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.⁵,⁶,⁷

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.
| Phytoconstituent                        | Class of compound | Isolated from          | Family                | IC<sub>50</sub> (µM) | Reference |
|----------------------------------------|-------------------|------------------------|-----------------------|-----------------------|-----------|
| Lycorine                               | Alkaloid          | Galanthus ikariae      | Amaryllidaceae        | 3.16                  | [13]      |
| Galanthamine                           | Alkaloid          | Galanthus ikariae      | Amaryllidaceae        | 3.2                   | [13]      |
| Tazettine                              | Alkaloid          | Galanthus ikariae      | Amaryllidaceae        | 3.2                   | [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        | 3.2                   | [13]      |
| Haemanthamine                          | Alkaloid          | Narcissus tazetta      | Amaryllidaceae        | 3.2                   | [13]      |
| 3-epi-hydroxybulbispermine             | Alkaloid          | Narcissus tazetta      | Amaryllidaceae        | 3.2                   | [13]      |
| Protopine                              | Alkaloid          | Corydalis ternata      | Papaveraceae          | 50                    | [14]      |
| Conympodiol                            | Alkaloid          | Asparagus adscendens   | Asparagaceae          | 2.17                  | [15]      |
| Bulbocapnine                           | Alkaloid          | Corydalis cava         | Fumariaceae           | 40                    | [16]      |
| Corydine                               | Alkaloid          | Corydalis cava         | Fumariaceae           | >100                  | [16]      |
| Cyclobuxoxviridine                     | 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-solane                              | Glyco alkaloid    | Solanum tuberosum      | Solanaceae            | -                     | [23,24]   |
| Coronarinidine                         | Indole alkaloid   | Tabernaemontana australis | Apocynaceae       | -                     | [25]      |
| Physostigmine                          | Indole alkaloid   | Physostigma venenosum  | Leguminosace          | 6x10⁻⁴                | [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]      |
| Corydalone                             | 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         | 191                   | [29]      |
| Anthrolycodoline                       | Lycopodane-type alkaloid | Lycopodium annotinum | Lycopodiaceae         | 1720                  | [29]      |
| Gnidioidine                            | Lycopodane-type alkaloid | Lycopodium annotinum | Lycopodiaceae         | 600                   | [29]      |
| Acrifoline                             | Lycopodane-type alkaloid | Lycopodium annotinum | Lycopodiaceae         | 1625                  | [29]      |
| Dehydroevodiamine                      | Quinazoline alkaloid | Evodia rutacearpa      | Rutaceae              | 37.8                  | [30]      |
| (−)-huperzine A                        | Quinolizidine alkaloid | Huperzia serrata     | Lycopodiaceae         | 10-4                  | [9,31,32] |
|                                      |                   | Huperzia dalhousieana |          |          |          |
| Assoanine                              | Steroidal alkaloid | Narcissus assoanus     | Amaryllidaceae        | 3.87                  | [7]       |
| Buxamine B                             | Steroidal alkaloid | Buxus hyrcana          | Buxaceae              | 7.56                  | [33]      |
| Buxamine                               | Steroidal alkaloid | Buxus papillosa        | Buxaceae              | 7.28                  | [33]      |
| N, N-dimethyl buxapapine               | Steroidal alkaloid | Buxus papillosa        | Buxaceae              | 7.28                  | [33]      |
| Epinorgalantamine                      | Steroidal alkaloid | Narcissus confuses     | Amaryllidaceae        | 9.60                  | [7]       |
| Galanthamine                           | Steroidal alkaloid | Galanthus nivalis      | Lycopodiaceae         | 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]       |
| Sarsaligone                            | 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]      |
| Phytoconstituent                      | Class of compound     | Isolated from       | Family     | IC₅₀ (µM) | Reference |
|--------------------------------------|-----------------------|---------------------|------------|----------|-----------|
| Cyclobuxophylline O                  | Steroidal alkaloid    | Buxus hyrcana       | Buxaceae   | 35.4     | [39]      |
| Isosarcodine                         | Steroidal alkaloid    | Sarcococa saligna   | Buxaceae   | 10.31    | [40]      |
| Sarcorine                            | Steroidal alkaloid    | Sarcococa saligna   | Buxaceae   | 69.99    | [40]      |
