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Chemistry of Natural Products

Contents

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7 Acetylcholinesterase inhibitory activity of spices and culinary herbs

7.1 Introduction

Cholinesterases play an important role in the area of neurobiology, toxicology, and pharmacology, out of which acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) are vital in nerve impulse transmission [1]. The enzyme AChE catalyzes the hydrolysis of the ester bond of acetylcholine to terminate the nerve impulse transmission at the cholinergic synapses [2]. Compounds that are capable of suppressing the activity of AChE are known as AChE inhibitors or anticholinesterases. Anticholinesterases inhibit AChE enzyme, thereby increase the levels of acetylcholine near the synaptic cleft of cholinergic neurons. Prolonged availability of acetylcholine facilitates the cholinergic nerve impulse transmission process in patients with cognitive decline. AChE inhibitors are used to treat many pathological conditions, including Alzheimer's disease (AD), Parkinson's disease, myasthenia gravis, postural tachycardia syndrome, etc. AD is one of the progressive neurodegenerative diseases that affect memory and cognitive behaviour [3–4]. People of age over 60 years are affected most and it is one of the major causes of dependency among elderly people. About 5% of the world's elderly population (47 million people) was affected with dementia in 2015, and this figure is predicted to increase to 75 million in 2030 and 132 million by 2050. At present nearly 60% of people with dementia live in low- and middle-income countries [5].

There are many synthetic and natural anticholinesterases. Donepezil, tacrine, metrifonate and galantamine are anticholinesterases approved by the United States Food and Drug Administration (FDA) and currently in use. Galantamine is a plant-derived natural product [6]. In traditional medicine, many plants have been used to treat cognitive disorders. A large number of plants have been screened using well-established *in vitro* methods. Ethnopharmacological approach and bioassay-guided fractionation have facilitated the identification of potential anticholinesterases [7]. The majority of plant-derived compounds with anticholinesterase activity can be

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categorized into alkaloids, terpenes, sulfur compounds, and phenolic compounds including flavonoids, benzenoids, stilbenes, lignans, oxygen heterocycles, etc [2].

Simple and rapid screening methods are essential for finding novel therapeutic agents with AChE inhibitory activity. Popular screening methods include UV-visible spectrometric assays, fluorimetric assays, diffractometric assays, mass spectrometric assays, histochemical localization of AChE, colorimetric sticks or strips, radiometric assays, TLC bioautography assays, biosensors and chip techniques [1]. Among these, common methods are UV spectrometric assays and TLC bioautography method based on Ellman's [8] and Marston's [9] methods.

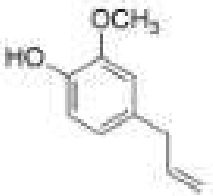
7.2 Spices with AChE inhibitory activity

Spices are a vital component in an everyday meal among South Asians and are culturally linked with the lifestyle. Recent studies have shown that spices provide much more health benefits than just a flavor in food [10]. Research findings over the past 10 years have indicated that phytochemicals derived from various spices such as *Cinnamomum zeylanicum*, *Coriandrum sativum*, *Curcuma longa*, *Garcinia cambogia*, *Myristica fragrans*, *Piper nigrum*, *Syzygium aromaticum*, and *Tamarindus indica* slow down or delay the onset of neurological diseases via multiple mechanisms [6].

a) *Cinnamomum zeylanicum* Blume (cinnamon)

Ceylon cinnamon or true cinnamon, is the dried bark of *Cinnamomum zeylanicum*, belongs to the family Lauraceae. *C. zeylanicum* is used both in the food industry and in indigenous medicine. *C. zeylanicum* is the most important spice, which was used since ancient times for many purposes such as medicine, spice, perfumery material, and soft drink. Sri Lanka is the world's largest producer and exporter of the best quality cinnamon to the world [11]. It possesses many medicinal properties such as sugar control, antioxidant, anti-inflammatory, and antimicrobial activity [12]. Traditionally it was also used for diabetes in Ayurveda and Chinese medicine. *C. zeylanicum* is used to treat stomachic and carminative for gastrointestinal complaints as well as other ailments, including toothache [13].

