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Study of the Alkaloid Polyneuridine as a Drug Candidate for Therapy of Alzheimer's Disease

Viviane Lima Silva[1]; Valéria Lima Silva[2]
[1]Degree in Chemistry, Centro Universitário FIEO, UNIFIEO, Osasco/SP, Brasil.
[1]viviannelyma956@gmail.com
[2]PhD Student in Biotechnology, Universidade Federal do Piauí, UFPI, Teresina/PI, Brasil.
[2]valeriafisiobr@hotmail.com

Abstract
Alzheimer's disease is characterized by the progressive and irreversible loss of natural cognitive functions in most elderly people. There is currently no cure for this neurodegenerative disorder, but there are therapies available on the market based on substances that inhibit acetylcholinesterase and cognitive symptoms as a way to improve cholinergic hypofunction. Polyneuridine is the main indole alkaloid extracted from the bark and leaves of Aspidosperma polyneuron, a brazilian plant species popularly known as peroba-rosa. The objective of this work is to investigate, through a scientific prospection, the polyneuridine alkaloid, as well as its anticholinesterase property, since it is known that the therapy of this disease is based on cholinesterase inhibitors. To carry out the study, two of the main publication databases of journals such as PubMed and Web of Science were analyzed. To search for scientific production, we inserted the following keywords combined with the terms in english to carry out the search in international databases: "Polyneuridine", "Polyneuridine AND anticholinesterase properties", "Polyneuridine AND Alzheimer's disease". The need for studies on this alkaloid is urgent, especially since Brazil holds the plant species that produces the most polyneuridine, but the plant species Aspidosperma polyneuron is on the red line of extinction due to the unbridled exploitation of its wood. It is concluded that if this exploration scenario continues, Brazil will lose a very important pharmacological genetic resource of its plant flora.

Key-words: Polyneuridine, Alzheimer's Disease, *Aspidosperma Polyneuron*, Prospection.

1. Introduction

Alzheimer's disease is characterized by the progressive and irreversible loss of natural cognitive functions in most elderly people. According to scientific studies, this type of dementia is due to the accumulation of β-amyloid peptide, originated from the cleavage of the amyloid precursor

protein that produces insoluble amyloid fibers in an agglutinated way, forming senile plaques, and the defibrillation of the TAU protein caused by abnormal phosphorylation of this protein causing the appearance of stable insoluble fibrils forming neurofibrillary tangles that disorganize the neural cytoskeleton and from this arises the development of a neuroinflammatory process, which decreases the levels of acetylcholine, which alters synaptic functions and triggers the neurodegenerative process, as well as we should remember that some factors such as genetic inheritance, psycho-emotional trauma, diabetes mellitus and nutritional quality can also contribute to the onset of this pathology (Fonseca-santos et al., 2015; Holtzman et al., 2016; Prince et al., 2014; Gonçalves & Carmo, 2012).

There is currently no cure for this neurodegenerative disorder, that is, current medications treat the symptoms of the disease, but are not able to suppress its development. However, there are therapies available on the market based on cholinergic inhibiting substances and also on cognitive symptoms as a way to improve cholinergic hypofunction. The most common chemical substances present in medications used in the therapy of Alzheimer's disease are donepezil, rivastigmine, galantamine, physostigmine and tacrine (Medeiros Filho, 2020).

Studies show that therapies adopted as a strategy in the treatment of Alzheimer's Disease also brought numerous side effects to patients, such as tacrine, the first drug authorized by the FDA to treat this pathology in mild to moderate cases, which administered in higher doses can cause nausea, vomiting, sweating, brachycardia, salivation, collapse, hypotension and seizure, and patients only showed cognitive improvement with the use of this drug consumed in high doses and because of these side effects, many patients abandoned the treatment (Knapp et al., 1994).

