Review / *Derleme*

Bezmialem Science 2014; 1: 1-25
DOI: 10.14235/bs.2014.233

Lamiaceae Family Plants as a Potential Anticholinesterase Source in the Treatment of Alzheimer's Disease

Alzheimer Hastalığı Tedavisinde Potansiyel Antikolinesteraz Bir Kaynak Olarak Lamiaceae Familyası Bitkileri

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ABSTRACT

Alzheimer's disease (AD) is one of the most common and progressive neurodegenerative disorders with dementia in the world. The precise causes of AD are not fully understood yet, although several important features of its pathophysiology are well described. Current AD treatment is symptomatic and is mainly, but not exclusively, focused on the inhibition of cholinesterases (ChEs). There are four cholinesterase inhibitors approved by the U.S. Food and Drug Administration (FDA): tacrine, donepezil, rivastigmine, and galantamine. Among them, galantamine is a natural drug, and rivastigmine is a derivative of the natural drug physostigmine. In addition, only an NMDA (N-methyl-D-aspartate) receptor antagonist, memantine, is also approved by the FDA in the treatment of patients with moderate to severe AD. However, none of them provides a satisfactory treatment for Alzheimer's disease, and studies are still going on to find new potential drugs from both synthetic chemicals and natural sources.

In this review, studies on the discovery of new cholinesterase inhibitors from natural sources, particularly from Lamiaceae family plants were evaluated, and a number of terpenoids and phenolics/flavonoids isolated are presented as potential drugs in the treatment of Alzheimer's disease.

Key Words: Alzheimer's disease, galantamin, NMDA reseptör antagonist, Lamiaceae, alkaloidler, terpenoidler

ÖZET

Alzheimer hastalığı (AH) demansla seyreden en yaygın ve gittikçe ilerleyen nörodejeneratif hastalıklardan biridir. Patofizyolojisi ile ilgili önemli özellikleri oldukça iyi belirlenmiş olmasına rağmen hala AH'nın kesin nedenleri tam olarak anlaşılamamıştır. Mevcut AH tedavisi semptomatiktir ve başlıca (fakat yegâne değil) kolinesteraz inhibitörleri üzerine odaklıdır. Amerikan Gıda ve İlaç Dairesi (FDA) tarafından onaylanmış olan dört kolinesteraz inhibitörü takrin, donepezil, galantamin, rivastigmindir ve bunlardan galantamin doğal, rivastigmin ise doğal antikolinesteraz olan fizostigminin bir türevidir. Bunlara ilaveten, bir NMDA (N-metil-D-aspartat) reseptör antagonisti olan memantin ortaileri derecede AH tedavisi için FDA tarafından onaylanmıştır. Fakat bunlardan hiçbiri tam anlamıyla Alzheimer hastalığını tatmin edici bir tedavi sunamamaktadır. Bu nedenle doğal ve sentetik kaynaklı yeni potansiyel ilaçlar üzerindeki çalışmalar devam etmektedir.

Bu derlemede yeni kolinesteraz inhibitörlerinin doğal kaynaklardan, özellikle Lamiaceae familyası bitkilerinden keşfedilmesi çalışmaları gözden geçirildi ve izole edilen pek çok terpenik, fenolik/flavonoid bileşik Alzheimer hastalığının tedavisi için potansiyel ilaç olarak sunuldu.

Anahtar Sözcükler: Alzheimer hastalığı, galantamine, NMDA receptor antagonist, Lamiaceae, alkaloids, terpenoids

Introduction

Alzheimer's disease (AD) is a neurodegenerative disease that primarily affects the elderly population over 65 years of age, is estimated to account for about 70% of the dementia cases, and now affects approximately 24 million people worldwide (1).

Alzheimer's disease (AD) is named after the German physician Aloes Alzheimer, who first described it in 1906. Alzheimer's disease (AD) is a slowly progressive disease of the brain that is characterized by memory loss, difficulty performing familiar tasks, problems with language, disorientation of time and place, poor or decreased judgment, problems with abstract thinking, misplacing things, changes in mood or behavior, changes in personality, and loss of initiative.

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Received / Geliş Tarihi : 05.02.2014
Accepted / Kabul Tarihi : 24.02.2014
Available Online Date/
Çevrimiçi Yayın Tarihi: 05.05.2014

Accumulation of the protein amyloid plays a significant role in the development of Alzheimer's disease, which is a characteristic hallmark, besides the protein tau angles in the patients with AD (2). However, Alzheimer's disease is diagnosed when a person has sufficient cognitive decline to meet the criteria for dementia or the clinical course is consistent with that of AD. Many other causes of dementia are screened for, prior to diagnosing Alzheimer's disease, and the period of the disease may extend to 3-10 years (2).

The acetylcholinesterase (AChE) enzyme predominates in a healthy brain, with the butyrylcholinesterase (BChE) enzyme considered to play a minor role in regulating brain acetylcholine (ACh) levels. The exact cause of AD is not well understood yet. The brains of those with mild-to-moderate Alzheimer's disease, a progressive type of dementia, have abnormally low acetylcholine concentrations. This means that any compound that enhances the cholinergic system in the brain may be useful in treating Alzheimer's disease and similar brain malfunctions. However, BChE activity progressively increases in patients with AD, while AChE activity remains unchanged or declines. The two enzymes differ in substrate specificity, kinetics, and activity in different brain regions. Recent evidence suggests that both AChE and BChE may have roles in the etiology and progression of AD beyond regulation of synaptic acetylcholine levels (2, 3).

Genetic factors correlate with early-onset AD, consisting of mutations in amyloid precursor protein (APP) and presenilins 1 and 2 (PS1 & PS2), along with APP gene duplication. However, factors of late-onset or sporadic AD are not understood enough yet (4), which requires further studies. Prevention of non-genetic AD can be managed with available drugs, to some degree. Elevated levels of tocopherol and tocotrienol forms are found to be associated with reduced risk of cognitive impairment in the elderly (5). In addition to vitamin E, vitamin C and beta carotene, as well as many natural compounds, may help in scavenging free radicals generated during the initiation and progression of this disease. Several natural substances with neuroprotective effects have been widely studied by a number of researchers. Most of the isolates have remarkable antioxidant properties, mainly by scavenging free radical species. Some of them increase cell survival and improve cognition by directly affecting amyloidogenesis and programmed cell death pathways (6). However, there is still an immediate requirement for both the diagnosis for patients with AD at the early stage and exploration of more efficient drugs than the ones prescribed by physcians at present, as known cholinesterase inhibitors and NMDA glutamate receptor antagonists can not provide a fully satisfactory cure for Alzheimer's disease. Besides AD, there are a number of neurodegenerative disorders and diseases with dementia, which are classified as senile; vascular; with Lewy bodies; mixed type; and dementia in Parkinson's disease (PD) and Huntington's disease (7, 8).

In this review article, natural plants have been evaluated for the treatment of AD, particularly Lamiaceae family plant extracts and their pure compounds, as potential anticholinesterase agents.

Present Treatment of AD

As it is known, two types of cholinesterases are present in the healthy human body, acetyl- and butyryl-cholinesterases. In the human brain, BChE (in some articles abbreviated as BuChE) predominantly appears to have a neuroglial distribution, whereas AChE is mainly located within cholinergic axons and the cell bodies of neurons. However, both enzymes are also found in neuritic plaques and tangles in patients with AD (9).

Butyrylcholine is not a physiological substrate in the human brain, and the only chemical difference from ACh is the presence of two additional methylene (CH_2) groups in BCh. Due to its predominantly neuronal distribution, AChE activity is higher than BChE activity in the human brain. Depending on the region, human brain AChE activity is 1.5-fold (temporal and parietal cortex) to 60-fold (caudate nucleus) higher than BChE activity (10).

The loss of memory is considered to be the result of a shortage of the nerve transmitter acetylcholine. It is possible to increase the level of this transmitter in the brain by inhibiting the activity of the enzyme acetylcholinesterase, which splits or breaks down the transmitter substance. Drugs that inhibit the breakdown of the messenger or transmitter acetylcholine delay the development of the disease (8), which explains the cholinesterase cascade in AD.

In order to find new natural agents for the treatment of AD based on the cholinesterase inhibitory mechanism, many research groups in the world study different plants from various families, including the Amaryllidaceae, Fumariaceae, Papaveraceae, and Lamiaceae (11) families. So far, some potential triterpenoids (12), such as ursolic acid and oleanolic acid, ginsenosides, gingkolides, and cannabinoids have been studied as potential cholinesterase inhibitors in AD treatment, but they are still awaiting clinical trials (12), as well as some plants that contain different types of alkaloids (11, 13).

Many drugs currently available in western medicine were originally isolated from plants or are derived from templates of compounds isolated from plants. The two major synthetic AD therapeutics available on the market are tacrine and donepezil as acetylcholinesterase inhibitors, besides a natural drug, galantamine, and a naturally derived compound, rivastigmine (Table 1) (14).

At present, two types of medications in AD treatment are approved by the FDA; these are cholinesterase inhibitors and a glutamate NMDA receptor antagonist.

Cholinesterase inhibitors

As cholinesterase inhibitors, donepezil (Aricept), rivastigmine (Exelon), galantamine (Razadyne, Reminyl), and tacrine (Cognex) are on the market, prescribed for early to moderate

Table 1. FDA Approved four anticholinesterase drugs in AD treatment

	Tacrine	Rivastigmine	Donepezil	Galanthamine
Brand name	Cognex	Exelon, generic	Aricept	Razadyne*, generic
Enzymes inhibited	AChE, BChE	AChE, BChE	AChE	AChE
Mechanism	Noncompetitive	Noncompetitive	Noncompetitive	Competitive
[a]Typical maintenance dose	20 mg four times daily	9.5 mg/24h (transdermal) 3-6 mg twice daily (oral)	10 mg once daily	8-12 mg twice daily (immediate release) 16-24 mg/day (extended release)
FDA-approved indications	Mild-moderate AD **	Mild-moderate AD Mild-moderate PD	Mild-severe AD	Mild-moderate AD
[b]Metabolism	CYP1A2	Esterases	CYP2D6 CYP3A4	CYP2D6 CYP3A4

**AD: Alzheimer's Disease; * It's original form: Reminyl

[a]Typical starting doses are one-half of the maintenance dose and are given for the first month of therapy

[b]Drugs metabolized by CYP2D6 and CYP3A4 are subject to increased serum levels when co-administered with drugs known to inhibit these enzymes, such as ketoconazole and paroxetine. Similarly, tacrine levels are increased by co-administration with the CYP1A2 inhibitors theophylline, cimetidine, and fluvoxamine (It's adopted by Standaert DG,Roberson ED 2010)

stages to treat symptoms related to memory, thinking, language, judgment, and some other thought processes, aiming to prevent the breakdown of acetylcholine, a chemical messenger that is important for learning and memory. Thus, communications among nerve cells are carried out by keeping acetylcholine levels high. However, a delayed worsening of symptoms may be realized 6 to 12 months or a maximum of 2 years for about half of people with AD.

According to the FDA, of the prescribed drugs, donepezil (Aricept) is approved to treat all stages of AD and rivastigmine (Exelon) and galantamine (Razadyne, Reminyl) are approved to treat mild to moderate AD. Cholinesterase inhibitors have some side effects, such as nausea, vomiting, loss of appetite, and increased frequency of bowel movements, but are generally tolerated. But, tacrine (Cognex) is now rarely prescribed by physicans because of hepatotoxicity and adverse effects, although it was the first its cholinesterase inhibitor approved by the FDA.

Galantamine

Several plant species contain alkaloids with cholinesterase inhibitor activity; for example, galantamine was discovered in the bulbs of *Galanthus nivalis* L. (snowdrop) (Figure 1), known as 'kardelen' in Turkey, which is one of the Amaryllidaceae family plants. Galantamine, with a similar structure to morphine (Figure 2), originally was found in species of *Narcissus tazetta* L. and *Leucojum aestivum* L. and *Lycoris radiata* Herb., belonging to the same family. Selective and competitive inhibition of AChE is considered the principal mode of action of galantamine, although other mechanistic effects have been suggested to contribute to observed cognitive improvements (2).

