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Review Article

Medicinal Plants with Acetylcholinesterase Inhibitory Activity: Therapeutic Potential of Brazilian Plants for the Treatment of Alzheimer's Disease

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ABSTRACT
Alzheimer's disease (AD) is characterized by persistent impairment of cognitive and psychomotor functions, resulting in reduced short-term memory. In current pharmacotherapy, some available acetylcholinesterase inhibitors (AChEi) have side effects, such as hepatotoxicity. Hence, it is necessary to investigate other sources to obtain compounds inhibiting AChE. In this context, the objective of this study was to review the main publications involving plants collected in Brazil tested for the inhibition of AChE, which may lead to new phytotherapeutic inhibitors. This review was carried out by searching the PubMed, Scopus, and Science Direct databases during September 2018, using several combinations of the following keywords: extract, AChE, Brazil and Alzheimer's. Inclusion criteria were articles with plant studies collected in Brazil for the inhibition of AChE (*in vivo* and/or *in vitro*), with keywords in the title, abstract, or full text. Articles with studies of purified, synthetic, or semi-synthetic compounds were excluded. In this research, 298 articles were identified and 31 articles were selected. More than forty species of the families *Fabaceae*, *Anacardiaceae*, *Annonaceae*, *Malvaceae*, *Myrtaceae*, *Arecaceae* and *Lauraceae* were found, and the most cited substances were the phenolic compounds and flavonoids. Alkaloids and steroids were also found in some active plants. The relevance and importance of this work lies in the review of new potential herbal drugs for the treatment of AD, and this survey could collaborate for the development of new medicinal alternatives for this and other neurodegenerative problems related to cerebral availability of acetylcholine.
Key words: Acetylcholinesterase, Alzheimer, Medicinal plants.

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INTRODUCTION

One of the major neurodegenerative dementias, Alzheimer's disease (AD), is characterized by persistent damage to cognitive and psychomotor functions, resulting in reduced short-term memory. Physiologically, it occurs with the deposition of senile plaques, originated by the extracellular accumulation of the amyloid beta protein (Ab), together with intracellular neurofibrillary tangles.[1] As a consequence, a cascade of biochemical processes occurs (generation of free radicals, inflammation, calcium deregulation, and synaptic damages), bringing damage to the cholinergic system.[2]

The elevation of synaptic levels of acetylcholine (ACh) in the brain helps restore cognitive function and reduces the effects of AD. Therefore, the use of AChsterase inhibitors (AChEi) stands out as the more efficient strategy. The enzyme acts on the rapid hydrolysis of ACh in the synaptic cleft and neuromuscular junction, promoting the termination of nerve impulse. However, individuals with AD have increased enzymatic activity of AChE, which causes a decrease in the rates of ACh in the brain.[3]

ACh is a molecule which has an ester group and a quaternary amine. In the presynaptic neuron, its synthesis occurs from choline and acetylcoenzyme A. When produced, the ACh is conditioned in vesicles, until a stimulus occurs that results in its release in the synaptic cleft and connection to the postsynaptic receptor, promoting the information. After conducting the message, the ACh molecule separates itself from the postsynaptic receptor and returns to the synaptic cleft, where it undergoes hydrolysis by AChE, giving rise to acetic acid and choline.[4] In the pharmaceutical market, some AChE inhibitors used for the treatment of AD are available such as Tacrine", Donepezil", Rivastigmine", and Galantamine". However, some of these inhibitors may promote side effects such as hepatotoxicity, cardiac arrhythmias, and urinary incontinence, what could result in the discontinuation of treatment.[2,3,5] It is, therefore, necessary to inves-

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tigate other sources for obtaining AChE inhibitor compounds that are nontoxic, are easy to access, and with a low cost.

