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Naturally Occurring Acetylcholinesterase Inhibitors and Their Potential Use for Alzheimer's Disease Therapy

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Alzheimer's disease (AD) is a main cause of dementia, accounting for up to 75% of all dementia cases. Pathophysiological processes described for AD progression involve neurons and synapses degeneration, mainly characterized by cholinergic impairment. This feature makes acetylcholinesterase inhibitors (AChEi) the main class of drugs currently used for the treatment of AD dementia phase, among which galantamine is the only naturally occurring substance. However, several plant species producing diverse classes of alkaloids, coumarins, terpenes, and polyphenols have been assessed for their anti-AChE activity, becoming potential candidates for new anti-AD drugs. Therefore, this mini-review aimed to recapitulate last decade studies on the anti-AChE activity of plant species, their respective extracts, as well as isolated compounds. The anti-AChE activity of extracts prepared from 54 plant species pertaining 29 families, as well as 36 isolated compounds were classified and discussed according to their anti-AChE pharmacological potency to highlight the most prominent ones. Besides, relevant limitations, such as proper antioxidant assessment, and scarcity of toxicological and clinical studies were also discussed in order to help researchers out with the bioprospection of potentially new AChEi.

Keywords: Alzheimer's disease, acetylcholinesterase inhibitors, anti-cholinesterase, plant species, secondary metabolites

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INTRODUCTION

Alzheimer's disease (AD) is a main cause of dementia, accounting for up to 75% of all dementia cases and has become a population aging-related concern for policymakers and public health systems around the world by its both direct and indirect costs (Takizawa et al., 2015; Fiest et al., 2016; Scheltens et al., 2016). Nowadays, AD prevalence among people over 60 years old is estimated in 40.2 per 1000, while its incidence proportion is 34.1 per 1,000 (Prince, 2015; Fiest et al., 2016). Those values mean that over 45 million people is suffering from AD symptoms worldwide, whereas this scenario is expected to double every 20 years until at least 2050 (Scheltens et al., 2016). AD is mainly characterized by progressive neurodegenerative disorder, clinically demonstrated by cognitive and memory decline, progressive impairment of daily activities, and a variety of neuropsychiatric symptoms and behavioral disturbances (Tarawneh and Holtzman, 2012).

Pathophysiological processes described for AD progression involve neurons and synapses degeneration resulting from beta-amyloid (Aβ) protein aggregation and neurofibrillary tangles, as well as, neuroinflammation, mitochondrial damage, oxidative stress and excitotoxicity, which interfere with several neurotransmitters signaling pathways (Madeo and Elsayad, 2013; Godyn et al., 2016; Henstridge et al., 2016). Among the latter, cholinergic dysfunction is the most studied and has been closely associated with the early cognitive decline found in AD patients (Craig et al., 2011). In fact, early in the 70's, it was observed that cholinergic neurons were prematurely lost in AD process, arising the Alzheimer's Cholinergic Hypothesis (Bartus et al., 1982). This hypothesis was further corroborated by observations that cholinergic neurons in basal forebrain are severely damaged during AD progression (Bartus, 2000).

Despite the huge research on AD, supportive care from family and other caregivers is still the mainstay treatment, though pharmacotherapy has importantly evolved during the last decade. Four drugs are currently used for the treatment of the dementia phase: the acetylcholinesterase (AChE) inhibitors (AChEi)–donepezil, rivastigmine, and galantamine–and the glutamate antagonist memantine. AChEi increase synaptic acetylcholine (ACh) levels and improve cholinergic function in the brain (Anand and Singh, 2013; Andrieu et al., 2015). Amongst those clinically relevant AChEi, galantamine is the only naturally occurring substance, consisting of an alkaloid extracted from Amaryllidaceae family (Heinrich, 2010; Murray et al., 2013). Galantamine reversibly and competitively inhibits AChE (Thomsen and Kewitz, 1990) and allosterically modulates nicotinic ACh receptors (Schrattenholz et al., 1996). Notwithstanding, besides its anti-AChE activity, most of natural AChEi molecules generally present additional pharmacological properties, particularly antioxidant, which enable them to be applied as multi-target strategies against AD onset and progression (Orhan et al., 2011; Ayaz et al., 2017; Sahoo et al., 2018).

Several studies have been carried out toward identification and isolation of natural molecules applicable for design and development of new anti-AD drugs, particularly those pertaining to the classes of alkaloids, terpenes, coumarins and polyphenols (Huang et al., 2013). Therefore, this mini-review recapitulates last decade studies on the anti-AchE activity of plant species, their respective extracts, as well as isolated compounds, in order to settle down the state-of-the-art in the field and to help researchers out with the bioprospection of potentially new AChEi candidates applicable for anti-AD drug design and pharmacotherapy.

METHODOLOGY

This mini-review revises published studies available in Pubmed between 2007 and 2018 (1st semester), which were retrieved by using the following descriptors combination: "anti-acetylcholinesterase and plant extract" and "acetylcholinesterase inhibitors and plant extract and Alzheimer." The only criterion for inclusion was that anti-AChE activity of the plant extract and/or isolated compounds had been assessed by Ellman's methodology (Ellman et al., 1961), which is considered a gold standard for AChEi screening (Holas et al., 2012). On the other hand, two criteria for exclusion were applied: the lack of reliable positive controls, which might include but are not limited to galantamine, huperzine A and B, or physostigmine (Mehta et al., 2012); and the absence of half maximal inhibitory concentration (IC_{50}) assessment, which allow us to compare the anti-AChE potencies among different plant extracts and/or isolated compounds (Colovic et al., 2013).

A total of 207 original studies were retrieved, from which 71 were considered appropriate. All the species Latin names were validated at The Plant List (2013); version 1.1.; http://www.theplantlist.org/ (accessed 15th August, 2018). When the Latin name provided by the study diverged from that accepted at The Plant List, the species was identified by the accepted one followed by the former, which was reported as synonym, between parenthesis. To improve the readability of the text, the identity of the plant taxonomist(s) for each species is informed only in **Table 1**, excepting those mentioned as the source of isolated compounds, but whose extracts were not assayed.

PLANT SPECIES WITH ANTI-ACETYLCHOLINESTERASE ACTIVITY

Amaryllidaceae is the leading family of genera holding anti-AChE activity, particularly *Galanthus* spp., which are the primordial source of galantamine (Heinrich, 2010). However, subsequently to galantamine's approval for the treatment of mild-to-moderate AD in 2001, a plethora of species have been assessed in a pursuit of new AChEi. In our survey timeframe, a total of 39 studies reporting the anti-AChE activity for 51 species, from 29 different families, were considered. The most prevalent families were Amaryllidaceae, Lycopodiaceae, and Polygonaceae, contributing with 5, 5, and 4 species, respectively. Noteworthy, *Huperzia* spp. keep drawing ethnopharmacology researchers' attention, despite the consistent basic and clinical evidence already available for Huperzine A on AD treatment (Ha et al., 2011; Sahoo et al., 2018).

Table 1 summarizes the contemplated species, which were classified in three categories, in accordance to the IC_{50} values determined for their respective extracts/fractions: high potency, $IC_{50} < 20\,\mu g/mL$; moderate potency, $20 < IC_{50} < 200\,\mu g/mL$; and low potency, $200 < IC_{50} < 1{,}000\,\mu g/mL$. Those cutoffs were set according to the average IC_{50} value described for galantamine in the literature ($\sim 2\,\mu M$ or $0.575\,\mu g/mL$) multiplied by a factor of 10 (Lopez et al., 2002; Ingkaninan et al., 2003; Berkov et al., 2008). Similar criteria have been previously applied by Murray et al. (2013), excepting that they included studies reporting only the maximal anti-AChE inhibitory activity and set the cutoff for low potency at $IC_{50} > 500\,\mu g/mL$.

Twenty-four plant species fell into high potency category, with IC_{50} values varying from $0.3\,\mu g/mL$ for ethyl acetate bulb extract of *Scadoxus puniceus* (Amaryllidaceae), ethyl acetate root extract of *Lannea schweinfurthii* (Anacardiaceae; Adewusi and Steenkamp, 2011), and ethyl acetate root fraction of

TABLE 1 | Plant extracts with *in vitro* anticholinesterase activity assessed by Ellman's Method reported in Pubmed from 2007 to 2018 (1st semester).

