg/mL	29.13 mg/mL	60% ETOH extract (S)	
	30.5 mg/mL	35.96 mg/mL	60% ETOH extract (FL)	
Ophrys lutea (Gouan*)* Cav	94.21 mg/mL	11.75 mg/mL	60% ETOH extract (FL)	Ali-Shtayeh et al., 2014
	26.5 mg/mL	46.4 mg/mL	60% ETOH extract (S)	
	97.12 mg/mL	5.08 mg/mL	60% ETOH extract (L)	
Orchis caspia Trautv	5.70 mg/mL	0.51 mg/mL	60% ETOH extract (L)	Ali-Shtayeh et al., 2014
	97.8 mg/mL	2.74 mg/mL	60% ETOH extract (FL)	
	47.4 mg/mL	57.88 mg/mL	60% ETOH extract (S)	
Orchis collina Banks &Sol.	11.5 mg/mL	19.67mg/mL	60% ETOH extract (FL)	Ali-Shtayeh et al., 2014
	98.4 mg/mL	3.2 mg/mL	60% ETOH extract (S)	
	21.85 mg/mL	70.81 mg/mL	60% ETOH extract (L)	
Oxalidaceae				
Oxalis pes-caprae L.	6.50 mg/mL	1.3 mg/mL	60% ETOH extract (L)	Ali-Shtayeh et al., 2014
Papaveraceae				
Papaver rhoeas L.	76.92 µg/mL		ETOH extract (Capsule/petal)	de Torre et al., 2022
	150.84 µg/mL		AQU Extract (Capsule/Petal)	
Papilionaceae				
Lupinus pilosus L. (*Lupinus varius* L.)	17.75 mg/mL	> 100 mg/mL	60% ETOH extract (FL)	Ali-Shtayeh et al., 2014
	3.49 mg/mL	1.15mg/mL	60% ETOH extract (L)	
Vicia hybrida L.	50.23 mg/mL	> 100 mg/mL	60% ETOH extract (L)	Ali-Shtayeh et al., 2014
Pinaceae				
Cedrus libani A.Rich.	1.91 % 100 µg/mL	63.83 % 1mg/ml	ACE (N)	Senol et al., 2015
	33.19 % 100 µg/mL	63.83 % 1mg/ml	ACE (SH)	
	44.07 % 100 µg/mL	37.84 % 1mg/ml	ETOH extract (SH)	
Cedrus deodera (Roxb.) G.Don	>1000 µg/mL	116.0 µg/mL	MOH extract (S)	Mathew & Subramanian ,2014
Picea pungens Engelm.	45.09 % at100 µg/mL	31.56 % 1mg/ml	ACE (N)	Senol et al., 2015
Polygalaceae				
Carpolobia lutea G. Don	140 µg/mL	343 µg/mL	ETOH extract (S, BR)	Nwidu et al., 2017
	472.0 µg/mL	675 µg/mL	EAC fraction (S)	
	140 µg/mL	>1000 µg/mL	n-hexane fraction oil (S)	
	503 µg/mL	123 µg/mL	EAC fraction oil (S)	
	912 µg/mL	>1000 µg/mL	n-hexane fraction (S)	
	142 µg/mL	118 µg/mL	MOH fraction (S)	
	472 µg/mL	825 µg/mL	MOH fraction oil (S)	
	811 µg/mL	351 µg/mL	crude saponin extract (S)	
	>1000 µg/mL	449µg/mL	dichloromethane fraction (S)	
	840 µg/mL	334 µg/mL	crude ethanol oil extract (S,BR)	
	547.0 µg/mL	504 µg/mL	hot AQU extract (S, BR)	
	>1000 µg/mL	196µg/mL	hot AQU extract (L)	
	478 µg/mL	849 µg/mL	crude butanol extract (L)	
	60.0 µg/mL	500 µg/mL	CHL fraction (L)	
	81 µg/mL	>1000 µg/mL	ETOH extract (L)	
	738 µg/mL	>1000 µg/mL	crude butanol extract (L)	
	461µg/mL	141 µg/mL	n-hexane fraction (L)	
	500 µg/mL	>1000 µg/mL	crude EAC extract (L)	
	3.0 µg/mL	509 µg/mL	crude MOH extract (RT)	
	137 µg/mL	849 µg/mL	CHL fraction (RT)	
	247 µg/mL	>1000 µg/mL	Butanol fraction (RT)	
	173.0 µg/mL	500 µg/mL	n-hexane fraction (RT)	