Plants as a source of anticholinesterase substances

Natural products are sources of great relevance for the search of new compounds with potential to inhibit or even delay the action of key enzymes in neurodegenerative diseases.[6–8] Phytochemical studies have enabled the discovery of new anticholinesterase substances. In this sense, examples of biodiversity have been studied due to its popular use, and one of the most widespread models in phytomedicines for the improvement of cognitive function is *Ginkgo biloba* extract.[9]

AChEis are the main class of drugs currently used to treat the dementia phase caused by AD. Among the substances approved and used in the clinic, Galantamine is a natural derivative. Several species of plants produce classes of secondary metabolites such as alkaloids, coumarins, terpenes, and polyphenols that have already been evaluated for their anticholinesterase activity and have become potential candidates for the treatment of AD.[10]

Flavonoids are secondary metabolites that can slow neurodegenerative processes such as AD because of their anti-amyloidogenic and antioxidant properties.[11] A group of researchers isolated 13 new flavonoid derivatives from the leaves of *G. biloba,* which showed efficiency by improving signal transmission at nerve synapses, expanding the effects of ACh.[12,13] Another group of researchers suggested that quercetin and tyloside are useful for the treatment of typical dementia of AD. The study also suggested that these inhibitors antagonized AChE by increasing the concentration of ACh at the synapses between cholinergic neurons.[14–15]

In a study carried out by Kongkiatpaiboon *et al.*,[16] the AChE inhibitory activity of root extracts of the *Stemona collinsiae* Craib species was tested. This activity was attributed to the presence of didehydrostemofoline and stemofolin alkaloids in the extract, and the activity was confirmed after the tests were performed with the isolated metabolites. Another study evaluated the activity of inhibition of the enzyme of five isolated alkaloids from *Holarrhena antidysenterica,* of which four of them presented strong inhibitory activity of AChE. The alkaloids conessine, conessimine, conamine, and conimine showed 50% inhibitory concentration (IC_{50}) values between 4 and 28 μM.[17]

Ginsenosides and terpenoids obtained from *Panax ginseng* have beneficial and neuroprotective effects. Other terpenoids with neuromodulatory activity are ginkgolides and cyclic diterpenes of the labdane type commonly isolated from *G. biloba.* In this species, the terpene trilactones, i.e., ginkgolides, are the main active substances that can enhance the production of acetylcholine.[18]

Coumarins also have potential biological properties for the treatment of AD. Substituted synthetic coumarins were synthesized and evaluated as inhibitors of monoamine oxidases and AChE by Vina *et al.*[19] Coumarins showed positive results for inhibition of the two enzymes. Other studies investigated the activity of coumarins after structural modifications in order to obtain additional biological activity of inhibition of beta-amyloid protein deposition and potentiated the effects of these metabolites for the treatment of AD.[20]

In this context, the aim of this study was to review the main publications involving plants collected in Brazil tested for the inhibition of AChE, to provide a deeper survey for new natural therapeutic source that might to lead to novel phytotherapic AChE inhibitors.

MATERIALS AND METHODS

This review was carried out by a search performed in September 2018, and there was no restriction in relation to the year of publication. This literature search was performed through specialized search databases (PubMed, Scopus, and Science Direct) using several combinations of the following keywords: extract, acetylcholinesterase, Brazil, and Alzheimer. The manuscript selection was based on the following inclusion criteria: articles with studies of plants collected in Brazil for the inhibition of AChE (in *vivo* and/or *in vitro),* with keywords in the title, abstract, or full text. Articles with studies of purified, synthetic, or semi-synthetic compounds were excluded. In this research, 298 articles were identified; however, 31 articles were selected as the others did not meet the inclusion criteria or were indexed in two or more databases and were considered only once.

RESULTS AND DISCUSSION

Several studies aimed to evaluate the inhibitory capacity of botanical extracts against AChE activity, and a lot of species were considered active to inhibit this enzyme. The extracts were prepared by several extractive procedures, and the maceration at room temperature was the most used method. The leaves were the most frequently cited plant parts. The main compounds found in the extracts were phenolic compounds, mainly flavonoids and anthocyanins. However, alkaloids and steroids were found in some active plant extracts [Table 1].