Plant species (Families)	Type of extract or fraction (plant's part)	IC_{50} (μg/mL)	Toxicological assessment[#]	References
Scadoxus puniceus (L.) Friis & Nordal (Amaryllidaceae)	Ethyl acetate extract (bulb)	0.3	Not assessed	Adewusi and Steenkamp, 2011
Lannea schweinfurthii Engl. (Anacardiaceae)	Ethyl acetate extract (root)	0.3	Not assessed	Adewusi and Steenkamp, 2011
Carpolobia lutea G. Don (Polygalaceae)	Ethyl acetate fraction (root)	0.3	≤100 μg/mL	Nwidu et al., 2017
Xysmalobium undulatum (L.) W. T. Aiton (Apocynaceae)	Ethyl acetate extract (root)	0.5	Not assessed	Adewusi and Steenkamp, 2011
Phlegmariurus tetragonus (Hook. & Grev.) B. Øllg. (Lycopodiaceae)*	Alkaloidal fraction (aerial parts)	0.9	Not assessed	Armijos et al., 2016
Esenbeckia leiocarpa Engl. (Rutaceae)	Alkaloidal fraction (stems)	1.6	Not assessed	Cardoso-Lopes et al., 2010
Melissa officinalis L. (Lamiaceae)	Ethanolic extract (leaves)	1.7	Not assessed	Dastmalchi et al., 2009
Carpolobia lutea G. Don (Polygalaceae)	Aqueous fraction (root)	2	≤100 μg/mL	Nwidu et al., 2017
Crinum bulbispermum (Burm. f.) Milne-Redh. & Schweick. (Amaryllidaceae)	Ethyl acetate extract (bulb)	2.1	Not assessed	Adewusi and Steenkamp, 2011
Morus alba L. (Moraceae)	Ethyl acetate fraction (root-bark)	2.5	Not assessed	Kuk et al., 2017
Angelica decursiva (Miq.) Franch. & Sav. (Apiaceae)	Aqueous fraction (whole plant)	2.6	Not assessed	Ali et al., 2015
Carpolobia lutea G. Don (Polygalaceae)	Methanolic extract (root)	3	≤100 μg/mL	Nwidu et al., 2017
Buchanania axillaris (Desr.) Ramamoorthy (Anacardiaceae)	Methanolic extract (aerial parts)	4.9	Not assessed	Penumala et al., 2018
Salvia miltiorrhiza Bunge (Lamiaceae)	Ethanolic extract (whole plant)	5.0	Not assessed	Lin et al., 2008
Huperzia serrata (Thunb.) Trevis. (Lycopodiaceae)	Alkaloids fraction (whole plant)	6.0	Not assessed	Ohba et al., 2015
Esenbeckia leiocarpa Engl. (Rutaceae)	Hexanic fraction (stems)	6.0	Not assessed	Cardoso-Lopes et al., 2010
Angelica decursiva (Miq.) Franch. & Sav. (Apiaceae)	Buthanolic fraction (whole plant)	6.0	Not assessed	Ali et al., 2015
Berberis aetnensis C. Presl (Berberidaceae)	Methanolic fraction (root)	7.6	Not assessed	Bonesi et al., 2013
Senna obtusifolia (L.) H. S. Irwin & Barneby. (Leguminosae)	Ethyl acetate fraction (leaves)	9.4	Not assessed	Jung et al., 2016
Angelica decursiva (Miq.) Franch. & Sav. (Apiaceae)	Ethyl acetate fraction (whole plant)	9.7	Not assessed	Ali et al., 2015
Senna obtusifolia (L.) H.S. Irwin & Barneby. (Leguminosae)	Buthanolic fraction (leaves)	9.9	Not assessed	Jung et al., 2016
Zanthoxylum davyi Waterm. (Rutaceae)	Methanolic extract (roots)	10	Not assessed	Adewusi and Steenkamp, 2011
Ziziphus mucronata Willd. (Rhamnaceae)	Ethyl acetate extract (root)	11.2	Not assessed	Adewusi and Steenkamp, 2011
Morus alba L. (Moraceae)	Methanolic extract (root-bark)	11.4	Not assessed	Kuk et al., 2017
Zanthoxylum davyi Waterm. (Rutaceae)	Ethyl acetate extract (roots)	11.6	Not assessed	Adewusi and Steenkamp, 2011
Buchanania axillaris (Desr.) Ramamoorthy (Anacardiaceae)	Chloroform fraction (aerial parts)	12.3	Not assessed	Penumala et al., 2018
Senna obtusifolia (L.) H.S. Irwin & Barneby. (Leguminosae)	Chloroform fraction (leaves)	12.7	Not assessed	Jung et al., 2016
Morus alba L. (Moraceae)	Chloroform fraction (root-bark)	13.4	Not assessed	Kuk et al., 2017
Angelica decursiva (Miq.) Franch. & Sav. (Apiaceae)	Chloroform fraction (whole plant)	13.7	Not assessed	Ali et al., 2015
Senna obtusifolia (L.) H. S. Irwin & Barneby. (Leguminosae)	Aqueous fraction (leaves)	14.5	Not assessed	Jung et al., 2016

(Continued)

TABLE 1 | Continued

Plant species (Families)	Type of extract or fraction (plant's part)	IC_{50} (μg/mL)	Toxicological assessment[#]	References
Crinum bulbispermum (Burm. f.) Milne-Redh. & Schweick. (Amaryllidaceae)	Methanolic extract (bulb)	14.8	Not assessed	Adewusi and Steenkamp, 2011
Scabiosa arenaria Forssk. (Caprifoliaceae)	Ethyl acetate fraction (stem and leaves)	16	Not assessed	Besbes Hlila et al., 2013
Angelica decursiva (Miq.) Franch. & Sav. (Apiaceae)	Methanolic extract (whole plant)	16.6	Not assessed	Ali et al., 2015
Berberis libanotica Ehrenb. ex C.K. Schneid. (Berberidaceae)	Methanolic fraction (root)	16.9	Not assessed	Bonesi et al., 2013
Pavetta indica L. (Rubiaceae)	Methanolic extract (aerial parts)	17.8	Not assessed	Penumala et al., 2017
Zephyranthes carinata Herb. (Amaryllidaceae)	Alkaloidal fraction (bulb)	18.0	Not assessed	Cortes et al., 2015
Crinum jagus (J. Thomps.) Dandy (Amaryllidaceae)	Alkaloidal fraction (bulb)	18.3	≤28.7 μg/mL	Cortes et al., 2015
Adenia gummifera (Harv.) Harms (Passifloraceae)	Ethyl acetate extract (root)	18.9	Not assessed	Adewusi and Steenkamp, 2011
Berberis libanotica Ehrenb. ex C.K. Schneid. (Berberidaceae)	Methanolic extract (root)	21.7	Not assessed	Bonesi et al., 2013
Huperzia squarrosa (G. Forst.) Trevis. (Lycopodiaceae)	Ethyl acetate fraction (aerial parts)	23.4	Not assessed	Tung et al., 2017
Berberis aetnensis C. Presl (Berberidaceae)	Alkaloidal fraction (root)	24.5	Not assessed	Bonesi et al., 2013
Ochna obtusata DC. (Ochnaceae)	Chloroform fraction (aerial parts)	25.7	Not assessed	Penumala et al., 2017
Gossypium herbaceum L. (Malvaceae)	Hydroalcoholic extracts (flowers)	28.1	Not assessed	Zhao et al., 2013
Hippeastrum puniceum (Lam.) Voss. (Amaryllidaceae)	Alkaloid fraction (bulb)	28.1	≤28.7 μg/mL	Cortes et al., 2015
Hemidesmus indicus (L.) R. Br. ex Schult. (Apocynaceae)	Chloroform fraction (aerial part)	28.1	Not assessed	Penumala et al., 2018
Scabiosa arenaria Forssk. (Caprifoliaceae)	Buthanolic fraction (stems and leaves)	29.0	Not assessed	Besbes Hlila et al., 2013
Senna obtusifolia (L.) H.S. Irwin & Barneby. (Leguminosae)	Methanolic fraction (leaves)	29.2	Not assessed	Jung et al., 2016
Morus alba L. (Moraceae)	Buthanolic fraction (root-bark)	36.6	Not assessed	Kuk et al., 2017
Ficus sur Forssk. (Moraceae)	Ethyl acetate extract (fruit)	31.9	Not assessed	Adewusi and Steenkamp, 2011
Rumex hastatus D. Don (Polygonaceae)	Essential Oils (aerial parts)	32.5	Not assessed	Ahmad et al., 2016
Acalypha alnifolia Klein ex Willd. (Euphorbiaceae)	Chloroform fraction (aerial parts)	32.9	Not assessed	Penumala et al., 2017
Olax nana Wall. ex Benth. (Olacaceae)	Methanolic extract (leaves)	33.2	Not assessed	Ovais et al., 2018
Nelumbo nucifera Gaertn. (Nelumbonaceae)	Buthanolic fraction (leaves)	33.2	Not assessed	Jung et al., 2015
Persicaria hydropiper (L.) Delarbre. (Polygonaceae)**	Hexanic fraction (whole plant)	35.0	Not assessed	Ayaz et al., 2014
Berberis aetnensis C. Presl (Berberidaceae)	Hexanic fraction (root)	36.5	Not assessed	Bonesi et al., 2013
Crinum bulbispermum (Burm. f.) Milne-Redh. & Schweick. (Amaryllidaceae)	Ethyl acetate extract (root)	39.3	Not assessed	Adewusi and Steenkamp, 2011
Huperzia brevifolia (Grev. & Hook.) Holub (Lycopodiaceae)	Alkaloidal fraction (aerial parts)	39.6	Not assessed	Armijos et al., 2016
Piper capense L. f. (Piperaceae)	Ethyl acetate extract (root)	40.7	Not assessed	Adewusi and Steenkamp, 2011

(Continued)

TABLE 1 | Continued

Plant species (Families)	Type of extract or fraction (plant's part)	IC_{50} (μg/mL)	Toxicological assessment[#]	References
Searsia mysorensis (G. Don) Moffett. (Anacardiaceae)	Chloroform fraction (aerial part)	41.3	Not assessed	Penumala et al., 2018
Morus alba L. (Moraceae)	Aqueous fraction (root-bark)	43.0	Not assessed	Kuk et al., 2017
Hemidesmus indicus (L.) R. Br. ex Schult. (Apocynaceae)	Methanolic extract (aerial part)	48.6	Not assessed	Penumala et al., 2018
Huperzia squarrosa (G. Forst.) Trevis. (Lycopodiaceae)	Buthanolic fraction (aerial parts)	50.1	Not assessed	Tung et al., 2017
Esenbeckia leiocarpa Engl. (Rutaceae)	Ethanolic extract (stems)	50.7	Not assessed	Cardoso-Lopes et al., 2010
Scabiosa arenaria Forssk. (Caprifoliaceae)	Ethyl Acetate fraction (flowers)	51.0	Not assessed	Besbes Hlila et al., 2013
Pavetta indica L. (Rubiaceae)	Chloroform fraction (aerial parts)	52.1	Not assessed	Penumala et al., 2017
Polygonum hydropiper L. (Polygonaceae)	Chloroform fraction (whole plant)	55.0	Not assessed	Ayaz et al., 2014
Acalypha alnifolia Klein ex Willd. (Euphorbiaceae)	Methanolic extrac (aerial parts)	59.2	Not assessed	Penumala et al., 2017
Carpolobia lutea G. Don (Polygalaceae)	Chloroform fraction (leaves)	60.0	≤100 μg/mL	Nwidu et al., 2017
Pavetta indica L. (Rubiaceae)	Buthanolic fraction (aerial parts)	60.1	Not assessed	Penumala et al., 2017
Nelumbo nucifera Gaertn. (Nelumbonaceae)	Ethylacetate fraction (leaves)	61.1	Not assessed	Jung et al., 2015
Huperzia compacta (Hook.) Trevis. (Lycopodiaceae)	Alkaloid fraction (aerial parts)	62.4	Not assessed	Armijos et al., 2016
Acalypha alnifolia Klein ex Willd. (Euphorbiaceae)	Aqueous fraction (aerial parts)	64.8	Not assessed	Penumala et al., 2017
Nelumbo nucifera Gaertn. (Nelumbonaceae)	Chloroform fraction (leaves)	67.3	Not assessed	Jung et al., 2015
Buchanania axillaris (Desr.) Ramamoorthy (Anacardiaceae)	Buthanolic fraction (aerial parts)	67.5	Not assessed	Penumala et al., 2018
Scabiosa arenaria Forssk. (Caprifoliaceae)	Buthanolic fraction (flowers)	74.0	Not assessed	Besbes Hlila et al., 2013
Rumex hastatus D. Don (Polygonaceae)	Chloroform fraction (whole plant)	75.0	Not assessed	Ahmad et al., 2015
Scabiosa arenaria Forssk. (Caprifoliaceae)	Methanolic extract (flowers)	80.0	Not assessed	Besbes Hlila et al., 2013
Carpolobia lutea G. Don (Polygalaceae)	Ethanolic fraction (leaves)	81.0	≤100 μg/mL	Nwidu et al., 2017
Ochna obtusata DC. (Ochnaceae)	Methanolic extrac (aerial parts)	82.2	Not assessed	Penumala et al., 2017
Berberis libanotica Ehrenb. ex C.K. Schneid. (Berberidaceae)	Alkaloidal extract (root)	82.4	Not assessed	Bonesi et al., 2013
Searsia mysorensis (G. Don) Moffett. (Anacardiaceae)	Buthanolic fraction (aerial part)	83.5	Not assessed	Penumala et al., 2018
Searsia mysorensis (G. Don) Moffett. (Anacardiaceae)	Aqueous fraction (aerial part)	93.7	Not assessed	Penumala et al., 2018
Berberis libanotica Ehrenb. ex C.K. Schneid. (Berberidaceae)	Hexanic extract (root)	95.5	Not assessed	Bonesi et al., 2013
Jatropha gossypifolia L. (Euphorbiaceae)	Ethyl acetate fraction (leaves)	95.7	Not assessed	Saleem et al., 2016
Polygonum hydropiper L. (Polygonaceae)	Aqueous fraction (whole plant)	100.0	Not assessed	Ayaz et al., 2014
Pavetta indica L. (Rubiaceae)	Aqueous fraction (aerial parts)	100.4	Not assessed	Penumala et al., 2017
Stemona sessilifolia (Miq.) Miq. (Stemonaceae)	Alkaloidal extracts (root)	102.6	Not assessed	Lai et al., 2013
Huperzia squarrosa (G. Forst.) Trevis. (Lycopodiaceae)	Ethanolic extract (aerial parts)	112.2	Not assessed	Tung et al., 2017