Water and ethanol (EtOH) extracts of bark of *C. zeylanicum* showed anticholinesterase activity of 46.84 ± 0.003% and 40.83 ± 0.005%, respectively, at 100 µg/mL [14]. Eugenol (Figure 7.1; **(1)**), one of the major components of the bark of *C. zeylanicum* showed anticholinesterase activity of 0.48 ± 0.16 mg/mL and the positive control galantamine 0.38 ± 0.16 µg/ml. [15].



1 **Figure 7.1:** Anticholinesterase active compound of *C. zeylanicum*.

b) *Coriandrum sativum* L. (coriander)

Coriandrum sativum belongs to the family of Apiaceae and is native to Western Asia, Eastern Mediterranean region and Europe. Leaves of *C. sativum* have a distinctive aroma. Both leaves and dried fruits are used as spice [16]. *C. sativum* is used in traditional Indian medicine to treat digestive, respiratory, and urinary system disorders. In the European traditional medical system, the fruits of *C. sativum* are used to strengthen memory [17]. *C. sativum* is reported to have interesting biological activities including antioxidant, anti-mutagenic, antihelmintic, sedative-hypnotic, anticonvulsant, antimicrobial, diuretic, cholesterol-lowering, hypolipidemic, hypoglycemic, antifeedant, anticancer, anxiolytic, hepatoprotective, cardioprotective, antiprotozoal, antiulcer, post-coital anti-fertility and heavy metal detoxification activities [18].

Methanol (MeOH) extract of Sri Lankan *C. sativum* seeds did not exhibit any AChE inhibitory activity in the assay, whereas *n*-hexane and dichloromethane (DCM) extracts showed low activity with IC_{50} values greater than 100 µg/mL. Ethyl acetate (EtOAc) extract showed the highest activity (IC_{50}, 63.51 ± 0.08 µg/mL) among the four extracts [19]. Previous studies have shown leaf MeOH extract to have AChE inhibitory activity of 36.25 ± 5.3% at 0.1 mg/mL where positive control physostigmine showed IC_{50} of 0.075 ± 0.003 µg/mL [20]. Further, fresh leaves of *C. sativum* showed a dose-dependent improvement in memory scores of young as well as aged rats [21].

c) *Curcuma longa* L. (turmeric)

Curcuma longa belongs to the family of ginger, Zingiberaceae, and it is indigenous to the Indian subcontinent [22]. Turmeric is widely used in the indigenous system of medicine and Ayurvedic systems for centuries to treat various ailments including inflammation and diseases such as biliary disorders, anorexia, cough, diabetic wounds, hepatic disorders, rheumatism, and sinusitis [18]. Turmeric is one of the most commonly used herbal medicine with various activities including antioxidant, apoptotic, antidepressant, antifungal, antiplatelet, antispasmodic, antiarthritic, hypoglycemic, hypotensive, antibacterial, leishmanicidal, antigenotoxicity, cardioprotective, neuroprotective, wound healing, cytoprotective by induction of heat shock protein [23]. Curcuminoid (Figure 7.2; curcumin (**2**), demethoxycurcumin (DMC) (**3**) and bisdemethoxycurcumin (BMC) (**4**)) is the important class of compounds that is responsible for most of the bioactivities mentioned above [24].

Kalaycıoğlu and co-workers reported BMC (4) to have the highest anticholinesterase activity (IC_{50} 2.14 ± 0.78 μM) while the positive control galantamine had IC_{50} 2.41 ± 0.12 μM. The lowest activity (IC_{50} 51.8 ± 0.6 μM) was found in curcumin (2) [25]. *In vitro* studies indicated that curcumin (2) has anti-amyloidogenic, antioxidative, anticholinesterase, β-secretase and anti-inflammatory properties while *in vivo* studies resulted in inhibition of amyloid beta (Aβ) deposition, Aβ oligomerization, and tau phosphorylation in the brains of AD animal models and improvements in behavioral impairment in animal models with the potential to prevent AD [24]. Though curcumin (2) is one of the promising candidates for AD, low bioavailability after oral administration limits its use. Many studies were conducted with intranasal route of administration for the central nervous system [26]. A study conducted in combination therapy of curcumin and donepezil supports the concept that the combination strategy might be an alternative therapy in the management/prevention of neurological disorders [27]. Several preclinical studies have resulted in beneficial effects of curcumin in AD, although the number of human studies is limited. According to these results, curcumin may stabilize or prevent cognitive decline [28].

