Cholinesterase inhibitors from botanicals

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ABSTRACT

Alzheimer's disease (AD) is a progressive neurodegenerative disease, wherein a progressive loss of cholinergic synapses occurs in hippocampus and neocortex. Decreased concentration of the neurotransmitter, acetylcholine (ACh), appears to be critical element in the development of dementia, and the most appropriate therapeutic approach to treat AD and other form of dementia is to restore acetylcholine levels by inhibiting both major form of cholinesterase: Acetylcholinesterase (AChE) and butyrylcholinesterase (BChE). Consequently, researches have focused their attention towards finding cholinesterase inhibitors from natural products. A large number of such inhibitors have been isolated from medicinal plants. This review presents a comprehensive account of the advances in field of cholinesterase inhibitor phytoconstituents. The structures of some important phytoconstituents (collected through www.Chemspider.com) are also presented and the scope for future research is discussed.

Key words: Acetylcholinesterase, alkaloids, alzheimer's disease, butyrylcholinesterase, buxaceae

INTRODUCTION

Alzheimer's disease (AD) is a neurodegenerative disease of the central nervous system, wherein cholinergic neurons projecting to the neocortex and hippocampus are predominantly affected causing profound memory impairment, emotional disturbance, and personality changes in late stages.[1,2] According to cholinergic hypothesis, memory impairment in Alzheimer's disease is due to the deficit of cholinergic function in the brain, thereby, reducing hippocampal and cortical levels of the neurotransmitter acetylcholine (ACh) and associated enzyme choline transferase.[3,4] In the healthy brain acetylcholinesterase (AChE) is the most important enzyme regulating the level of ACh, while butyrylcholinesterase (BChE) plays a minor role. In patients with AD, the level of AChE activity declines and the activity of BChE increases and the ratio between BChE and AChE can change from 0.6 in the normal brain to as high as 11 in cortical areas affected by the disease.[5] Therefore, inhibition of AChE and BChE is the most effective therapeutic approach to treat the symptoms of AD.[5,6] Consequently, cholinesterase inhibitors are the only approved drugs for treating patients with mild to moderately severe Alzheimer's disease.[3,4,7]

Although, synthetic drugs such donepezil, neostigmine, and rivastigmine are available for the symptomatic treatment of AD, search for newer molecules from natural products has gained much attention by the researchers worldwide. As a result, a number of botanicals used in various traditional systems of medicines as memory enhancers have been tested for anticholinesterase activity. *Bacopa monniera*, *Ginkgo biloba*, *Acorus calamus*, *Epimedium koreanum*, *Rhododendron ponticum*, *Rhododendron luteum*, *Corydalis solida*, *Glaucium corniculatum,* and *Buxus sempervirens* are some of the medicinal plants used as cognitive enhancers by traditional healers which have been found to posses moderate to excellent anticholinesterase activity.[8-12] Further, a number of active compounds with good cholinesterase activity have been isolated from medicinal plants. With this background, the present review was planned to comprehend the fragmented information available on the cholinesterase inhibitors from medicinal plants.

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Table 1: Acetylcholinesterase inhibitors from medicinal plants