Family Plant species	AChE inhibition (%)/ IC50	Antioxidant activity (IC50)	Method of extraction (Part tested)	Reference
	0.30 µg/mL	>1000µg/mL	EACfraction (RT)	
	2.0 µg/mL	141 µg/mL	AQU fraction (RT)	
Polygonaceae				
Emex spinosa (L.) Campd.	142.38 µg/mL	10.89 µg/mL	MOH extracts	Shahat et al., 2015
Persicaria hydropiper (L.) Delarbre.	35 µg/mL	135 µg/mL	Hexanic fraction (WP)	Ayaz et al., 2014
	130 µg/mL	20 µg/mL	EO (L)	
Persicaria minor (Huds.) Opiz.	234.0 µg/mL	74.131 µg/mL	AQU extract (L)	Ahmad et al., 2014
Polygonum hydropiper L.	55 µg/mL	10 µg/mL	CHL fraction (WP)	
	330 µg/mL	140 µg/mL	MOH extract (WP)	Ayaz et al., 2015
	310 µg/mL	15 µg/mL	EACfraction (WP)	
	240 µg/mL	3 µg/mL	BUT fraction (WP)	
	100.0 µg/mL	60 µg/mL	AQU fraction (WP)	
	225 µg/mL	200 µg/mL	EO (FLs)	
Polygonum minus Huds.	342.8 µg/mL	38.309 µg/mL	MOH extract (L)	Ahmad et al., 2014
	809.0 µg/mL	37.154 µg/mL	MOH extract (S)	
	930.0 µg/mL	30.430 µg/mL	ETOH extract (S)	
	910.0 µg/mL	31.864 µg/mL	ETOH extract (L)	
	581.0 µg/mL	99.243 µg/mL	AQU extract (S)	
	478.0 µg/mL		Dichloromethane extract (L)	
	770.0 µg/mL		Dichloromethane extract (L)	
Rheum officinale Baill.	341.7 µg/mL		50% MOH(RTs)	Jazayeri et al. 2014
Rumex hastatus D. Don	115.0 µg/mL		EACfraction (WP)	Ahmad et al., 2015
	75.0 µg/mL		Chloroform fraction (WP)	
	218.0 µg/mL		MOH extract (WP)	
	32.5 µg/mL	3.71 µg/ml	Essential Oils (AP)	
Primulaceae				
Anagallis arvensis L.	57.94 µg/mL		ETOH extract (AP)	de Torre et al., 2022
	102.89 µg/mL		AQU Extract (AP)	
Punicaceae				
Punica granatum L.	77.0 µg/mL	54.5 µg/mL	MOH extract (F)	Mathew & Subramanian ,2014
Ranunculaceae				
Anemone coronaria L.	71.5 mg/mL	1.7 mg/mL	60% ETOH extract (FL)	Ali-Shtayeh et al., 2014
	71.5 mg/mL	60.17 mg/mL	60% ETOH extract (L)	
Nigella sativa L.	69.5 mg/mL	3.62 mg/mL	60% ETOH extract (SD)	Ali-Shtayeh et al., 2014
Ranunculus asiaticus L.	14.3 mg/mL	> 100 mg/mL	60% ETOH extract (FL)	Ali-Shtayeh et al., 2014
Resedaceae				
Caylusea hexagyna M.L. Green	264.56 µg/mL	12.33 µg/mL	MOH extracts	Shahat et al., 2015
Rhamnaceae				
Ziziphus jujuba Mill. (Zizyphus vulgaris (Lam.)	24.37 µg/ml		50% MOH(F)	Jazayeri et al. 2014
Rhizophoraceae				
Rhizophora mucronata Poir.	5.75 µg/mL	60.97%	Donepezil extract (L)	Suganthy & Devi, 2016
	117.86 µg/mL	84.76%	CHL	
	69.21 µg/mL	60.75%	EAC(L)	
	259.56 µg/mL	48.34%	ACE (L)	
	59.31 µg/mL	91.05%	MOH extract (L)	
Rosaceae				
Rosa damascena Mill.	93.10 µg/mL		50% MOH(FLs)	Jazayeri et al. 2014
Sorbus torminalis (L.) Grantz	(38.84 % at 5mg/mL)	5.69 mg/mL	Aquous extract (F)	Hasbal et al., 2015
Rubiaceae				
Cinchona officinalis L.	187.6 µg/mL		50% MOH(BR)	Jazayeri et al. 2014
Galium pisiferum Boiss.	8.45 mg/mL	24.16 mg/mL	60% ETOH extract (FL)	Ali-Shtayeh et al., 2014
	10.45 mg/mL	45.53 mg/mL	60% ETOH extract (L)	
Macrosphyra Longistyla (DC) Hiern	0.556 µg/mL	0.09 mg/mL	crude methanol extract (L)	Elufioye et al., 2019
	0.846 µg/mL	0.89 mg/mL	AQU fraction	
	0.914 µg/mL	0.079 mg/mL	EACfraction (L)	
Pavetta indica L.	17.8 µg/mL		MOH extract (AP)	Penumala et al., 2018
	52.1 µg/mL	204.4 µmol AAE/g	Chloroform fraction (AP)	
	60.1 µg/mL		BUT fraction (AP)	
	100.4 µg/mL		AQU fraction (AP)	
Rutaceae				
Citrus aurantiifolia (Christm.) Swingle	19.57 µg/ml		50% MOH(F)	Jazayeri et al. 2014
Citrus aurantium L.	226.1 µg/mL		50% MOH(FLs)	Jazayeri et al. 2014
Haplophyllum myrtifolium Boiss.	5.70 mg GALAEs*/g	43.77 mg TEs/g	Pertolium Ether (AP)	Zengin et al. 2014
	5.51 mg GALAEs*/g	67.45 mg TEs**/G	EAC(AP)	
	4.65 mg GALAEs*/g	84.49 mg TEs/g	MOH extract (AP)	
	5.70 mg GALAEs*/g	43.77 mg TEs/g	Pertolium Ether (AP)	

