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Acetylcholinesterase Inhibitory Potential in Cinnamon Seed Oil (*Cinnamomum zeylanicum* Nees) Lauraceae from Roraima, Brazil

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One of the oldest plants known and considered a symbol of wisdom in antiquity especially in China is cinnamon (*Cinnamomum zeylanicum* Nees). The objective of this work was to study the fixed oil extracted from cinnamon (*Cinnamomum zeylanicum* Nees) seeds regarding its biological potential for inhibition of acetylcholinesterase. The inhibitory activity test of hexane extract studied on the enzyme acetylcholinesterase was conducted based on Ellman spectrophotometric method. The percentage of acetylcholinesterase enzyme inhibition was 65.5%, being considered a potent inhibitor according to the literature standarts. In conclusion, the results indicate that the oil can be used in the pharmaceutical industry as part or to develop drugs for treatment of certain neurodegenerative diseases, such as Alzheimer's disease.
Keywords: Fixed oil, Biological activity, Neurodegenerative diseases, Alzheimer, Natural products.

1. Introduction

Cinnamomum zeylanicum, popularly known as cinnamon, belongs to Lauraceae family and genus *Cinnamomum* comprises about 250 species. This species grows as a tree and is native to India and Indochina, with the three main species of interest *C. zeylanicum* (Figure 1), *C. cassia* Blume and *C. camphora* L. *Cinnamon* have biological activities, such as analgesic, antiseptic, antispasmodic, aphrodisiac, astringent, carminative, hemostatic, insecticidal, parasiticidal, and, also, have functional and nutraceutical properties of biotechnological interest (Ostroschi et al., 2018; Abdeen et al., 2019).
Cinnamon's oil can be obtained from different parts of the fruit such as the seeds and has great biotechnological importance, due differences in the characteristics of aroma, flavor and mainly chemical composition (Legge, 1974). It is a yellowish or brownish liquid that darkens and thickens over time or by prolonged exposure to air. Its smell and taste are very characteristic, being little soluble in water and quite soluble in alcohol and glacial acetic acid (Saltos, 2001).
The most common applications of this oil is the use in perfumery, food industry, pharmaceutical, compositions for dentists and beverages, among other products, that can be still characterized as having a sweet, spicy and powerful taste (Molinas, 1970). The *C. zeylanicum* species is described to contain eugenol as the main

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component (75-85%), which has high antibacterial activity. It also contains cinnamaldehyde (5%), which contributes to its aromatic character and antimicrobial properties (Saltos, 2001).
In addition, it has great medicinal interest, due its therapeutic use as carminative and the diluted essential oil can also be applied to the skin in the form of massage, to improve circulation. It has been reported as an excellent bactericidal, antifungal, antiviral, and possess anti-hepatotoxicity and nephrotoxicity (Hussain et al., 2019), acaricide, antioxidant (Mahomoodally et al., 2018), nematicide, insecticide (Jumbo et al., 2018) activities and combats bacterial dental plaque. It has also been shown to inhibit fungi, such as *Aspergillus niger*, *A. fumigatus*, *A. nidulans*, *A. falvus*, *Candida albicans*, *C. tropicalis*, *C. pseudotropicalis*, *Histoplasma capsulatum,* as well as *Fusarium proliferatum* (Velluti, 2003).
An important line which is emerging is the research in the potential of oils and extracts to combat neurodegenerative diseases, such as Alzheimer. This illness constitutes one of the most worrisome diseases worldwide, since it is neurodegenerative and irreversible, characterized by the formation of senile plaques where □-amyloid is the main constituent (Dos Santos et al., 2017). In order to treat this problem, numerous approaches have been carried out to restore central cholinergic function including the utilization of acetylcholinesterase (AChE) inhibitory substances, since that enzyme is the main protein responsible for the hydrolysis of acetylcholine (Lopez et al., 2005; Mirmosayyeb et al., 2017; Momtaz et al., 2018).
In Alzheimer's disease, the key hypothesis is that inhibition of acetylcholinesterase, the enzyme that catalyzes the hydrolysis of acetylcholine, increases the acetylcholine in the brain by improving the cholinergic functions in patients with that disease (Boaventura et al., 2018). In the search for inhibitors of acetylcholinesterase, natural products, usually plant extracts or different oils providing bioactive secondary metabolites, can be studied for the development of new drugs (Cahliková et al., 2015).
The bioactivity of botanical oils and extracts of *C. zeylanicum* specifically, are extensively studied in different areas of knowledge (Saeed et al., 2018; Vallianou et al., 2018; Khater, Geden, 2018; De Souza et al., 2018). These studies also demonstrate the potential of the botanical genus *Cinnamomum* in the inhibition of AChE and induction of epigenetic modifications of Alzheimer's disease (Mesripour et al., 2016; Ribeiro-Santos et al., 2017). However, there are not enough studies on the potential of *C. zeylanicum* for inhibition of acetylcholinesterase and antiamyloidogenic activity (Madhavadas, Subramanian, 2017; Omar, 2017), especially on chephotypes submitted to the edaphoclimatic and ecophysiological conditions of the Brazilian tropical savannah. Knowing this, the objective of this work was to study the potential of the oil extracted from seeds of cinnamon to inhibit AChE. Figure 1 shows images of trees, leaves and flowers of Cinnamon.