Phytoconstituent	Class of compound	Isolated from	Family	IC_{50} (μM)	Reference
Lycorine	Alkaloid	*Galanthus ikariae* *Narcissus tazetta*	Amaryllidaceae	3.16	[13]
Galanthamine	Alkaloid	*Galanthus ikariae*	Amaryllidaceae	3.2	[13]
Tazettine	Alkaloid	*Galanthus ikariae* *Narcissus tazetta*	Amaryllidaceae	-	[13]
Crinine	Alkaloid	*Galanthus ikariae*	Amaryllidaceae	-	[13]
3-epi-hydroxybulbispermine	Alkaloid	*Galanthus ikariae*	Amaryllidaceae	-	[13]
2-demethoxy-montanine	Alkaloid	*Galanthus ikariae*	Amaryllidaceae	-	[13]
N-nor-galanthamine	Alkaloid	*Narcissus tazetta*	Amaryllidaceae	-	[13]
Haemanthamine	Alkaloid	*Narcissus tazetta*	Amaryllidaceae	-	[13]
3-epi-hydroxybulbispermine	Alkaloid	*Narcissus tazetta*	Amaryllidaceae	-	[13]
Protopine	Alkaloid	*Corydalis ternata*	Papaveraceae	50	[14]
Conypododiol	Alkaloid	*Asparagus adscendens*	Asparagaceae	2.17	[15]
Bulbocapnine	Alkaloid	*Corydalis cava*	Fumariaceae	40	[16]
Corydine	Alkaloid	*Corydalis cava*	Fumariaceae	>100	[16]
Cyclobuxoviridine	Alkaloid	*Buxus hyrcana*	Buxaceae	179.7	[17,18]
Moenjodaramine	Alkaloid	*Buxus hyrcana*	Buxaceae	25.0	[17,19]
Buxamine A	Alkaloid	*Buxus hyrcana*	Buxaceae	81.4	[17,20]
Buxamine B	Alkaloid	*Buxus hyrcana*	Buxaceae	79.6	[17,21]
Spirofornabuxine	Alkaloid	*Buxus hyrcana*	Buxaceae	6.3	[22]
α-solanine	Glyco alkaloid	*Solanum tuberosum*	Solanaceae	-	[23,24]
Coronaridine	Indole alkaloid	*Tabernaemontana australis*	Apocynaceae	-	[25]
Physostigmine	Indole alkaloid	*Physostigma venenosum*	Leguminosae	6×10^{-4}	[26]
Rupicoline	Indole alkaloid	*Tabernaemontana australis*	Apocynaceae	-	[25]
Voacangine	Indole alkaloid	*Tabernaemontana australis*	Apocynaceae	-	[25]
Voacangine hydroxyindolenine	Indole alkaloid	*Tabernaemontana australis*	Apocynaceae	-	[25]
Corynoline	Isoquinoline alkaloid	*Corydalis incisa*	Papaveraceae	30.6	[27]
Palmatine	Isoquinoline alkaloid	*Corydalis speciosa*	Papaveraceae	5.8	[28]
Protopine	Isoquinoline alkaloid	*Corydalis speciosa*	Papaveraceae	16.1	[28]
Corydaline	Isoquinoline alkaloid	*Corydalis cava*	Fumariaceae	15	[16]
Annotinine	Lycopodane-type alkaloid	*Lycopodium annotinum*	Lycopodiaceae	>2,000	[29]
Annotine	Lycopodane-type alkaloid	*Lycopodium annotinum*	Lycopodiaceae	860	[29]
Annotine N-oxide	Lycopodane-type alkaloid	*Lycopodium annotinum*	Lycopodiaceae	404	[29]
Lycodoline	Lycopodane-type alkaloid	*Lycopodium annotinum*	Lycopodiaceae	>2,000	[29]
Lycoposerramine M	Lycopodane-type alkaloid	*Lycopodium annotinum*	Lycopodiaceae	>2,000	[29]
Anhydrolycodoline	Lycopodane-type alkaloid	*Lycopodium annotinum*	Lycopodiaceae	191	[29]
Gnidioidine	Lycopodane-type alkaloid	*Lycopodium annotinum*	Lycopodiaceae	1720	[29]
Lycofoline	Lycopodane-type alkaloid	*Lycopodium annotinum*	Lycopodiaceae	600	[29]
Acrifoline	Lycopodane-type alkaloid	*Lycopodium annotinum*	Lycopodiaceae	1625	[29]
Dehydroevodiamine	Quinazoline alkaloid	*Evodia rutaecarpa*	Rutaceae	37.8	[30]
(–)-huperzine A	Quinolizidine alkaloid	*Huperzia serrata* *Huperzia dalhousieana*	Lycopodiaceae	10-4	[9,31,32]
Assoanine	Steroidal alkaloid	*Narcissus assoanus*	Amaryllidaceae	3.87	[7]
Buxamine B	Steroidal alkaloid	*Buxus hyrcana* *Buxus papillosa*	Buxaceae	7.56	[33]
N, *N*-dimethyl buxapapine	Steroidal alkaloid	*Buxus papillosa*	Buxaceae	7.28	[33]
Epinorgalantamine	Steroidal alkaloid	*Narcissus confuses* *Narcissus perezchiscanoi* *Narcissus leonensis* *Narcissus legionensis* *Narcissus poeticus*	Amaryllidaceae	9.60	[7]
Galanthamine	Steroidal alkaloid	*Galanthus nivalis* *Narcissus confuses* *Lycorus radiate*	Amaryllidaceae	1.07	[7,34-36]
11-hydroxygalantamine	Steroidal alkaloid	*Narcissus poeticus*	Amaryllidaceae	1.61	[7]
Oxoassoanine	Steroidal alkaloid	*Narcissus assoanus*	Amaryllidaceae	47.2	[7]
Sanguinine	Steroidal alkaloid	*Eucharis grandiflora*	Amaryllidaceae	0.10	[7]
Sarsalignone	Steroidal alkaloid	*Sarcococca saligna*	Buxaceae	7.02	[33]
Vaganine	Steroidal alkaloid	*Sarcococca saligna*	Buxaceae	8.59	[33]
E-buxenone	Steroidal alkaloid	*Buxus hyrcana*	Buxaceae	71.0	[17]
Z-buxenone	Steroidal alkaloid	*Buxus hyrcana*	Buxaceae	87.4	[17]
31-hydroxybuxamine B	Steroidal alkaloid	*Buxus hyrcana*	Buxaceae	61.3	[17,37]
N20-formylbuxaminol E	Steroidal alkaloid	*Buxus hyrcana*	Buxaceae	25.5	[17,38]
Buxrugulosamine	Steroidal alkaloid	*Buxus hyrcana*	Buxaceae	24.8	[39]

Contd...

Table 1: Contd...