The tolerability and safety of galantamine in AD have not been compared with those of the synthetic AChE inhibitor donepezil (15). Optimization of the drug delivery and formulation of galantamine has extended investigations into the intranasal route (16) and prodrugs.

Figure 1. *Galanthus nivalis* L.

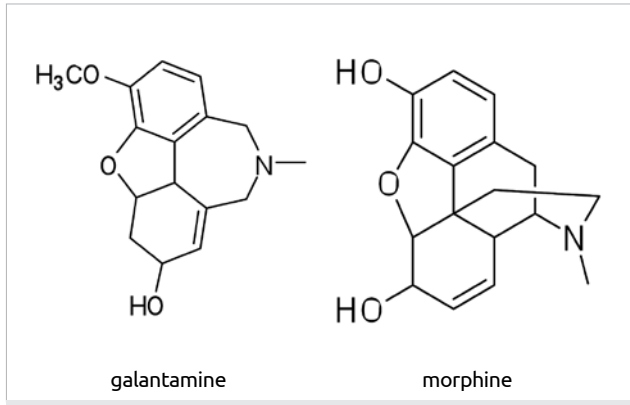


Figure 2. Structures of galantamine and morphine

Although numerous synthetic derivatives of galantamine have been developed to obtain more potent and selective AChE inhibitory properties, their clinical potential has yet to be explored. Other Amaryllidaceae alkaloids and synthetic derivatives have been shown to inhibit AChE (17), including ungeremine (Figure 3) from *Nerine bowdenii* W. Watson, *Galanthus,* and *Narcissus* species, which is a more potent AChE inhibitor than galantamine (4). Lycorine (Figure 3) inhibits AChE but is also cytotoxic, which probably limits any clinical potential (17).

Physostigmine and derivatives

Physostigmine (Figure 4) is a pyrroloindole alkaloid, isolated from the calabar bean (*Physostigma venenosum* Balf.), having a carbamate moiety that is principally responsible for reversible inhibition of AChE (17). It was presented as the first known AChE inhibitor; however, it inhibited both AChE and BChE in a smilar submicromolar range (IC_{50}= 0.015 and 0.016 µM, respectively) (18).

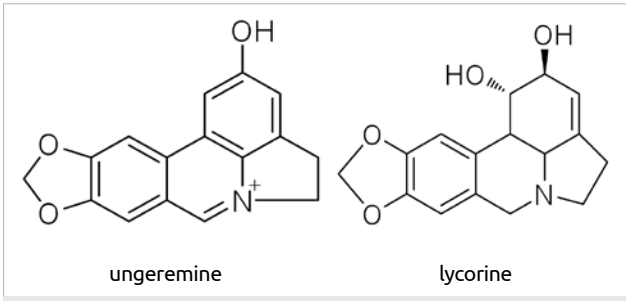


Figure 3. Structures of ungeremine and lycorine

This alkaloid improved cognitive functions in rats with scopolamine-induced cognitive impairment and in AD patients (19). However, a Cochrane review concluded later on that the evidence for efficacy of physostigmine on AD is limited and that adverse effects are common (20).

To improve the pharmacokinetic and therapeutic profiles, synthetic derivatives of physostigmine have been investigated.

One of the physostigmine derivatives, eptastigmine (heptylphysostigmine tartrate) (Figure 4), inhibited both AChE and BChE and improved cognition in AD, however, its hematological effects halted further study (21).

Other derivatives (Figure 5) of physostigmine including cymserine, bisnorcymserine (N-demethylated cymserine), and tetrahydrofurobenzofuran cymserine inhibited BChE (22). Another derivative, phenserine, an inhibitor of AChE and amyloid precursor protein (APP), has lower toxicity than physostigmine (Figure 4), tacrine (23), and rivastigmine (Figure 6). Some other alkaloids, such as steroidal alkaloids and huperzine A, which is a sesquiterpene alkaloid, have also been detected for anticholinesterase properties (1). Huperzine A (Figure 7) has been obtained from *Huperzia serrata* (Thunb. ex Murray) Trevis and some other *Huperzia* species (Lycopodiaceae family), used in Indian and Chinese traditional medi-

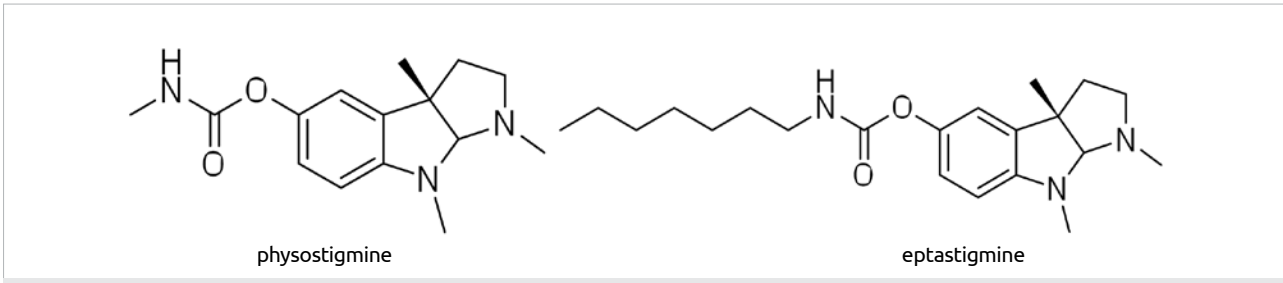


Figure 4. Structures of physostigmine and its derivative eptastigmine

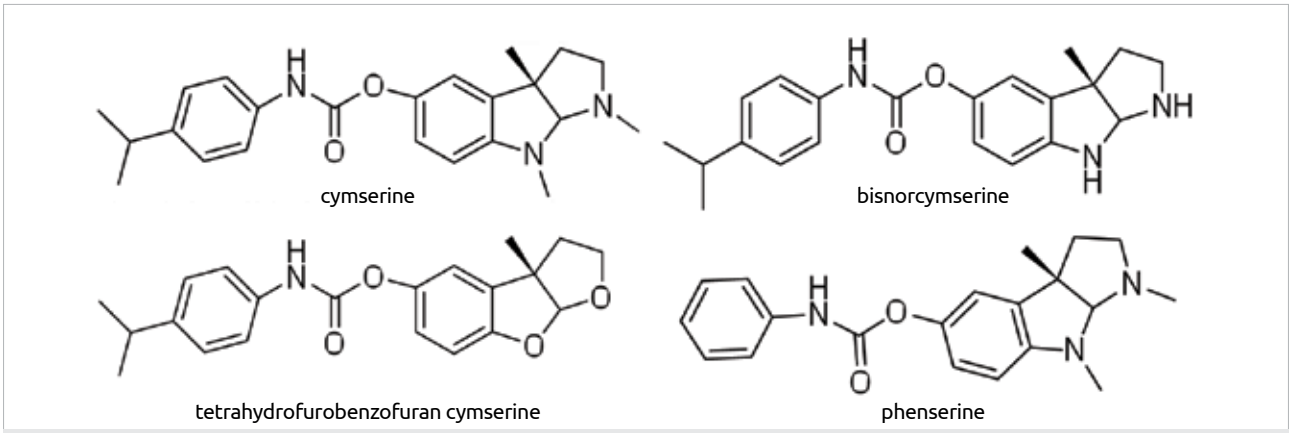


Figure 5. Structures of pysostigmine derivatives: cymserine, bisnorcymserine, tetrahydrofurobenzofuran cymserine, phenserine

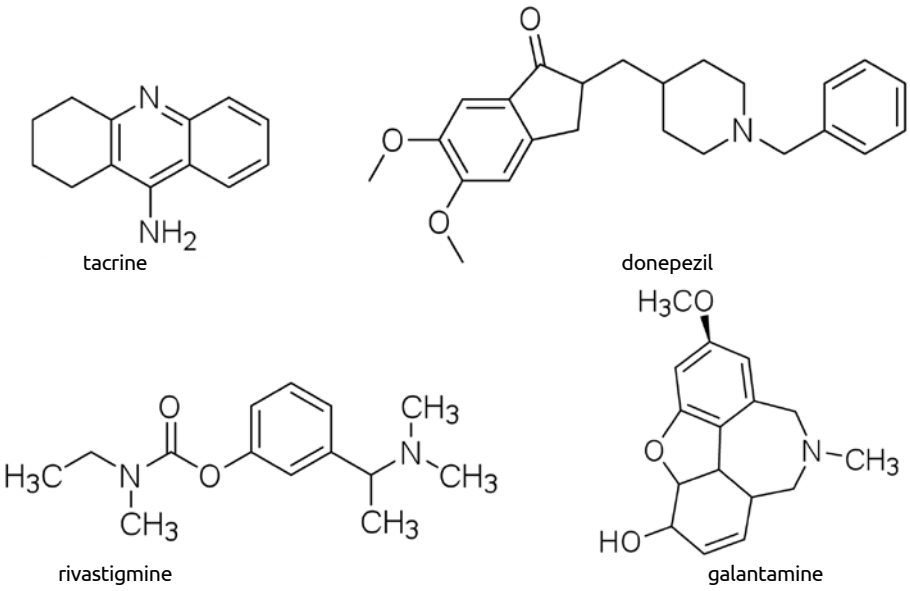


Figure 6. The FDA approved cholinesterase inhibitors

cine and widely distributed over the counter as a nootropic and dietary supplement. It is an AChE inhibitor and NMDA receptor antagonist and now under phase III trial stage studies to become a drug in the treatment of AD.

N-methyl-D-aspartate (NMDA) glutamate receptor antagonist

Memantine (an NMDA glutamate receptor antagonist) (trade name Namenda, or Ebixa) is the only non-cholinesterase inhibitor (non-ChEI) drug currently approved for the treatment of AD, particularly for the cognitive symptoms of Alzheimer's disease, covering memory loss, confusion, and problems with thinking and reasoning (Figure 7).

Both types of drugs may only help lessen or stabilize symptoms. Memantine improves memory, attention, language, and the ability to perform simple tasks in the treatment of moderate to severe stages of AD. It can be used either alone or with other AD drugs that regulate the activity of glutamate, another chemical messenger involved in learning and memory. However, it has some disturbing side effects, including headache, constipation, confusion, and dizziness (24).

Types of targets in the discovery/development of new AD drugs

Various synthetic and natural drugs are in development for dementia, covering a wide range of targets. They are classified by Howes and Perry (2) as follows:

1. New ChEIs; β-Amyloid (Ab) modulators [bapineuzumab, solanezumab], including β-and g-secretase inhibitors [semagacestat]
2. Muscarinic and nicotinic receptor ligands
3. AMPA (amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) and NMDA receptor modulators [neramexane]

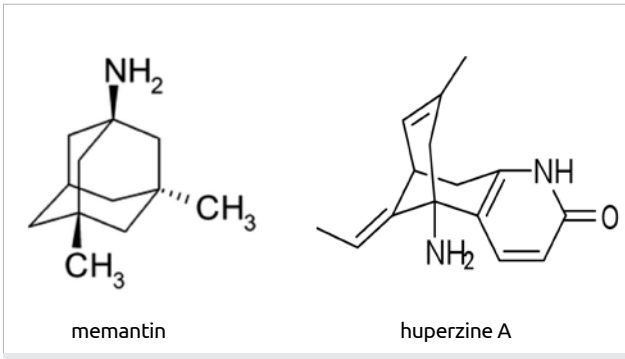


Figure 7. Structures of memantine and huperzine A

4. Cytokine synthesis inhibitors
5. Astrocyte modulators [arundic acid]
6. COX-2 (cyclo-oxygenase-2) inhibitors [celecoxib]
7. Calcineurin modulators
8. ApoE (apolipoprotein E) modulators
9. Tau protein modulators, including GSK3 (glycogen synthase kinase 3) inhibitors
10. Microtubule stabilizers
11. Calcium metabolism modulators
12. Chelating agents
13. Cannabinoid CB1 receptor antagonists
14. Platelet-activating factor (PAF) receptor antagonists
15. Monoamine oxidase (MAO) inhibitors
16. GABA receptor modulators
17. a-synuclein modulators

In addition to the drugs above (2), antioxidants, energy metabolism modulators [latrepirdine, formerly dimebon], neu-

ronal growth factors, monoclonal antibodies, and gene and stem cell therapies should be considered as potential AD drugs. In the classification above, drugs that have reached the phase III trial stage are shown in brackets.