Donepezil was the second drug authorized for use in the therapy of Alzheimer's disease in mild to moderate cases, where the studies and development of this drug were carried out by Rogers et al. (1998), who published data showing that donepezil performed better in the treatment of Alzheimer's disease than tacrine, because while tacrine was administered in high daily doses of 80mg, 120mg and 160mg and a half-life of 3,5 hours, donepezil was administered in lower daily doses, that is, between 5mg and 10mg and a half-life of 70 hours, being more effective in the treatment of patients diagnosed with Alzheimer's disease, also causing side effects in patients who ingested the highest dosage, such as nausea, vomiting, diarrhea and colic.

Research promoted by Higgins and Flicker (2000) pointed out rivastigmine as a promising drug in the treatment of Alzheimer's disease in mild to moderate cases, showing, according to studies, encouraging results with the use of daily doses between 6mg and 12mg, but the drug also had side effects such as nausea, vomiting, diarrhea, weight loss, dizziness and stomach cramps, while

physostigmine, another drug used in this therapy, caused nausea, vomiting and diarrhea as side effects when using the highest dose, which can be taken in daily doses of 18mg, 24mg and 30mg according to studies presented by Christopher (2000).

In the more advanced stages of Alzheimer's Disease, the use of memantine is recommended as an effective strategy, being administered in doses of 10mg twice a day and with a half-life between 60 and 80 hours, with tolerable side effects such as vomiting, diarrhea, insomnia, anxiety, hallucination, tiredness and dizziness. Galantamine is a natural alkaloid approved in 2001 for use in the therapy of Alzheimer's Disease, which acts on the central nervous system by binding to nicotinic cholinergic receptors, thus contributing to the increase in cholinergic neurotransmission, making it an effective drug in the treatment cognitive symptoms of Alzheimer's disease (Araújo & Pondé, 2006; Vale et al., 2011; Sharma, 2019; Toublet et al., 2019).

Polyneuridine is the main indole alkaloid extracted from the bark and leaves of *Aspidosperma polyneuron*, a brazilian plant species that reaches from 20m to 30m in height, popularly known as peroba-rosa, belonging to the Apocinaceae family that occurs in the states of Bahia. Espírito Santo, Rio de Janeiro, Santa Catarina, Minas Gerais, São Paulo, Mato Grosso do Sul, Paraná and Rondônia (KLEIN et al., 2016).

Some indole alkaloids are natural bioactives that act preferentially on the central nervous system, such as ibogaine, which has a bicyclic nitrogenous subunit incorporated into the 5-methoxy-indole system, which has an aminoethyl unit similar to the chemical structure of serotonin (5-hydroxytryptamine). An endogenous neuroregulator of paramount importance, and this structural similarity explains the activity of this alkaloid in central serotonergic receptors, as well as the similarity of polyneuridine, an alkaloid similar to normacusin, with a serotonin structure (Barreiro) & Bolzani, 2009).

The objective of this work is to investigate, through a scientific prospection, data on the use of the polyneuridine alkaloid, as well as its anticholinesterase property, as it is known that the therapy of Alzheimer's disease is based on cholinesterase inhibitors, which depending on the therapy chosen, cause several side effects to the patient, which justifies the need for researchers to seek new effective therapies for this type of pathology.

2. Methodology

To carry out this research, it was necessary to carry out a scientific survey in two of the main databases of journal publications, such as PubMed and Web of Science. To search for scientific

production, the following keywords were used combined with english terms to perform the search in international databases: "*Polyneuridine*", "*Polyneuridine and anticholinesterase properties*" "*Polyneuridine and Alzheimer's disease*". To ensure the refinement of the research, the articles were screened by two researchers, independently and blindly, using as inclusion criteria articles from scientific studies published on any date, excluding from the research, uncontrolled trials, and works that were incomplete and results not detailed.

3. Results and Discussion

3.1. Scientific Prospecting Using Key Terms

All searches found were in english and to carry out this scientific prospecting, the keywords were first entered in the PubMed database and no article was found that highlighted the alkaloid in question. It was also found in PubMed that there is no scientific study involving polyneuridine in the treatment of neurogenerative diseases, nor have pharmacological studies been developed to test its anticholinesterase and antioxidant activities.