| Sarcodine                            | Steroidal alkaloid    | Sarcococa saligna   | Buxaceae   | 49.77    | [40]      |
| Sarcocine                            | Steroidal alkaloid    | Sarcococa saligna   | Buxaceae   | 20.0     | [40]      |
| Alkaloid-C                           | Steroidal alkaloid    | Sarcococa 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]      |
| Buxakarachimine                      | Triterpenoid alkaloid | Buxus papillosa     | Buxaceae   | 143      | [42]      |
| Buxaheramaine                        | Triterpenoid alkaloid | Buxus papillosa     | Buxaceae   | 162      | [42]      |
| Cyclopropobuxine-C                   | Triterpenoid alkaloid | Buxus papillosa     | Buxaceae   | 38.8     | [42]      |
| Cyclovirrobuxine-A                   | Triterpenoid alkaloid | Buxus papillosa     | Buxaceae   | 105.7    | [42]      |
| Cyclicomophylline-A                  | Triterpenoid alkaloid | Buxus papillosa     | Buxaceae   | 235      | [42]      |
| (+)-homoenjodaramine                 | Triterpenoid alkaloid | Buxus hyrcana       | Buxaceae   | 19.2     | [43]      |
| (+)-moenjodaramine                   | Triterpenoid alkaloid | Buxus hyrcana       | Buxaceae   | 50.8     | [43]      |
| 17-oxo-3-benzoylbutadine             | Triterpenoid alkaloid | Buxus hyrcana       | Buxaceae   | 17.6     | [17]      |
| buxhyrcamine                         | Triterpenoid alkaloid | Buxus hyrcana       | Buxaceae   | 18.2     | [17]      |
| 31-demethylcyclobuxoviridine         | Triterpenoid alkaloid | Buxus hyrcana       | Buxaceae   | 298.3    | [17]      |
| Homomoenjodarine                     | Triterpenoid alkaloid | Buxus hyrcana       | Buxaceae   | 19.5     | [17,43]   |
| Papillozine C                        | Triterpenoid alkaloid | Buxus hyrcana       | Buxaceae   | 47.8     | [43]      |
| Buxmicrophylline F                   | Triterpenoid 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] |
| Lawssaritol                          | Sterol                | Haloxylon recurvum  | Chenopodiaceae | 15.2    | [45]      |
| 24-ethyl-cholesterol-7-en-3,5,6-triol| Sterol                | Haloxylon recurvum  | Chenopodiaceae | 13.7    | [45]      |
| 24-ethylcholesterol                  | Sterol                | Haloxylon recurvum  | Chenopodiaceae | 3.5     | [45]      |
| 6-en-3,5-diol                        | Sterol                | Haloxylon recurvum  | Chenopodiaceae | 200     | [46]      |
| 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                                | Flavone               | Micromeria cilicica  | Lamiaceae | >200     | [46]      |
| Isomucronulatol                      | Isolavone             | Micromeria cilicica  | Lamiaceae | 118      | [46]      |
| Osajin                               | Isolavonoid           | Maclura pomifera    | Moraceae   | 2.239**  | [48]      |
| Pomiferin                            | Isolavonoid           | Maclura pomifera    | Moraceae   | 0.096**  | [48]      |
| Sudachitin                           | Polymethoxy flavone   | Micromeria cilicica  | Lamiaceae | 140      | [46]      |
| Ferulic acid                         | Phenolic acid         | Impatiens bicolor   | Balsaminaceae | 81.7    | [49]      |
| α-pinene                             | Monoterpenes          | Salvia potentillifolia | Lamiaceae | >200     | [50]      |
| β-pinene                             | Monoterpenes          | Salvia potentillifolia | Lamiaceae | >200     | [50]      |
| 1,8-cineole                          | Monoterpenes          | Salvia lavandulaefolia | Lamiaceae | 0.67     | [10]      |
| α-pinen                              | Monoterpenes          | Salvia lavandulaefolia | Lamiaceae | 0.63     | [10]      |
| Ursolic acid                         | Pentacyclic triterpene| Micromeria cilicica  | Lamiaceae | 93.8     | [46]      |
| Ursolic acid                         | Pentacyclic triterpene| Origanum majorana   | Lamiaceae | 7.5**    | [51]      |
| (+)-limonene                         | Terpene               | Pinimpinella anisoides | Apiaceae | 225.9    | [52]      |
| trans-anethole                        | Terpene               | Pinimpinella anisoides | Apiaceae | 134.7    | [52]      |
| (+)-sabinene                         | Terpene               | Pinimpinella anisoides | Apiaceae | 176.5    | [52]      |
| Arbor-1,9 (11)-dien-3-one             | Terpene               | Buxus hyrcana       | Buxaceae   | 47.9     | [53]      |
| α-onocerin                           | Terprenedioid         | Lycopodium clavatum | 5.2    | [54]      |
| Swertianolin                          | Bellidifolin          | Gentiana cambpestris | Coniferae | -        | [55]      |
| Norswertianolin                      | Bellidin              | Gentiana cambpestris | Coniferae | -        | [55]      |
| pipertone 7-O-b-D-glucoside          | Glycoside             | Micromeria cilicica  | Lamiaceae | >200     | [46]      |
| 1,2,3,4,8-penta-O-galloyl-β-D-glucone | Glycoside             | Terminalia chebula   | Combretaceae | 29.9    | [56]      |
### Table 1: Butyrylcholinesterase inhibitors from medicinal plants

