Journal of Pharmaceutical and Scientific Innovation

www.jpsionline.com (ISSN : 2277 -4572)

Review Article

A REVIEW ON RECENT UPDATES OF ACETYLCHOLINESTERASE INHIBITORS FROM PLANT SOURCES

Balamurugan K [1], Sathya B *[2], Anbazhagan S [3]

[1]Assistant Professor, Department of Pharmacy, Annamalai University, Chidambaram, Tamilnadu, India

[2]Research Scholar, Department of Pharmacy, Annamalai university, Chidambaram, Tamilnadu, India

[3]Professor, Department of Pharmaceutical Chemistry, Surya School of Pharmacy, Surya Group of Institutions, Vikravandi, Villupuram, Tamil Nadu, India

*Corresponding Author Email: sathiya.y2k@gmail.com

DOI: 10.7897/2277-4572.07489

Received on: 20/06/18 Revised on: 14/07/18 Accepted on: 18/07/18

ABSTRACT

Acetylcholinesterase, the key enzyme, terminates the impulse transmission in numerous cholinergic pathways by rapid hydrolysis of the neurotransmitter acetylcholine. The enzyme inactivation by cholinesterase inhibitors increases the concentration of acetylcholine in the synapse eliciting neurohumoral transmission both in the central and peripheral nervous system. Several synthetic cholinesterase inhibitors like Tacrine, Donepezil and Galantamine were in existence with unpleasant side effects like weird dreams, muscle pain and gastrointestinal disturbances as well. Medicinal plants are found to be the valuable source of acetylcholinesterase inhibitors with minimal side effects. Many medicinal plants have been used traditionally for the treatment of various neurodegenerative disorders like Alzheimer's disease, dementia and cognitive impairments. The aim of the present review is to provide a comprehensive literature survey of plants that have been tested for acetylcholinesterase inhibitory activity along with other numerous phytoconstituents, which may aid researchers in their study of natural products for management of number of central nervous system disorders.

Keywords: Acetylcholinesterase inhibitors, acetylcholine, medicinal plants, neurodegenerative disorders, cognitive impairments.

INTRODUCTION

The cholinergic hypothesis implies that the Acetylcholine (ACh), a neurotransmitter synthesized in cholinergic nerve terminals play an important role in learning, memory and mood. ACh, increases the synaptic transmission in neuromuscular junction of central nervous system (CNS) thereby regulates its functions[1,2]. The enzyme acetylcholinesterase (AChE) inhibits the ACh mediated neuronal impulse transmission by triggering fast hydrolysis of ACh in the cholinergic nerve endings[3]. The decreased level of ACh in the cortex region of brain results in insufficient cholinergic functions originating many pathological features in the CNS disorders like Alzheimer's disease and dementia[4]. The AChE inhibitors deactivate AChE and increase the availability and duration of action of ACh at the synaptic nerve terminals[5].

Acetylcholine

Acetylcholine is discovered as the first neurotransmitter, an organic molecule released at nerve endings of all autonomic ganglia and at many synapses in the central nervous system. In the peripheral nervous system, ACh is responsible for skeletal muscle movement. The smooth and cardiac muscle movement is also regulated by ACh. In the central nervous system ACh play a chief role in memory and cognition[6]. ACh is synthesized from choline and acetyl coenzyme A by the biosynthetic enzyme Choline acetyltransferase (ChAT) in the cytosol of several cholinergic neurons. From the cytosol, ACh is transported by the vesicular ACh transporter (an energy - dependent pump), actively and stored as the synaptic vesicle in the presynaptic terminal[7]. The arrival of an action potential at the nerve terminals causes opening of voltage sensitive Ca^{2+} channels present in presynaptic membrane thereby permitting an influx of Ca^{2+} into the terminals. The released Ca^{2+} thus facilitates the fusion of synaptic vesicles triggering the exocytosis of ACh from the storage vesicles into the synaptic cleft at the neuronal junction. Following its release from the nerve terminal, ACh diffuses across the synaptic cleft and bind to the receptors on the post synaptic terminal membrane. Upon activation of the receptors ACh elicits several cellular responses[8]. The signal transmission effect of ACh is rapidly terminated by the enzyme AChE located on the post – synaptic membrane, by hydrolyzing ACh into acetate and choline. The liberated choline is transported back into the nerve terminals by the high – affinity choline transporter and used for resynthesis of ACh by combining with acetyl coenzyme A in the presence of the enzyme ChAT[9]. Cholinergic function of ACh is required for the short term memory function, thus its deficiency may leads to short term memory deficit, a central nervous system disorder[10]. The drugs that are enhancing and inhibiting cholinergic transmission are shown in table 1 and 2, respectively[11].