(Continued)

TABLE 1 | Continued

Plant species (Families)	Type of extract or fraction (plant's part)	IC_{50} (μg/mL)	Toxicological assessment[#]	References
Hemidesmus indicus(L.) R. Br. ex Schult. (Apocynaceae)	Buthaolic fraction (aerial part)	113.5	Not assessed	Penumala et al., 2018
Rumex hastatus D. Don (Polygonaceae)	Ethyl acetate fraction (whole plant)	115.0	Not assessed	Ahmad et al., 2015
Nelumbo nucifera Gaertn. (Nelumbonaceae)	Aqueous fraction (leaves)	119.6	Not assessed	Jung et al., 2015
Persicaria hydropiper (L.) Delarbre. (Polygonaceae)***	Essential Oils (leaves)	130.0	Not assessed	Ayaz et al., 2015
Hemidesmus indicus(L.) R. Br. ex Schult. (Apocynaceae)	Aqueous fraction (aerial part)	129.4	Not assessed	Penumala et al., 2018
Buchanania axillaris (Desr.) Ramamoorthy (Anacardiaceae)	Aqueous fraction (aerial parts)	136.2	Not assessed	Penumala et al., 2018
Carpolobia lutea G. Don (Polygalaceae)	Ethanolic extract (stem-bark)	140.0	≤100 μg/mL	Nwidu et al., 2017
Carpolobia lutea G. Don (Polygalaceae)	Hexanic fraction oil (stem)	140.0	≤100 μg/mL	Nwidu et al., 2017
Carpolobia lutea G. Don (Polygalaceae)	Methanolic fraction (stem)	142.0	≤100 μg/mL	Nwidu et al., 2017
Elatostema papillosum Wedd. (Urticaceae)	Methanolic extract (leaves)	165.4	Not assessed	Reza et al., 2018
Scabiosa arenaria Forssk. (Caprifoliaceae)	Aqueous fraction (flowers)	170	Not assessed	Besbes Hlila et al., 2013
Ochna obtusata DC. (Ochnaceae)	Buthanolic fraction (aerial parts)	174.4	Not assessed	Penumala et al., 2017
Jatropha gossypifolia L. (Euphorbiaceae)	Dichloromethane extract (root)	176.0	Not assessed	Saleem et al., 2016
Nelumbo nucifera Gaertn. (Nelumbonaceae)	Methanolic fraction (leaves)	184.5	Not assessed	Jung et al., 2015
Rumex hastatus D. Don (Polygonaceae)	Methanolic extract (whole plant)	218.0	Not assessed	Ahmad et al., 2015
Jatropha gossypifolia L. (Euphorbiaceae)	Methanolic extract (root)	222.0	Not assessed	Saleem et al., 2016
Polygonum hydropiper L. (Polygonaceae)	Essential Oils (flowers)	225.0	Not assessed	Ayaz et al., 2015
Scabiosa arenaria Forssk. (Caprifoliaceae)	Methanolic extract (stems and leaves)	230.0	Not assessed	Besbes Hlila et al., 2013
Diplotaxis simplex Asch. ex Rohlfs (Brassicaceae)	Aqueous extract (seeds)	233.0	Not assessed	Bahloul et al., 2016
Persicaria minor (Huds.) Opiz. (Polygonaceae)****	Aqueous extract (leaves)	234.0	Not assessed	Ahmad et al., 2014
Scabiosa arenaria Forssk. (Caprifoliaceae)	Buthanolic fraction (fruits)	240.0	Not assessed	Besbes Hlila et al., 2013
Polygonum hydropiper L. (Polygonaceae)	Buthanolic fraction (whole plant)	240.0	Not assessed	Ayaz et al., 2014
Huperzia squarrosa (G. Forst.) Trevis. (Lycopodiaceae)	Hexanic fraction (aerial parts)	257.0	Not assessed	Tung et al., 2017
Acalypha alnifolia Klein ex Willd. (Euphorbiaceae)	Buthanolic fraction (aerial parts)	257.5	Not assessed	Penumala et al., 2017
Atriplex laciniata L. (Amaranthaceae)	Aqueous fraction (whole plant)	267.0	Not assessed	Kamal et al., 2015
Scabiosa arenaria Forssk. (Caprifoliaceae)	Methanolic extract (fruits)	270.0	Not assessed	Besbes Hlila et al., 2013
Atriplex laciniata L. (Amaranthaceae)	Ethyl acetate fraction (whole plant)	270.0	Not assessed	Kamal et al., 2015
Atriplex laciniata L. (Amaranthaceae)	Methanolic extract (whole plant)	280.0	Not assessed	Kamal et al., 2015
Jatropha gossypifolia L. (Euphorbiaceae)	Dichloromethane extract (leaves)	289.0	Not assessed	Saleem et al., 2016
Justicia adhatoda L. (Acanthaceae)	Methanolic extract (leaves)	294.0	Not assessed	Ali et al., 2013

(Continued)

TABLE 1 | Continued

Plant species (Families)	Type of extract or fraction (plant's part)	IC_{50} (μg/mL)	Toxicological assessment[#]	References
Polygonum hydropiper L. (Polygonaceae)	Ethyl acetate fraction (whole plant)	310.0	Not assessed	Ayaz et al., 2014
Atriplex laciniata L. (Amaranthaceae)	Hexanic fraction (whole plant)	310.0	Not assessed	Kamal et al., 2015
Diplotaxis harra (Forssk.) Boiss. (Brassicaceae)	Aqueous extract (seeds)	313.0	Not assessed	Bahloul et al., 2016
Polygonum hydropiper L. (Polygonaceae)	Methanolic extract (whole plant)	330.0	Not assessed	Ayaz et al., 2014
Polygonum minus Huds. (Polygonaceae)	Methanolic extract (leaves)	342.8	Not assessed	Ahmad et al., 2014
Ochna obtusata DC. (Ochnaceae)	Aqueous fraction (aerial parts)	369.1	Not assessed	Penumala et al., 2017
Atriplex laciniata L. (Amaranthaceae)	Chloroform fraction (whole plant)	390.0	Not assessed	Kamal et al., 2015
Scabiosa arenaria Forssk. (Caprifoliaceae)	Aqueous fraction (stems and leaves)	410.0	Not assessed	Besbes Hlila et al., 2013
Diplotaxis simplex Asch. ex Rohlfs (Brassicaceae)	Aqueous extract (flowers)	420.0	Not assessed	Bahloul et al., 2016
Salsola vermiculata L. (Amaranthaceae)	Methanol extract (roots)	450.0	Not assessed	Rasheed et al., 2013
Polygonum minus Huds. *(Polygonaceae)*	Dichloromethane extract (leaves)	478.0	Not assessed	Ahmad et al., 2014
Scabiosa arenaria Forssk. (Caprifoliaceae)	Ethyl acetate fraction (fruits)	500.0	Not assessed	Besbes Hlila et al., 2013
Polygonum minus Huds. (Polygonaceae)	Aqueous extract (stem)	581.0	Not assessed	Ahmad et al., 2014
Salvia leriifolia Benth. (Lamiaceae)	Hexane fraction (leaves)	590.0	Not assessed	Loizzo et al., 2010
Jacaranda caroba (Vell.) DC. (Bignoniaceae)	Aqueous extract (leaves)	670.2	Not assessed	Ferreres et al., 2013
Polygonum minus Huds. *(Polygonaceae)*	Dichloromethane extract (leaves)	770.0	Not assessed	Ahmad et al., 2014
Diplotaxis harra (Forssk.) Boiss. (Brassicaceae)	Aqueous extract (flowers)	760.0	Not assessed	Bahloul et al., 2016
Polygonum minus Huds. (Polygonaceae)	Methanolic extract (stem)	809.0	Not assessed	Ahmad et al., 2014
Salvia leriifolia Benth. (Lamiaceae)	Dichloromethane fraction (leaves)	840.0	Not assessed	Loizzo et al., 2010
Salvia leriifolia Benth. (Lamiaceae)	Ehtyl acetate fraction (leaves)	870.0	Not assessed	Loizzo et al., 2010
Rhizophora lamarckii Montrouz. (Rhizophoraceae)	Methanol extract (leaves)	910.0	Not assessed	Suganthy et al., 2009
Polygonum minus Huds. *(Polygonaceae)*	Ethanolic extract (leaves)	910.0	Not assessed	Ahmad et al., 2014
Polygonum minus Huds. *(Polygonaceae)*	Ethanolic extract (stem)	930.0	Not assessed	Ahmad et al., 2014
Jacaranda caroba (Vell.) DC. (Bignoniaceae)	Hydromethanolic extracts (leaves)	1000.4	Not assessed	Ferreres et al., 2013

AChE, acetylcholinesterase; IC_{50}, half maximal inhibition concentration.