Phytoconstituent	Class of compound	Isolated from	Family	IC_{50} (μM)	Reference
Cyclobuxophylline O	Steroidal alkaloid	*Buxus hyrcana*	Buxaceae	35.4	[39]
Isosarcodine	Steroidal alkaloid	*Sarcococca saligna*	Buxaceae	10.31	[40]
Sarcorine	Steroidal alkaloid	*Sarcococca saligna*	Buxaceae	69.99	[40]
Sarcodine	Steroidal alkaloid	*Sarcococca saligna*	Buxaceae	49.77	[40]
Sarcocine	Steroidal alkaloid	*Sarcococca saligna*	Buxaceae	20.0	[40]
Alkaloid-C	Steroidal alkaloid	*Sarcococca saligna*	Buxaceae	42.2	[40]
Nb-dimethylcyclobuxoviricine	Triterpenoid alkaloid	*Buxus hyrcana*	Buxaceae	45.5	[17,41]
Buxakashmiramine	Triterpenoid alkaloid	*Buxus papillosa*	Buxaceae	25.4	[42]
Buxakarachiamine	Triterpenoid alkaloid	*Buxus papillosa*	Buxaceae	143	[42]
Buxahejramine	Triterpenoid alkaloid	*Buxus papillosa*	Buxaceae	162	[42]
Cycloprotobuxine-C	Triterpenoid alkaloid	*Buxus papillosa*	Buxaceae	38.8	[42]
Cyclovirobuxeine-A	Triterpenoid alkaloid	*Buxus papillosa*	Buxaceae	105.7	[42]
Cyclomicrophylline-A	Triterpenoid alkaloid	*Buxus papillosa*	Buxaceae	235	[42]
(+)-homomoenjodaramine	Triterpenoidal alkaloid	*Buxus hyrcana*	Buxaceae	19.2	[43]
(+)-moenjodaramine	Triterpenoidal alkaloid	*Buxus hyrcana*	Buxaceae	50.8	[43]
17-oxo-3-benzoylbuxadine	Triterpenoidal alkaloid	*Buxus hyrcana*	Buxaceae	17.6	[17]
buxhyrcamine	Triterpenoidal alkaloid	*Buxus hyrcana*	Buxaceae	18.2	[17]
31-demethylcyclobuxoviridine	Triterpenoidal alkaloid	*Buxus hyrcana*	Buxaceae	298.3	[17]
Homomoenjodarmine	Triterpenoidal alkaloid	*Buxus hyrcana*	Buxaceae	19.5	[17,43]
Papillozine C	Triterpenoidal alkaloid	*Buxus hyrcana*	Buxaceae	47.8	[43]
Buxmicrophylline F	Triterpenoidal alkaloid	*Buxus hyrcana*	Buxaceae	22.4	[44]
Haloxysterols A	Sterol	*Haloxylon recurvum*	Chenopodiaceae	8.3	[45]
Haloxysterols B	Sterol	*Haloxylon recurvum*	Chenopodiaceae	0.89	[45]
Haloxysterols C	Sterol	*Haloxylon recurvum*	Chenopodiaceae	1.0	[45]
Haloxysterols D	Sterol	*Haloxylon recurvum*	Chenopodiaceae	17.2	[45]
5a, 8a-epidioxy-(24S)-ethylcholesta-6,9 (11), 22 (E)-triene-3b-ol	Sterol	*Haloxylon recurvum*	Chenopodiaceae	26.4	[45]
(24S)-ethylcholesta-7,9 (11), 22 (E)-triene-3b-ol	Sterol	*Haloxylon recurvum*	Chenopodiaceae	19.2	[45]
Lawsaritol	Sterol	*Haloxylon recurvum*	Chenopodiaceae	15.2	[45]
24-ethyl-cholest-7-ene-3,5,6-triol	Sterol	*Haloxylon recurvum*	Chenopodiaceae	13.7	[45]
24-ethylcholest-6-ene-3,5-diol	Sterol	*Haloxylon recurvum*	Chenopodiaceae	3.5	[45]
Isothymonin 40-methyl ether	Flavone	*Micromeria cilicica*	Lamiaceae	>200	[46]
Tiliroside	Flavonoid	*Agrimonia pilosa*	Rosaceae	23.5	[47]
3-Methoxy quercetin	Flavonoid	*Agrimonia pilosa*	Rosaceae	37.9	[47]
Quercitrin	Flavonoid	*Agrimonia pilosa*	Rosaceae	66.9	[47]
Quercetin	Flavonoid	*Agrimonia pilosa*	Rosaceae	19.8	[47]
Rutin	Flavonol	*Micromeria cilicica*	Lamiaceae	>200	[46]
Isomucronulatol	Isoflavone	*Micromeria cilicica*	Lamiaceae	118	[46]
Osajin	Isoflavonoid	*Maclura pomifera*	Moraceae	2.239*	[48]
Pomiferin	Isoflavonoid	*Maclura pomifera*	Moraceae	0.096*	[48]
Sudachitin	Polymethoxy flavone	*Micromeria cilicica*	Lamiaceae	140	[46]
Ferulic acid	Phenolic acid	*Impatiens bicolor*	Balsaminaceae		[49]
α-pinene	Monoterpene	*Salvia potentillifolia*	Lamiaceae	81.7	[50]
β-pinene	Monoterpene	*Salvia potentillifolia*	Lamiaceae	>200	[50]
1,8-cineol	Monoterpene	*Salvia lavandulaefolia*	Lamiaceae	0.67	[10]
α-pinen	Monoterpene	*Salvia lavandulaefolia*	Lamiaceae	0.63	[10]
Ursolic acid	Pentacyclic triterpene acid	*Micromeria cilicica*	Lamiaceae	93.8	[46]
Ursolic acid	Pentacyclic triterpene acid	*Origanum majorana*	Lamiaceae	7.5**	[51]
(+)-limonene	Terpene	*Pimpinella anisoides*	Apiaceae	225.9	[52]
trans-anethole	Terpene	*Pimpinella anisoides*	Apiaceae	134.7	[52]
(+)-sabinene	Terpene	*Pimpinella anisoides*	Apiaceae	176.5	[52]
Arbora-1,9 (11)-dien-3-one	Triterpene	*Buxus hyrcana*	Buxaceae	47.9	[53]
α-onocerin	Triterpenoid	*Lycopodium clavatum*		5.2	[54]
Swertianolin	Bellidifolin 8-O-β-glucopyranoside	*Gentiana cambpestris*	Coniferae	-	[55]
Norswertianolin	Bellidin 8-O-β-glucopyranoside	*Gentiana cambpestris*	Coniferae	-	[55]
piperitone 7-O-b-D-glucoside	Glycoside	*Micromeria cilicica*	Lamiaceae	>200	[46]
1,2,3,4,6-penta-O-galloyl-β-D-glucose	Glycoside	*Terminalia chebula*	Combretaceae	29.9	[56]