Plant Extracts and Phytochemicals as Potential Therapeutic Agents in Alzheimer's Disease

A number of scientific studies have been carried out on medicinal herbs. Herbs have anti-inflammatory, antioxidant, cognitive-enhancing, neuroprotective, and antiaging effects that may be used in the treatment of AD (25). Anti-inflammatory herbs may reduce inflammation of the brain tissue in AD, such as German chamomile (*Matricaria chamomilla*), ginseng (*Panax ginseng*), licorice (*Glycyrrhiza glabra*), turmeric (*Curcuma longa*), and white willow bark (*Salix alba*), which also afforded the active principal of aspirin. Acetylcholine is a neurotransmitter that plays a key role in cognitive function and reasoning. However, the brains of those with mild to moderate Alzheimer's disease, a progressive type of dementia, have abnormally low acetylcholine concentrations. This means that any compound that enhances the cholinergic system in the brain may be useful in treating Alzheimer's disease and similar brain malfunctions. The herbs, such as COX-2 inhibitors, were also reported to inhibit acetylcholinesterase (AChE) for AD indications (8).

Free radicals occur in body chemistry in processes, such as the destruction of invading organisms by white blood cells. Free radicals might play a role in various diseases, such as arthritis, heart disease, and Alzheimer's disease (AD). When natural enzyme controls fail, free radicals in the body attack lipids, proteins, and nucleic acids. Oxidative stress is one of the first steps of AD, which may play a pathogenic role in its progress.

Plants and their constituents with pharmacological activities may be relevant for the treatment of cognitive disorders, including enhancement of cholinergic function in the central nervous system (CNS) and anti-inflammatory and antioxidant activities. In Ayurvedic and Chinese medicine, numerous plants have been used to treat CNS disorders, indicating the potential for therapeutic use in neurodegenerative diseases, such as AD, Parkinson, and some other diseases (26).

Lamiaceae family plants

The Lamiaceae or Labiatae (the mint family) is one of the largest families, with around 7000 species worldwide (27). Lamiaceae plants are widely used in traditional medicine since antiquity, especially the aromatic and culinary herbs, such as mint, rosemary, sage, savory, marjoram, oregano, thyme, and lavender. Many members of the family are widely cultivated, owing not only to their aromatic qualities but also their ease of cultivation. Besides those grown for their edible leaves, some are also used for decorative purposes, including catmint (*Nepeta*), sage (*Salvia*), yellow-flowered sage (*Phlomis*), and bugle (*Ajuga*). Many of these and related species are also important bee plants, providing the nectar and pollen to support bee colonies and provide honey. The essential oils (secreted from glands on the leaves and stems of the plant) are commercially extracted from many species. Menthol and thymol and many other monoterpenes are used in medicine and the food industry.

Some Lamiaceae plant seeds, such as chia (*Salvia hispanica* L.), are used instead of leaves for food purposes. Many spices have been shown to impart an antioxidative effect in foods (28). The term "spice" is defined as dry plant material that is normally added to food to impart flavor. Lamiaceae plants are rich in terpenoids, not only monoterpenes but also sesqui, di-, and triterpenoids, along with flavonoids and other phenolics (29) having a number of biological activities, including antimicrobial, anti-inflammatory, antioxidant, antiviral, cytotoxic, wound healing, neuroprotective, and anticholinesterase (30).

Members of the Lamiaceae family and their phytochemicals have been studied for pharmacological and some clinical effects relevant to dementia, reviewed by Perry and Howes (30). Among Lamiaceae plants, especially *Salvia, Rosmarinus,* and *Melissa* species, have been known to have neuroprotective properties for many years, besides some other Lamiaceae plants, such as *Teucrium* species, especially *T. polium* L. Those four mentioned genera were also reported to be used in Anatolia for memory enhancement in a very old book, written in the 17th century by an Ottoman herbalist-physician (31).

Lamiaceae family plants have been used in Turkey as folk medicines (32) to treat various disorders, such as common cold, throat infections, psoriasis, seborrheic eczema, hemorrhage, menstrual disorders, miscarriage, ulcer, spasm, and stomach problems, since ancient times. Lamiaceae plants are represented by 45 genera and 550 species with over 735 taxa in Turkey. From this family, 28 genera are widely distributed, and over 240 species are endemic (29). They have been searched for secondary metabolites, particularly di- and triterpenoids and flavonoids and other phenolic compounds, as well as for the essential oil contents that have various activities-namely antioxidant, anticholinesterase, antimicrobial, anti-inflammatory, and cytotoxic (29).

Table 2 shows potential Lamiaceae plants having anticholinesterase and/or other related activities in the treatment of Alzheimer's disease.

Lavandula species

In traditional medicine, *Lavandula officinalis* Chaix ex Villars has been used in neurological disorders, like epilepsy, dementia, depression, and chest and rib pains, in extract form for internal use and in the form of ointment for external use (33). *L. officinalis* has generally been considered as a medicinal agent with sedative, antidepressive, antispasmodic, antiflatulent, antiemetic, diuretic, anticonvulsant, antibacterial, and general tonic properties (33).

L. officinalis suppressed brain NO level and showed low antiepileptic activity in a study carried out by Rahmati et al.

Table 1. FDA Approved four anticholinesterase drugs in AD treatment

Lamiaceae Plants	Antioxidant	Nitric oxide (NO) inhibition	Anti-inflammatory	Neuroprotective	Cerebral vascular disorders	Anticholinesterase	Anticholinesterase related disorders	Other neuronal disorders
Lavandula sp.	*L. angustifolia* Potent antioxidant and antiapoptotic activities	*L. officinalis* NO suppressing and anti-epileptogenic effect	*L. stoechas* Potential anti-inflammatory activity	*L. angustifolia* Potent neuroprotective effects	-	*L. angustifolia* Moderate inhibition of the AChE enzyme	-	-
Leonurus heterophyllus	-	-	-	-	-	Significant AChE inhibitory activity	-	-
Melissa officinalis	Inhibition on XO	-	Nephroprotective against the lesions induced by the APAP; Anti-inflammatory and an antinociceptive activity	Protect neurons from oxidative stress	-	Beneficial activity mild to moderate AD patients with a positive effect on agitation -	MAO-A inhibitory effects	
Micromeria cilicica	-	-	-	-	-	*M. cilicica* Against cholinesterase enzymes *M. juliana* Active against BChE	-	-
Nepeta sorgerae	-	-	-	-	-	*N. sorgerae* Against cholinesterase enzymes	-	-
Origanum sp.	*Origanum majorana* L. Potential natural antioxidant	-	-	-	-	*O. syriacum* L. Strong activity aga inst cholinesterase enzymes	-	-
Rosmarinus officinalis	-	-	COX-2 inhibitors	Against cellular stress insults and increase neuro-thermotolerance; Prevention of disorders due to angiogenesis	For circulatory disorders, hypertension	-	Pain of nervous origin, neuralgia and for general symptoms of old age	-
Salvia officinalis	Antioxidant activity	-	Significant anti-inflammatory effect	-	-	Against memory loss	-	-

Salvia fruticosa L. (Mediterranean sage)	Antioxidant activity	-	Against inflammatory disorders	-	-	Moderate activity to the GABA(A)-benzodiazepine receptor site; Against AChE and BChE	-	Antiamnesic experiment
Salvia lavandulifolia Vahl. (Spanish sage)	-	-	-	-	-	Against memory loss	-	-
Salvia miltiorrhiza	-	Inhibition of NO formation	Alleviation of inflammation	Against cerebral ischemia	Treatment of cerebrovascular disease	AD prevention	-	Insomnia, neurasthenia
Salvia nipponica Miq. var. *formosana*	Significant antioxidant activity	-	-	-	-	Significant anticholinesterase activity	-	-
Satureja thymbra L.	Lipid peroxidation inhibitory activity	-	-	-	-	Against cholinesterase enzymes	-	-
Scutellaria sp.	-	-	-	*S. baicalensis* Neuroprotective effect	-	*S. orientalis* subsp. *macrostegia* Against cholinesterase enzymes	-	-
Sideritis sp.	*S. congesta* Significant antioxidant activity	-	-	-	-	*S. arguta* Against AChE and BChE *S. ceasarea* Against AChE and BChE	-	*S. scardica* Anxiolytic-like effects; Act as triple monoamine reuptake inhibitors
Stachys sp.	*S. byzantina* Strong antioxidant activity	-	-	-	-	-	-	*S. lavandulifolia* Sedative and anxiolytic activities
Thymus species	*T. vulgaris* L. Antioxidant activity	-	*Thymus kotschyanus* Anti-inflammatory effects *T. vulgaris* Inhibition of inflammatory edema and leukocyte migration	-	-	*T. lotocephalus* Against cholinesterase enzymes	-	-

(34), suggesting that the NO-suppressing effect of the extract is partly responsible for antiepileptic property of *L. officinalis.*

In a study, *L. stoechas* L. was found to be active against dermatophyte strains and showed potential anti-inflammatory activity, since it inhibited NO production at concentrations without affecting cell viability. Therefore, *L. stoechas* may be considered as a potential agent in the treatment of AD (35), as well as *L. viridis* L'Hér extracts.

The genus *Lavandula* (known as lavanta in Turkish) is represented by two species in Turkey: *L. angustifolia* Mill. and *L. stoechas* with two subspecies. Triterpenoids from the roots of *L. stoechas* L. ssp *stoechas* L. with cytotoxic properties were reported by Topcu et al. (36).

In another study, in scopolamine-treated rats, lavender essential oils showed potential antioxidant and antiapoptotic activities. The study showed that antioxidant and antiapoptotic activities are the major mechanisms for their potent neuroprotective effects against scopolamine-induced oxidative stress in the rat brain (37). Aqueous and methanolic extracts of *L. angustifolia* have been shown to possess significant acetylcholinesterase inhibitory activity in a dose-dependent manner (38) (Table 2).

***Leonurus heterophyllus* L.**

L. heterophyllus is known as 'Ich mau thao' (motherwort) in Vietnamese traditional medicine. *L. heterophyllus* ethanol extract has shown significant AChE inhibitory activity (39). Also, its seven isolates were investigated *in vitro* for their anticholinesterase activity using the mouse cortex AChE enzyme, and two of them, leoheteronin A and leopersin G (Figure 8), were found to be potent in the inhibition of AChE.

***Melissa officinalis* L.**

Melissa officinalis (Lemon balm, oğul otu in Turkish) (Figure 9) is one of the important Lamiaceae family plants. Its essential oil is used as an antibacterial, sedative, and spasmolitic agent, and research on oil of lemon balm has continued intensively (40). Lemon balm can also temporarily improve cognitive decline as well as improve the mood for Alzheimer's patients. A study addressing the use of lemon balm for AD concluded that *M. officinalis* is one of several plants that may be useful in the prevention and treatment of AD due to its ability to inhibit AChE along with antioxidant activity (8).

Akhondzadeh et al. (41) carried out a study on *M. officinalis* extract, which indicated its value in the management of mild to moderate AD and that it has a positive effect on agitation in patients. Kennedy et al. (42) have suggested the potential of lemon balm to mitigate the effects of stress. Bolkent et al. (43) reported that the administration of *M. officinalis* extract reduced total cholesterol, total lipid, ALT, AST, and ALP levels in serum and LPO levels in liver tissue and increased glutathione levels in the tissue. Therefore, it was suggested that *M. officinalis* extract exerted a hypolipidemic effect and showed a protective effect on the liver of hyperlipidemic rats (40).

M. officinalis extracts have been shown to bind directly to both nicotinic and muscarinic receptors in human brain tissue. Robust anxiolytic effects have also been demonstrated following acute administration to healthy humans. In a study, aromatherapy with *M. officinalis* reduced agitation, because its essential oil attenuates cognitive declines in patients with dementia (44).

M. officinalis has shown protective effects in the PC12 cell line, MAO-A-inhibitory effects, and free radical scavenging properties (45).