**Syn, Huperzia tetragona (Hook. & Grev.) Trevis. **Syn, Polygonum hydropiper L. ***Syn, Polygonum hydropiper L. ****Syn, Polygonum minus Huds. [#]Maximal concentration assessed for the absence of cytotoxicity.*

Plant species and their respective extracts were classified in accordance with the criteria described at Section Plant Species With Anti-Acetylcholinesterase Activity in: high potency (green background), moderate potency (orange background), and low potency (red background).

Carpolobia lutea G. Don (Polygalaceae; Nwidu et al., 2017); to 18.9 μg/mL for the ethyl acetate root extract of *Adenia gummifera (Harv.) Harms (Passifloraceae;* Adewusi and Steenkamp, 2011; **Table 1**). Both *S. puniceus* and *L. schweinfurthii* ethyl acetate extracts showed very-limited antioxidant activity, leading the authors to attribute the strong anti-AChE activity to the extract alkaloid-content (Adewusi and Steenkamp, 2011). However, primary extraction with ethyl acetate hardly renders alkaloid-rich extracts, which demands an extraction scheme outlined to adjustable acid and basic pH values during partitioning (Sarker et al., 2005), therefore further validation for those species is advisable. Notwithstanding, analyzing the solvents employed for preparation of the potent extracts within this category (**Table 1**), there is no direct correlation between solvent

polarity and anti-AChE activity, supporting the assumption that non-alkaloidal secondary metabolites, such as terpenoids, flavonoids and other phenolic compounds, would be as active as the classic alkaloidal AChEi (Murray et al., 2013).

For instance, the ethyl acetate root fraction of *Carpolobia lutea* (Polygalaceae)–whose total phenolic content was 296.5 mg EAG/g–presented IC_{50} = 0.3 μg/mL (Nwidu et al., 2017); virtually the same value determined to the essential oil from *Salvia leriifolia* (Lamiaceae) aerial parts, which presented IC_{50} = 0.32 μL/mL and had camphor (10.5%), 1,8-cineole (8.6%), camphene (6.2%) and α-pinene (4.7%) as main components (Loizzo et al., 2009). Contrarily, the n-Hexane whole plant fraction of *Polygonum hydropiper* (Polygonaceae) crude extract presented moderate anti-AChE activity with IC_{50} = 35 μg/mL (Ayaz et al., 2014), meanwhile the essential oil from its leaves showed a potency nearly four times lower (IC_{50} = 120 μg/mL; Ayaz et al., 2015). The alkaloid fraction of *Esenbeckia leiocarpa* (Rutaceae), obtained by acid-base partition of the ethanol stem extract, presented IC_{50} = 1.6 μg/mL, which corresponded to an inhibitory potency 30-fold higher than the original crude extract (IC_{50} = 50.7 μg/mL; Cardoso-Lopes et al., 2010). Still, the assessment of anti-AChE activity of *Berberis aetnensis* and *Berberis libanotica* root extracts, whose major constituent was the alkaloid berberine, showed 3-fold higher activity for the methanol fraction (IC_{50} = 7.6 and 16.9 μg/mL, respectively) than for alkaloid-rich fraction (IC_{50} = 24.5 and 82.4 μg/mL, respectively), supporting the synergy between alkaloid and non-alkaloid components within methanol fraction from both species (Bonesi et al., 2013).

Huperzia spp. (Lycopodiaceae) have been used for over 1,000 years in China for diverse neuronal- and cognitive-based illnesses (Ma et al., 2007), becoming of major interest for the pharmaceutical industry upon the isolation of the alkaloid Huperzine A from *H. serrata* (Liu et al., 1986). Thenceforth, huge research has focused on the isolation of Huperzine A and other Lycopodium alkaloids from *Huperzia* spp. and other Lycopodiaceae species (Ha et al., 2011; Damar et al., 2016; Sahoo et al., 2018). In spite of that, our survey retrieved recent relevant studies on anti-AChE activity of five *Huperzia* spp.: *H. serrata* (Ohba et al., 2015), *H. squarrosa* (Tung et al., 2017), *H. brevifolia*, *H. compacta*, and *H. tetragona* (Armijos et al., 2016; **Table 1**). In the study by Ohba et al. (2015), alkaloid enriched fraction of *H. serrata* aerial parts, whose major alkaloidal constituent was Huperzine A (∼0.5%), presented IC_{50} = 5.96 μg/mL. On the other hand, in the study by Armijos et al. (2016), alkaloid fraction of *H. tetragona* aerial parts strongly inhibited AChE (IC_{50} = 0.9 μg/mL), meanwhile *H. brevifolia* and *H. compacta* presented moderate potency (IC_{50} = 39.6 and 62.4 μg/mL, respectively). The authors ascribed the high potency of *H. tetragona* to other Lycopodium alkaloids, mainly lycopodine, 6-OH-lycopodine and des-*N*-methyl-α-obscurine, since Huperzine A was not detected in any of the assessed species. Tung et al. (2017) assessed anti-AChE activity in three different fractions obtained from the ethanol extract of *H. squarrosa* aerial parts. EtOAc and BuOH fractions presented moderated activity, whose IC_{50} values were 23.44 and 50.11 μg/mL, respectively. The n-hexane fraction otherwise presented the lowest AChE inhibitory activity (IC_{50} = 257.03 μg/mL).

As showed in the abovementioned studies, anti-AChE activity of plant extracts is significantly variable regardless of the predominant secondary metabolite class or the polarity of the extracting solvent. To cope with these limitations and still screen potentially applicable species, most researchers have also assessed the extracts antioxidant capacity, in order to demonstrate their dual efficacy. Although the present mini-review does not aim to discuss antioxidant aspects, it is noticeable that most studies cited in **Table 1** have either quantified total phenolic content or measured antioxidant capacity in their extracts. Such assessments require appropriate methods that address the mechanism of antioxidant activity and focus on the kinetics of the reactions involving the antioxidants (Amorati and Valgimigli, 2018). Contrariwise, phenolic content was predominantly measured by Folin-Ciocalteu method, which also quantifies nonphenolic compounds, such as aromatic amino acids, sugars, ascorbic acid, and organic acids (Pueyo and Calvo, 2009), reason why it is not advisable for total phenol quantification. Similarly, antioxidant capacity was mostly assessed by trapping of the radicals $DPPH^{\bullet}$ and $ABTS^{\bullet+}$, which are non-biologically relevant oxidants (Amorati and Valgimigli, 2018). Thus, most plant extracts propelled as dually efficient (Anti-AChE and antioxidant) much probably deserve a biological approach to characterize their preventive instead of scavengering antioxidant capacity.

NATURAL AChEi COMPOUNDS

The active site of AChE contains two main subsites, the "esteratic" and "anionic" subsites, corresponding to the catalytic machinery and the choline-binding pocket, respectively. As illustrated in **Figure 1A**, the "esteratic" subsite consists in a histidine residue (His_{447}), whereas the "anionic" subsite is an tryptophan residue (Trp_{84}) able to bind quaternary ligands, which may act as competitive inhibitors (Dvir et al., 2010). Most of natural AChEi reported during our delimited survey period belong to the alkaloid group. Anti-AChE activity of alkaloids is ascribed to their complex nitrogen structures, which once positively charged bind to the "anionic" subsite on AChE active site (Hostettmann et al., 2006; Houghton et al., 2006). For instance, galantamine inhibits AChE by stably binding to Trp_{84}, as well as phenylalanine residues on the acyl-binding pocket (Greenblatt et al., 1999). On the other hand, non-alkaloidal AChEi, which include terpenes, flavonoids and other phenolic compounds, seem to act as non-competitive inhibitors that bind to peripheral anionic sites (PAS) mainly represented by the residues Tyr_{70}, Asp_{74}, Try_{121}, Trp_{279}, and Tyr_{334} (Johnson and Moore, 2006).

Figure 1B shows the isolated compounds identified as potential natural AChEi, which were classified in three categories, in accordance to their IC_{50} values: high potency, $IC_{50} < 15$ μM; moderate potency, $15 < IC_{50} < 50$ μM; and low potency, $50 < IC_{50} < 1{,}000$ μM. As a comparative reasoning, IC_{50} values described for galantamine in the surveyed studies where it was used as positive control were averaged, resulting in

