Mini Review Article
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Anticholinesterase potential of phytoextracts and their bioactive compounds: a promising therapeutic agent against Alzheimer's disorder

Abstract

Alzheimer's disease (AD) is a dynamic neurodegenerative pathological condition described by low level of neurotransmitter acetylcholine (ACh) in the cerebrum. It is an irreversible age-related type of dementia that gradually dissolves the mind and burglarizes the individual memory and psychological abilities and causes changes in identity and conduct. Amid a decade ago, critical development in Alzheimer's commonness has lighted the significance of more looks into in the pursuit of new medication. One of the major clinical advances in the treatment of AD have been the utilization of acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) inhibitors to reduce ACh level in cerebrum albeit cholinergic mixes with nicotinic and muscarinic agonist properties additionally have pulled in some intrigue. At present, there are extremely constrained drugs accessible to treat AD and the greater part of the treatment is accessible just to postpone the progress of indications and symptomatic alleviation for a brief timeframe. Restorative plants speak to a lot of undiscovered store of characteristic prescriptions and potential wellspring of common AChE inhibitors. The basic assorted variety of their phytoconstituents makes them an important wellspring of novel lead mixes for the mission of medications to treat AD. Consequently, methodical ethnopharmacological screening of these plants may give valuable leads in the disclosure of new medications for AD treatment. With this background, a precise review is prepared to deliver up to date information in different phytoextracts and their derivatives alongside their conceivable activity on cholinergic sensory system to ease AD treatment. Electronic database were used for searching the information related to studies performed in plants during last decades.

Keywords: Alzheimer's disease, Acetylcholine, Acetylcholinesterase, Butyrylcholinesterase, Medicinal plant.

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Introduction

Alzheimer's disease (AD) is a neurodegenerative brain disorder associated with progressive dementia, a deterioration of memory and cognition.[1] AD causes changes in normal physiological behaviors of elderly patients, with duration of 09 years between beginning of symptoms and demise and has been risen as one of the deadliest issue in created countries. By 2040, World Health Organization (WHO) evaluated around 71% of the dementia cases will happen in developing nations.[2–4] The role of neurotransmitter acetylcholine (ACh) with cognitive function is clinically established now.[5] One of the neurotic signs of AD is loss of cholinergic cell in basalis of Meynert and hippocampus resulting reduce level of Ach in cerebrum.[6] Subsequently, repletion of Ach levels in brain has been exploited therapeutically amid most recent couple of decades to accomplish symptomatic help in AD.[7] In light of these etiologies a few pharmacological procedures with various conceivable targets are under scrutiny[8] and the main line remedial approach includes re-foundation of ACh levels, with the hindrance of cholinesterases viz. acetylcholinesterase (AChE), butyrylcholinesterase (BChE) and also monoamine oxidase (MAO) enzymes.[9,10] AChE basically acts by termination of nerve impulses at the cholinergic neural connections by quick hydrolysis of Ach to choline and acetic acid. This inhibition alleviates half-life of AChE and in this manner increasing concentration at synapses.[11] In fact, tacrine was the first clinically proven AChE inhibitor acquainted with enhances Ach level at the nerve ending. Afterward, second era inhibitors are presented however coming about symptoms and cost factor made their use constrained.[12] Medicinal plants and their concentrates are assuming an indispensable part in the present treatment of psychological issue either as standard or integral drug with specific reference to their ethnopharmacological perspectives.[13,14] Basically, in Ayurveda (Traditional Indian medicinal system), these restorative plants were named "medharasayanas" (Sanskrit: "medha" implies intellect/cognition and "rasayana" implies revival.[15] Medharasayanas incorporate a gathering of four therapeutic plants with multifold benefits, particularly to enhance memory and acumen by Prabhava (specific action) viz. Mandukaparni (*Centella asiatica*; Family: Umbelliferae), Yastimadhu (*Glycirrhiza glabra*; Family: Leguminosae), Guduchi (*Tinospora cordifolia*; Family: Menispermaceae) and Shankhapushpi (*Convolvulus pleuricaulis*; Family: Convolvulaceae).[16] Traditional Indian medicinal plants like Ashwagandha (*Withania somnifera*; Family: Solanaceae), Brahmi (*Bacopa monnieri*; Family: Scophulariaceae), Jyothishmati (*Celastrus panniculata*; Family: Celastraceae), Kushmanda (*Benincasa hispida*; Family: Cucurbitaceae), Vacha (Acorus calamus; Family: Araceae) and Jatamamsi (*Nardostachys jatamamsi*; Family: Valerianaceae) are very much archived in Ayurveda and other traditional messages as brain tonics and memory enhancers.[17] Indian turmeric (*Curcuma*