Flavonoids are the largest group of phenolic compounds originated from plants, accounting for more than half of the 8000 phenolic compounds that occur naturally. The basic chemical structure of flavonoids is based on two aromatic rings A and B, joined by a 3-carbon bridge, generally a heterocyclic ring. These substances exhibit a characteristic antioxidant activity, which is related to their ability to eliminate free radicals and to donate hydrogen atoms or electrons or chelates of cations of metal compounds.[39]

The complex chemical structure of flavonoids, as well as the diversity of their molecules, makes this class of secondary metabolites great candidates for the search for new bioactive molecules. Some of the structural features and nature of the substitutions in rings B and C may determine the antioxidant activity of flavonoids. The degree of hydroxylation and the positions of the hydroxyl groups on ring B (in particular, the "catechol" group) can increase the bioactivities. This could be explained by the greater radical stability conferred by relocation or may also act as a preferred bonding site for metals.[39]

With the major number of studies found, 11 species from *Fabaceae* family were considered active for enzyme inhibition. From this family, a great number of plants were active for the inhibition of AChE: the barks of *Anadenanthera peregrina, Bauhinia forficata, Copaifera langsdorffii, Plathymenia reticulata, Senna alata, Senna cana* and the leaves of *Caesalpinia ferrea, Cassia fistula, Senna pendula,* and *Stryphnodendron coriaceum.* The main compounds found in this family were phenolic compounds, anthraquinones, steroids, flavonoids, tannins, triterpenoids, and xanthones.[22,28,29]

From *Anacardiaceae* family, the extract from the cashew nutshell from *Anacardium occidentale* and the leaves of *Mangifera indica* could inhibit AChE, and phenolic compounds and flavonoids were found.[21,22] The seeds of *Spondias tuberosa* and *Spondias purpurea* were also active for the inhibition of the enzyme, and phenolic compounds, tannins, leucoanthocyanidins, catechins, flavones, anthraquinones, triterpenoids, and sterols were present in the extracts, showing the importance of these secondary metabolite for the family's bioactivity.[40]

In a screening of five species from *Annonaceae* family, only *Annona cacans* was active. *Acacia coriacea* seed extract presented the greatest inhibition, with 52%, followed by *Duguetia furfuracea* and *Annona crassiflora.* Phenolic acids were found in the phytochemical analysis of these species (caffeic acid, p-coumaric acid, ferulic acid, sinapic acid, and rutin).[23]

Table 1: Medicinal plants from Brazil found in the literature for acetylcholinesterase inhibition