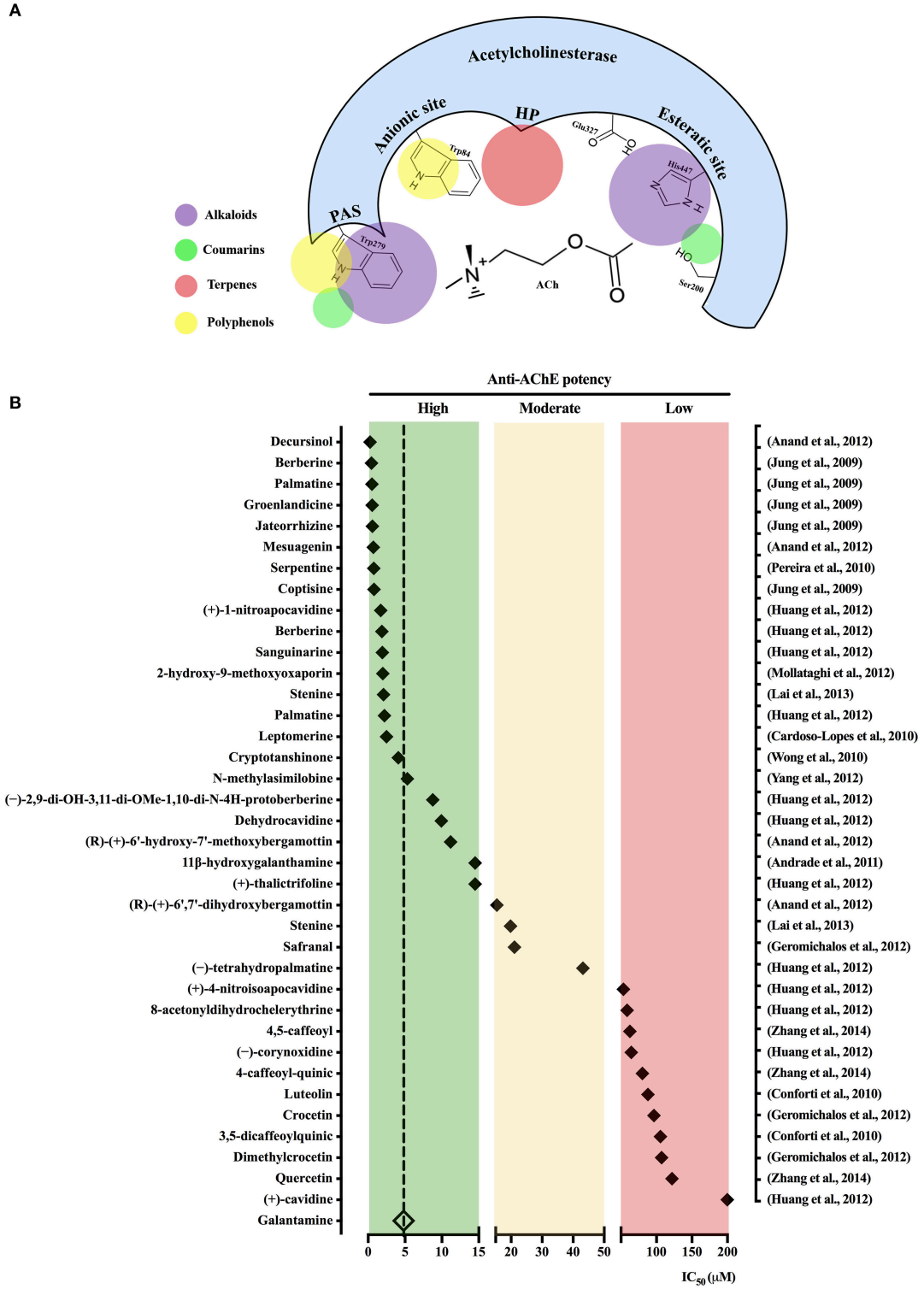

FIGURE 1 | Schematic view of acetylcholinesterase active binding sites for the main natural acetylcholinesterase inhibitors (AChEi) classes. **(A)** Acetylcholinesterase gorge pocket composed by the following binding sites: esteratic site, anionic site, peripheral anionic site (PAS), as well as hydrophobic pocket (HP) is shown. Colored circles represent the main binding sites for compounds pertaining to the indicated classes. **(B)** Natural AChEi reported in Pubmed from 2007 to 2018 (1st semester) were classified in accordance with the criteria described at Section Natural AChEi Compounds in: high potency (green background), moderate potency (orange background), and low potency (red background). The diamond symbol represents the IC_{50} value for each compound (in the left) as described in the respective study (in the right).

IC_{50} = 4.82 ± 1.29 μM. Studies describing discrepant IC_{50} values for galantamine were not considered. Sixteen compounds presented anti-AChE potency higher than galantamine, which include 01 terpene, 2 coumarins, and 13 alkaloids. Other 20 compounds, additionally pertaining to flavonoids and phenolic acids, were also selected with IC_{50} ranging from 5.33 to >200 μM (**Figure 1B**). The dihydropyranocoumarin decursinol isolated from *Angelica gigas* Nakai (Apiaceae) was the most potent AChEi (IC_{50} = 0.28 μM; Anand et al., 2012), such high potency had been previously attributed to characteristics of cyclization of the isoprenyl unit at C-6 and the functional groups attached to the coumarin nucleus, which differ from other coumarins (Kang et al., 2001).

The major alkaloids with recognized anti-AChE activity are the classical galantamine and huperzine A, which have been elegantly reviewed by Gulcan et al. (2015) and Qian and Ke (2014), respectively. However, other recently described alkaloids of various subclasses deserve special emphasis because of their important inhibitory action on AChE. Jung et al. (2009) assessed the anti-AChE activity of five protoberberine alkaloids isolated from the rhizome of *Coptis* spp. (berberine, palmatine, groenlandicine, jateorrhizine, and coptisine), with IC_{50} ranging from 0.44 to 0.80 μM. Interestingly, groenlandicine also strongly inhibited the enzyme responsible for cleaving the β-site of the amyloid precursor protein, adding an important property against AD pathogenesis (Jung et al., 2009). The potentialities of protoberberines alkaloids as natural AChEi were further supported by isolation of 12 isoquinoline alkaloids, including two new nitrotetrahydroprotoberberines (2,9-dihydroxy-3,11-dimethoxy-1,10-dinitrotetrahydroprotoberberine and 4-nitroisoapocavidine), from *Corydalis saxicola* Bunting (Papaveraceae). All the alkaloids were selectively active against AChE with IC_{50} < 10 μM. Structure-activity relationship study indicated that potency differences were related to the presence of phenolic hydroxy groups, which could reduce the anti-AChE activity, whereas nitro substitutions at ring A, especially at C-1, in the tetrahedroprotoberberines could increase it (Huang et al., 2012).

Studies on the molecular mechanisms by which natural AChEi interact with AChE binding subsites are still scant. Nevertheless, some studies have offered important insights on this matter. Serpentine, the main alkaloid found in the roots of *Catharanthus roseus* (L.) G. Don (Apocynaceae) presented high anti-AChE potency (IC_{50} = 0.77 μM), which was attributed to the binding of its quaternary nitrogen to an Asp residue at AChE peripheral anionic site (Pereira et al., 2010). Lai et al. (2013) when evaluating alkaloids from *Stemona sessilifolia* (Miq.) Miq. roots (Stemonaceae) identified the AChEi stenine B (IC_{50} = 2.10 μM) and stenine (IC_{50} = 19.8 μM). Authors attributed the stronger activity of stenine B to its ability to build hydrogen bonds with Tyr_{130}, similarly to huperzine A. Lastly, bioactivity-guided chromatographic fractionation of *Nelumbo nucifera* Gaertn. (Nelumbonaceae) leaf extract led to isolation of three aporphine-type alkaloids, an important subclass of natural inhibitors of AChE. Amongst them, N-methylasimilobine displayed a significant anti-AChE activity with IC_{50} = 5.33 μM. According to their *in silico* studies, such potency was due to a hydroxyl group at the alkaloid C-2 position, which makes hydrogen bond with a carbonyl group on Ser_{293} in association with another hydrogen bond between its alkaloidal quaternary nitrogen and the hydroxyl group of Tyr_{124} (Yang et al., 2012).

Salvia spp. (Lamiaceae) have been used for centuries for its beneficial effects on memory disorders (Hamidpour et al., 2014). Wong et al. (2010) demonstrated that the diterpene cryptotanshinone extracted from the root of *Salvia miltiorrhiza* Bunge is a reversible inhibitor of human AChE (IC_{50} = 4.09 μM) and that chronic oral administration can reverse cognitive deficits induced by scopolamine in rats. Flavonoids, a heterogeneous group of polyphenols, are currently considered a prominent source of anti-AD compounds (Khan et al., 2018) because of their potential AChE inhibitory activity allied to the well-known antioxidant activity and low toxicity (Uriarte-Pueyo and Calvo, 2011). However, our survey did not identify any highly potent, and consequently prominent AChEi pertaining to the flavonoid class (**Figure 1**). For instance, luteolin and 3,5-dicaffeoylquinic acid, phenolic compounds extracted from *Phagnalon saxatile* Cass. (Compositae) exhibited low activity against AChE with an IC_{50} of 88.00 and 105 μM, respectively (Conforti et al., 2010).

CLINICAL STUDIES

Besides galantamine, huperzine A is the most clinically studied alkaloidal AChEi (Qian and Ke, 2014). The efficacy of huperzine A was demonstrated in the treatment of 447 patients with age-related memory impairment or dementia (Shu, 1998; Ma et al., 2007). However, in another phase II study, the results were not conclusive on its beneficial cognitive effects for patients with moderate AD, requiring further investigation (Rafii et al., 2011). A clinical trial with *Salvia officinalis* L. administered to patients with mild to moderate AD for a 16-weeks period led to improved cognitive performance (Perry et al., 2003). Of importance, *S. officinalis* also attenuated cognitive impairment in patients suffering from moderate to severe AD when used for up to 1 year. However, authors recognized that long-term efficacy, safety and administration strategy still require further investigation (Tune, 2001). *Salvia* spp. are particularly rich in terpenes, whose anti-AChE capacity has been assessed through enough pre-clinical tests, but are awaiting clinical trials (Rollinger et al., 2004; Kennedy and Scholey, 2006). On the other hand, a 22-weeks randomized, double-blind, multicenter trial, including 54 individuals suffering from mild-to-moderate AD, showed that daily intake of *Crocus sativus* L. (Iridaceae) dried extract (30 mg/day) significantly improved cognitive capacity comparable to that observed in donepezil-treated patients (Akhondzadeh et al., 2010).

TOXICOLOGICAL STUDIES

A recent systematic review and meta-analysis of 43 randomized placebo-controlled clinical trials showed that AChEi improved cognitive function, global symptomatology, and functional capacity, as well as decreased patients' mortality (Blanco-Silvente et al., 2017). However, patients taking AChEi presented

higher discontinuation due to adverse events, denoting an important issue on anti-AChE therapy. As showed in **Table 1**, the majority of the plant extract-based studies mentioned in this mini-review has not assessed their toxicity in animals or humans, although species like *S. officinalis* (Kennedy and Scholey, 2006) and *P. hydropiper* (Huq et al., 2014) have been considered as non-toxic. Amongst the main natural AChEi compounds herein mentioned, berberine and safranal seem to ally more advantages than disadvantages. Nevertheless, berberine has been shown to cause mild gastrointestinal reactions, including diarrhea and constipation, besides other less frequent side effects (Imenshahidi and Hosseinzadeh, 2016); and safranal has toxic effects on hematological and biochemical indices, as well as induced embryonic malformation in animal's models at high doses (Bostan et al., 2017).

CLOSING REMARKS AND PERSPECTIVES

The present mini-review demonstrated that during last decade several plant species and their potentially active compounds have been screened for anti-AChE activity. Amongst the most active extracts (**Table 1**), it is noticeable the use of extracting solvents of distinct polarities, which suggests that their active compounds might pertain to a wide range of secondary metabolites classes. However, having a look at the isolated substances summarized in **Figure 1B**, most high potent compounds assessed during this period pertain to alkaloid class, exception made to the highest potent decursinol, a dihydropyranocoumarin. Alkaloids indisputably are the most studied class of natural AChEi, what seemly has trapped the researcher's attention in this class when in pursuit of new potential AChEi candidates, a vision that urges to be changed. Notwithstanding, the search for secondary AD-relevant pharmacological properties, such as antioxidant, deserves experimental approaches addressing their capacity to prevent oxidants generation and oxidative damage, instead of their mere scavengering capacity.