TABLE 1: DRUGS THAT ENHANCE CHOLINERGIC TRANSMISSION

Mode of Action	Drug
Nicotinic agonists	Nicotine
Muscarinic agonists	Bethanechol
Cholinesterase inhibitor	Physostigmine

TABLE 2: DRUGS THAT INHIBIT CHOLINERGIC TRANSMISSION

Mode of Action	Drug
Inhibitors of vesicular storage	Vesamicol
Inhibitors of release	Botulinium toxin
Nicotinic antagonists	Trimethaphan
Muscarinic antagonists	Atropine
Inhibitors of high – affinity choline transport	Hemicholinium
Inhibitors of pyruvate dehyrogenase	Bromopyruvate

Acetylcholinesterase Enzyme

AChE is a membrane – bound enzyme belonging to the family of serine hydrolase present in neuromuscular junction and cholinergic synapses. AChE inhibits the synaptic transmission of cholinergic neurons by rapid hydrolysis of ACh[12]. The enzyme AChE is a protein complex of α/β hydrolase fold type with an overall ellipsoid shape having a deep groove of above 20 Å deep, called the gorge. The "peripheral site" of the outer rim is the initial binding site of ACh, which then migrates to the bottom where hydrolysis takes place. The four essential sub sites of gorge are the esteric site, the oxyanion hole, anionic site and the acyl pocket[13]. The catalytic triad Ser200-His440-Glu327 of the esteric site promotes the nucleophilicity of catalytic serine. The hydrogen bond between His and Ser is strong which improves the ability of Ser for a nucleophilic attack on the substrate. The transition state of histidinium cation is stabilized by Glutamate[14]. During this catalytic process, the tetrahedral intermediate of ACh thus formed is stabilized by the hydrogen bond donors containing Gly 118, Gly 119 and Ala 201 residues of the "oxyanion hole" (OH)[15]. The choline binding site is the "anionic subsite" having Trp84, Phe330 and Glu199, which upon π-cation interactions binds to quaternary ammonium ligands of ACh[16]. The dimension of the substrates, entering the active site is controlled by the acyl binding pocket having Phe288 and Phe290. The three existing isoforms of AChE are G1 in brain; G4 in brain and the neuromuscular endplate and G2 in skeletal muscles and blood forming cells. The single AChE molecule can hydrolyze nearly 2.4×10^4 molecules of ACh per second[17]. It is much more important to inhibit AChE both medically and toxicologically. The well thorough knowledge of AChE and about its structure is essential for finding out the mechanism of action underlying the pharmacological and toxicological action of certain AChE inhibitors for the purpose of rational drug design[13].

Acetylcholinesterase Inhibitors

AChE inhibitors or anti-cholinesterases (anti-ChE) promotes the accumulation of ACh in the vicinity of cholinergic nerve terminals and are potentially capable of producing effects equivalent to excessive stimulation of cholinergic receptors throughout the central nervous system. The anti-ChE agents have received extensive application as toxic agents, in the form of agricultural insecticides, pesticides and potential chemical warfare "nerve gases". Nervertheless, several compounds of this class are widely used therapeutically; others that cross the blood- brain barrier have been approved or are in clinical trial for the treatment of neurodegenerative disorders[18]. According to the mode of action, AChE inhibitors are divided in to two main types, reversible and irreversible.