| Phytoconstituent                   | Class of compound | Isolated from          | Family              | IC₅₀ (µM) | Reference |
|-----------------------------------|-------------------|------------------------|---------------------|----------|-----------|
| Cynatroside A                     | Pregnane glycoside| *Cynanchum atratum*    | Asclepiadaceae      | 6.4      | [57]      |
| Cynatroside B                     | Pregnane glycoside| *Cynanchum atratum*    | Asclepiadaceae      | 3.6      | [57]      |
| (+)-α-viniferin                    | Sterilene oligomer| *Caragana chamlaque*   | Fabaceae            | 2.0      | [58]      |
| kobopholin A                      | Sterilene oligomer| *Caragana chamlaque*   | Fabaceae            | 115.8*   | [58]      |
| Bellidin                           | Xanthone          | Gentiana campestris    | Coniferae           | -        | [51]      |
| Bellidifolin                       | Xanthone          | Gentiana campestris    | 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]      |

*IC₅₀ reflects the concentration at which 50% inhibition of the enzyme is observed.*

### Table 2: Butyrylcholinesterase inhibitors from medicinal plants

| Phytoconstituent                   | Class of compound | Isolated from          | Family              | IC₅₀ (µM) | Reference |
|-----------------------------------|-------------------|------------------------|---------------------|----------|-----------|
| Corypodiol                        | Alkaloid          | *Asparagus adscendens*  | Asparagaceae        | 11.21    | [15]      |
| Bulboapline                       | Alkaloid          | *Corydalis cava*       | Fumariaceae         | >100     | [16]      |
| Corydine                          | Alkaloid          | *Corydalis cava*       | Fumariaceae         | >100     | [16]      |
| Cyclobuxoviridine                 | Alkaloid          | *Buxus hycran*         | Buxaceae            | 304.5    | [17,18]  |
| Moenjodaramine                    | Alkaloid          | *Buxus hycran*         | Buxaceae            | 102.4    | [17,19]  |
| Buxamine A                        | Alkaloid          | *Buxus hycran*         | Buxaceae            | 100.2    | [17,20]  |
| Buxamine B                        | Alkaloid          | *Buxus hycran*         | Buxaceae            | 100.5    | [17,21]  |
| Spirofornabuxine                  | Alkaloid          | *Buxus hycran*         | Buxaceae            | 125.2    | [22]      |
| Corydine                          | Isoquinoline alkaloid | *Corydalis cava*           | Fumariaceae         | 52.0     | [16]      |
| 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       | 667.0    | [29]      |
| Lycopersidramine M                | Lycopodane-type alkaloid | *Lycopodium annotinum* | Lycopodiaceae       | >2,000   | [29]      |
| Anthydrinol                       | Lycopodane-type alkaloid | *Lycopodium annotinum* | Lycopodiaceae       | >2,000   | [29]      |
| Gnidioline                        | 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 hycran*         | Buxaceae            | 200.7    | [17]      |
| Z-buxenone                        | Steroidal alkaloid | *Buxus hycran*         | Buxaceae            | 155.8    | [17]      |
| 31-hydroxybuxamine B              | Steroidal alkaloid | *Buxus hycran*         | Buxaceae            | 112.1    | [17,37]  |
| N20-formylbuxaminol E             | Steroidal alkaloid | *Buxus hycran*         | Buxaceae            | 120.9    | [17,38]  |
| Buxrugulosamine                   | Steroidal alkaloid | *Buxus hycran*         | Buxaceae            | 160.2    | [39]      |
| Cyclobuxophylline O               | Steroidal alkaloid | *Buxus hycran*         | Buxaceae            | 45.0     | [39]      |
| Isosarcodine                      | Steroidal alkaloid | *Sarcococca saligna*   | Buxaceae            | 1.893    | [40]      |
| Sarcorine                         | Steroidal alkaloid | *Sarcococca saligna*   | Buxaceae            | 10.33    | [40]      |