Finally, despite the undoubted relevance of new AChEi discovery for AD palliative pharmacotherapy, there is scanty knowledge on their structure-activity relationships, as well as toxicological assessments that would enable them to phase II studies. For instance, berberine and related protoberberine alkaloids have been consistently assessed for their anti-AChE activity, but no phase II study has been conducted so far. Such knowledge is capital both to promote higher safety and to guide the design of new (semi-) synthetic AChEi. Thus, given the plethora of plant species and compounds already described, their assessment through clinical trials certainly represent the main barrier to be transposed in order to expand and improve the pharmacological care of AD patients.

AUTHOR CONTRIBUTIONS

TS conceived the proposal, discussed mini-review's structure, surveyed and selected relevant articles, tabulated the data and drafted the manuscript. TG surveyed and selected relevant articles, tabulated the data. BP supervised articles selection, analysis and data tabulation. AC discussed mini-review's structure, supervised articles selection, analysis and data tabulation. AP conceived the proposal, discussed mini-review's structure, oriented the selection of relevant articles, analyzed tabulated data, and drafted the manuscript. All authors read and approved the final format of the manuscript.

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REFERENCES

Adewusi, E. A., and Steenkamp, V. (2011). *In vitro* screening for acetylcholinesterase inhibition and antioxidant activity of medicinal plants from southern Africa. *Asian Pacif. J. Trop. Med.* 4, 829–835. doi: 10.1016/S1995-7645(11)60203-4

Ahmad, R., Baharum, S. N., Bunawan, H., Lee, M., Mohd Noor, N., Rohani, E. R., et al. (2014). Volatile profiling of aromatic traditional medicinal plant, Polygonum minus in different tissues and its biological activities. *Molecules* 19, 19220–19242. doi: 10.3390/molecules191119220

Ahmad, S., Ullah, F., Ayaz, M., Sadiq, A., and Imran, M. (2015). Antioxidant and anticholinesterase investigations of Rumex hastatus D. Don: potential effectiveness in oxidative stress and neurological disorders. *Biol. Res.* 48:20. doi: 10.1186/s40659-015-0010-2

Ahmad, S., Ullah, F., Sadiq, A., Ayaz, M., Imran, M., Ali, I., et al. (2016). Chemical composition, antioxidant and anticholinesterase potentials of essential oil of Rumex hastatus D. Don collected from the North West of Pakistan. *BMC Complement. Altern. Med.* 16:29. doi: 10.1186/s12906-016-0998-z

Akhondzadeh, S., Shafiee Sabet, M., Harirchian, M. H., Togha, M., Cheraghmakani, H., Razeghi, S., et al. (2010). A 22-week, multicenter, randomized, double-blind controlled trial of Crocus sativus in the treatment of mild-to-moderate Alzheimer's disease. *Psychopharmacology* 207, 637–643. doi: 10.1007/s00213-009-1706-1

Ali, M. Y., Jung, H. A., and Choi, J. S. (2015). Anti-diabetic and anti-Alzheimer's disease activities of Angelica decursiva. *Arch. Pharmacal. Res.* 38, 2216–2227. doi: 10.1007/s12272-015-0629-0

Ali, S. K., Hamed, A. R., Soltan, M. M., Hegazy, U. M., Elgorashi, E. E., El-Garf, I. A., et al. (2013). *In-vitro* evaluation of selected Egyptian traditional herbal medicines for treatment of Alzheimer disease. *BMC Complement. Alter. Med.* 13:121. doi: 10.1186/1472-6882-13-121

Amorati, R., and Valgimigli, L. (2018). Methods to measure the antioxidant activity of phytochemicals and plant extracts. *J. Agric. Food Chem.* 66, 3324–3329. doi: 10.1021/acs.jafc.8b01079

Anand, P., and Singh, B. (2013). A review on cholinesterase inhibitors for Alzheimer's disease. *Arch. Pharmacal Res.* 36, 375–399. doi: 10.1007/s12272-013-0036-3

Anand, P., Singh, B., and Singh, N. (2012). A review on coumarins as acetylcholinesterase inhibitors for Alzheimer's disease. *Bioorg. Med. Chem.* 20, 1175–1180. doi: 10.1016/j.bmc.2011.12.042

Andrieu, S., Coley, N., Lovestone, S., Aisen, P. S., and Vellas, B. (2015). Prevention of sporadic Alzheimer's disease: lessons learned from clinical trials and future directions. *Lancet Neurol.* 14, 926–944. doi: 10.1016/S1474-4422(15)00153-2

Armijos, C., Gilardoni, G., Amay, L., Lozano, A., Bracco, F., Ramirez, J., et al. (2016). Phytochemical and ethnomedicinal study of Huperzia species used in the traditional medicine of Saraguros in Southern Ecuador; AChE and MAO inhibitory activity. *J. Ethnopharmacol.* 193, 546–554. doi: 10.1016/j.jep.2016.09.049

Ayaz, M., Junaid, M., Ahmed, J., Ullah, F., Sadiq, A., Ahmad, S., et al. (2014). Phenolic contents, antioxidant and anticholinesterase potentials of crude extract, subsequent fractions and crude saponins from *Polygonum hydropiper* L. *BMC Complement. Altern. Med.* 14:145. doi: 10.1186/1472-6882-14-145

Ayaz, M., Junaid, M., Ullah, F., Sadiq, A., Khan, M. A., Ahmad, W., et al. (2015). Comparative chemical profiling, cholinesterase inhibitions and anti-radicals properties of essential oils from Polygonum hydropiper L: a preliminary anti-Alzheimer's study. *Lipids Health Dis.* 14:141. doi: 10.1186/s12944-015-0145-8

Ayaz, M., Sadiq, A., Junaid, M., Ullah, F., Subhan, F., and Ahmed, J. (2017). Neuroprotective and anti-aging potentials of essential oils from aromatic and medicinal plants. *Front. Aging Neurosci.* 9:168. doi: 10.3389/fnagi.2017.00168

Bahloul, N., Bellili, S., Aazza, S., Chérif, A., Faleiro, M. L., Antunes, M. D., et al. (2016). Aqueous extracts from tunisian diplotaxis: phenol content, antioxidant and anti-acetylcholinesterase activities, and impact of exposure to simulated gastrointestinal fluids. *Antioxidants* 5:12. doi: 10.3390/antiox5020012

Bartus, R. T. (2000). On neurodegenerative diseases, models, and treatment strategies: lessons learned and lessons forgotten a generation following the cholinergic hypothesis. *Exp. Neurol.* 163, 495–529. doi: 10.1006/exnr.2000.7397

Bartus, R. T., Dean, R. L., Beer, B., and Lippa, A. S. (1982). The cholinergic hypothesis of geriatric memory dysfunction. *Science* 217, 408–414. doi: 10.1126/science.7046051

Berkov, S., Codina, C., Viladomat, F., and Bastida, J. (2008). N-Alkylated galanthamine derivatives: potent acetylcholinesterase inhibitors from Leucojum aestivum. *Bioorg. Med. Chem. Lett.* 18, 2263–2266. doi: 10.1016/j.bmcl.2008.03.008

Besbes Hlila, M., Omri, A., Ben Jannet, H., Lamari, A., Aouni, M., and Selmi, B. (2013). Phenolic composition, antioxidant and anti-acetylcholinesterase activities of the Tunisian Scabiosa arenaria. *Pharmaceutical. Biol.* 51, 525–532. doi: 10.3109/13880209.2012.746713

Blanco-Silvente, L., Castells, X., Saez, M., Barcelo, M. A., Garre-Olmo, J., Vilalta-Franch, J., et al. (2017). Discontinuation, efficacy, and safety of cholinesterase inhibitors for Alzheimer's disease: a meta-analysis and meta-regression of 43 randomized clinical trials enrolling 16 106 patients. *Int. J. Neuropsychopharmacol.* 20, 519–528. doi: 10.1093/ijnp/pyx012

Bonesi, M., Loizzo, M. R., Conforti, F., Passalacqua, N. G., Saab, A., Menichini, F., et al. (2013). Berberis aetnensis and B. *libanotica:* a comparative study on the chemical composition, inhibitory effect on key enzymes linked to Alzheimer's disease and antioxidant activity. *J. Pharmacy Pharmacol.* 65, 1726–1735. doi: 10.1111/jphp.12172

Bostan, H. B., Mehri, S., and Hosseinzadeh, H. (2017). Toxicology effects of saffron and its constituents: a review. *Iran J. Basic Med. Sci.* 20, 110–121. doi: 10.22038/ijbms.2017.8230

Cardoso-Lopes, E. M., Maier, J. A., Silva, M. R. D., Regasini, L. O., Simote, S. Y., Lopes, N. P., et al. (2010). Alkaloids from stems of *Esenbeckia leiocarpa* Engl. (Rutaceae) as potential treatment for Alzheimer disease. *Molecules* 15, 9205–9213. doi: 10.3390/molecules15129205

Colovic, M. B., Krstic, D. Z., Lazarevic-Pasti, T. D., Bondzic, A. M., and Vasic, V. M. (2013). Acetylcholinesterase inhibitors: pharmacology and toxicology. *Curr. Neuropharmacol.* 11, 315–335. doi: 10.2174/1570159X11311030006

Conforti, F., Rigano, D., Formisano, C., Bruno, M., Loizzo, M. R., Menichini, F., et al. (2010). Metabolite profile and *in vitro* activities of *Phagnalon saxatile* (L.) Cass. relevant to treatment of Alzheimer's disease. *J. Enz. Inhibit. Med. Chem.* 25, 97–104. doi: 10.3109/14756360903018260

Cortes, N., Posada-Duque, R. A., Alvarez, R., Alzate, F., Berkov, S., Cardona-Gómez, G. P., et al. (2015). Neuroprotective activity and acetylcholinesterase inhibition of five Amaryllidaceae species: a comparative study. *Life Sci.* 122, 42–50. doi: 10.1016/j.lfs.2014.12.011

Craig, L. A., Hong, N. S., and Mcdonald, R. J. (2011). Revisiting the cholinergic hypothesis in the development of Alzheimer's disease. *Neurosci. Biobehav. Rev.* 35, 1397–1409. doi: 10.1016/j.neubiorev.2011.03.001