Family Plant species	AChE inhibition (%)/ IC50	Antioxidant activity (IC50)	Method of extraction (Part tested)	Reference
Salicaceae				
Salix alba BR	989.1 µg/mL		50% MOH(BR)	Jazayeri et al. 2014
Salvadoraceae				
Retama raetam (Forssk.) Webb	85.83 mg/mL	60.2 mg/mL	60% ETOH extract (FL)	Ali-Shtayeh et al., 2014
Sapotaceae				
Englerophytum magalismontanum (Sonder) T.D.Penn.	160.19 µg/mL	10.80 µg/mL	ACE (L)	Dzoyem & Eloff, 2015
Scrophulariaceae				
Bacopa monnieri (L.) Pennell	523.0 µg/mL	115.0 µg/mL	MOH extract (WP)	Mathew & Subramanian ,2014
Scrophularia syriaca Benth	310.03 µg/mL	11.88 µg/mL	MOH extracts	Shahat et al., 2015
Solanaceae				
Mandragora autumnalis Bertol	10.06 mg/mL 48.1 mg/mL 5.10 mg/mL 34.85 mg/mL	> 100 mg/mL > 100 mg/mL 1.17 mg/mL 5.17 mg/mL	60% ETOH extract (F) 60% ETOH extract (RT) 60% ETOH extract (L) 60% ETOH extract (F)	Ali-Shtayeh et al., 2014
Withania somnifera (Linn.) Dunal.	124.0 µg/mL	850 µg/mL	MOH extract (RT)	Mathew & Subramanian ,2014
Taxaceae				
Taxus baccata L.	(27.24 % at 100 µg/mL) (31.54 % at 100 µg/mL) (43.65 % at 100 µg/mL)	87.95 % at 1000 µg/ml 91.57 % at 1 000 µg/ml 91.57 % at 1000 µg/mL	ETOH extract (SH) ACE (N) ACE (SH)	Senol et al., 2015
Theaceae				
Camellia sinensis (L.) Kuntze	5.96 µg/mL		50% MOH (L)	Jazayeri et al. 2014
Urticaceae				
ElatoSa papillosum Wedd.	165.4 µg/mL		MOH extract (L)	Ali Reza et al., 2018
Parietaria judaica L.	70.30 mg/mL	> 100 mg/mL	60% ETOH extract (L)	Ali-Shtayeh et al., 2014
Urtica pilulifera L.	10.25 mg/mL	38.32 mg/mL	60% ETOH extract (L)	Ali-Shtayeh et al., 2014
Valerianaceae				
Nardostachys jatamansi (D. Don) DC.	(83.83 % at 100 µg/ml)	295.0 µg/mL	MOH extract (R)	Mathew & Subramanian ,2014
Valeriana wallichii DC.	715.0 µg/mL	215.0 µg/mL	MOH extract (RT)	Mathew & Subramanian ,2014
Verbenaceae				
Verbena officinalis L.	166.83 µg/mL 140.85 µg/mL		ETOH extract (AP) AQU Extract (AP)	de Torre et al., 2022