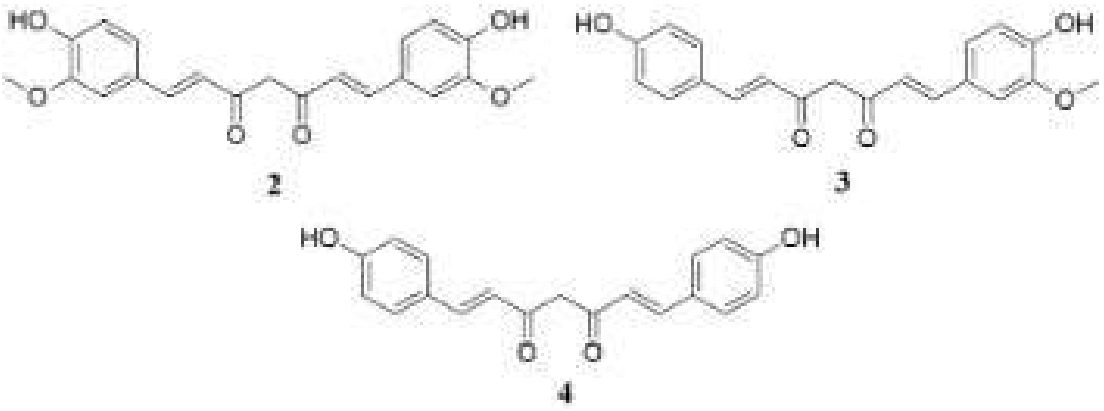


Figure 7.2: Structures of anticholinesterase active curcuminoids.

d) *Garcinia cambogia* Desr. (garcinia)

Garcinia cambogia (formally *Garcinia gummi-gutta*) belongs to the family Clusiaceae and is grown in South Asian countries. The herbal preparations made using *G. cambogia* rinds are used to treat inflammatory ailments, rheumatic pains, and bowel complaints. The fruit is considered to be anthelmintic and cardiotonic. The juice (sherbet) made from the rind is used for piles, hemorrhoids, colic problems, ulcers, inflammations, treat sores, dermatitis, diarrhea, dysentery, ear infections, to facilitate digestion and to prevent hyper perspiration [29]. Biological activities of *G. cambogia* include appetite-suppressant, antiobesity, hypolipidemic, antidiabetic, anti-inflammatory, antioxidant, hepatoprotective, anticancer, antiulcer, anticholinesterase, antimicrobial, anthelmintic, and diuretic activities, and effects on fertility such as increasing sperm count and

acylphenol moiety; malabaricones A, B, and C (Figure 7.4; (7–9)) exhibited significant interaction with AChE, showing IC_{50} values 11.0 ± 2.1 µM, 9.0 ± 1.6 µM, 11.7 ± 2.5 µM, respectively (IC_{50}, 0.11 ± 0.02 µM for positive control tacrine) [40]. *n*-Hexane, DCM, EtOAc and MeOH extracts of dried fruit aril of Sri Lankan *M. fragrans* showed high AChE inhibitory activity with IC_{50} values of 29.03 ± 0.11 µg/mL, 21.37 ± 0.07 µg/mL, 18.29 ± 0.04 µg/mL and 13.44 ± 0.13 µg/mL respectively in modified Ellman's method. Chromatographic separation of the combined EtOAc (87.51% inhibition at 100 µg/mL) and MeOH (96.75% inhibition at 100 µg/mL) extracts yield six compounds, out of which malabaricone C (9) showed highest anticholinesterase activity with IC_{50} 2.06 ± 0.04 µg/mL while donepezil showed IC_{50} 0.03 ± 0.00 µg/mL [41].