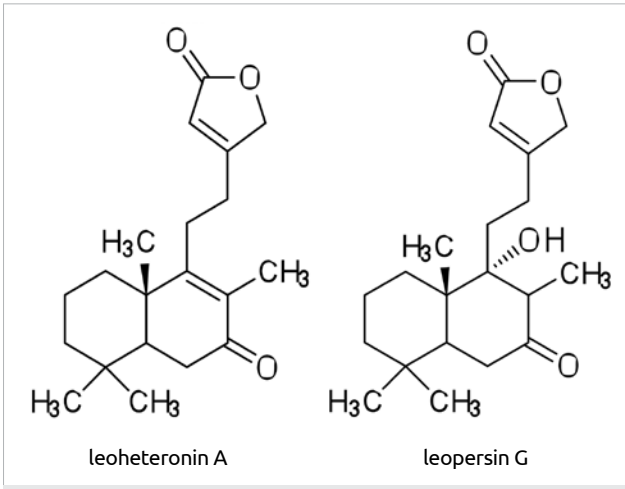
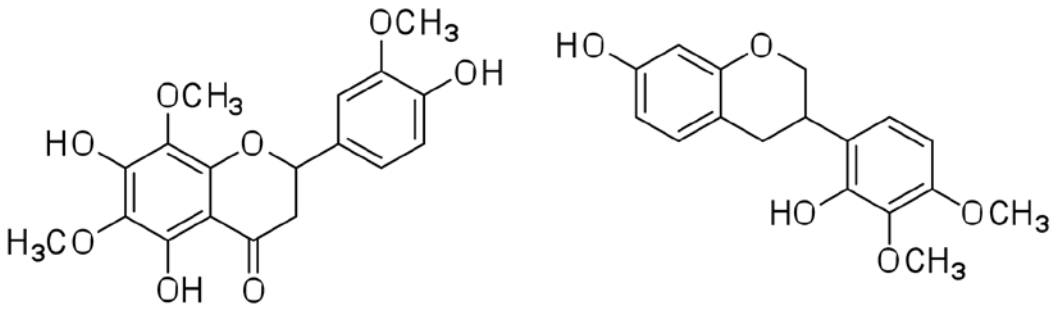


Figure 8. Structures of leoheteronin A and leopersin G

Figure 9. *Melissa officinalis* L.



sudachitin isomucronulatol

Figure 10. Structures of flavonoids sudachitin and isomucronulatol

An aqueous extract of *M*. officinalis has nephroprotective effect against the lesions induced by acetaminophen (APAP) and showed an anti-inflammatory effect on carrageenan-induced pleurisy (46, 47).

Micromeria species

***M. cilicica* Hausskn. ex P.H. Davis**

M. cilicica (Syn. *Clinopodium cilicicum* (Hausskn. ex P. H. Davis) Bräuchler & Heubl) is grown in Mersin, Turkey. Its extracts and seven isolated constituents were tested against both cholinesterase enzymes. While all the tested compounds exhibited only weak inhibition against the AChE enzyme, three of them, including two flavonoids, sudachitin and isomucronulatol (Figure 10), and a triterpene, ursolic acid, exhibited moderate-high inhibition against BChE enzyme (Table 3) (48).

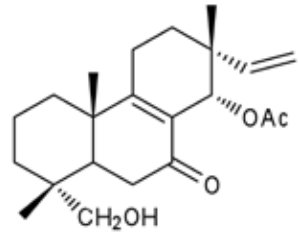
***M. juliana* (L.) Bentham ex Reichb.**

Acetyl- and butyryl-cholinesterase inhibitory activities of the aerial parts of *M. juliana* were investigated, and the petroleum ether and acetone extracts were found to be moderately active against BChE. Antioxidant activity results, obtained by using a series of antioxidant tests, namely lipid peroxidation inhibition activity (beta-carotene-linoleic acid assay), DPPH radical scavenging, ferric reducing power, and metal chelating capacity, supported potential use of *Micromeria* species as cholinesterase-inhibitory agents (49).

***Nepeta* species**

In Turkey, *Nepeta* species are represented by 41 taxa, of which 18 are endemic. The endemic and non-endemic species of the genus *Nepeta* mostly grow in East Anatolia and the Taurus mountains. Some *Nepeta* species are used in folk medicine as a diuretic, diaphoretic, antitussive, antispasmodic, antiasthmatic, febrifuge, emmenagogue, sedative, and spice and herbal tea (50).

In a study, the BChE inhibition activity of the dichloromethane and methanol extracts of *N. sorgerae* Hedge et Lamond, grown in Anatolia (Nemrut mountain), was not found to be high (13.9±0.4 µg/mL and 5.3±0.4 µg/mL %, respectively), but their AChE inhibition activity was found at a higher percentage (55.9±1.2 µg/mL and 66.7±0.7 µg/mL %, respectively). The isolated new compound isopimarane diterpene sorgerolone (Figure 11) showed high inhibition against AChE ($IC_{50=}$17.8 µg/mL) and BChE enzymes (IC_{50}=120 µg/mL) (50).



sorgerolone

Figure 11. Structure of sorgerolone

Extracts of a series *Nepeta* species have been searched for anticholinesterase and antioxidant activities and exhibited fairly promising results, except for *N. baytopii* Hedge et Lamond and *N. fissa* C. A. Meyer. Inhibition was observed, particularly against AChE enzyme, ranging from 55.91% to 74.12%, probably due to their rich contents in phenolics (rosmarinic acid) and triterpenoids (oleanolic and ursolic acids and their derivatives). The studies are going to be completed by our group. Terpenoids and steroids as nepetalic acid esters were obtained from *N. caesarea* Boiss., besides several known terpenoids and rosmarinic acid, which is a common phenolic compound with high antioxidant activity in some Lamiaceae plants (51).

***Origanum* species**

The genus Figure 11 (sorgerolone) *Origanum* (Lamiaceae), known as kekik in Turkish, is represented in Turkey by 23 species with 32 taxa, 21 being endemic. *Origanum* species have been referred to as one of the memory-enhancing plants. They also have antioxidant, antibacterial, anti-inflammatory, and antispasmodic effects (52).

O. ehrenbergii Boiss and *O. syriacum* L. oils were evaluated for their anticholinesterase, NO production-inhibitory, and antioxidant activities. *O. ehrenbergii* oil exhibited strong ac-

Table 3. Potential pure compounds isolated from Lamiaceae plants having anticholinesterase and/or other related activities in the treatment of Alzheimer's Disease

Plant name	Pure Compound	Antioxidant activity	AChE (Inhibition %) 100 µg/mL or IC_{50} (µg/mL)	BChE (Inhibition %) 100 µg/mL or IC_{50} (µg/mL)	Anti-inflammatory
Salvia fruticosa	oleanolic acid	37.35±1.23[a]	77.26±0.59	20.16±0.31	
	ursolic acid	31.14±0.92[a] 0.22±0.02[b]	75.87±0.92	32.21±0.88	
	α-amyryltetracosanoate	57.48±1.54[a]	45.19±0.75	38.89±0.78	
	3-acetylsitosterol		54.70±0.75	54.45±0.37	
S. nipponica var. *formosana*	taxodione			2.88 (IC_{50})	
	(+)-valeranone	23.86±2.17[b]		114.12(IC_{50})	36.68±4.36[e]
	nubiol	–9.16±5.11 [b]		77.15 (IC_{50})	10.22±2.98 [e]
	methyl rosmarinate	11.11 (IC_{50})[c]		108.51(IC_{50})	1.46±0.42 [e]
	rosmarinic acid	11.89 (IC_{50})[c]		46.70 (IC_{50})	6.66±0.87 [e]
	salvianolic acid B	26.00±1.57 [b]			2.03±0.37 [e]
	β-sitosteroyl-3-O-β-D-glucoside	14.64±4.23 [b]			12.14±0.82 [e]
	3-epi-corosolic acid	0.71±0.05 [b]			1.29±0.15 [e]
	ursolic acid				0.33±0.12
	2α,3α-23-trihydroxy-urs-12-en-28-oic acid	6.18±0.19 [b]			6.00±0.65[e]
	oleanolic acid 3-O-ferulate	2.13±0.44[b]			1.23±0.30 [e]
	caffeic acid methyl ester	0.44±0.05[b]			20.67±3.00 [e]
	vanillic acid	22.48 (IC_{50})[c]			
		11.76±1.01[b] 23.82 (IC_{50})[c]			17.79±2.24 [e]
S. potentillifolia	α-pinene		87.2±0.50	17.5±1.18	
	β-pinene		NA	NA	
S. poculata	ursolic acid	94.43 (IC_{50})[b]	50.72±0.53	66.70±0.89	
	5-hydroxy 7,4'dimethoxyflavone	71.65 (IC_{50})[b] 44.80 (IC_{50})[d]	NA	NA	
	eupatilin	59.14 (IC_{50})[b] 22.34 (IC_{50})[d]	0.94±0.63	32.22±0.24	
	salvigenin	78.46 (IC_{50})[b] 78.68 (IC_{50})[d]	NA	7.96±0.67	
	sclareol	48.74 (IC_{50})[b] >100 (IC_{50})[d]	NA	7.99±0.73	
	β-sitosterol	>100 (IC_{50})[b] >100 (IC_{50})[d]	NA	6.80±0.82	
Micromeria cilicica	piperitone 7-O-β-D-glucoside	164.0 (IC_{50})[a] 49.0 (IC_{50})[b] >200 (IC_{50})[c] 69.1 (IC_{50})[d]	3.05±0.08	8.00±1.66	
	isothymonin 4'-methyl ether	79.1(IC_{50})[a] 56.8 (IC_{50})[b] 61.4 (IC_{50})[c] 38.1 (IC_{50})[d]	5.25±0.87	26.0±0.99	
	sudachitin	38.4 (IC_{50})[a] 36.4 (IC_{50})[b] 17.2 (IC_{50})[c] 4.91 (IC_{50})[d]	65.2±0.82	78.3±1.70	

	isomucronulatol	44.0 (IC_{50})[a] 39.4 (IC_{50})[b] 15.2 (IC_{50})[c] 4.22 (IC_{50})[d]	75.2±0.78	81.3±1.33	
	rutin	13.5 (IC_{50})[a] 20.6 (IC_{50})[b] 9.87 (IC_{50})[c] 12.8 (IC_{50})[d]	28.2±1.45	44.6±2.05	
	ursolic acid	>200 (IC_{50})[a] 94.4 (IC_{50})[b] >200 (IC_{50})[c] >200 (IC_{50})[d]	54.3±0.21	78.8±0.62	
	saccharose	72.3 (IC_{50})[a] 47.7 (IC_{50})[b] >200 (IC_{50})[c] 106.0 (IC_{50})[d]	6.09±2.00	3.90±0.07	
Sideritis congesta	ent-7α-acetoxy-16β, 18-dihydroxy-kaurane	94.52 (IC_{50})[a] 303.53 (IC_{50})[b] NA[c]	1.89 (IC_{50})	1.19 (IC_{50})	
	epoxyisolinearol	195.17 (IC_{50})[a] 337.52 (IC_{50})[b] NA[c]	0.87 (IC_{50})	0.43 (IC_{50})	
	sideroxol	NA[a] 388.30 (IC_{50})[b] NA[c]	1.27 (IC_{50})	0.024 (IC_{50})	
	siderol	NA[a] 298.95 (IC_{50})[b] NA[c]	0.69 (IC_{50})	0.65 (IC_{50})	
	sideridiol	NA[a] 273.85 (IC_{50})[b] NA[c]	8.04 (IC_{50})	3.67 (IC_{50})	
	7-epicandicandiol	53.82 (IC_{50})[a] 514.38 (IC_{50})[b] NA[c]	0.23 (IC_{50})	0.022 (IC_{50})	
	linearol	271.70 (IC_{50})[a] 571.05 (IC_{50})[b] NA[c]	2.66 (IC_{50})	0.15 (IC_{50})	
	sidol	355.82 (IC_{50})[a] 548.14 (IC_{50})[b] NA[c]	0.92 (IC_{50})	0.05 (IC_{50})	
Nepeta sorgerae	14α-Acetoxy-18-hydroxyisopimara-8, 15-diene-7-one	59.5 (IC_{50})[a] NA (IC_{50})[c]	17.8 (IC_{50})	120 (IC_{50})	
	oleanolic acid	NA(IC_{50})[a] NA(IC_{50})[c]	28.37 (IC_{50})	NA (IC_{50})	
	ursolic acid	NA (IC_{50})[a] NA (IC_{50})[c]	39.19 (IC_{50})	NA (IC_{50})	
Sideritis arguta	diacetyldistanol		NA	175.8±2.0(IC_{50})	
	eubotriol		NA	98.1±2.6(IC_{50})	
	sideroxol		14.5 (IC_{50})	25.0 (IC_{50})	
	7-epi-candicandiol	43.1 (IC_{50})[a]	22.8 (IC_{50})	21.1 (IC_{50})	
	eubol		NA	23.2±3.2	
Sideritis cesarea	penduletin		21.03±0.99	66.58±1.42	
	apigenin		24.21±0.28	12.33±1.02	