Figure 1: Tree, flowers and fruits of Cinnamomum zeylanicum.

2. Materials and methods

2.1 Collection and processing of cinnamon seeds

The collection of the plant for morphological identification was carried out from a 7 m high tree showing white flowers and purple fruits in the municipality of Boa Vista, urban perimeter, Roraima, Brazil (Caimbé neighbourhood, Jorge Fraxe street No. 1092, geographical coordinates, 2°49'46"N, 60°43'11"W), being identified at the National Institute of Amazonian Research (INPA) in Manaus as *Cinnamomum zeylanicum* Nees, with the common name cinnamon, belonging to the Lauraceae family. An exsiccate was deposited in the INPA herbarium under Nº 268121. The climate of the collection zone is characterized as rainy tropical (Aw), according to the classification of Köppen on climatic types. The access was duly registered in the National System of Management of Genetic Heritage and Associated Traditional Knowledge - SisGen linked to the Ministry of the Environment - MMA, according to specific Brazilian legislation, under number A87FF8B.

Once collected the seeds were washed with distilled water and the particles and impurities were removed as part of hygienization process. Then, they were dried in a circulation oven air at 40 °C for 72 hours until reaching constant. Finally, the seeds were milled and screened in a stainless steel sieve with a grain size of 20-40 Mesh, after which the powder was weighed and stored in amber flask until the analyzes were carried out (Matos, 1988; Jorge; Luzia, 2012). These procedures were taken in the Laboratory of Environmental Chemistry of the Federal University of Roraima.

2.2 Extraction of fixed oil from seeds

The extraction of the oil from cinnamon seeds was performed in triplicate, using a Soxhlet system and solvent hexane. Initially, the solid powdered material stored was weighed in triplicate and placed in cartridges that were placed in Soxhlet apparatus and together with 500 mL of hexane. The system was heated to the boiling point of the solvent (65 °C). The system was switched off after six hours of extraction, cooled to room temperature and then filtered obtaining the cinnamon oil dissolved in hexane. Immediately after this, solvent was removed through a rotatory-evaporatory system. Procedure was carried out in triplicate and the oils free of excess solvent were transferres to three amber vials previously weighed. The remaining hexane was removed through gaseous nitrogen; finally the three samples were weighted. Samples were stored in amber flasks under nitrogen atmosphere until further analysis (Jorge, Luzia, 2012).

2.3 Acetilcolinesterase (AChE) inhibition assay

Aliquots of a working solution (25 µL) (sample in DMSO 10 mg mL^{-1}) were added to microplate wells and positive and negative controls were also prepared. To the first five wells of a column (positive control) 25 µL of an eserine (positive control) solution prepared at 10 mg mL^{-1} (31 mM; 2.7 mM in the whole reaction mixture 275 µL) in Tris/HCl at pH 8.0) was added. Then, 25 µL of acetylthiocholine iodide (ATChI, Sigma A5751) 15 mM; the reaction mixture, 125 µL of 5',5-dithio-bis (2-nitrobenzoate) (DTNB, Sigma D8130) (3 mM) and 50 µL of Tris/HCl (50 mM, pH 8) containing 0.1% (m/v) bovine serum albumin was added to each well. Absorbance was measured at 405 nm every 1 min for 8 times. Then 25 µL (0.226 U mL^{-1}) of Electric eel AChE (type VI-S) provided by Sigma (C3389-500UN) in Tris/HCl was added to each well. Absorbance was measured at 405 nm by 10 times (Frank,Gupta, 2005; Ellman et al.,1961) and described by Dos Santos et al. (2015).