longa; Family: Zingiberaceae) contains curcumin, a demonstrated cell reinforcement and anticholinesterase activity, is observed to be exceptionally compelling to defer the movement of AD.[18] Cholinesterase inhibitors inhibit the hydrolysis of ACh by inhibitin AChE and thereby increase the availability of acetylcholine in brain specifically in cholinergic synapse.[19] However, this approach is limited to patients who have intact and functionally active presynaptic neurons capable of synthesizing and releasing ACh. Therefore, AChE inhibitors are useful in the early and moderate stages of AD.[20] Recent studies indicated that cholinesterase inhibitors might play a modulatory role on Aβ plaque deposition via suppressing amyloid precursor protein (APP) expression.[21] Medicinal plants have been the single most productive source of lead molecule for the development of drugs, and over a hundred new products are already in clinical development.[22] Indeed, several pharmacological screenings showed the efficacy of these medicinal plants extracts alone or in combination along with their active constituents to encounter AD.[23] The discoveries of exploratory results on different medicinal plants influencing cholinergic neurotransmission pertinent to the treatment of AD are given underneath (Table 1).

Table1 Medicinal plants affecting cholinergic neurotransmission

Family	Common name	Source	Parts used	Type of extract	Method and % of cholinesterase inhibition		Reference
					AchE	BchE	
Araceae	Sweet Flag	*Acorus calamus*	Rhizome	Methanol	96 well plate; 50% (791.35µg/ml)*	ND	8
Brassicaceae	White mustard	*Brassica alba*	Seed	Ethanol	UV spectroscopy; 50% (84.3±1.36µg/ml)*	ND	24
Capparidaceae	Varuna	*Crataeva nurvala*	Stem bark	Chloroform	UV spectophotometry; 2.38±0.160 (µMoles/min/g of tissue)	ND	11
Caryophyllaceae	Clove	*Eugenia caryophyllus*	Flower bud	Essentail oil	96 well plate; 50.45±0.003 (100µg/ml)	96 well plate; 49.76±0.005 (100 µg/ml)	25
Combretaceae	Bohera	*Terminalia bellirica*	Fruit	Methanol	TLC and 96 well plate; 39.68±8.15 (0.1mg/ml)	ND	26
	Haritaki	*Terminalia chebula*	Fruit	Methanol	96 well plate; 89.00±1.00 (5 mg/ml)	96 well plate; 95.00±1.00 (5mg/ml)	26
Convolvulaceae	Shankhapushpi	*Convolvulus pluricaulis*	Whole plant	Methanol	TLC and 96 well plate; 2.22±1.17 (100µg/ml)	ND	26
Dioscoreaceae	Aerial yam	*Dioscorea bulbifera*	Whole plant	Methanol	96 well plate; 79.00±2.00 (5mg/ml)	96 well plate; 82.00±2.00 (5mg/ml)	26
Fumariaceae	Indian Fumitory	*Fumaria asepala*	Whole plant	Chloroform: methanol (1:1)	96 well plate; 91.99±0.70 (1mg/ml)	96 well plate; 93.12±0.28 (1mg/ml)	26
Ginkgoaceae	Ginkgo	*Ginkgo biloba*	Whole plant	Ethanol	96 well plate; 50% (268.33µg/ml)*	ND	26
Hyperaceae	St. Johns Wort	*Hypericum perforatum*	Aerial part	Methanol	UV spectophotometry; 73.5±2.40 (400µg/ml)	UVspectophotometry; 50.5 ± 0.70 (400mg/ml)	26
Lamiaceae	Lavender	*Lavandula angustifolia*	Aerial parts	Ethanol	UV spectophotometry; 64.30±9.00 (1mg/ml)	ND	26
	Menthe/Pudina	*Mentha spicata*	Whole plant	Methanol	TLC and 96 well plate; 15.00±0.00 (0.1mg/ml)	ND	26
	Sage	*Salvia albimaculata*	Whole plant	Petroleum ether	96 well plate; 89.40±2.07 (1mg/ml)	96 well plate; 73.90±0.76 (1 mg/ml)	26
Leguminosae	White siris	*Albizia procera*	Bark	Methanol	TLC and 96 well plate; 40.71±0.46 (0.1mg/ml)	ND	26
	Indian Laburnum	*Cassia fistula*	Root	Methanol	TLC and 96 well plate; 54.13±3.90 (0.1mg/ml)	ND	26
	Touch me not/ Lajjavati	*Mimosa pudica*	Whole plant	Water	TLC and 96 well plate; 1.68±0.22 (100µg/ml)	ND	26
	Licorice	*Glycyrrhiza glabra*	Root	Methanol	96 well plate; 50% (418±30.7µg/ml) *	ND	27
Fagaceae	Menthi	*Trigonella foenum graecum*	Seeds	Hydro alcohol	TLC and 96 well plate; 50% (6±0.9µg/ml)	ND	28
Lythraceae	Pomegranate	*Punica granatum*	Fruit	Methanol	96 well plate; 50% (77± 6.2µg/ml) *	ND	26
Nelumbonaceae	Indian lotus	*Nelumbo nucifera*	Stamen	Methanol	TLC and 96 well plate; 23.77±2.83 (0.1mg/ml)	ND	23