Reversible Acetylcholinesterase Inhibitors

The activities of the enzyme AChE are manipulated pharmacologically by reversible AChE inhibitors. These inhibitors include compounds like carbamate, quaternary or tertiary ammonium group that are applied in the diagnostic and/or treatment of various neurodegenerative disorders, as well as antidote to anticholinergic overdoses[19]. Reversible inhibitors are further divided into competitive enzyme inhibitors and substrate inhibitors. Examples of reversible cholinesterase inhibitors includes, Carbamates like Physostigmine, Neostigmine, Pyridostigmine, Edrophonium**,** Rivastigmine**,** Donepezil**,** Galanthamine and Acridine derivative – Tacrine[20]. The novel donepezil-tacrine and oxoisoaporphine-tacrine congeners hybrid related derivatives, coumarin and hyperzine A derivatives are able to bind simultaneously to both peripheral and catalytic sites of the enzyme and thus exhibits high AChE inhibitory activity with IC_{50} value in the nanomolar range. In addition, the newly synthesized symmetrical bispyridinium and carbamate anti-AChE compounds can inhibit the enzyme even in micromolar concentrations, making them the novel candidates for the treatment of many CNS disorders.

Irreversible Acetylcholinesterase Inhibitors

Organophosphorus compounds (OPs) are esters or thiols derived from phosphoric, phosphonic, phosphinic or phosphoramidic acid and the compounds includes organophosphorus insecticides like parathion, malathion, chlorpyrifos, diazinon, dichlorvos, phosmet, fenitrothion, tetrachlorvinphos, azinphos methyl, pirimiphos-methyl, dimethoate, phosalone and organophosphorus nerve gases like tabun, sarin, soman, cyclosarin. The organophosphates acts by non-reversible phosphorylation of esterases in the central nervous system and their toxic effects are due to irreversible inactivation of AChE. The OPs and ACh are substrate analogues and thus OPs enters the active site like natural substrate and binds covalently to the hydroxyl group of serine. since the phosphorylated enzyme cannot hydrolyze the neurotransmitter, leads to accumulation of ACh in the synaptic cleft results in neurotransmission[19].

The biochemical properties and physiological role of AChE is found to be unique, made it an attractive topic of intensive investigations throughout the world. The research is under progress to discover new AChE inhibitors from both synthetic and natural origin. This review is highly focused on certain newly existing natural bioactive compounds with AChE inhibitory activity along with a brief discussion about the traditional AChE inhibitors from natural source that are already in use.

ACETYLCHOLINESTERASE INHIBITORS FROM PLANTS

The history of drug discovery shown that the plants are being an important sources in the search for new bioactive compounds with AChE inhibitory property[5]. Based on the several neuropharmacological activities including cognitive repair that have been documented in folk medicine, the following plants have been described as potential leads for the development of new drugs for CNS disorders. The list of some plants that have been reported to exhibit AChE inhibitor activity are also been given in table 3.

TABLE 3: PLANTS WITH ACETYLCHOLINESTERASE INHIBITORY ACTIVITY

Plant	Family	Parts used	Type of extract	Activity (%inhibition) (concentration)	References
Acacia nilotica	Mimosaceae	Leaf	Ethyl acetate	53.00±3.70 (1 mg/ml)	21
Arnica chamissonis	Asteraceae	Flower	Methanolic	95.0±1.1 (400 µg/ml)	22
Bacopa monnieri	Scrophulariaceae	Whole plant	Ethanolic	42.9±1.2 (0.1 mg/ml)	23
Combretum kraussii	Combretaceae	Leaf	Ethyl acetate	96.00±4.60 (1 mg/ml)	24
Corydalis solida	Papaveraceae	Whole plant	Methanolic	89.00±0.00 (0.1 mg/ml)	25
Crinum jagus	Amaryllidaceae	Leaf	Methanolic	74.25±6.42 (42.5 µg/ml)	26
Dioscorea bulbifera	Dioscoreaceae	Whole plant	Methanolic	79.00±2.00 (5 mg/ml)	27
Embelia ribes	Myrsinaceae	Root	Methanolic	50.82±0.71 (100 µg/ml)	28
Fumaria capreolata	Fumariaceae	Fruit	Ethanolic	97.37±0.52 (100 mg/ml)	29
Galium odoratum	Rubiaceae	Herb	Hexane	53.1±1.1 (400 µg/ml)	22
Laurus nobilis	Lauraceae	Leaf	Ethanolic	65.80±3.70 (2 mg/ml)	30
Myricaria elegans	Tamariacaceae	Aerial parts	Methanolic	74.80±0.00 (0.2 µg/ml)	31
Nelumbo nucifera	Nelumbonaceae	Flower	Methanolic	61.73±7.6 (0.1 mg/ml)	32
Punica granatum	Punicaceae	Whole fruit	Methanolic	62.4±5.3 (0.1 mg/ml)	32
Salvia officinalis	Lamiaceae	Whole plant	Ethanolic	68.20±15.60 (2.5 mg/ml)	33
Terminalia chebula	Combrateceae	Fruit	Methanolic	89.00±1.00 (5 mg/ml)	27
Tinospora cordifolia	Manispermacea	Stem	Methanolic	89.00±1.00 (5 mg/ml)	28
Withania somnifera	Solanaceae	Root	Methanolic	75.95±0.16 (100 µg/ml)	28