Damar, U., Gersner, R., Johnstone, J. T., Schachter, S., and Rotenberg, A. (2016). Huperzine A as a neuroprotective and antiepileptic drug: a review of preclinical research. *Expert Rev. Neurother.* 16, 671–680. doi: 10.1080/14737175.2016.1175303

Dastmalchi, K., Ollilainen, V., Lackman, P., Af Gennäs, G. B., Dorman, H. D., Järvinen, P. P., et al. (2009). Acetylcholinesterase inhibitory guided fractionation of *Melissa officinalis* L. *Bioorg. Med. Chem.* 17, 867–871. doi: 10.1016/j.bmc.2008.11.034

Dvir, H., Silman, I., Harel, M., Rosenberry, T. L., and Sussman, J. L. (2010). Acetylcholinesterase: from 3D structure to function. *Chem. Biol. Interact.* 187, 10–22. doi: 10.1016/j.cbi.2010.01.042

Ellman, G. L., Courtney, K. D., Andres V. Jr., and Featherstone, R. M. (1961). A new and rapid colorimetric determination of acetylcholinesterase activity. *Biochem. Pharmacol.* 7, 88–95. doi: 10.1016/0006-2952(61)90145-9

Ferreres, F., Grosso, C., Gil-Izquierdo, A., Valentão, P., and Andrade, P. B. (2013). Phenolic compounds from Jacaranda caroba (Vell.) A. *DC.*: approaches to neurodegenerative disorders. *Food Chem. Toxicol.* 57, 91–98. doi: 10.1016/j.fct.2013.03.012

Fiest, K. M., Roberts, J. I., Maxwell, C. J., Hogan, D. B., Smith, E. E., Frolkis, A., et al. (2016). The prevalence and incidence of dementia due to Alzheimer's disease: a systematic review and meta-analysis. *Can. J. Neurol. Sci.* 43, S51–S82. doi: 10.1017/cjn.2016.36

Godyn, J., Jonczyk, J., Panek, D., and Malawska, B. (2016). Therapeutic strategies for Alzheimer's disease in clinical trials. *Pharmacol. Rep.* 68, 127–138. doi: 10.1016/j.pharep.2015.07.006

Greenblatt, H. M., Kryger, G., Lewis, T., Silman, I., and Sussman, J. L. (1999). Structure of acetylcholinesterase complexed with (-)-galanthamine at 2.3 A resolution. *FEBS Lett.* 463, 321–326. doi: 10.1016/S0014-5793(99)01637-3

Gulcan, H. O., Orhan, I. E., and Sener, B. (2015). Chemical and molecular aspects on interactions of galanthamine and its derivatives with cholinesterases. *Curr. Pharm. Biotechnol.* 16, 252–258. doi: 10.2174/1389201015666141202105105

Ha, G. T., Wong, R. K., and Zhang, Y. (2011). Huperzine a as potential treatment of Alzheimer's disease: an assessment on chemistry, pharmacology, and clinical studies. *Chem. Biodivers.* 8, 1189–1204. doi: 10.1002/cbdv.201000269

Hamidpour, M., Hamidpour, R., Hamidpour, S., and Shahlari, M. (2014). Chemistry, pharmacology, and medicinal property of sage (Salvia) to prevent and cure illnesses such as obesity, diabetes, depression, dementia, lupus, autism, heart disease, and cancer. *J. Tradit. Complement. Med.* 4, 82–88. doi: 10.4103/2225-4110.130373

Heinrich, M. (2010). Galanthamine from galanthus and other amaryllidaceae–chemistry and biology based on traditional use. *Alkaloids Chem. Biol.* 68, 157–165. doi: 10.1016/S1099-4831(10)06804-5

Henstridge, C. M., Pickett, E., and Spires-Jones, T. L. (2016). Synaptic pathology: a shared mechanism in neurological disease. *Ageing Res. Rev.* 28, 72–84. doi: 10.1016/j.arr.2016.04.005

Holas, O., Musilek, K., Pohanka, M., and Kuca, K. (2012). The progress in the cholinesterase quantification methods. *Expert Opin. Drug Discov.* 7, 1207–1223. doi: 10.1517/17460441.2012.729037

Hostettmann, K., Borloz, A., Urbain, A., and Marston, A. (2006). Natural product inhibitors of acetylcholinesterase. *Curr. Org. Chem.* 10, 825–847. doi: 10.2174/138527206776894410

Houghton, P. J., Ren, Y., and Howes, M.-J. (2006). Acetylcholinesterase inhibitors from plants and fungi. *Nat. Product Rep.* 23, 181–199. doi: 10.1039/b508966m

Huang, L., Su, T., and Li, X. (2013). Natural products as sources of new lead compounds for the treatment of Alzheimer's disease. *Curr. Top. Med. Chem.* 13, 1864–1878. doi: 10.2174/15680266113139990142

Huang, Q.-Q., Bi, J.-L., Sun, Q.-Y., Yang, F.-M., Wang, Y.-H., Tang, G.-H., et al. (2012). Bioactive isoquinoline alkaloids from Corydalis saxicola. *Planta Med.* 78, 65–70. doi: 10.1055/s-0031-1280126

Huq, A. K., Jamal, J. A., and Stanslas, J. (2014). Ethnobotanical, phytochemical, pharmacological, and toxicological aspects of persicaria hydropiper (l.) delarbre. *Evid. Based Complement. Alternat. Med.* 2014:782830. doi: 10.1155/2014/782830

Imenshahidi, M., and Hosseinzadeh, H. (2016). Berberis vulgaris and berberine: an update review. *Phytother. Res.* 30, 1745–1764. doi: 10.1002/ptr.5693

Ingkaninan, K., Temkitthawon, P., Chuenchom, K., Yuyaem, T., and Thongnoi, W. (2003). Screening for acetylcholinesterase inhibitory activity in plants used

in Thai traditional rejuvenating and neurotonic remedies. *J. Ethnopharmacol.* 89, 261–264. doi: 10.1016/j.jep.2003.08.008

Johnson, G., and Moore, S. W. (2006). The peripheral anionic site of acetylcholinesterase: structure, functions and potential role in rational drug design. *Curr. Pharm. Des.* 12, 217–225. doi: 10.2174/138161206775193127

Jung, H. A., Ali, M. Y., Jung, H. J., Jeong, H. O., Chung, H. Y., and Choi, J. S. (2016). Inhibitory activities of major anthraquinones and other constituents from *Cassia obtusifolia* against β-secretase and cholinesterases. *J. Ethnopharmacol.* 191, 152–160. doi: 10.1016/j.jep.2016.06.037

Jung, H. A., Karki, S., Kim, J. H., and Choi, J. S. (2015). BACE1 and cholinesterase inhibitory activities of Nelumbo nucifera embryos. *Arch. Pharm. Res.* 38, 1178–1187. doi: 10.1007/s12272-014-0492-4

Jung, H. A., Min, B.-S., Yokozawa, T., Lee, J.-H., Kim, Y. S., and Choi, J. S. (2009). Anti-Alzheimer and antioxidant activities of Coptidis Rhizoma alkaloids. *Biol. Pharm. Bull.* 32, 1433–1438. doi: 10.1248/bpb.32.1433

Kamal, Z., Ullah, F., Ayaz, M., Sadiq, A., Ahmad, S., Zeb, A., et al. (2015). Anticholinesterse and antioxidant investigations of crude extracts, subsequent fractions, saponins and flavonoids of *Atriplex laciniata* L.: potential effectiveness in Alzheimer's and other neurological disorders. *Biol. Res.* 48:21. doi: 10.1186/s40659-015-0011-1

Kang, S. Y., Lee, K. Y., Sung, S. H., Park, M. J., and Kim, Y. C. (2001). Coumarins isolated from Angelica gigas inhibit acetylcholinesterase: structure-activity relationships. *J. Nat. Prod.* 64, 683–685. doi: 10.1021/np000441w

Kennedy, D. O., and Scholey, A. B. (2006). The psychopharmacology of European herbs with cognition-enhancing properties. *Curr. Pharm. Design* 12, 4613–4623. doi: 10.2174/138161206779010387

Khan, H., Amin, S., Kamal, M. A., and Patel, S. (2018). Flavonoids as acetylcholinesterase inhibitors: current therapeutic standing and future prospects. *Biomed. Pharmacother.* 101, 860–870. doi: 10.1016/j.biopha.2018.03.007

Kuk, E. B., Jo, A. R., Oh, S. I., Sohn, H. S., Seong, S. H., Roy, A., et al. (2017). Anti-Alzheimer's disease activity of compounds from the root bark of *Morus alba* L. *Arch. Pharm. Res.* 40, 338–349. doi: 10.1007/s12272-017-0891-4

Lai, D.-H., Yang, Z.-D., Xue, W.-W., Sheng, J., Shi, Y., and Yao, X.-J. (2013). Isolation, characterization and acetylcholinesterase inhibitory activity of alkaloids from roots of Stemona sessilifolia. *Fitoterapia* 89, 257–264. doi: 10.1016/j.fitote.2013.06.010

Lin, H. Q., Ho, M. T., Lau, L. S., Wong, K. K., Shaw, P. C., and Wan, D. C. (2008). Anti-acetylcholinesterase activities of traditional chinese medicine for treating Alzheimer's disease. *Chem. Biol. Interact.* 175, 352–354. doi: 10.1016/j.cbi.2008.05.030

Liu, J.-S., Zhu, Y.-L., Yu, C.-M., Zhou, Y.-Z., Han, Y.-Y., Wu, F.-W., et al. (1986). The structures of huperzine A and B, two new alkaloids exhibiting marked anticholinesterase activity. *Can. J. Chem.* 64, 837–839. doi: 10.1139/v86-137

Loizzo, M. R., Menichini, F., Tundis, R., Bonesi, M., Conforti, F., Nadjafi, F., et al. (2009). *In vitro* biological activity of Salvia leriifolia Benth essential oil relevant to the treatment of Alzheimer's disease. *J. Oleo Sci.* 58, 443–446. doi: 10.5650/jos.58.443

Loizzo, M. R., Tundis, R., Conforti, F., Menichini, F., Bonesi, M., Nadjafi, F., et al. (2010). *Salvia leriifolia* Benth (Lamiaceae) extract demonstrates *in vitro* antioxidant properties and cholinesterase inhibitory activity. *Nutri. Res.* 30, 823–830. doi: 10.1016/j.nutres.2010.09.016