Table 1 - Keywords used for Searching the Databases

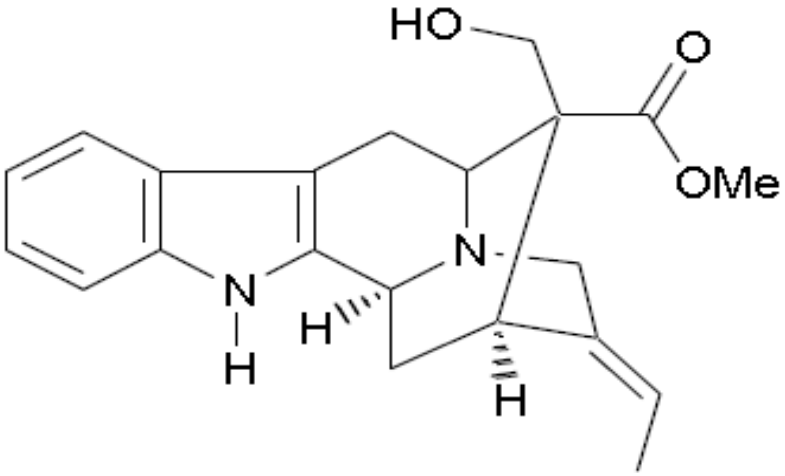
Keywords	**PubMed**	**Web of Science**
polyneuridine	0	10
Polyneuridine AND anticholinesterase activity	0	0
Polyneuridine AND Alzheimer's disease	0	0

Source: Prepared by the authors with data from PubMed and Web of Science (2021)

3.2. *Aspidosperma Polyneuron* and the Polyneuridine Alkaloid

In the Web of Science database 10 articles associated with the keyword polyneuridine were found, where the first publication reported the discovery, for the first time, of the polyneuridine alkaloid in the plant species *Aspidosperma polyneuron* by Antonaccio et al. (1962). This plant species is native to brazilian forests, but is in extinction due to intense logging for commercial purposes (MAZAROTTO et al., 2020). Already the research developed by Guimarães et al. (2012) alluded to the genus *Aspidosperma* in order to review ^{1}H and ^{13}C NMR data up to 2011 and describe the skeleton of 35 different plumeran indole alkaloids and highlight the main spectral differences between them.

Figure 1- Chemical Structure of Polyneuridine



Source: MARQUES et al., 1988.

A survey developed by Coatti et al. (2015) mentions the *Aspidosperma polyneuron* species in a study, which evaluated the cytotoxicity, genotoxicity and the analysis of gene expression for the qRT-PCR in HepG2 human cells of the alkaloid aspidospermine, showing that it presents cytotoxicity from 75 μM, genotoxicity from 50 μM and with no significant modulation of GSTP1 and GPX1 genes (xenobiotic metabolism); CAT (oxidative stress); TP53 and CCNA2 (cell cycle); HSPA5, ERN1, EIF2AK3 and TRAF2 (endoplasmic reticulum stress); CASP8, CASP9, CASP3, CASP7, BCL-2, BCL-XL BAX and BAX (apoptosis); and PCBP4, ERCC4, OGG1, RAD21 and MLH1 (DNA repair).

The plant species *Aspidosperma polyneuron* was highlighted in a study by Alzate-Marin et al. (2011) in order to provide information for the *ex situ* conservation of this plant that is on the red list of endangered species as an important genetic resource. Ferreira-Ramos et al. (2011) published a study that provides a new set of local microsatellites for *Aspidosperma polyneuron* that can be used to estimate genetic parameters, such as genetic diversity, population structure, gene flow and reproduction systems. A study published by Celloto et al. (2012), who used *Klebsiella oxytoca* cells isolated from the rhizosphere of *Aspidosperma polyneuron* immobilized by adsorption on different inorganic matrices in order to produce indole-3-acetic acid, which is the auxin responsible for plant growth. After 90 days of immobilized cells and stored at 4º C, there was a slight reduction in the production of indole-3-acetic acid without significant loss of activity.