Contd...

Table 1: Contd...

Phytoconstituent	Class of compound	Isolated from	Family	IC_{50} (μM)	Reference
Cynatroside A	Pregnane glycoside	*Cynanchum atratum*	Asclepiadaceae	6.4	[57]
Cynatroside B	Pregnane glycoside	*Cynanchum atratum*	Asclepiadaceae	3.6	[57]
(+)-α-viniferin	Stilbene oligomer	*Caragana chamlague*	Fabaceae	2.0	[58]
kobophenol A	Stilbene oligomer	*Caragana chamlague*	Fabaceae	115.8*	[58]
Bellidin	Xanthone	*Gentiana cambpestris*	Coniferae	-	[51]
Bellidifolin	Xanthone	*Gentiana cambpestris*	Coniferae	-	[51]
Bracteosin A	Withanolide	*Ajuga bracteosa*	Labiatae	25.2	[59]
Bracteosin B	Withanolide	*Ajuga bracteosa*	Labiatae	35.2	[59]
Bracteosin C	Withanolide	*Ajuga bracteosa*	Labiatae	49.2	[59]

*mM, **nM

Table 2: Butyrylcholinesterase inhibitors from medicinal plants

Phytoconstituent	Class of compound	Isolated from	Family	IC_{50} (μM)	Reference
Conypododiol	Alkaloid	*Asparagus adscendens*	Asparagaceae	11.21	[15]
Bulbocapnine	Alkaloid	*Corydalis cava*	Fumariaceae	83	[16]
Corydine	Alkaloid	*Corydalis cava*	Fumariaceae	>100	[16]
Cyclobuxoviridine	Alkaloid	*Buxus hyrcana*	Buxaceae	304.5	[17,18]
Moenjodaramine	Alkaloid	*Buxus hyrcana*	Buxaceae	102.4	[17,19]
Buxamine A	Alkaloid	*Buxus hyrcana*	Buxaceae	100.2	[17,20]
Buxamine B	Alkaloid	*Buxus hyrcana*	Buxaceae	100.5	[17,21]
Spirofornabuxine	Alkaloid	*Buxus hyrcana*	Buxaceae	125.2	[22]
Corydaline	Isoquinoline alkaloid	*Corydalis cava*	Fumariaceae	52	[16]
Annotinine	Lycopodane-type alkaloid	*Lycopodium annotinum*	Lycopodiaceae	>2,000	[29]
Annotine	Lycopodane-type alkaloid	*Lycopodium annotinum*	Lycopodiaceae	>2,000	[29]
Annotine N-oxide	Lycopodane-type alkaloid	*Lycopodium annotinum*	Lycopodiaceae	>2,000	[29]
Lycodoline	Lycopodane-type alkaloid	*Lycopodium annotinum*	Lycopodiaceae	667	[29]
Lycoposerramine M	Lycopodane-type alkaloid	*Lycopodium annotinum*	Lycopodiaceae	>2,000	[29]
Anhydrolycodoline	Lycopodane-type alkaloid	*Lycopodium annotinum*	Lycopodiaceae	>2,000	[29]
Gnidioidine	Lycopodane-type alkaloid	*Lycopodium annotinum*	Lycopodiaceae	>2,000	[29]
Lycofoline	Lycopodane-type alkaloid	*Lycopodium annotinum*	Lycopodiaceae	>2,000	[29]
Acrifoline	Lycopodane-type alkaloid	*Lycopodium annotinum*	Lycopodiaceae	>2,000	[29]
E-buxenone	Steroidal alkaloid	*Buxus hyrcana*	Buxaceae	200.7	[17]
Z-buxenone	Steroidal alkaloid	*Buxus hyrcana*	Buxaceae	155.8	[17]
31-hydroxybuxamine B	Steroidal alkaloid	*Buxus hyrcana*	Buxaceae	112.1	[17,37]
N20-formylbuxaminol E	Steroidal alkaloid	*Buxus hyrcana*	Buxaceae	120.9	[17,38]
Buxrugulosamine	Steroidal alkaloid	*Buxus hyrcana*	Buxaceae	160.2	[39]
Cyclobuxophylline O	Steroidal alkaloid	*Buxus hyrcana*	Buxaceae	45.0	[39]
Isosarcodine	Steroidal alkaloid	*Sarcococca saligna*	Buxaceae	1.893	[40]
Sarcorine	Steroidal alkaloid	*Sarcococca saligna*	Buxaceae	10.33	[40]
Sarcodine	Steroidal alkaloid	*Sarcococca saligna*	Buxaceae	18.31	[40]
Sarcocine	Steroidal alkaloid	*Sarcococca saligna*	Buxaceae	3.86	[40]
Alkaloid-C	Steroidal alkaloid	*Sarcococca saligna*	Buxaceae	22.13	[40]
N-b-dimethylcyclobuxoviricine	Triterpenoid alkaloid	*Buxus hyrcana*	Buxaceae	133.8	[17,41]
Buxakashmiramine	Triterpenoid alkaloid	*Buxus papillosa*	Buxaceae	0.74	[42]
Buxakarachiamine	Triterpenoid alkaloid	*Buxus papillosa*	Buxaceae	ND	[42]
Buxahejramine	Triterpenoid alkaloid	*Buxus papillosa*	Buxaceae	ND	[42]
Cycloprotobuxine-C	Triterpenoid alkaloid	*Buxus papillosa*	Buxaceae	2.73	[42]
Cyclovirobuxeine-A	Triterpenoid alkaloid	*Buxus papillosa*	Buxaceae	2.05	[42]
Cyclomicrophylline-A	Triterpenoid alkaloid	*Buxus papillosa*	Buxaceae	2.43	[42]
17-oxo-3-benzoylbuxadine	Triterpenoidal alkaloid	*Buxus hyrcana*	Buxaceae	186.8	[17]
buxhyrcamine	Triterpenoidal alkaloid	*Buxus hyrcana*	Buxaceae	209	[17]
31-demethylcyclobuxoviridine	Triterpenoidal alkaloid	*Buxus hyrcana*	Buxaceae	15.4	[17]
Homomoenjodarmine	Triterpenoidal alkaloid	*Buxus hyrcana*	Buxaceae	52.2	[17,43]
Papillozine C	Triterpenoidal alkaloid	*Buxus hyrcana*	Buxaceae	35.2	[43]
Buxmicrophylline F	Triterpenoidal alkaloid	*Buxus hyrcana*	Buxaceae	154.2	[44]
Haloxysterols A	Sterol	*Haloxylon recurvum*	Chenopodiaceae	4.7	[45]
Haloxysterols B	Sterol	*Haloxylon recurvum*	Chenopodiaceae	2.3	[45]
Haloxysterols C	Sterol	*Haloxylon recurvum*	Chenopodiaceae	17.8	[45]
Haloxysterols D	Sterol	*Haloxylon recurvum*	Chenopodiaceae	2.5	[45]
5a, 8a-epidioxy-(24S)-ethylcholesta-6,9 (11), 22 (E)-triene-3b-ol	Sterol	*Haloxylon recurvum*	Chenopodiaceae	6.9	[45]