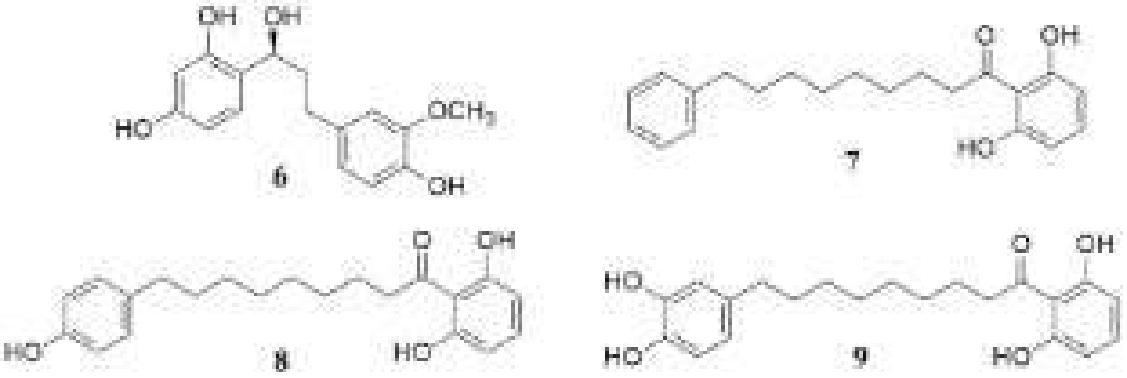


Figure 7.4: Anticholinesterase active compounds of *M. fragrans*.

f) *Piper nigrum* L. (pepper)

Piper nigrum, known as the king of spices, belongs to the family of Piperaceae. *P. nigrum* is a widely used spice around the world and occupies a large percentage of the spice trade. Mature dried berries of the woody perennial evergreen climbing vine are used as the spice. *P. nigrum* is used as a medicinal agent, a preservative and perfumery ingredient [42]. *P. nigrum* is used in a variety of traditional medicinal systems such as Traditional Chinese Medicine, the Indian Ayurvedic system, and folklore medicine of Latin America and West Indies [43]. It is used in folk medicine for stomach disorders, digestive problems, neuralgia, and as a central nervous system depressant [12] *P. nigrum* is used in the treatment of pain relief, chills, rheumatism, flu, muscular aches, colds, exhaustion, and fevers, as a nerve tonic, to increase circulation of blood, increase the flow of saliva, stimulate appetite and to encourage peristalsis [44]. *P. nigrum* shows a diverse array of bioactivities including antihypertensive, antiasthmatic, cognitive and fertility improvement, antimicrobial, antioxidant, anticancer, anti-inflammatory, hepatoprotective, antidiarrheal, antidepressant, immunomodulatory, anticonvulsant and analgesic activities [42]. Aqueous and EtOH extract of *P. nigrum* seeds showed 52.25 ± 0.002% and 50.72 ± 0.002% inhibition respectively at 100 µg/mL, following modified Ellman's method [14]. Seed MeOH extract of *P. nigrum*

showed 34% inhibition of AChE at 1,000 µg/mL while galantamine showed an IC_{50} value of 9.4 µg/mL [45]. *n*-Hexane, DCM, EtOH and aqueous extracts of *P. nigrum* seeds showed inhibition of 48.7 ± 3.4%, 42.3 ± 1.3%, 46.8 ± 2.7%, 48.8 ± 2.1% respectively at 500 µg/mL [46]. *n*-Hexane, DCM, EtOAc and MeOH extracts of Sri Lankan *P. nigrum* seeds showed low anticholinesterase activity as their IC_{50} values were higher than 100 µg/mL [19]. Piperine (Figure 7.5; (**10**)) an active alkaloid in *P. nigrum* improves cognitive deficit condition. The mechanism of action of piperine on cognitive improvement is based on the increase of neuron density and anticholinesterase activity in the hippocampus [47].