Table contiuned

Family	Common name	Source	Parts used	Type of extract	Method and % of cholinesterase inhibition		Reference
Rubiaceae	Indian Madder	*Rubia cordifolia*	Stem	Methanol	TLC and 96 well plate; 22.12±2.22 (100µg/ml)	ND	22
Scrophulariaceae	Brahmi	*Bacopa monniera*	Whole plant	Ethanol	96 well plate; 42.90±1.20 (0.1mg/ml)	ND	18
Solanaceae	Aswagandha	*Withania somnifera*	Root	Methanol	TLC and 96 well plate; 75.95±0.16 (100µg/ml)	ND	26
			Root	Aqueous	TLC and 96 well plate; 24.60±0.38 (100µg/ml)	ND	26
Umbelliferae	Mandookparni	*Centella asiatica*	Whole plant	Hydroalcohol	96 well plate; 50% (106.55µg/ml)*	ND	26
Valerianaceae	Indian Valerian	*Nardostachys jatamansi*	Rhizomes	Methanol	96 well plate; 50% (562.21µg/ml)*	ND	26
Zingiberaceae	Galanga	*Alpinia galanga*	Rhizomes	Methanol	TLC and 96 well plate; 16.98±0.37 (100µg/ml)	ND	26
Zygophyllaceae	Land-Caltrops/ Gokhru	*Tribulus terrestris*	Whole plants	Chloroform: methanol (1:1)	96 well plate; 37.89±0.77 (1mg/ml)	96 well plate; 78.32±1.27 (1mg/ml)	26

ND, not done; *, represents IC50

Lead phytomolecules affecting cholinergic neurotransmission

Bioactive phytoconstituents resulted from isolation and characterization of natural flora and fauna have always been an important reservoir of drugs. The majority of the compounds examined till date affecting cholinergic neurotransmission and aiding protection against AD are primarily derived from plants sources.[24] A list of phytoconstituents having significant AChE inhibitory activity is provided in Table 2. Natural alkaloids with AChE inhibitory activity viz. physostigmine, huperzine-A, galan- thamine, are successfully practiced to encounter progression of AD.[25–29] Stilbene oligomer viz. α-viniferin and triterpenoid viz. ursolic acid are another highly potential lead molecule with AChE inhibitory activity.[30,31] The other major classes of phytoconstituents reported to have such activity are the flavonoids, glycosides and coumarins.[32] Although, with enormous efforts structure activity relationship (SAR) of few isolated bioactive compounds have been established but most of them are yet to be finalized. Moreover, cellular based mechanism of action, clinical efficacy and toxicity profile of these phytoextracts and their derivatives requires further assessment, before proceeding towards clinical trials and final approval to encounter AD.