Abbreviations: Plants parts: WP, Whole plant; R, Rhizome; L, Leaves; FL, Flowers; B, Bulbs; AP, Areal parts; H, Hull; G, Gumm resin; RT, Roots; S, Stem; I, Inflorescence; F, Fruits; SD, Seeds; BR, Bark; SH, Shoots; N, Needle. Solvents: MOH, Methanol; EtOH, Ethanol; AQU, Aqueous; ALK, Alkaloidal; ACE, Acetone; CHL, Chloroform; BUT Buthanolic; EAC, Ethyl acetate; EO, Essential oil. Units: GALAEs, Galanthamine equivalent; TEs, Trolox equivalent

مراجعة علمية

رؤى إثنوبوتانية حول مثبطات الأسيتيل كولين إستراز الطبيعية: نحو استراتيجيات بديلة في معالجة مرض ألزهايمر

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Natural AChE Inhibitors, Alzheimer's Disease Management, Cognitive Enhancement, Oxidative Stress and Neurodegeneration

الملخص

جاموس، ر. م.، قاســم، أ. ب.، أبوزيتون، س.ي.، ، اشــتيه، م. س. (2024) رؤى إثنوبوتانية حول مثبطات الأسيتيل كولين إستراز الطبيعية: نحو استراتيجيات بديلة في معالجة مرض ألزهايمر. سلسلة دراسات التنوع الحيوي البيئة. 19(1): 1-27.

تلعب مثبطات إنزيم الأسيتيل كولين إستراز (AChE) دورًا محوريًا في علاج الاضطرابات التنكسية العصبية، وخاصة مرض ألزهايمر، من خلال منع تحلل الأسيتيل كولين وبالتالي تعزيز الذاكرة والأداء المعرفي. تُعد النباتات الطبية والغذائية التقليدية، وخصوصًا تلك المستخدمة في الطب الشعبي الفلسطيني، مصدرًا غنيًا بالمركبات الفعالة حيويًا التي تمتلك خصائص مثبطة لإنزيم AChE. وقد تمثل هذه البدائل الطبيعية خيارات علاجية أكثر أمانًا وتوفرًا وتوافقًا ثقافيًا مقارنةً بالعقاقير الاصطناعية، مع آثار جانبية أقل. تستعرض هذه المراجعة إمكانيات النباتات، وخصوصًا المستخدمة في الطب الشعبي العشبي العربي الفلسطيني(TAPHM) ، كمصادر طبيعية لمثبطات إنزيم AChE في إدارة مرض ألزهايمر. تم إجراء مراجعة منهجية للأدبيات العلمية المنشورة بين عامي 2014 و2022 باستخدام قواعد بيانات مثل Google Scholar و PubMedو Scopusو Web of Science، وشملت الكلمات المفتاحية "تثبيط إنزيم الأسيتيل كولين إستراز"، "مرض ألزهايمر"، و"النباتات الطبية". وتم التحقق من هوية النباتات من خلال قاعدة بياناتWorld Flora Online ، كما تم تحليل المركبات النباتية الثانوية لخصائصها المثبطة للإنزيم والمضادة للأكسدة. تم تحديد 361 مستخلصًا نباتيًا من 180 نوعًا نباتيًا تنتمي إلى 63 فصيلة نباتية، وقد أظهرت فصائل Lamiaceae و Asteraceaeو Polygonaceaeأعلى مستويات النشاط المثبط. ومن بين المركبات الفعالة الرئيسية التي تم تحديدها: القلويدات والفلافونويدات والتربينات، والتي أظهرت خصائص متعددة تشمل الحماية العصبية، والأنشطة المضادة للأكسدة، وتثبيط إنزيم .AChE بشكل عام، تُظهر المستخلصات النباتية الطبيعية، خاصة من فصيلةLamiaceae ، إمكانيات واعدة كمركبات متعددة الوظائف في إدارة مرض ألزهايمر. هناك حاجة إلى إجراء دراسات سريرية مستقبلية لتأكيد فعاليتها وسلامتها العلاجية، مع تعزيز دمج المعرفة العشبية التقليدية في إطار البحث الدوائي الحديث.