3. Results and discussion

After extraction, the yield of crude hexane extracts was 50.29 ± 1.12%, which represents a good yield. The percentage of acetylcholinesterase inhibition obtained for cinnamon seeds oil in this work was 65.5% According to Vinutha et al. (2007) acetylcholinesterase inhibitory potential can be classified as high when percent inhibition is greater than 50% (potent inhibition); moderate when inhibition varies from 30 to 50%; and weak for inhibition values below 30%. Although serine, the positive control used as reference in this assay was 97.55 ± 1.52%, it must be considered that serine is a chemical in its pure form while cinnamon's oil is a mixture of several components.

In this line of research, investigations related to the inhibition potential of extracts and oils of *C. zeylanicum* on the enzyme AChE demonstrate the antiamiloidogenic (Madhavadas, Subramanian, 2017), biochemical and enzymatic effects of this botanical species. This confirms its potential for systematic studies in a therapeutic and pharmacological approach for the prevention and treatment of Alzheimer's disease and the importance of the present study. From the results found in the literature and confronted with the responses of this work, it was verified equivalent or inferior effects related to the bioactivity of the cinnamon seed oil for inhibition of AChE when compared with other natural products of the same species.

When assessing the inhibitory potential on the acetylcholinesterase enzyme of the essential oil of leaves and barks of *C. zeylanicum* fruits, Aumeeruddy-Elalfi et al. (2018) found inhibition effect of 61.36%. Approximate value to that found in the inhibitory response promoted by cinnamon seeds oil. The authors corroborates that the pharmacological activities of AChE inhibitors are important in the inactivation of the enzymatic activity, resulting in the accumulation of acetylcholine in the synaptic regions, which leads to a better stimulation of the cholinergic receptors.

Inhibitory responses of acetylcholinesterase from aqueous and ethanolic extracts of *C. zeylanicum* were also studied by Kumar et al. (2012), where they found an effect of 46.84 ± 0.003 40.83 ± 0.005%, respectively, being smaller when compared to the present approach. However, the same researchers reported inhibition activity of the butyrylcholinesterase enzyme (BChE) in both treatments was greater than 50%. Arachchige et al. (2017) corroborate that AChE activity can be compensated for by increased BChE activity, since BChE may even hydrolyze acetylcholine when AChE levels are depleted in Alzheimer's patients. These same

authors also observed that ethanol and methanol extracts of leaves of *C. zeylanicum* barks showed enzymatic inhibitory action on acetylzolinasterase of a maximum of 52.13%, considering different dose-responses.

Evaluating the inhibitory activity of acetylcholinesterase from the essential oil and methanol extract from *C. zeylanicum* leaves, Dalai et al. (2014) found that the oil (IC_{50}: 45.88 ± 1.94 μg mL^{-1}) had better anticholinesterase activity than the methanolic extract (IC_{50}: 77.78 ± 0.03 μg mL^{-1}). This work reported that the inhibitory effect was also superior to the isolated compound, Eugenol, as well as the control treatment (Galantamine).

Other studies also reveal that species of *Cinnamomum* genus such as cinnamon contain potentially valuable anti-amyloidogenic agents for the prevention and treatment of Alzheimer's disease. Kang et al. (2016) demonstrated that methanol extract from cinnamon bark efficiently reduced the production of amyloid (Aβ40) - a substance generated through the amyloidogenic pathway of amyloid precursor protein (APP) by β-secretase and γ-secretase. The authors concluded that inhibition of Aβ production is also a potential therapeutic approach to Alzheimer's disease.

It is also noteworthy that the value of inhibition found for cinnamon oil in this research is higher than that obtained for other plant species, such as *Maximiliana maripa* (Arecaceae), for which the percentage of inhibition was 63.76% (Fernadez et al., 2016) or for *Inga cinnamomea* pulp ((Mimosaceae) with inhibition of 54.81% (Abreu et al., 2018), but lower than that obtained for the chloroform extract of *Annona hypoglauca* (Annonaceae) (88.47%) (Santos et al., 2018). It was also lower than the ethanolic extract of the residue of *Brassica napus* (Brassicaceae) oil which inhibited in 85% acetylcholinesterase activity *in vitro* (Yates et al., 2019).

This study of the inhibition potential of acetylcholinesterase has its importance, given that Alzheimer's is a disease that affected approximately 35 million people in the world by the year 2010 (Querfurth et al., 2010). One of the mechanisms of Alzheimer's disease is the reduction of acetylcholine production, which implies a gradual loss of memory and learning capacity along with other risk factors (Craig et al., 2011).

4. Conclusions

The activity of oil from seeds of cinnamon brings perspectives in the prospection of new leads for the development of drugs capable of treating patients with Alzheimer's disease, since it was able to inhibit acetylcholinesterase. Further studies are needed to establish the therapeutic safety and efficacy of its secondary metabolites aiming at development of a possible pharmaceutical agent.

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