Species	Extraction	Results	Chemical constituents	References
A. occidentale	Maceration (72 h) in an amber vessel using a proportion of 3 ml of ethanol 70% for each gram of drug	Active	Phenolic compounds, coumarins, quinones, anthocyanidins, triterpenes, steroids, flavonoids, saponins, and lipid substances	[21]
M. indica, S. tuberosa, and *S. purpurea*	Maceration with 70% ethanol for 7 days	Active	Phenolic compounds, tannins, leucoanthocyanidins, catechins, flavones, anthraquinones, triterpenoids, and sterols	[22]
A. coriacea, A. crassiflora, A. sylvatica, and *D. furfuracea*	Maceration with methanol at room temperature	Active	Phenolic compounds (caffeic acid, sinapic acid, p-coumaric acid, and acido ferulico), and flavonoids (rutin)	[23]
T. catharinensis	Extraction with a Soxhlet apparatus using ethanol as extraction solvent (10 mL ethanol/g) for 12 h at a temperature of nearly 70°C	Active	Alkaloids (6-epi-affinine, coronaridine-hydroxyindolenine, voachalotine, voacristine-hydroxyindolenine, and 12-methoxy-n-methyl-voachalotine)	[24]
I. paraguariensis	Infusion in aqueous medium using 7 g of herb per 100 mL of ultra-purified water at 65°C and at 75°C for 15 min	Active after acute exposure	Methylxanthines (caffeine and theobromine), phenolic compounds, and flavonoids	[25]
E. oleracea	Maceration with 70% ethanol for 7 days	Active	Phenolic compounds and flavonoids	[22]
V. polystachya	Maceration with 3 L n-Hex at room temperature once a day for 15 days; then resubmitted to ethanol 95% extraction (6 L) at room temperature once a day for 15 days	Active	Iridoids, terpenes, and phenolic acids (ursolic acid)	[26]
C. coriaceum	Maceration, with 96% ethanol, at 12 h cycle of light, without agitation for 7 days	Active	Alkaloids, steroids, saponins, tannins, phenols, and flavonoids (rutin, quercetin, and isoquercetin)	[27]
I. asarifolia, I. batatas, K. brasiliensis, K. gastonis-bonnieri, J. curcas, J. gossypiifolia, J. pohliana, and *P. amarus*	Extracted with EtOAc and methanol	Active	Not investigated in this study	[28]
A. peregrina	Maceration with 70% ethanol for 7 days	Active	Phenolic compounds and flavonoids	[22]
C. ferrea	Extracted with methanol	Active		[28]
B. forficata	Maceration with 70% ethanol for 7 days	Active	Phenolic compounds and flavonoids	[22]
C. fistula	Extracted with EtOAc and	Active	Not investigated in this study	[28]
C. langsdorffii	Methanol Maceration with 70% ethanol for 7 days	Active	Phenolic compounds and flavonoids	[22]
L. leucocephala	Extracted with methanol	Active		[28]
P. reticulata	Maceration with 70% ethanol for 7 days	Active	Phenolic compounds and flavonoids	[22]
S. alata	Extracted with EtOAc and methanol	Active	Not investigated in this study	[28]
S. cana	Maceration with n-Hex for 7 days	Active	Anthraquinones and triterpenoids	[29]
S. pendula	Maceration with n-Hex for 7 days and maceration with ethanol for 7 days	Active	Anthraquinones and triterpenoids	[29]
S. coriaceum	Maceration with 70% ethanol for 7 days	Active	Phenolic compounds and flavonoids	[22]
O. aciphylla	Maceration with absolute ethanol for 72 h using solvents of increasing polarity (Hex, EtOAc, ethanol, and water)	Active for all extracts	Flavonoids (procyanidin B-type dimer, propelargonidin dimer, flavan-3-ol catechin, and a flavone methoxy-luteolin-deoxyhexose-hexose)	[30]
G. herbaceum	Extracted with methanol	Active	Not investigated in this study	[28]
G. ulmifolia	Maceration with ethanol for 7 days	Active	Phenolic compounds (chlorogenic acid and caffeic acids) and flavonoids (catechin, rutin, quercetin, quercetin, and luteolin)	[31]
L. divaricata	Decoction for 10 min in distilled water at 100°C	Active	Phenolic compounds (gallic acid, chlorogenic acid, caffeic acid, and rosmarinic acid) and flavonoids (catechin, epicatechin, vitexin, rutin, quercetin, and luteolin)	[33]
L. divaricata	Maceration with 70% ethanol for 7 days	Active	Phenolic compounds and flavonoids	[22]

continued...

Table 1: Contd...

Species	Extraction	Results	Chemical constituents	References
E. dysenterica	Infusion of powdered leaves (0.1 kg) was soaked in 0.5 L of water at 70°C	Active	Flavonoids (catechin and quercetin)	[34]
E. uniflora	Unprocessed frozen fruits (30 g) were sonicated for 30 min at 25°C in 90 mL 70:30 v/v ethanol-water (pH 1.0)	Active	Phenolic compounds and flavonoids (anthocyanins: Delphinidin-O-glucoside, cyanidin-3-O-glucoside, cyanidin-O-galactoside, petunidin-O-hexoside, pelargonidin-3-O-glucoside, pelargonidin-O-rutinoside, malvidin-3-O-glucoside, malvidin-O-pentoside, and malvidin-O-acetylhexoside)	[35]
P. guajava	Maceration with 70% ethanol for 7 days	Active	Phenolic compounds and flavonoids	[22]
-	Maceration with 50% ethanol for 72 h	Active	Phenolic compounds	[36]
S. aromaticum	Maceration with 70% ethanol for 7 days	Active	Phenolic compounds and flavonoids	[22]
B. glabra	Extracted with EtOAc	Active	Not investigated in this study	[28]
B. glabra	Maceration with 99% ethanol (1:10) for 15 days	Active	Terpenoids (phytol, squalene, stigmasterol, and geranylgeraniol), carotenoids (a, y-tocopherol), phenolic compounds (caffeic, vanillic, coumaric, and ferulic acids), and flavonoids (quercetin)	[37]
C. limmonia	Extracted with EtOAc	Active	Not investigated in this study	[28]
Prockia crucis	Maceration with absolute ethanol for 7 days	Active	Phenolic compounds (gallic acid, chlorogenic acid, and caffeic acid), flavonoids (rutin, quercetin, kaempferol, luteolin, and apigenin), and coumarin	[38]