[a]β-Carotene-linoleic acid (Inhibition %)100 μM
[b]Superoxide anion IC_{50}(μM) or (Inh %)
[c]DPPH free radical scavenging assay
[d]ABTS cation IC50(μM)
[e]inhibitory effect on elastase release by human neutrophils in response to fMLP/CB.
NA: Not active

tivity against both cholinesterases, with IC_{50} values of 0.3 µg/mL. Essential oil of *O. syriacum* also exhibited high activity. Interestingly, *O. ehrenbergii* oil inhibited NO production in the murine monocytic macrophage cell line RAW 264.7, with an IC_{50} value of 66.4 µg/mL. In addition, both *O. ehrenbergii* and *O. syriacum* oils moderately inhibited oxidation of linoleic acid after incubation. Furthermore, *O. ehrenbergii* showed strong scavenging effects on DPPH, with an IC_{50} value of 0.99 µg/mL. All the data together suggest that *O. ehrenbergii* and *O. syriacum* oils might be used as valuable new flavors in functional foods and nutraceutical products, with particular relevance to supplements for the elderly (53).

In another study, essential oil of marjoram (*O. majorana* L.) had significant potential as a natural antioxidant and anti-AChE agent (54).

***Rosmarinus officinalis* L.**

R. officinalis (known as biberiye/kuşdili in Turkey) (Figure 12) is a dietary herb that possesses high antioxidant activity and was first marketed as a source of natural antioxidants. It has been used as a medicinal herb since early times, and it has received increasing attention due to its antimicrobial, anti-inflammatory, and antioxidative constituents. Rosemary contains a large number of compounds consisting of phenolics and abietane diterpenes, which are responsible for its antioxidant and cytotoxic activity, such as rosmarinic acid (Figure 13), carnosic acid, and carnosol (Figure 14).

R. officinalis is used in connection with AD and dementia for general symptoms of old age, debility, and fatigue. It was also applied for neuralgia, indigestion, pain of nervous origin, circulatory disorders, and hypertension (55).

In a study (56), rosmarinic acid inhibited β-secretase 1 enzyme, which is beta-site amyloid precursor protein-cleaving enzyme 1 (BACE1), in a non-competitive manner. It was also found in the same study to exhibit weaker inhibition against other enzymes, such as TNF-α-converting enzyme (TACE), acetylcholinesterase (AChE), chymotrypsin, and elastase, along with luteolin, indicating that they were relatively specific inhibitors of BACE1.

The anticholinesterase activity of the essential oil of *R. officinalis* most likely depends on a synergistic mechanism of oil components. In contrast to the essential oil, the major compound rosmarinic acid (Figure 13) in the methanolic extract of the plant was considered to be responsible for strong anti-BChE activity (57).

In another study, treatment with extract of *R. officinalis* in cirrhotic animals modifies the expression of subunits of the NMDA receptor, with an improvement in hepatocellular function due to the presence of antioxidant compounds and flavonoids (58). *R. officinalis* is able to protect neuronal cells against hydrogen peroxide-induced injury, and it is suggested that *R. officinalis* might potentially serve as an agent for prevention of several human neurodegenerative diseases caused by oxidative stress and apoptosis (59).

The downregulation effect of *R. officinalis* polyphenols on cellular stress proteins in rat pheochromocytoma PC12 cells was investigated, and results suggested that an abietane diterpene, carnosic acid (Figure 14); a stilbene, rosmarinic acid (Figure 13); and a flavone, luteolin (Figure 15) may modulate the neuroprotective defense system against cellular stress (60).

Activated glutathione metabolism participates in protective effects of carnosic acid against oxidative stress in neuronal HT22 cells (61). Carnosic acid is also involved in the synthesis of nerve growth factor (NGF), which is necessary for the growth and maintenance of nerve tissue. Carnosic acid and carnosol (Figure 14) have the potential to protect cortical neuronal cells by activation of the Keap1/Nrf2 pathway (62).

Some *Salvia* species, particularly *S. officinalis* L. and *S. triloba* L., showed similar chemical composition to *R. officinalis*. However, *R. officinalis* leaves are especially much more rich in carnosic acid and carnosol, which are the main abietane diterpenes responsible for prevention of membrane damage and vascular brain circulation, with high antioxidant and neuroprotective properties.

Figure 12. *Rosmarinus officinalis* L.

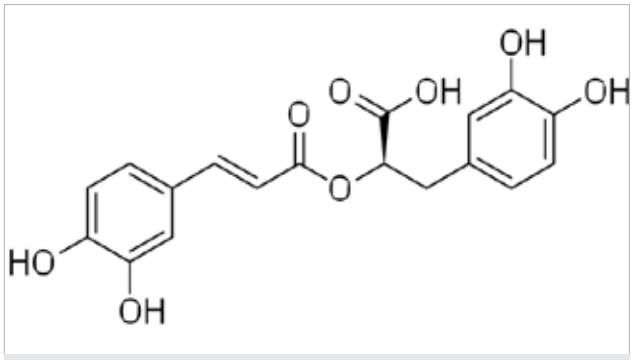


Figure 13. Structure of rosmarinic acid

A patented study showed that carnosic acid protects neurons both in vitro and in vivo through activation of the Keap1/Nrf2 pathway via S-alkylation of targeted cysteines on Keap1 (63).

The alcoholic extract of *R. officinalis* at 150 and 300 mg/kg modulated the short- and long-term memories of mice in a social recognition and inhibitory avoidance task, respectively. This modulatory effect was shown to improve learning and memory processes (64).

According to Duke's claim in 2007-"*If a synthetic COX-2 inhibitor could prevent Alzheimer's Disease, so could a natural COX-2 inhibitor*"-rosemary should be considered a good agent for the treatment of AD due to the presence of the following natural COX-2 inhibitors (65) in its content: namely, the monoterpenes thymol, carvacrol, and eugenol (Figure 16); a flavone, apigenin (Figure 15); the triterpenoids oleanolic acid and ursolic acid (Figure 17); and several phenolic compounds. In fact, in addition to *Rosmarinus* species, many aromatic culinary herbs of Lamiaceae plants, especially *Salvia, Mentha, Thymus,* and *Origanum* species, contain the monoterpenic compounds mentioned above.

***Salvia* species**

One of the most well-known Lamiaceae family plants is the genus *Salvia,* which has wide distribution, with nearly 1000 species in three regions of the world: Central and South America (500 spp.), Central Asia/Mediterranean (250 spp.), and Eastern Asia (90 spp.) (66). *Salvia* (sage) species have been used since ancient times in folk medicine for cognitive brain function, along with various biological activities. Sage extracts possess antioxidant, estrogenic, and anti-inflammatory properties, which may help strong anticholinesterase effects by inhibiting both butyryl- and acetyl-cholinesterases (67).

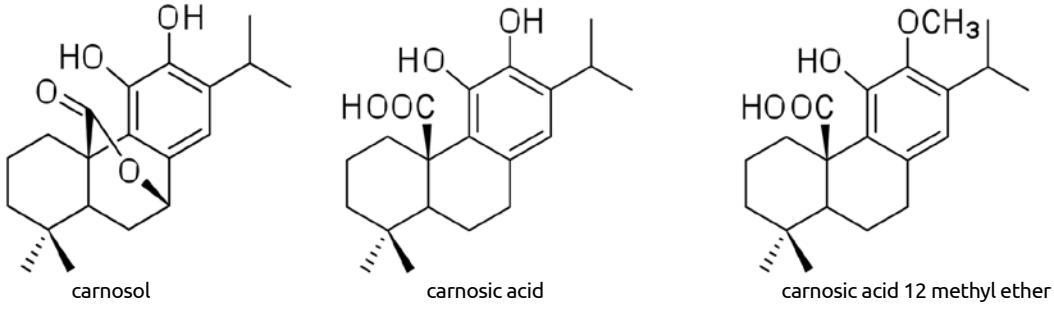


Figure 14. Structures of carnosol, carnosic acid and carnosic acid 12 methyl ether

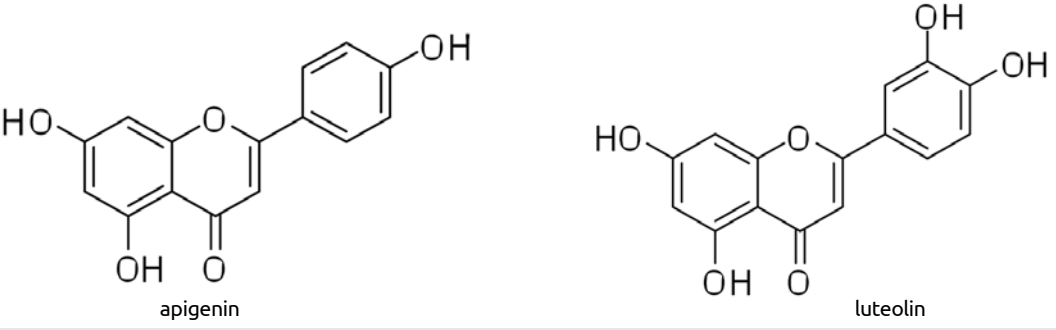


Figure 15. Structures of apigenin and luteolin

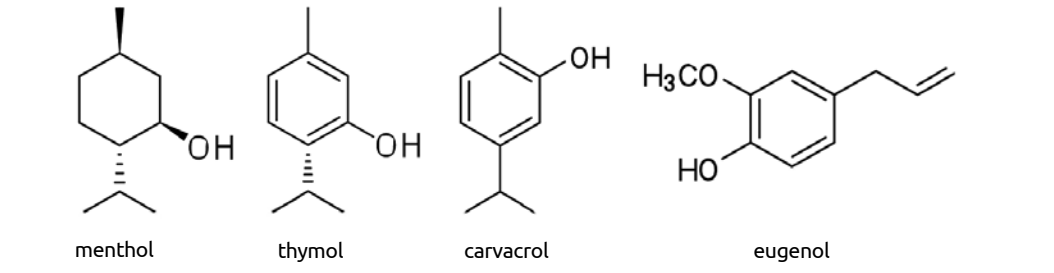


Figure 16. Structures of common monoterpenoids in Lamiaceae plants

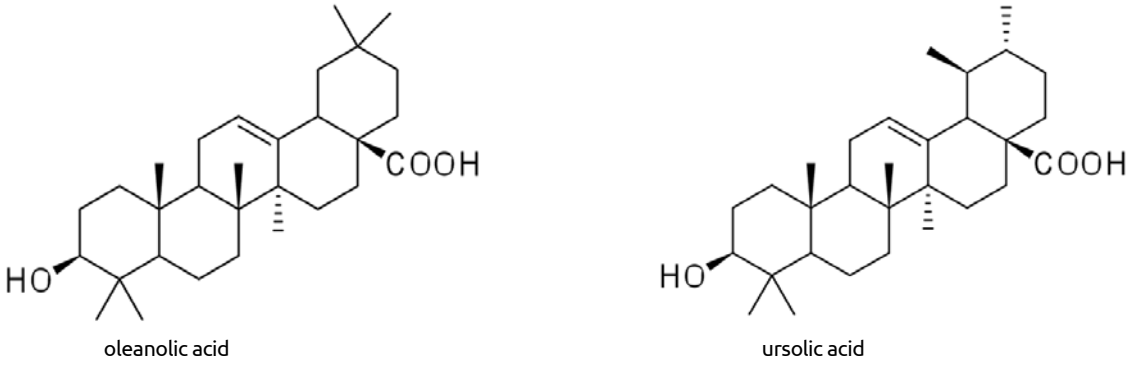


Figure 17. Structures of most common two triterpenoids in Lamiaceae family plants

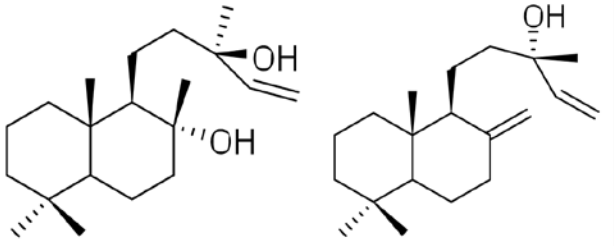


Figure 18. Structures of labdane diterpenoids sclareol and manool

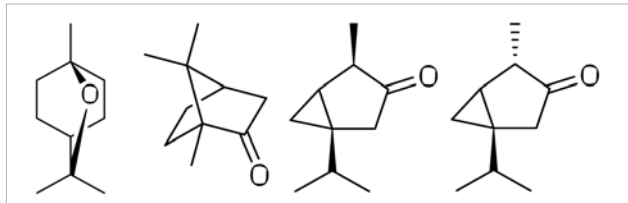


Figure 20. Structures of some monoterpenoids found in *Salvia* species

Figure 19. *Salvia fruticosa* Mill. (*S. triloba* L.)