Table 2 Lead phytomolecules affecting cholinergic neurotransmission

Chemical nature of phytoconstituents					
Alkaloid					
	Class	*Source*	**Family**	**Activity on AchE**	**References**
Assoanine	*Steroidal alkaloid*	*Narcissus assoanus*	Amaryllidaceae	50% inhibition at 3.87±0.24 pM	29
Buxamine B	*Steroidal alkaloid*	*Bums hyrcana*	Buxaceae	50% inhibition at 7.56±0.008 pM	29
Epinorgalantamine	*Steroidal alkaloid*	*Narcissus confuses*	Amaryllidaceae	50% inhibition at 9.60±0.65 pM	29
Galantamine	*Steroidal alkaloid*	*Galanthus nivalis*	Amaryllidaceae	50% inhibition at 1.07±0.18 pM	29
Sanguinine	*Steroidal alkaloid*	*Eucharis grandeora*	Amaryllidaceae	50% inhibition at 0.10±0.01 pM	29
Oxoassoanine	*Steroidal alkaloid*	*Narcissus assoanus*	Amaryllidaceae	50% inhibition at 47.21±1.13 pM	29
α-Solanine	*Glycoalkaloid*	*Sarcococca saligna*	Buxaceae	50% inhibition at 8.59±0.155 pM	30
Vaganine	*Steroidal alkaloid*	*Solanum tuberosum*	Solanaceae	50% inhibition at 7.028±0.007 pM	30
Physostigmine	*Indole alkaloid*	*Physostigtna venenosiun*	Fabaceae	50% inhibition at 6±1.0 pM	31
Coronaridine	*Indole alkaloid*	*Tabernaernontana austral*	Apocynaceae	Minimum concentration of 25 pM to produce detectable spot in TLC	28
Voacangine	*Indole alkaloid*	*Tabernaentontana austral*	Apocynaceae	Minimum concentration of 25pM to produce detectable spot in TLC	28
Rupicoline	*Indole alkaloid*	*Tabernaetnontana australis*	Apocynaceae	Minimum concentration of 25µM to produce detectable spot in TLC	6
Retamine	*Quinolizidine alkaloid*	*Genista aucheri*	Fabaceae	AchE and BchE inhibition (%) at 1 mg/ml at 15.0±1.08 & 66.3±0.88 respectively	17

Table Continued

Chemical nature of phytoconstituents					
Alkaloid					
	Class	*Source*	**Family**	**Activity on AchE**	**References**
Corynoline	*Isoquinoline alkaloid*	*Corydalis incisa*	Papaveraceae	50% inhibition at 30.6 pM	28
Palmatine	*Isoquinoline alkaloid*	*Corydath speciosa*	Papaveraceae	50% inhibition at 5.8 pM	28
(-)-Huperzine A	*Quinolizidine alkaloid*	*Huperzia serrate*	Lycopodiaceae	50% inhibition at 10.1 pM	31
Glycoside					
Cynatroside A	*Pregnant glycoside*	*Cynanchum frown*	Asclepiadaceae	50% inhibition at 6.4 pM	31
Cynatroside B	*Pregnant glycoside*	*Cynanchum stratum*	Asclepiadaceae	50% inhibition at 3.6pM	31
Norswertianolin	*Ggluco pyranoside*	*Gentiana cambpestris*	Coniferae	Minimum concentration of 1.20nM to produce detectable spot in TLC	31
Swertianolin	*Bellidifolin 8-o-13 glucopyranoside*	*Gentians cambpestris*	Coniferae	Minimum concentration of 0.18nM to produce detectable spot in TLC	31
Others					
Scopoletin	*Coumarin*	*Vaccinium oldhami*	Ericaceae	IC50 value of 79µM	14
Murranganin	*Coumarins*	*Murraya paniculata*	Rutaceae	IC50 value of 79.1µM	7
Viniferin	*Stilbene oligomer*	*Caragana chantlague*	Leguminosae	50% inhibition at 2.0pM	5
Bellidin	*Xanthone*	*Centime cambpestris*	Coniferae	Minimum concentration of 0.03 nM to produce detectable spot in TLC bioassay	14
Ursolic acid	*Triterpenoids*	*Origami majorana*	Lamiaceae	50% inhibition of AChE and BchE at 75.87±0.92 & 32.21±0.88 respectively	18
Capsaicin	*Pungent principle*	*Capsicum annum*	Solanaceae	50% inhibition of AChE and BchE at 62.7±0.79 and 75.3±0.98 respectively	18
Viniferin	*Polyphenol*	*Caragana chamlague*	Leguminosae	IC50 values of 2.0mM	31
Kobophenol A	*Polyphenol*	*Caragana chamlague*	Leguminosae	IC50 value of 115.8mM	31
Curcuminoids	*Triterpene*	*Curcuma longa*	Ziniberaceae	IC50 value of 19.67mM	31

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Conflict of interest

There is no conflict of interest.

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