10

Figure 7.5: Anticholinesterase active compounds of *P. nigrum*.

g) *Syzygium aromaticum* (L.) Merr. & L.M. Perry (clove)

Syzygium aromaticum (formally *Eugenia caryophyllus*) is one of the economically important crops in Asian countries, belongs to the family of Myrtaceae. Fully grown, unopened flower buds of this plant are used as a spice all over the world [48]. Whole dried bud or ground powder of *S. aromaticum* is extensively used in Asian cuisine to enhance flavor due to its aroma. Clove oil is obtained by the steam distillation of flower buds, inflorescence branches left after the removal of flower buds. *S. aromaticum* oil is used in the pharmaceutical industry and for perfumery purposes [49]. Dried flower buds of *S. aromaticum* are traditionally used as a carminative to treat hypochlorhydria by increasing hydrochloric acid in the stomach and increasing peristalsis [50]. Ayurvedic uses include antispasmodic, antiemetic, stimulant, dyspepsia, gastric irritation [51]. Several biological activities such as anticancer, antidiabetic, anti-inflammatory, antioxidant, antiulcerogenic, antithrombotic, antifungal, antiviral, antiseptic, antimutagenic, and antiparasitic activities have been reported [52].

A study conducted on aqueous and EtOH extracts of flower bud showed 50.45 ± 0.003% and 59.09 ± 0.006% inhibition respectively at 100 µg/mL [14]. Cold and hot extracts of flower bud showed 90% and 73.7% of inhibition at 100 µg/mL for *in vitro* AChE assay [53]. The essential oil fraction of *S. aromaticum* had 31.94 ± 1.91% inhibition at 120 µg/mL [54]. In another study, MeOH extract showed 47.0% inhibition at 1,000 µg/mL [45]. A study revealed that *S. aromaticum* oil, MeOH extract of the dried flower bud of *S. aromaticum* and eugenol has potential anticholinesterase activity. Essential oil of the clove bud showed high anticholinesterase activity (IC_{50} 49.73 ± 1.33 µg/mL), compared to MeOH extract (IC_{50} 61.5 ± 1.88 µg/mL) while standard compound eugenol (**1**) showed IC_{50} of 49.73 ± 1.33 µg/mL and positive control galantamine had IC_{50} value of 10.14 ± 0.71 µg/mL. Further TLC bioautography method following Ellman's protocol confirmed the potential anticholinesterase activity of the

MeOH extract of *S. aromaticum* [55]. A study on the leaves (*n*-hexane, EtOAc and MeOH extracts) and bud (MeOH extract) of *S. aromaticum*, revealed that MeOH extract of leaves showed slightly higher activity (IC_{50} 42.10 ± 0.41 µg/mL) than MeOH extract of bud (IC_{50} 45.25 ± 0.07 µg/mL). EtOAc extract of leaves (IC_{50} 55.90 ± 3.82 µg/mL) and *n*-hexane (IC_{50} 62.5 ± 16.62 µg/mL) extract of leaves [56]. *n*-Hexane, DCM, EtOAc and MeOH extracts of Sri Lankan *S. aromaticum* showed IC_{50} value higher than 100 µg/mL with 36.19%, 34.95%, 42.45%, 31.94% inhibitions at 100 µg/mL [19].

h) *Tamarindus indica* L. (tamarind)

Tamarindus indica is a large evergreen tree belonging to the family of Fabaceae and native to African and Asian countries. The fruit pulp of *T. indica* is used as a flavoring agent in food, beverages and lozenges due to the taste of tartaric acid and reducing sugars. Fruits, seeds, leaves, bark, and flowers of *T. indica* are used for various purposes including culinary and medicine [57, 58] Tamarind products, leaves, fruits, and seeds have been extensively used in Indian Ayurvedic medicine and traditional African medicine. Tamarind seeds are used in Cambodia and India, in powdered form, to treat boils and dysentery. Boiled and pounded seeds are reported to treat ulcers and bladder stones and powdered seed husks are used to treat diabetes [58].

DCM extract of *T. indica* fruit pulp showed an inhibition of 26.64% at 100 µg/mL, while MeOH extract of *T. indica* seeds showed significant AChE inhibitory activity with IC_{50} 15.88 ± 0.01 µg/mL [19]. Previous studies indicated that MeOH extract from bark had more potent AChE inhibitory activity (IC_{50} of 268.09 µg/mL) than seed MeOH extract (IC_{50} 287.15 µg/mL). Donepezil inhibited the AChE activity with almost 92.57% inhibition at 100 µg/mL [59].