Vanda roxburghii

The chloroform extract of *Vanda roxburghii* (Orchidaceae) acts as an important source of polyphenols with antioxidant and choliesterase inhibitory activity. The bioassay-guided separation using column chromatography let to the isolation of gigantol, a bibenzyl stilbinoid as a phenolic component from the active subfraction. Due to its phenolic compounds *Vanda roxburghii*, possess a combination of antioxidant properties and choliesterase inhibitory activities supported its traditional utilization in Bangladesh in the treatment of Alzheimer's disease[34].

Pluchea indica

In a study performed by Noridayu et.al., the methanolic extract of stem of *Pluchea indica* (Asteraceae) and hexane extract of both the leaves and stems were found to inhibit acetylcholinesterase potentially. Its methanolic extract of leaves also showed highest antioxidant activity. This study revealed that the *Pluchea indica* may provide a potential source of bioactive compounds and thus it may be benificial to human health[35].

Jatropha gossypifolia

Jatropha gossypifolia belonging to the family Euphorbiaceae, shown to have a potent acetylcholinesterase inhibitory activity was screened by Ellman's assay method. The dichloromethane fraction of root, methanol fraction of root, and dichloromethane fraction of leaves shown significant acetylcholinesterase inhibitory activity when compared with the standard eserine. The dichloromethane fraction of root contains butyrylcholinesterase (BuChE) inhibitory action as well. This study thus explained about the significant AChE and BuChE inhibitory action of the plant *Jatropha gossypifolia*, supporting its traditional use for the management of Neurodegenerative disorders like Alzheimer's disease[36].

Arnica montana

Arnica montana belongs to family Asteraceae is a valuable medicinal plant for its strong anti-inflammatory activity[37]. Its main application is for treatment of injuries like sprains, bruises and hematomas[38]. The acetylcholinesterase inhibitory potential of *Arnica montana* was assessed quantitatively by modified Ellman's colorimetric method. The result demonstrated that *Arnica montana* extract has strong antioxidant activity and moderate AChE inhibitory ability[39].

Agrimonia pilosa

In a study performed by Mankil jung et.al., an ethyl acetate extract of whole plants of *Agrimonia pilosa* (Rosaceae) yielded four flavonol compounds as tiliroside, 3-methoxy quercetin, quercitrin and quercetin. All the four flavonoids shown significant inhibitory effect on AChE. The fourth flavonoid – quercetin was twice as active against AChE, shown more anti-amnesic activity than the clinically useful tacrin[40]. Thus quercetin or its derivatives might have therapeutic potential for the treatment of Alzheimer's disease[41]. The leaves and stems of the plant also shown various pharmacological activities such as anti-tumour, analgesic, anti-bacterial, anti-inflammatory[42], hypoglycemic and vasoconstrictor activities. The plant also cures abdominal pain, sore throat, headaches, bloody and mucoid dysentery and heat stroke[43-45].

Beilschmiedia species

Among all the three species of Beilschmiedia which are *Beilschmiedia glabra*, *B. madang* and *B. pulverulenta* belonging to the family Lauraceae, the methanolic extract of stem bark of *B. madang* showed highest AChE inhibitory activity with percentage inhibition of 62.8%**,** which may be due to their alkaloidal content as its phytoconstituents. The extract also exhibited highest free radical scavenging activity (IC_{50} of 63.2 µg/ml) and total phenolic content (163.4 mg GA/g) assay[46].

Emex spinosa

Emex spinosa (Polygonaceae), used as a purgative, diuretic, stomach disorders, dyspepsia and colic in traditional medicine. The maximal inhibitory effect of the plant was found at 400 µg/ml by 81.92%. The plant also exhibited the most chelation and reduction capability which confirm its antioxidant property[47].