The genus *Salvia* is a huge and important source, rich in terpenoids and flavonoids and other phenolics with antioxidant, anti-tuberculous, anti-inflammatory, neuroprotective, and anticholinesterase properties (68). Species of this genus, such as *S. officinalis*, possess significant pharmacological activities as well as economic value.

Some *Salvia* species (*S. officinalis, S. lavandulifolia* L.) have been used against memory loss in Europe. The anticholinesterase and anti-Alzheimer activities of *Salvia* species have been investigated for the last 15 years by some researchers (69) in the world, including several groups from Turkey (70).

Sage has a reputation in traditional European medicine with two species-*S. officinalis* and *S. lavandulifolia*-especially the aerial parts. In Europe, *S. sclarea* L. also has an important place in the food industry with its nice aroma and high antioxidant properties. In traditional Chinese medicine, *S. miltiorrhiza* Bunge roots have effects on improving memory/brain circulation. *Salvia* is also reported to have antioxidant, estrogenic (71), and anti-inflammatory properties (72). Oxidative stress has been strongly implicated in the pathophysiology of neurodegenerative disorders, such as Alzheimer's disease (AD) (69).

Many studies support traditional uses of European *Salvia* species grown in Europe, with some of their components reported as follows: cholinesterase inhibition by the monoterpenoids of the essential oil and the extracts from *S. officinalis* and *S. lavandulifolia*, antioxidant (73) and anti-inflammatory activity of *S. lavandulifolia* oil (74) and di- and triterpenoids from *S. fruticosa* Mill. (75), as well as diterpenoids with acetylcholinesterase inhibitory activity from a Chinese sage, *S. miltiorrhiza* (76).

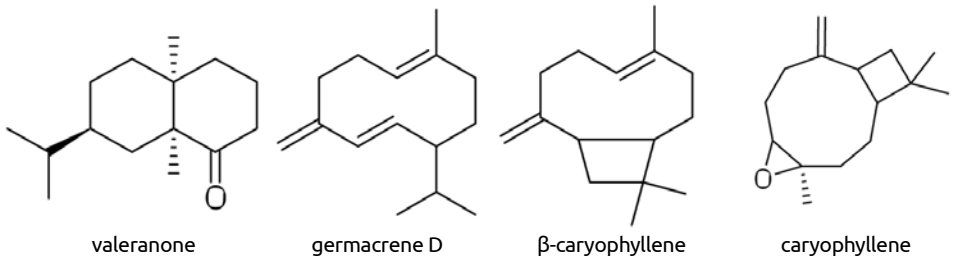


Figure 21. Structures of sesquiterpenoids

In a study, 56 extracts prepared by organic solvents from 14 *Salvia* species growing in Turkey were studied for anticholinesterase activity. The most active extracts at 1 mg/mL for AChE inhibition were observed to be a petroleum ether extract of *S. albimaculata* Hedge and Huber-Morath (89.4%) and a chloroform extract of *S. cyanescens* Boiss. et Bal. (80.2%), while ethyl acetate extracts of *S. frigida* Boiss. and *S. migrostegia* Boiss and Bal., chloroform extracts of *S. candidissima* Vahl ssp. *occidentalis* Hedge and *S.ceratophylla* L., and a petroleum ether extract of *S. cyanescens* were found to inhibit BChE potently (92.2%, 89.6%, 91.1%, 91.3%, and 91.8%, respectively), (70) as observed in most of the extracts studied of *Salvia* species growing in Turkey (77-79).

***Salvia chionantha* Boiss**

The essential oil and methyl ester of hexane extract of Anatolian *S. chionantha* were analyzed by GC and GC-MS to investigate the volatile constituents and fatty acid composition. Germacrene D (Figure 21) was found to be an important sesquiterpene in its essential oil, and it demonstrated larvicidal activity against *Aedes aegypti* and *Anopheles stephensi* as well as effective inhibition of aphid alarm pheromone activity. Moreover, the essential oil showed moderate inhibitory activity against both cholinesterases AChE (56.7±1.9%) and BChE (41.7±2.9%), while the hexane extract only exhibited activity against BChE enzyme at 0.5 mg/mL concentration (63.1±0.8%) (78). Hence, the essential oil may be useful as a moderate anticholinesterase agent, particularly against AChE enzyme.

***Salvia chrysophylla* Stapf.**

Sclareol (Figure 18), a labdane diterpene, was found in a number of *Salvia* species and also in many plant species belonging to other families. It was first isolated from *S. sclarea* L. and then from some other *Salvia* species, including *S. chrysophylla,* in a recent study, which reports its high anticholinesterase activity against both AChE and BChE enzymes, by Çulhaoğlu et al. (79). Sclareol also showed significant cytostatic and cytotoxic effects against leukemic cell lines, and it was found to induce cell cycle arrest and apoptosis (80).

***Salvia fruticosa* Mill. (*S. triloba* L.)**

S. fruticosa (synonym; *S. triloba*) (Figure 19) tea, called "Adaçayı" or "Elmaçayı," is commonly used to cure colds and stomach ache (73). In Anatolian folk medicine, the leaves of *S. fruticosa* are used as infusion (1-5%) for simple disorders,

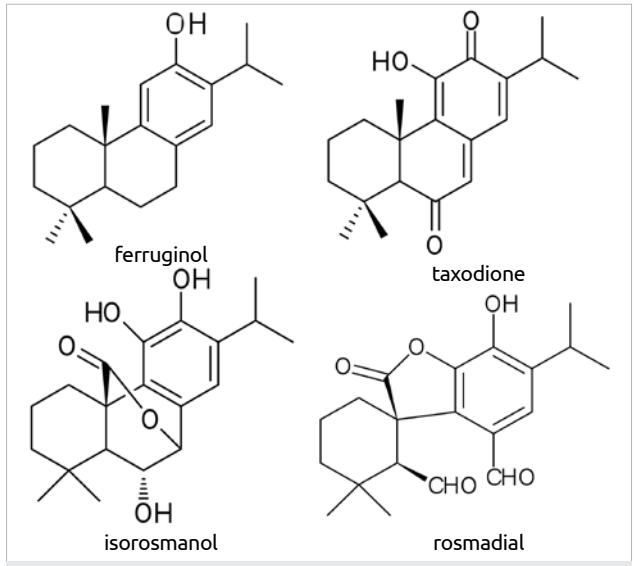


Figure 22. Structures of abietane diterpenoids

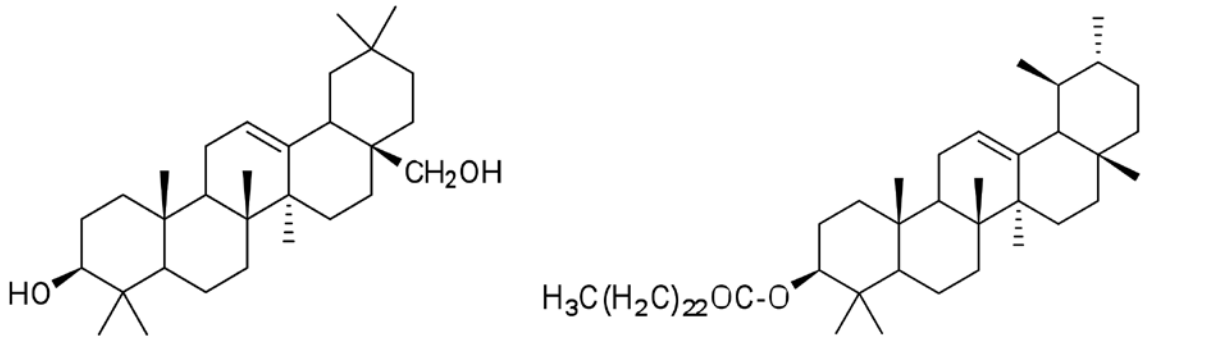
and it is one of the plants used for memory enhancing and is neuroprotective in Anatolia (75).

Many studies on the essential oil of *S. fruticosa* reported 1,8-cineole to be the main component, followed by camphor, α-thujone, β-thujone (Figure 20), and β-caryophyllene (Figure 21). The species is known to contain biologically active sesquiterpenes and diterpenes, besides the high content of oxygenated monoterpenes (75).

In an evaluation of cholinesterase inhibitory and antioxidant properties of wild and cultivated samples of *S. fruticosa* by activity-guided fractionation, *S. fruticosa* extracts showed moderate anti-cholinesterase activity (73). However, one of our very recent studies, a methanol extract of *S. fruticosa* showed strong activity against both AChE and BChE as well as strong antioxidant activity (75).

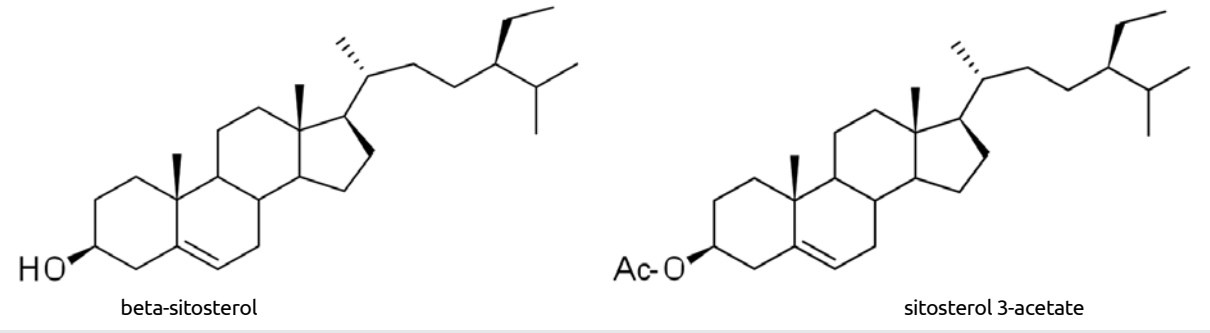
On the other hand, ethanolic extract of *S. fruticosa* had moderate activity the GABA (A)-benzodiazepine receptor site (81), and furthermore, the ethanol extract of *S. fruticosa* was found to be active in an antiamnesic experiment (82).