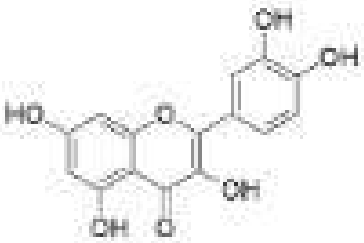
7.3 Other culinary herbs with AChE inhibitory activity

a) *Allium cepa* L. (onion)

Allium cepa is one of the oldest cultivated plants, belongs to the family of Amaryllidaceae which is utilized worldwide as a culinary herb. The bulb of *A. cepa* has a characteristic flavor and odor due to sulfur compounds present. Apart from the culinary virtues, it is widely used in traditional medicine in a wide variety of internal and external preparations to treat various ailments, including digestive problems, skin diseases, metabolic diseases, insect bites, and others. Experimental studies have proven the pharmacological properties of *A. cepa* including anticancer, antihypertensive, antidiabetic, antimicrobial, analgesic, antioxidant, immunomodulatory, anti-inflammatory, antioxidant, and neuroprotective activities. *A. cepa* is a rich source of phenolic compounds, especially quercetin, anthocyanins, kaempferol and their glycosides, phenolic

acids, thiosulfinates, vitamins, and minerals [60]. Most of the reported activities are due to the bioactive polyphenolic compounds present in onion.

Anticholinesterase activity of *Allium cepa* has been investigated using aqueous methanol extract following Ellman's method. Significant AChE inhibitory activity was observed with IC_{50} of 51.78 ± 1.05 µg/mL. Hence onion is considered an excellent candidate for developing as a drug for the management of AD [61]. The same research group has further investigated anticholinesterase activities of standardized EtOAc fraction obtained from aqueous methanol extract. Activity guided fractionation followed by the evaluation of AChE inhibitory potential revealed that the most active fraction had an IC_{50} value of 18.33 ± 1.36 µg/mL, whereas positive control donepezil had an IC_{50} value of 7.06 ± 0.13 µg/mL. Quercetin (Figure 7.6; **(11)**) and quercetin 4′ *O*-glucoside (spiraeoside) content in the active fraction was determined using a validated thin layer chromatography densitometric method. The active fraction was further examined using a streptozotocin (STZ) induced mice model of Alzheimer's disease. AChE inhibitory activity and oxidative stress markers were assessed in the brain homogenates of mice. This study indicated quercetin significantly improves the spatial learning and memory impairments caused by STZ. In addition, quercetin was found to act as a good AChE inhibitor in the cerebral cortex and hippocampus [62].



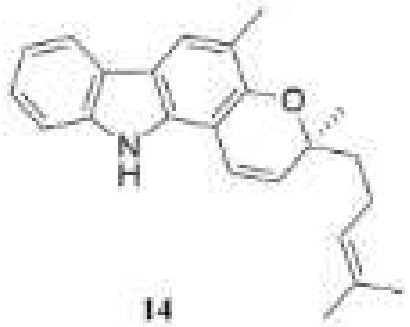
11

Figure 7.6: Anticholinesterase active compounds of *A. cepa*.

b) *Allium sativum* L. (garlic)

Allium sativum is one of the most researched herbal medicines and belongs to the family Amaryllidaceae. It is frequently used as a food and a condiment worldwide. In traditional medicine, garlic is used to treat infections, heart disease, diabetes, diarrhea, rheumatism, and many other disorders. The health benefits of *A. sativum* have been scientifically proven. Scientific and clinical studies have demonstrated that garlic possesses cardioprotective, antihypertensive, anticarcinogenic, immunostimulant, antibacterial, antilipidemic, and hypoglycemic properties [63].

The majority of the compounds reported from *A. sativum* are sulfur compounds including ajoenes, thiosulfinates, vinyldithiins, and various sulfides. Studies have shown that the characteristic pungent odor and many medicinal properties are due to the sulfur compounds. Alliin (*S*-allyl cysteine sulfoxide) (Figure 7.7; **(12)**) is the main sulfur compound, which is transformed to allicin (Figure 7.7; **(13)**) by allinase enzyme released during injuring the garlic bulb through cutting or crushing. Allicin



14

Figure 7.8: Anticholinesterase active compounds of *M. koenigii*.