Citrullus colocynthis

Citrullus colocynthis belongs to the family Cucurbitaceae is traditionally used to treat constipation, diabetes, edema, fever, jaundice, bacterial infection, cancer, etc. The plant was screened for its anticholinesterase activity and found that it inhibits acetylcholine iodide hydrolysis at 400 µg/ml by 83.54% to a

maximum. The plant also contains greater potential of antioxidant activity that may help in alleviating patients suffering from Alzheimer's disease[47].

Magnolia officinalis

The plant bark of *Magnolia officinalis* belongs to the family Magnoliaceae, is used as a memory enhancing agent for the treatment of neurosis, anxiety, dementia, stroke, etc., in chinese medicine. The ethanolic extract of the bark of the plant inhibits the cognitive impairment induced by scopolamine by inhibiting AChE. The extract contains magnolol and honokiol as constituents that are responsible for antioxidant activity both in vitro and in vivo[48,49].

Thymbra capitata

The essential oils and decoction waters of *Thymbra capitata* (Lauriaceae) was evaluated for antioxidant and antiacetylcholinesterase activity. The essentials oils of the plant shown the presence of carvacrol, the active constituent is responsible for its antiacetylcholinesterase activity at IC_{50} of 52±1 µg/ml. The plant also screened for its free radical scavenging, anti-inflammatory and superoxide anion scavenging activity[50].

Acorus calamus

Acorus calamus (Acoraceae) is widely used in Indian traditional system of medicines like Ayurveda, Unani, Siddha. It is also used to treat various CNS disorders like depression in chinese medicine[51]. The α and β-asarone are the major constituents present in *Acorus calamus*, inhibits AChE[48]. The plant also shows antioxidant, anti-spasmodic, cardiovascular hypolipidemic, immunosuppressive, anti-inflammatory, cytoprotective, anti-diarrhoeal, anthelmintic and antimicrobial activities[52].

Melissa officinalis

The traditional use of *Melissa officinalis* (lemon balm), Lamiaceae, was to sharpen memory. It also improves cognitive decline as well as the mood for Alzheimer's patients, temporarily. Another study revealed that the plant due to its AChE inhibitory ability and its antioxidant activity, helps in prevention and treatment of Alzheimer's disease[53,54].

Lepidium meyenii

Lepidium meyenii (Maca) belongs to Brassicaceae, the plant in the Andes of Peru, able to survive even in the undesirable condition of high altitude, burning sun, hot days, cold nights and dry winds[55]. The study done by Rubio J et.al. revealed that the aqueous and hydroalcoholic extracts of black maca improved scopolamine-induced memory impairment in mice by reducing brain AChE activity by 45%[56]. Rubio J et.al. also studied that Maca by its antioxidant and AChE inhibitory activities improved experimental memory impairment induced by ovareictomy in mice[57].

Lycopodium serratum

Lycopodium serratum belonging to the family Lycopodiaceae yeilds an alkaloid Huperizine A, a potential therapeutic agent used in the therapy of Alzheimer's disease[58]. Huperizine A, has been used traditionally to treat fever, inflammation, blood disorders and schizophrenia[59]. It is a potent, reversible, AChE inhibitor whose potency is similar to that of physostigmine, galantamine, denepezil and tacrine[60]. Huperizine A also confers certain protective effects such as regulating amyloid precursor protein metabolism, anti-inflammatory as well as apoptosis and mitochondrial dysfunction[61].

CONCLUSION

The known AChE inhibitors that are available in the market for the treatment of various neurodegenerative disorders are with several side effects such as high toxicity, low bioavailability, short duration of action and narrow therapeutic effects. The need arises for the development of new AChE inhibitors with less toxicity and more potent activity. Nature provides large number of bioactive compounds with greater AChE inhibitory potential those are desirable for human health. This review may provide information about the plants with AChE inhibitory activity which may contribute to the design of new pharmaceuticals from natural origin with minimal side effects.

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How to cite this article:
Balamurugan K *et al*. A review on recent updates of acetylcholinesterase inhibitors from plant sources. J Pharm Sci Innov. 2018;7(4): 98-103.
http://dx.doi.org/10.7897/2277-4572.07489

Source of support: Nil, Conflict of interest: None Declared