Salvia fruticosa Mill. (known as elma çalbasi in Anatolia) extracts afforded six abietane diterpenoids (carnosol, carnosic



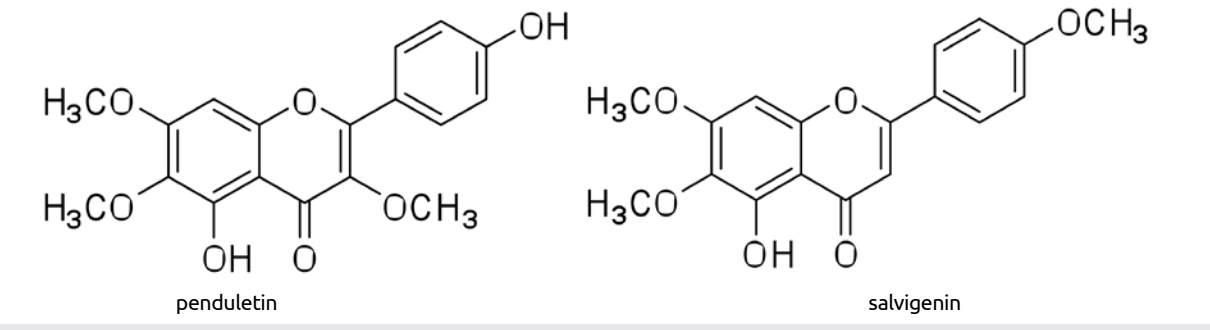
erythrodiol α-amiryl-tetracosanoate

Figure 23. Structures of erythrodiol and α-amiryl-tetracosanoate



beta-sitosterol sitosterol 3-acetate

Figure 24. Structures of some triterpenoids and steroids



penduletin salvigenin

Figure 25. Structures of penduletin and salvigenin

acid, carnosic acid 12-methyl ether, rosmadial, isorosmanol, ferruginol) (Figures 14 and 22); a labdane diterpene manool (Figure 18); four triterpenoids, oleanolic acid, ursolic acid (Figure 17), erythrodiol, and α-amyryltetracosanoate (Figure 23); a steroid (3-acetylsitosterol) (Figure 24); and salvigenin, which is a characteristic flavone of *Salvia* species (Figure 25). The fatty oil of apples of the plant exhibited high anticholinesterase activity, particularly against BChE. The essential oil, consisting mainly of 1.8-cineol (58.89%), obtained from the aerial parts of the plant, exhibited high AChE inhibitory activity (Figure 20). The antioxidant activity and anticholinesterase potential of the methanol extract and the triterpenoids α-amyryltetracosanoate, oleanolic acid, ursolic acid, and 3-acetylsitosterol were also investigated, and the methanol extract exhibited the highest antioxidant and anticholinesterase activity, surpassing those of pure compounds, probably due to synergistic effects of all components together (75).

In another study, n-butanol extract of *S. fruticosa* has shown an antiedematogenic effect on paw edema induced by carrageenan (83).

***Salvia lavandulifolia* Vahl.**

Salvia species (*S. officinalis* L., *S. lavandulifolia* and *S. miltiorrhiza* Bunge) are prominent for their reputed beneficial effects on memory disorders, depression, and cerebral ischemia (69). These actions are considered to be of potential value in AD therapy.

S. lavandulifolia (Spanish sage) extracts and constituents have demonstrated anticholinesterase, antioxidant, anti-inflammatory, estrogenic, and CNS-depressant (sedative) effects, relevant to the treatment of AD. The essential oil inhibited the enzyme AChE from human brain tissue and bovine erythrocytes, and monoterpenoid constituents inhibit AChE with varying degrees of potency; particularly, 1,8-cineole (eucalyptol) (Figure 20) and a- pinene (Figure 26) showed high activity (69). Also, essential oil administration to healthy volunteers produced significant effects on cognition. In a pilot open-label study involving oral administration of the essential oil to patients with AD, a significant increase in diastolic and systolic blood pressure was observed in two patients; however, this may be attributed to pre-existing hypertension, and there were no abnormalities in other vital signs or blood samples during the trial period, and statistically significant differences were observed between baseline and 6-week treatment, with a reduction in neuropsychiatric symptoms and an improvement in attention (69).

The ability of *S. lavandulifolia* to inhibit the activity of AChE in the hippocampus is consistent with the reported memory-enhancing properties of sage. It is also of potential significance in improving cognitive function in AD, which plays a major role in memory processing. *S. lavandulifolia* and *S. officinalis* have similar essential oil compositions, with the exception of the thujone content. *S. officinalis* oil was found to be toxic in large doses (84) due to high concentration of thujone; therefore, it is considered that *S. lavandulifolia* may be a more suitable treatment for AD (69). Also Anatolian *S. fruticosa* (*S. triloba)* has thujone at a low percentage, which may be advantageous in use of the treatment of AD (75).

***Salvia miltiorrhiza* Bunge**

S. miltiorrhiza (Chinese sage), particularly its root, which has numerous pharmacological activities, and which may be relevant in CNS disorders, including AD, has been used for the treatment of various medical conditions, including AD (30).

S. miltiorrhiza dried roots are red in color and therefore are used in Chinese folk medicine for the management of blood disorders and prescribed to stabilize the heart and calm the nerves (85). The roots also have indications to treat blood circulation disorders, insomnia, neurasthenia, and alleviation of inflammation. *S. miltiorrhiza* has been employed for the treatment of cerebral vascular disorders and has shown benefits in some patients (86).

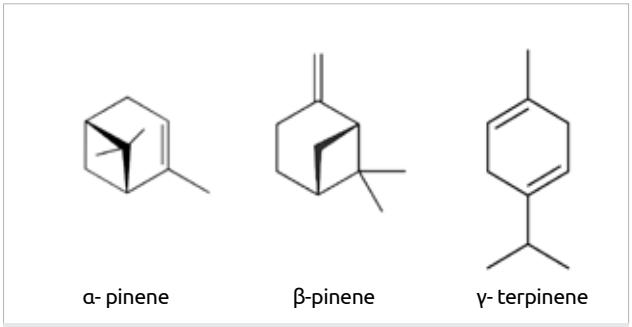


Figure 26. Structures of some monoterpenoids

S. miltiorrhiza root has been implicated in decreasing dysfunction of vasoactive intestinal peptide (VIP), a neuropeptide found within the gastrointestinal tract and CNS; it may play a role in the changes that occur in cerebral ischemia (87). Thus, *S. miltiorrhiza* root conserves neurons from cerebral ischemia and other CNS disorders, which can be attributed to the tanshinone diterpenes as the main constituents of the root. One of the tanshinones, tanshinone IIA, the major active diterpene of *S. miltiorrhiza,* inhibited human aortic smooth muscle cell migration and MMP-9 activity, which was carried out by Jin et al. [88]. Further assessment of the relevance of *Salvia* species in CNS disorders is discussed by Perry and Howes (36).

S. miltiorrhiza root may offer an additional therapeutic approach to the management of stroke and ischemia. During reperfusion, metabolism of free fatty acids from the breakdown of lipid membranes in ischemia has been proposed to generate oxygen free radicals, leading to further brain injury. *S. miltiorrhiza* root has been shown to protect against this process by reducing lipid peroxidation (89).

S. miltiorrhiza roots probably inhibit neuronal cell death by inhibition of presynaptic glutamate release (87). Thus, modulation of glutamatergic activity is also recognized as a therapeutic target in AD.

Salvianolic acid B (SalB) is a polyphenolic compound found in *S. miltiorrhiza* that has several anti-oxidative and anti-inflammatory effects. SalB administration significantly rescued the Ab25-35 peptide-induced decrease of choline acetyltransferase and brain-derived neurotrophic factor protein levels. These results suggest that SalB exerts neuroprotective activity via anti-inflammatory and anti-oxidative effects and that SalB may be a potential candidate for AD therapy (90).

The inhibition of NO formation may also explain the CNS-protective effects of *S.miltiorrhiza* root**.** Further investigations on *S. miltiorrhiza* may modify ischemic cell changes by modulating somatostatin (91).

***Salvia nipponica* Miq. var. *formosana* (Hayata) Kudo**

The extracts of the roots and the leaves of *Salvia nipponica* var. *formosana* showed potent inhibitory effects on superoxide anion production in fMLP/CB-activated human neutrophils, as well as other anti-inflammatory effects. Among the isolated 25 compounds, seven of them exhibited more potent inhibitory effects on superoxide anion generation and elastase release by human neutrophils in response to fMLP/CB. Moreover, those isolated compounds also showed significant anticholinesterase and antioxidative activities (92).

***Salvia officinalis* L.**

S. officinalis is the main medicinal *Salvia* species, but its native distribution is more or less restricted to the western part

of the Balkan Peninsula (93), including Turkey. However, it is cultivated in many European and Middle Eastern countries, even all over the world. Just as mint, it is known for its soothing and carminative effects.

Pharmacological activities of sage relevant to AD include antioxidant activity, anti-inflammatory effects, and cholinesterase inhibition (94).

S. officinalis, like *S. fruticosa,* has many antioxidant compounds, particularly a diterpene carnosic acid and a stilbene rosmarinic acid with high activity. These compounds are thought to protect the brain from oxidative damage (68, 69).

S. officinalis is used as an herbal medicine for neuronal dysfunction. Its ability to act as an AChE inhibitor made it a natural remedy for the prevention of AD. A clinical trial with *S. officinalis* that was given to mild and moderate AD patients for a period of 16 weeks showed improved cognitive performance (69).

S. officinalis extract showed potentiation of memory retention of passive avoidance learning in rats, associated with cholinergic effects and a neuroprotective effect (2). The latter effect was attributed particularly to its constituent rosmarinic acid and abietane diterpenes, also found in some other *Salvia* species (2). Evidence for the cognitive effects of *S. officinalis* extract has also been observed in a double-blind RCT (randomized control trial) of AD patients (2). In addition, it has been reported that *S. officinalis* exhibits CNS acetylcholine receptor activity, with demonstration of both nicotinic and muscarinic binding properties (87). Moreover, a recent study showed that *Melissa officinalis* L.*,* another herb from this family with the same CNS acetylcholine receptor activity, modulated mood and cognitive performance in acute administration in healthy young volunteers. No side effects or symptoms of toxicity were reported with the use of *S. officinalis* (95).

One of the major active compounds of *S. officinalis* is rosmarinic acid, which has a phenolic structure and has reduced a number of events induced by AD. These include reactive oxygen species formation, lipid peroxidation, DNA fragmentation, caspase-3 activation, and tau protein hyperphosphorylation. Moreover, rosmarinic acid inhibited phosphorylated p38 mitogen-activated protein kinase but not glycogen synthase kinase 3 activation. These data showed the neuroprotective effect of sage, which could validate the traditional use of this plant in the treatment of AD, through one of the active ingredients, rosmarinic acid (96), which is also a main active principle of rosemary.

In a study carried out by Iuvone et al. (96), the effect of a standardized extract from the leaves of *S. officinalis* and its rosmarinic acid were evaluated for 1) cell viability, 2) oxidative stress and phosphorylated p38 (p-p38) MAP kinase activation, 3) tau protein phosphorylation, and 4) neuronal apoptosis in cultured rat pheochromocytoma (PC12) cells exposed to Aβ, and rosmarinic acid was found to protect PC12 cells from amyloid peptide-induced neurotoxicity.

A randomized double-blind clinical study has recently shown that an ethanolic extract from *S. officinalis* is effective in the management of mild to moderate AD (44). The clinical relevance of these findings was emphasized by the observation that the patients did not experience any adverse effect while taking sage.

***Salvia potentillifolia* Boiss et Heldr. ex Bentham**

The essential oil of *S. potentillifolia* showed meaningful butyrylcholinesterase inhibitory activity (65.7 ± 0.21% inhibition), while one of the main constituents, α-pinene, exhibited high AChE-inhibitory activity (IC_{50}=86.2 ± 0.96 μM). Antimicrobial activity was also investigated on several microorganisms, and the essential oil showed high activity against *Bacillus subtilis* and *B. cereus*. It also exhibited remarkable anticandidal activity against *Candida albicans* and *C. tropicalis* with MIC values of 18.5 and 15.5 μg/ml, respectively, while the monoterpenes a- and β-pinenes (Figure 26) showed moderate activity (97).

***Satureja* species**

In Turkey, there are 15 *Satureja* species, five of them being endemic. Among them, *S. thymbra* L.*, S. spicigera* (C. Koch) Boiss, *S. cuneifolia* Ten.*, S. boissieri* Hausskn. ex Boiss, *S. coerulea* Janka*, S. pilosa* Velen., *S. icarica* P.H. Davis, *S. wiedemanniana* (Lallem.) Velen., *S. hortensis* L., and *S. cilicica* P. H. Davis are consumed as spices or herbal teas by the local people (98).