Lopez, S., Bastida, J., Viladomat, F., and Codina, C. (2002). Acetylcholinesterase inhibitory activity of some Amaryllidaceae alkaloids and Narcissus extracts. *Life Sci.* 71, 2521–2529. doi: 10.1016/S0024-3205(02)02034-9

Ma, X., Tan, C., Zhu, D., Gang, D. R., and Xiao, P. (2007). Huperzine A from Huperzia species—an ethnopharmacolgical review. *J. Ethnopharmacol.* 113, 15–34. doi: 10.1016/j.jep.2007.05.030

Madeo, J., and Elsayad, C. (2013). The role of oxidative stress in Alzheimer's disease. *J. Alzheimers Dis. Parkinsonism* 3, 116–121. doi: 10.4172/2161-0460.1000116

Mehta, M., Adem, A., and Sabbagh, M. (2012). New acetylcholinesterase inhibitors for Alzheimer's disease. *Int. J. Alzheimers Dis.* 2012:728983. doi: 10.1155/2012/728983

Murray, A. P., Faraoni, M. B., Castro, M. J., Alza, N. P., and Cavallaro, V. (2013). Natural AChE inhibitors from plants and their contribution to Alzheimer's disease therapy. *Curr. Neuropharmacol.* 11, 388–413.doi: 10.2174/1570159X11311040004

Nwidu, L. L., Elmorsy, E., Thornton, J., Wijamunige, B., Wijesekara, A., Tarbox, R., et al. (2017). Anti-acetylcholinesterase activity and antioxidant properties of extracts and fractions of Carpolobia lutea. *Pharm. Biol.* 55, 1875–1883. doi: 10.1080/13880209.2017.1339283

Ohba, T., Yoshino, Y., Ishisaka, M., Abe, N., Tsuruma, K., Shimazawa, M., et al. (2015). Japanese Huperzia serrata extract and the constituent, huperzine A, ameliorate the scopolamine-induced cognitive impairment in mice. *Biosci. Biotechnol. Biochem.* 79, 1838–1844. doi: 10.1080/09168451.2015.1052773

Orhan, I. E., Orhan, G., and Gurkas, E. (2011). An overview on natural cholinesterase inhibitors–a multi-targeted drug class–and their mass production. *Mini. Rev. Med. Chem.* 11, 836–842. doi: 10.2174/138955711796575434

Ovais, M., Ayaz, M., Khalil, A. T., Shah, S. A., Jan, M. S., Raza, A., et al. (2018). HPLC-DAD finger printing, antioxidant, cholinesterase, and α-glucosidase inhibitory potentials of a novel plant Olax nana. *BMC Complement. Alter. Med.* 18:1. doi: 10.1186/s12906-017-2057-9

Penumala, M., Zinka, R. B., Shaik, J. B., and Amooru Gangaiah, D. (2017). *In vitro* Screening of three indian medicinal plants for their phytochemicals, anticholinesterase, antiglucosidase, antioxidant, and neuroprotective effects. *Biomed. Res. Int.* 2017:5140506. doi: 10.1155/2017/5140506

Penumala, M., Zinka, R. B., Shaik, J. B., Mallepalli, S. K. R., Vadde, R., and Amooru, D. G. (2018). Phytochemical profiling and *in vitro* screening for anticholinesterase, antioxidant, antiglucosidase and neuroprotective effect of three traditional medicinal plants for Alzheimer's disease and diabetes mellitus dual therapy. *BMC Complement. Alter. Med.* 18:77. doi: 10.1186/s12906-018-2140-x

Pereira, D. M., Ferreres, F., Oliveira, J. M., Gaspar, L., Faria, J., Valentão, P., et al. (2010). Pharmacological effects of Catharanthus roseus root alkaloids in acetylcholinesterase inhibition and cholinergic neurotransmission. *Phytomedicine* 17, 646–652. doi: 10.1016/j.phymed.2009.10.008

Perry, N. S., Bollen, C., Perry, E. K., and Ballard, C. (2003). Salvia for dementia therapy: review of pharmacological activity and pilot tolerability clinical trial. *Pharmacol. Biochem. Behav.* 75, 651–659. doi: 10.1016/S0091-3057(03)00108-4

Prince, M. J. (2015). *World Alzheimer Report 2015: The Global Impact of Dementia: An Analysis of Prevalence, Incidence, Cost and Trends*. London: Alzheimer's Disease International.

Pueyo, I. U., and Calvo, M. I. (2009). Assay conditions and validation of a new UV spectrophotometric method using microplates for the determination of polyphenol content. *Fitoterapia* 80, 465–467. doi: 10.1016/j.fitote.2009.06.008

Qian, Z. M., and Ke, Y. (2014). Huperzine A: is it an effective disease-modifying drug for Alzheimer's disease? *Front. Aging Neurosci.* 6:216. doi: 10.3389/fnagi.2014.00216

Rafii, M., Walsh, S., Little, J., Behan, K., Reynolds, B., Ward, C., et al. (2011). A phase II trial of huperzine A in mild to moderate Alzheimer disease. *Neurology* 76, 1389–1394. doi: 10.1212/WNL.0b013e318216eb7b

Rasheed, D. M., El Zalabani, S. M., Koheil, M. A., El-Hefnawy, H. M., and Farag, M. A. (2013). Metabolite profiling driven analysis of Salsola species and their anti-acetylcholinesterase potential. *Nat. Prod. Res.* 27, 2320–2327. doi: 10.1080/14786419.2013.832676

Reza, A. A., Hossain, M. S., Akhter, S., Rahman, M. R., Nasrin, M. S., Uddin, M. J., et al. (2018). *In vitro* antioxidant and cholinesterase inhibitory activities of Elatostema papillosum leaves and correlation with their phytochemical profiles: a study relevant to the treatment of Alzheimer's disease. *BMC Complement. Alter. Med.* 18:123. doi: 10.1186/s12906-018-2182-0

Rollinger, J. M., Hornick, A., Langer, T., Stuppner, H., and Prast, H. (2004). Acetylcholinesterase inhibitory activity of scopolin and scopoletin discovered by virtual screening of natural products. *J. Med. Chem.* 47, 6248–6254. doi: 10.1021/jm049655r

Sahoo, A. K., Dandapat, J., Dash, U. C., and Kanhar, S. (2018). Features and outcomes of drugs for combination therapy as multi-targets strategy to combat Alzheimer's disease. *J. Ethnopharmacol.* 215, 42–73. doi: 10.1016/j.jep.2017.12.015

Saleem, H., Ahmad, I., Shahid, M. N., Gill, M., Nadeem, M. F., Mahmood, W., et al. (2016). *In vitro* acetylcholinesterase and butyrylcholinesterase inhibitory potentials of Jatropha gossypifolia plant extracts. *Acta Poloniae Pharmaceut. Drug Res.* 73, 419–423.

Sarker, S. D., Latif, Z., and Gray, A. I. (2005). *Natural Products Isolation*. Totowa, NJ: Humana Press.

Scheltens, P., Blennow, K., Breteler, M. M., De Strooper, B., Frisoni, G. B., Salloway, S., et al. (2016). Alzheimer's disease. *Lancet* 388, 505–517. doi: 10.1016/S0140-6736(15)01124-1

Schrattenholz, A., Pereira, E. F., Roth, U., Weber, K. H., Albuquerque, E. X., and Maelicke, A. (1996). Agonist responses of neuronal nicotinic acetylcholine receptors are potentiated by a novel class of allosterically acting ligands. *Mol. Pharm.* 49, 1–6.

Shu, Y.-Z. (1998). Recent natural products based drug development: a pharmaceutical industry perspective. *J. Nat. Prod.* 61, 1053–1071. doi: 10.1021/np9800102

Suganthy, N., Pandian, S. K., and Devi, K. P. (2009). Cholinesterase inhibitory effects of rhizophora lamarckii, avicennia officinalis, sesuvium portulacastrum and suaeda monica: mangroves inhabiting an Indian coastal area (Vellar Estuary). *J. Enz. Inhibit. Med. Chem.* 24, 702–707. doi: 10.1080/14756360802334719

Takizawa, C., Thompson, P. L., Van Walsem, A., Faure, C., and Maier, W. C. (2015). Epidemiological and economic burden of Alzheimer's disease: a systematic literature review of data across Europe and the United States of America. *J. Alzheimers Dis.* 43, 1271–1284. doi: 10.3233/JAD-141134

Tarawneh, R., and Holtzman, D. M. (2012). The clinical problem of symptomatic Alzheimer disease and mild cognitive impairment. *Cold Spring Harbor Perspect. Med.* 2:a006148. doi: 10.1101/cshperspect.a006148

Thomsen, T., and Kewitz, H. (1990). Selective inhibition of human acetylcholinesterase by galanthamine *in vitro* and *in vivo*. *Life Sci.* 46, 1553–1558. doi: 10.1016/0024-3205(90)90429-U

Tune, L. E. (2001). Anticholinergic effects of medication in elderly patients. *J. Clin. Psychiatry* 62, 11–14.

Tung, B. T., Hai, N. T., and Thu, D. K. (2017). Antioxidant and acetylcholinesterase inhibitory activities *in vitro* of different fraction of *Huperzia* squarrosa (Forst.) Trevis extract and attenuation of scopolamine-induced cognitive impairment in mice. *J. Ethnopharmacol.* 198, 24–32. doi: 10.1016/j.jep.2016.12.037

Uriarte-Pueyo, I., and Calvo, M. (2011). Flavonoids as acetylcholinesterase inhibitors. *Curr. Med. Chem.* 18, 5289–5302. doi: 10.2174/092986711798184325

Wong, K. K.-K., Ho, M. T.-W., Lin, H. Q., Lau, K.-F., Rudd, J. A., Chung, R. C.-K., et al. (2010). Cryptotanshinone, an acetylcholinesterase inhibitor from *Salvia miltiorrhiza*, ameliorates scopolamine-induced amnesia in Morris water maze task. *Planta Med.* 76, 228–234. doi: 10.1055/s-0029-1186084

Yang, Z.-D., Zhang, X., Du, J., Ma, Z.-J., Guo, F., Li, S., et al. (2012). An aporphine alkaloid from *Nelumbo nucifera* as an acetylcholinesterase inhibitor and the primary investigation for structure–activity correlations. *Nat. Prod Res.* 26, 387–392. doi: 10.1080/14786419.2010.487188

Zhao, Y., Dou, J., Wu, T., and Aisa, H. A. (2013). Investigating the antioxidant and acetylcholinesterase inhibition activities of *Gossypium herbaceam*. *Molecules* 18, 951–962. doi: 10.3390/molecules18010951

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