Contd...

Table 2: Contd...

Phytoconstituent	Class of compound	Isolated from	Family	IC_{50} (μM)	Reference
(24S)-ethylcholesta-7,9 (11), 22 (E)-triene-3b-ol	Sterol	*Haloxylon recurvum*	Chenopodiaceae	4.5	[45]
lawsaritol	Sterol	*Haloxylon recurvum*	Chenopodiaceae	3.9	[45]
24-ethyl-cholest-7-ene-3,5,6-triol	Sterol	*Haloxylon recurvum*	Chenopodiaceae	2.0	[45]
24-ethylcholest-6-ene-3,5-diol	Sterol	*Haloxylon recurvum*	Chenopodiaceae	3.5	[45]
α-pinene	Monoterpene	*Salvia potentillifolia*	Lamiaceae	>200	[50]
β-pinene	Monoterpene	*Salvia potentillifolia*	Lamiaceae	>200	[50]
Ursolic acid	Pentacyclic triterpene acid	*Micromeria cilicica*	Lamiaceae	41.1	[46]
(+)-limonene	Terpene	*Pimpinella anisoides*	Apiaceae	456.2	[52]
trans-anethole	Terpene	*Pimpinella anisoides*	Apiaceae	209.6	[52]
(+)-sabinene	Terpene	*Pimpinella anisoides*	Apiaceae	218.6	[52]
Arbora-1,9 (11)-dien-3-one	Triterpene	*Buxus hyrcana*	Buxaceae	220.1	[53]
Isothymonin 40-methyl ether	Flavone	*Micromeria cilicica*	Lamiaceae	>200	[46]
Rutin	Flavonol	*Micromeria cilicica*	Lamiaceae	>200	[46]
Isomucronulatol	Isoflavone	*Micromeria cilicica*	Lamiaceae	56.2	[46]
Sudachitin	Polymethoxy flavone	*Micromeria cilicica*	Lamiaceae	60.1	[46]
Bracteosin A	Withanolide	*Ajuga bracteosa*	Labiatae	38.9	[59]
Bracteosin B	Withanolide	*Ajuga bracteosa*	Labiatae	29.4	[59]
Bracteosin C	Withanolide	*Ajuga bracteosa*	Labiatae	39.1	[59]
Piperitone 7-O-b-D-glucoside	Glycoside	*Micromeria cilicica*	Lamiaceae	>200	[46]
1,2,3,4,6-penta-O-galloyl-β-D-glucose	Glycoside	*Terminalia chebula*	Combretaceae	27.6	[56]