In a study, the essential oil of *S. thymbra* showed AChE (IC_{50}=150 μg/mL)- and BChE (IC_{50}=166 μg/mL)-inhibitory activities. In contrast, the methanol extract exhibited weak activity, particularly against AChE enzyme. Among the constituents of the essential oil, thymol (Figure 16) showed the best AChE- and BChE-inhibitory activities, demonstrating IC_{50} values of 47.5 μg/mL and 80.1 μg/mL, respectively. Under the same conditions, the IC_{50} values of carvacrol (Figure 16) were found to be 182 and 177 μg/mL against AChE and BChE, respectively. Other monoterpenes, such as γ-terpinene (Figure 26), however, exhibited nearly the same activity as that of carvacrol against AChE enzyme (IC_{50}= 181 μg/mL) and very close activity to that of thymol (Figure 16) against BChE enzyme (IC_{50}= 85.8 μg/mL) (99).

***Scutellaria* species**

The members of *Scutellaria* (Lamiaceae) are known to be rich, particularly in flavonoids. Among *Scutellaria* species, *S. baicalensis* Georgi, a famous Chinese medicinal plant, has been prescribed for treatment of memory deficit in traditional Chinese medicine. To date, there have been a number of studies performed on *S. baicalensis* and their constituents for their memory-enhancing effects. The ethanol extract of the roots of *S. baicalensis* of Korean origin was shown to possess neuroprotective effects, tested by passive avoidance test in ibotenic acid-induced amnesia in rats. In a study, methanol extracts of the aerial parts of 33 Turkish *Scutellaria* species were screened for their anticholinesterase activity, and all extracts exhibited only weak AChE and BChE inhibition, indicating that the

memory-enhancing property of *Scutellaria* species may not result from AChE and/or BChE inhibition but by some other mechanisms, as suggested in different reports (100).

***Sideritis* Species**

Sideritis species are very popular and marketed as mountain tea, plateau tea, malotira, te´de Puerto, and dag cayi in Turkey. Plants of the genus *Sideritis* are widely used in folk medicine in the Mediterranean region. The decoction and/or the infusion of aerial parts is traditionally used as an antimicrobial, anti-inflammatory, antiulcerative, anticonvulsant, antispasmodic, and carminative agent (101).

One of our recent studies on *Sideritis* species, *S. arguta* Boiss et Heldr. (Figure 27) extracts, and pure ent-kaurene diterpenes (Figure 28) has come into focus due to the observed inhibitory effects on both cholinesterase enzymes *in vitro* (102).

The extracts of *S. congesta* P. H. Davis & Hub.-Mor. and its eight isolated diterpenes with an ent-kaurane structure were investigated for antioxidant potential by three methods, including beta-carotene bleaching method, DPPH free radical-scavenging activity, and superoxide anion-scavenging activity. The anticholinesterase activity was also evaluated for the ent-kauranes, and most of the diterpenes exhibited weak AChE inhibitory activity. However, almost all diterpenes exhibited some inhibitory activity against BChE enzyme; particularly sideroxol and 7-epicandicandiol (Figure 28) exhibited better BChE-inhibitory activity than the drug galantamine (103).

Aqueous and alcoholic extracts of *S. scardica* Griseb. (Figure 25) have turned out to act as triple monoamine reuptake inhibitors in the phytochemical therapy of mental disorders with neurodegenerative disorders (104).

The AChE and BChE inhibitory activities of the acetone, methanol, and water extracts of *S. caesarea* Duman, Aytac & Baser and the flavones penduletin and apigenin were evaluated at 200 µg/mL, and penduletin (Figure 25) exhibited significant activity against BChE (66.58%), while apigenin showed weak activity against both enzymes (105).

***Stachys lavandulifolia* Vahl.**

More than 270 plant species constitute the genus *Stachys*, which is one of the largest genera of the mint family, Labiatae.

The hydroalcoholic extract of the aerial parts of *S. lavadulifolia* posseses sedative and anxiolytic activities in mice, based on spontaneous motor activity and elevated plus maze assays; petroleum ether, ethyl acetate, and water fractions also showed

Figure 27. *Sideritis arguta* Boiss. et Heldr.

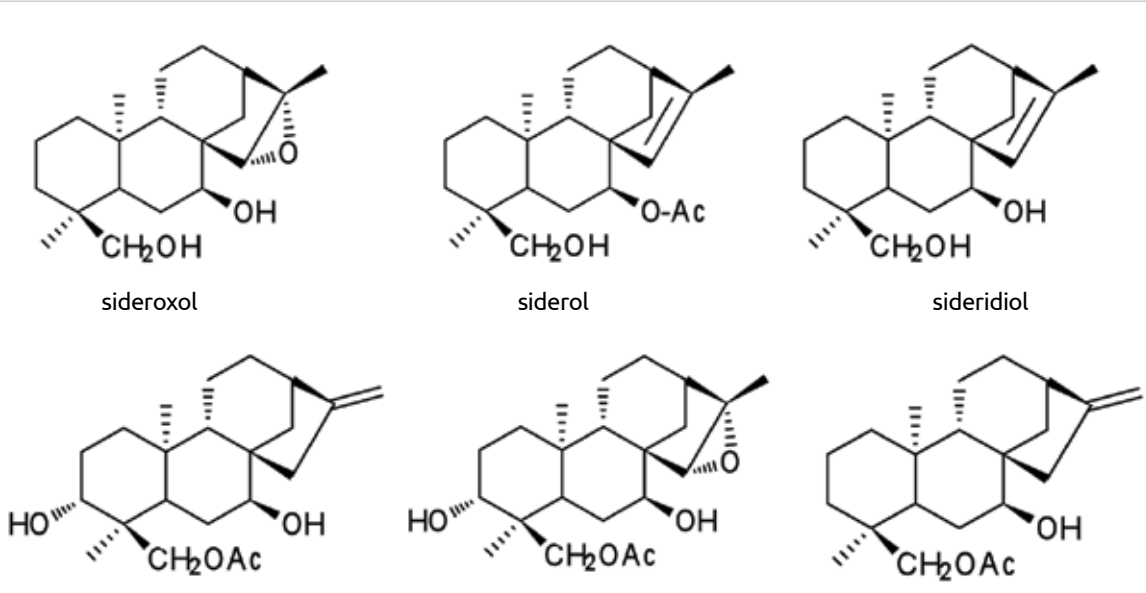


Figure 28. Structures of ent-kaurane diterpenoids

anxiolytic activity in mice (106). Therefore, this plant has great potential as a source for natural health products.

A study suggested that *S. byzantina* K. Koch has strong antioxidant activity (107).

***Thymus* species**

The genus *Thymus* (known as kekik in Turkey) is widely distributed in the Mediterranean region, with a characteristic aroma and great value as culinary herbs, ornamental plants, and flavoring agents (108). In addition, these plants possess an array of biological properties that positively impact human health (109).

The genus *Thymus* is represented by 41 species in Turkey, and 24 of them are endemic. Amongst them, *Thymus praecox* Opiz subsp. *caucasicus* (Ronniger) Jalas var. *caucasicus* (Ronniger) Jalas is consumed as "Anzer tea" in Anatolia (110).

The extracts of *T. lotocephalus,* obtained by SFE (super critical fluid extraction) method, exhibited high anticholinesterase activity, with IC_{50} values of 1.54±0.04 and 0.14±0.02 µg/mL against AChE and BChE, respectively. The essential oil of *T. lotocephalus* also strongly inhibited cholinesterases, with IC_{50} values of 0.90±0.04 and 0.50±0.12 µg/mL against AChE and BChE, respectively. This effect might be attributed to its major constituents, 1,8-cineole (eucalyptol) (Figure 20) and caryophyllene oxide (Figure 21) (109).

Anti-inflammatory properties of the essential oil of *T. vulgaris* L. were shown through its ability to repress the enzymatic activity of 5-lipoxygenase and to reduce the secretion of the pro-inflammatory cytokines TNF-, IL-1, and IL-8 in THP-1 cells, which may contribute to its potential anti-Alzheimer effect. Furthermore, the *T. vulgaris* essential oil, which possesses a high percentage of thymol, exhibited the highest antioxidant activity (111).

The anti-inflammatory effect of *T. kotschyanus* Boiss. extract on rat hind paw edema has been induced by carrageenan (112).

Based on epidemiological evidence, various environmental toxins, including pesticides, may have a role in the etiology of idiopathic neurodegenerative diseases (113). The antioxidant effects of a series of plant extracts and/or their bioactive components against neurotoxicity induced by pesticides (paraquat and rotenone) using the Drosophila model system were presented in a recent study, indicating that the fruit fly (*Drosophila melanogaster*) can be used for early-stage drug discovery and development for identification of novel plant-derived compounds to protect against neurodegeneration in AD and Parkinson's disease and other neurological disorders caused by oxidative stress (114).

Conclusion

One of the most active phytochemical products from the Lamiaceae family plants is rosmarinic acid, which displays a number of mechanistic effects relevant to dementia. Some Lamiaceae plants, particularly rosemary (*Rosmarinus*), sage (*Salvia*), lemon balm (*Melissa officinalis*), catmint (*Nepeta*), and lavender (*Lavandula*), are rich in rosmarinic acid and other phenolics that have strong antioxidant, anti-inflammatory, and neuroprotective effects in the treatment of neurological disorders, particularly AD [2]. As terpenoids, triterpenoids, especially oleane, ursane, and lupane triterpenoids, have high potential in the treatment of AD in the future. Ursolic/oleanolic acid or betulinic acid and their derivatives are important potential agents in the treatment of AD and maybe in other neurodegenerative diseases with dementia.

Diterpenes, especially phenolic ring-containing diterpenes, such as abietanes, were tested for anticholinesterase activity, and most abietanes have been found to be active against BChE particularly rather than AChE (75, 79, 92). Ferruginol and taxodione are fairly common abietanes isolated from a number of *Salvia* species that exhibited high BChE inhibition activity and weak-moderate AChE inhibition activity, indicating their dual inhibition properties. Several abietane diterpenoids, including carnosol and carnosic acid, and quinoid abietanes, such as tanshinones, should also be considered potential anti-Alzheimer agents.

Essential oils of *Satureja, Thymus, Origanum,* and *Thymbra* (all called kekik in Turkey) species are known to be rich in the monoterpenes thymol and carvacrol as well as β-pinene. Volatile constituents of the essential oils are likely to readily cross the blood-brain barrier due to their small molecular size and lipophilicity. Their volatile nature may also enable their administration as an inhaled vapor (115). Therefore, consumption of Lamiaceae plants rich in thymol and carvacrol is useful in the treatment of AD (99).

According to the results above, nonpolar extracts of the Lamiaceae family plants for anticholinesterase activity and the polar extracts for antioxidant activity are found to be effective and *complement* each other. From Anatolian *Salvia* species, triterpenic acids (oleanolic and ursolic acids) have been isolated in huge amounts (range 0.01-0.1% yield) in general, even at a higher yield in some species (1%), especially from aerial parts of the plants. Abietane diterpenes were also isolated from *Salvia* species in high yield but especially from their roots. The triterpenes isolated were found to be responsible for AChE inhibition, while diterpenes were found to be responsible for BChE inhibition, in general. As a conclusion, a number of Lamiaceae plants that have been investigated might be considered as potential anticholinesterase agents in the treatment of AD with dual inhibition on AChE and BChE, which requires immediate clinical trials.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - G.T.; Design - T.K.; Supervision - G.T.; Funding - G.T.; Analysis and/or Interpretation - G.T.; Literature Review - T.K.; Writing - G.T.; Critical Review - G.T.; Other - T.K.

Acknowledgements: The authors would like to thank the Scientific and Technological Research Council of Turkey (TUBITAK) to support this study with a project TBAG-107T592.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

Hakem değerlendirmesi: Dış bağımsız.

Yazar Katkıları: Fikir - G.T.; Tasarım - T.K.; Denetleme - G.T.; Kaynaklar - G.T.; Analiz ve/veya yorum - G.T.; Literatür taraması - T.K.; Yazıyı yazan - G.T.; Eleştirel İnceleme - G.T.; Diğer - T.K.

Teşekkür: Yazarlar TBAG-107T592 projesi ile bu çalışmaya destek veren Türkiye Bilimsel ve Teknolojik Araştırma Kurumu'na (TUBITAK) teşekkür eder.

Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

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