The phenolic compounds and flavonoids were also the components found in several active plants: the seeds from *Euterpe oleracea (Arecaceae)*[22] and leaves of *Ocotea aciphylla (Lauraceae)*.[30] From *Malvaceae* family, these compounds were also related to the activity of the leaves of *Guazuma ulmifolia*[31] and the leaves of *Luehea divaricata*[22–32–33] From *Myrtaceae* family, some extracts were active, and a characteristic composition of phenyl compounds, flavonoids, and anthocyanins was found: the leaves of *Eugenia dysenterica,*[34] the fruits of *Eugenia uniflora,*[35] the leaves of *Psidium guajava,* and the fruits of *Syzygium aromaticum*.[22,36]

In a screening study of 18 species collected in the state of Ceara, Brazil, the most active plants were *Ipomoea asarifolia, Jatropha curcas, Jatropha gossypiifolia, Kalanchoe brasiliensis,* and *S. alata,* with IC_{50} ranging from 0.08 mg/mL to 0.12 mg/mL.[28] These values were close to those of synthetic compounds currently used in AD pharmacotherapy, which demonstrate the importance of these species (Tacrine IC_{50} = 0.1 mM, Galantamine IC_{50} = 0.3 μM, Rivastigmine IC_{50} = 0.7 μM, and donepezil IC_{50} = 0.002 μM).[41]

Despite the main compounds found in this review were phenolic compounds, alkaloids were also found. From *Tabernaemontana catharinensis* five alkaloids were identified by mass spectrometry (6-epi-affinine, coronaridine-hydroxyindolenine, voachalotine, voacristine-hydroxyindolenine, and 12-methoxy-n-methyl-voachalotine), and an unknown compound with m/z 385.21 were identified by mass spectrometry, whose spectrum suggests a derivative of voacristine or voacangine. The fractions with the best results for anticholinesterase activity (IC_{50} = 7.7-8.3 μg/mL) were composed by 16-epi-affinine.[24] Alkaloids were also positive in the phytochemical screening in the peels and pulp extracts of *Caryocar coriaceum (Caryocaraceae),* and these extracts were also active for AChE inhibition.[27]

Methylxanthines were found in the extract of *Ilex paraguariensis,* prepared by infusion following the traditional method for tea preparation. The anticholinesterase activity was tested in aluminum toxicity *in vivo,* using strains of *Caenorhabditis elegans,* and the extract was considered active for the inhibition of AChE after acute exposure.[25] Iridoids, terpenes, and phenolic acids (ursolic acid) were found in the active extracts of the roots and rhizomes of *Valeriana polystachya (Caprifoliaceae).*[26]

CONCLUSIONS

In view of the results found with this survey, it was possible to observe that several species of medicinal plants in Brazil were investigated regarding their potential for the inhibition of AChE enzyme. These studies aimed to evaluate the ability of plant extracts to inhibit the AChE activity, and many species were considered active. The extraction method most commonly used for the extraction of secondary metabolites was cold maceration, and the aerial parts of the plants were the most cited. Among the species investigated, those belonging to the *Fabaceae* family were the most studied, with approximately 11 species active against the enzyme. In this review, phenolic compounds, anthraquinones, steroids, flavonoids, tannins, triterpenoids and xanthones were presented as the main active compounds found.

It was also possible to verify that most of the studies carried out on these species in Brazil only investigated the potential of the crude extracts obtained, presenting assumptions about the observed activity and correlating this activity with the presence of the secondary metabolites identified in the extract. These results highlight the importance of investigating these compounds in an isolated way to better understand the compound responsible for the activity, bringing knowledge to the development of phytopharmaceuticals.

The relevance and importance of this work lies in the review of new potential herbal drugs for the treatment of AD, and this survey could collaborate for the development of new medicinal alternatives for this and other neurodegenerative problems related to the cerebral availability of ACh.

CONFLICTS OF INTEREST

The Authors declare no conflict of interest.

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