| Sarcodeine                        | Steroidal alkaloid | *Sarcococca saligna*   | Buxaceae            | 18.31    | [40]      |
| Sarcothen                         | Steroidal alkaloid | *Sarcococca saligna*   | Buxaceae            | 3.86     | [40]      |
| Alkaloid-C                        | Steroidal alkaloid | *Sarcococca saligna*   | Buxaceae            | 22.13    | [40]      |
| N-b-dimethylcyclobuxoviricine     | Triterpenoid alkaloid | *Buxus hycran*         | Buxaceae            | 133.8    | [17,41]  |
| Buxakashmiramine                  | Triterpenoid alkaloid | *Buxus papillosa*      | Buxaceae            | 0.74     | [42]      |
| Buxakarachamine                   | Triterpenoid alkaloid | *Buxus papillosa*      | Buxaceae            | ND       | [42]      |
| Buxahejamine                      | Triterpenoid alkaloid | *Buxus papillosa*      | Buxaceae            | ND       | [42]      |
| Cycloprobutoxine-C                | Triterpenoid alkaloid | *Buxus papillosa*      | Buxaceae            | 2.73     | [42]      |
| Cyclovibuxamine-A                 | Triterpenoid alkaloid | *Buxus papillosa*      | Buxaceae            | 2.05     | [42]      |
| Cycloicynophylline-A              | Triterpenoid alkaloid | *Buxus papillosa*      | Buxaceae            | 2.43     | [42]      |
| 17-oxo-3-benzoylbuxadine           | Triterpenoid alkaloid | *Buxus hycran*         | Buxaceae            | 186.8    | [17]      |
| buxhyrycine                       | Triterpenoid alkaloid | *Buxus hycran*         | Buxaceae            | 209.0    | [17]      |
| 31-demethylcyclobuxoviridine      | Triterpenoid alkaloid | *Buxus hycran*         | Buxaceae            | 15.4     | [17,43]  |
| Homomoenjodarmine                 | Triterpenoid alkaloid | *Buxus hycran*         | Buxaceae            | 52.2     | [17,43]  |
| Papilozine C                      | Triterpenoid alkaloid | *Buxus hycran*         | Buxaceae            | 35.2     | [43]      |
| Buxmicophylline F                 | Triterpenoid alkaloid | *Buxus hycran*         | Buxaceae            | 154.2    | [44]      |
| Haloxysters A                     | Sterol            | *Haloxylon recurvum*   | Chenopodiaceae      | 4.7      | [45]      |
| Haloxysters B                     | Sterol            | *Haloxylon recurvum*   | Chenopodiaceae      | 2.3      | [45]      |
| Haloxysters C                     | Sterol            | *Haloxylon recurvum*   | Chenopodiaceae      | 17.8     | [45]      |
| Haloxysters D                     | Sterol            | *Haloxylon recurvum*   | Chenopodiaceae      | 2.5      | [45]      |
| 5a,8-epidioxy-(24S)-ethylcholesta- | Sterol            | *Haloxylon recurvum*   | Chenopodiaceae      | 6.9      | [45]      |
| 6,9 (11), 22 (E)-triene-3b-ol     | Sterol            | *Haloxylon recurvum*   | Chenopodiaceae      |          |          |

*Contd...*
ANTICHLINOSTERASE 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, steroids, flavonoids, and glycosides. Triterpenoid alkaloids, steroid-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. [13,17,18,23,27,29] Following are three of the important families having potential compounds to be used as anticholinesterase 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. [62] 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. [63]

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. [64] 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. [65,66] Galanthamine is an important reversible, long-lasting, selective, and competitive inhibitor of AChE isolated from Amaryllidaceae plant species such as Amaryllis, Galanthus, Lecocoum, 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., Phyllocladus 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 inhibitor 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
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 anticholinesterase 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-amylloid 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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