ANTICHOLINESTERASE PHYTOCHEMICAL CLASSES

In this review, 119 compounds having anti-AChE activity [Table 1] and 67 compounds having anti-BChE activity are presented [Table 2]. The structures of some important anticholinesterase compounds are presented in Figures 1a-c. Majority of these phytochemicals with potential AChE and BChE inhibitory activity are alkaloids followed by terpenes, sterols, flavanoids, and glycosides. Triterpenoid alkaloids, steroidal alkaloids, indole alkaloids, isoquinoline alkaloid, and lycopodane-type alkaloid are the major types of alkaloids having significant anticholinesterase activity making them promising candidates to be used as cholinesterase inhibitors in clinical practice. Most of the compounds having potential anticholinesterase activity are isolated from *Buxaceae, Amaryllidaceae, Lycopodiaceae, Lamiaceae, Chenopodiaceae, Papaveraceae, Apocynaceae,* and *Labiatae* species.[13,17,18,25,27,29,45,59] Following are three of the imporant families having potential compounds to be used as anticholonesterase inhibitors.

Buxaceae

Buxaceae is a small family of 4-5 genera consisted of about 90-120 species of flowering plants which are usually shrubs or small trees with a cosmopolitan distribution.[60] The plants of this family find extensive uses in the folkloric medicine particularly for memory-related disorders. Furthermore, studies have evidenced that terpenoidal alkaloids are the major chemical constituents responsible for the biological activities of the plants of this family.[61]

Amaryllidaceae

The plants of Amaryllidaceae family are well-known for their ornamental value and medicinal properties. The family has attracted considerable attention due to the content of alkaloids of its species, which showed interesting biological properties.[62] The chemical structures of these alkaloids are very variable as well as their pharmacological properties. Some species of this family contain galanthamine, an acetylcholinesterase inhibitor approved for the treatment of AD, as well as other alkaloids with interesting pharmacological activities: Antimalarial, antiviral, and antiproliferative.[63-66] Galanthamine is an important reversible, long-lasting, selective, and competitive inhibitor of AChE isolated from Amaryllidaceae plant species such as *Amaryllis, Galanthus, Leucojum, Pancratium, and Zephyranthes*.[67] It is a good example of a natural product substituting synthetic drugs in the treatment of AD.

Lycopodiaceae

Lycopodiaceae family is comprised of four genera: *Huperzia Bernh., Phylloglossum Kunze, Lycopodium L.*, and *Lycopodiella Holub* and has a wide distribution throughout the world.[68] *Lycopodium* species are used widely in Argentinian traditional medicine for memory improvement and Huperzine A is an alkaloid having potent, specific, and reversible acetylcholinesterase inhibiton isolated from *Huperzia serrata*.[69] Extensive studies on Huperzine A as a lead compound for the development of more effective anti-AChE drugs for the treatment of AD relative to those approved by the Food and Drug Association (FDA), such as donepezil, (–)-galanthamine, and rivastigmine, have been attributed to its better penetration through the blood brain barrier, its higher oral bioavailability and its longer duration of AChE inhibitory action.[70-76]