and aged mice, significant improvement in memory scores of both mice was observed for 20 and 30 mg/kg doses. Further, the brain cholinesterase activity was significantly reduced, thus suggesting the potential therapeutic activity of the alkaloidal extract in managing the symptoms of AD and dementia. This study revealed the alkaloids extract of *M. koenigii* leaves increased the brain acetylcholine levels and thereby improved the cognitive function of both young and aged mice. *In vitro* evaluation of the same extract showed ChE inhibition through a non-competitive mechanism. This study further supported the therapeutic potential of *M. koenigii* for the management of Alzheimer patients [69].

d) *Zingiber officinale* Roscoe (ginger)

Zingiber officinale belongs to the family Zingiberaceae and originated in East Asia. The rhizome of this plant is popular around the world due to its pungency and typical aroma. *Z. officinale* is one of the most famous medicinal herbs in the Indian Ayurvedic system and Traditional Chinese Medicine for centuries. Oleoresin of *Z. officinale* is used in food, beverages, soft drinks, and in herbal drugs/products as bioavailability enhancer in anti-inflammatory herbal products. The rhizome of *Z. officinale* is used to treat a wide range of ailments, including the common cold, fever, sore throat, pain, rheumatism, bronchitis as well as carminative for gastrointestinal disorders, nausea and vomiting. In addition, it is used to treat toothache, gingivitis, bronchitis, hypertension, dementia, helminthiasis, constipation, asthmatic respiratory disorders, antispasmodic, expectorant, peripheral circulatory stimulant and astringent [70]. *Z. officinale* possess a wide range of biological activities such as cardioprotective, anticonvulsant, anxiolytic, antiemetic, antidiabetic, hypolipidemic, anti-inflammatory, antithrombotic, antiobesity, antioxidant, antitumor, anti-atherosclerotic, radioprotective, hypotensive, antiulcer, hepatoprotective, etc.

A recent study has shown that a standardized extract of the dry rhizomes of *Z. officinale* affects the initiation and development of neurodegeneration by inhibiting messenger ribonucleic acid (mRNA) expression of pro-inflammatory mediators and amyloid β-induced inflammatory mediators with good potential in the prevention and treatment of AD [70–72]. A study reported negative inhibition for MeOH extract of *Z. officinale* rhizobium [45] while in another study IC_{50} of 41 ± 1.2 µg/mL was

observed for MeOH extract of *Z. officinale* rhizobium and 0.075 ± 0.003 µg/mL for physostigmine [73]. 60% EtOH extract of *Z. officinale* showed an inhibition of 48.04 ± 0.06% at 100 µg/mL while galantamine showed 93.44 ± 2.21% of inhibition at the same concentration [74]. Zerumbone (Figure 7.9: (15)) present in the *Z. officinale* exhibited AChE inhibitory activity through TLC bioautographic method following Ellman's method [75]. In a comparative molecular docking approach using AutoDock, it was proposed that gingerenone A (Figure 7.9: (16)) binds to the active site of AChE and appears to interact with AChE conferring minimum binding energy among the docked compounds which facilitate the AChE inhibitory activity [76].

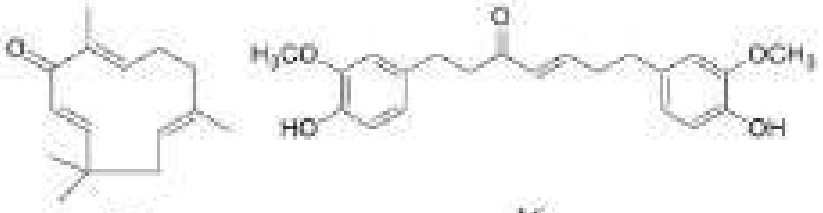


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Figure 7.9: Anticholinesterase active compounds of *Z. officinale*.

7.4 Conclusion

Selected examples given in this brief chapter indicate the therapeutic potential of spices and other culinary plants used in South Asian cuisine. Most of the investigations were conducted using *in vitro* testing using enzyme assays or using mouse models. However, further investigations, including bioavailability studies, are required to confirm the effectiveness of the active compounds or extracts.

Abbreviations

AChE	Acetylcholinesterase
AD	Alzheimer's disease
BChE	Butyrylcholinesterase
DCM	Dichloromethane
EtOAc	Ethyl acetate
MeOH	Methanol