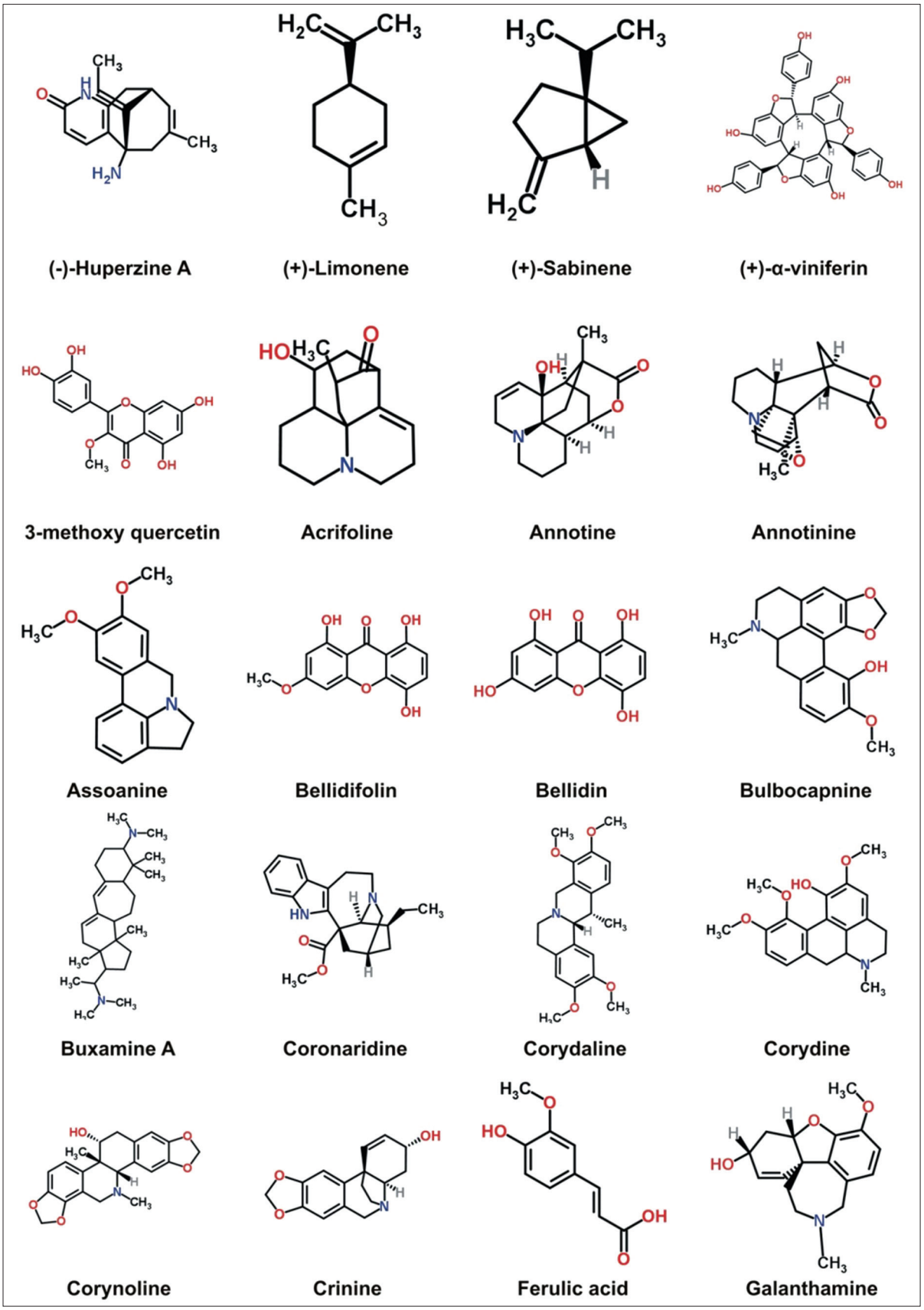

Figure 1a: Structures of some important anticholinesterase compounds

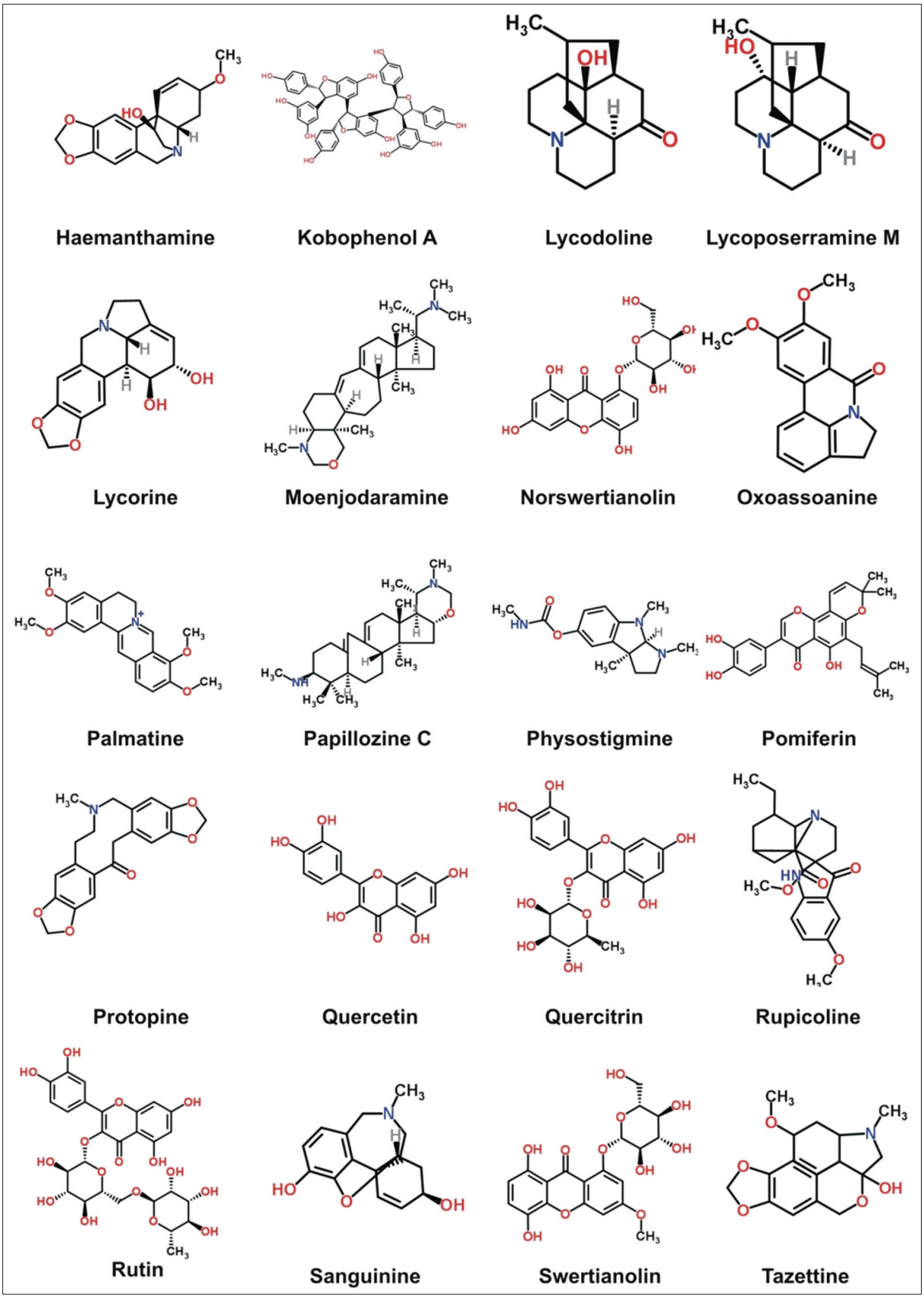

Figure 1b: Structures of some important anticholinesterase compounds

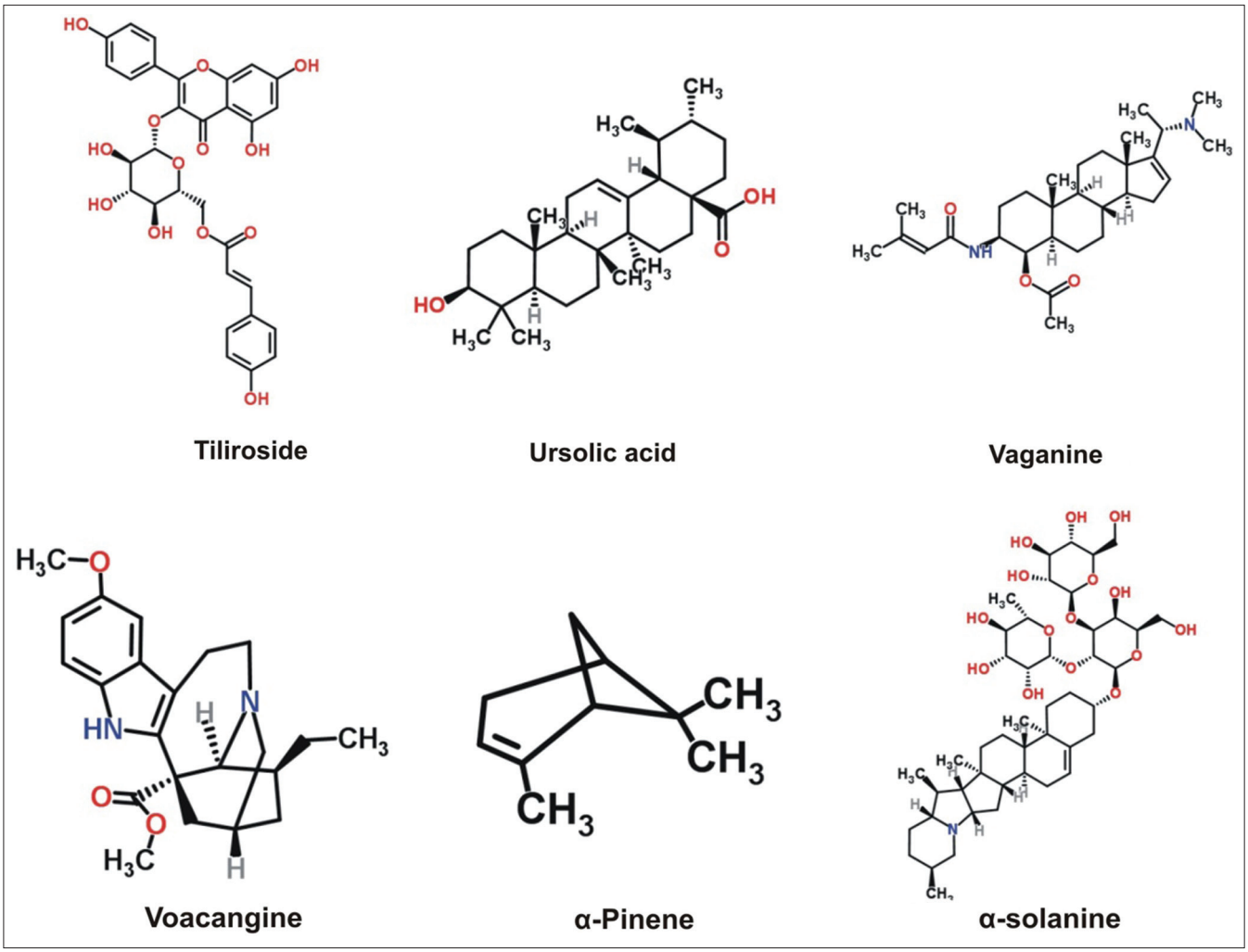

Figure 1c: Structures of some important anticholinesterase compounds

CONCLUSIONS

AD has great impact on the personal and social life of human beings and no doubt, cholinesterase inhibitors offer great help in the effective management and treatment of AD. It is clearly evidenced that alkaloids are the major phytoconstituents responsible for the anticholiesterase activity of plant extracts and this information could be exploited for the synthesis of novel anticholinesterase drugs using alkaloids as intermediate compounds. Although, large number of natural plants extracts has been found to effective inhibitors of AChE and BChE, very few plants have been studied in-depth. Thus, detailed studies involving β-amyloid and receptor binding studies are warranted for optimum therapeutic utilization of these phytoconstituents. Further, limited data is available on the safety aspects of both the plant extracts and the isolated phytoconstituents. Since, very few animal studies and clinical trials are available; scope exists to undertake extensive research in these areas. It was also noted that, the alkaloids are the major compounds responsible for the anticholinesterase activity of plant extracts and these alkaloids can be used as starting materials for new classes of synthetic drugs for the treatment of AD.

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