According to Ferreira et al. (2003) from studies carried out using roots, leaves and the stem of *Aspidosperma polyneuron*, the ethanol extract of the parts of this plant was produced for fungal inhibition tests against *Clasdoporium herbarum*, *Aspergillus Niger*, *Penicilium chrysogenum*,

Candida albicans, *Trichoderma Harzianum* and *Rhizoctonia sp*, but the only extract that showed good results was the ethanolic stem extract, which was able to inhibit the growth of the fungus *Clasdoporium herbarum*.

In 2005, new studies were carried out with *Aspidosperma polyneuron*, where an ethanol extract was prepared from wood waste discarded by a company in the industrial sector, using violet spectroscopy and comparison with data from the literature proposed by Marques et al. (1988) where polyneuridine was the main inhibitory agent for the growth of these bacteria (GRANATO et al., 2005).

3.3. Cholinesterase Inhibitor Drugs

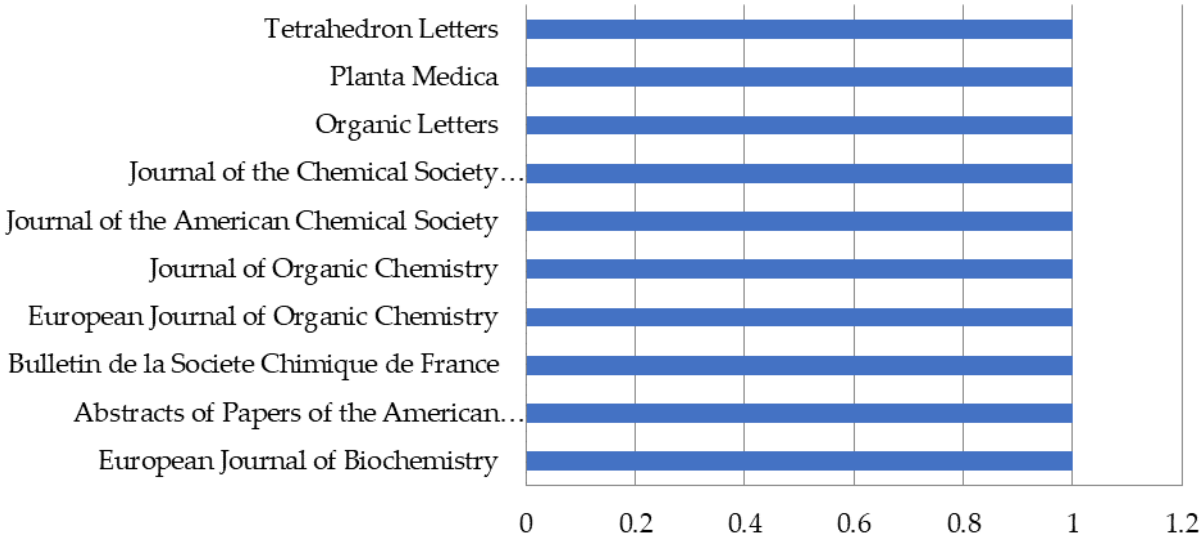
In the current context of Alzheimer's disease we can mention rivastigmine, donepezil and galantamine as inhibitors of the acetylcholine enzyme, as the neurodegenerative process occurs by the significant destruction of the number of neurons causing a decrease in acetylcholine levels in different regions of the brain, for example, in the cerebral cortex, hippocampus, entorhinal cortex and ventral striatum, the role of these drugs is to correct the insufficiency of the neurotransmitter in these brain regions, in this case acetylcholine, leads to a cognitive and behavioral improvement of the patient's functions at the stage of disease in mild to moderate cases (MULLER, 2007; CASTELLANI, 2010; FONSECA-SANTOS, 2015).

Many studies are being developed on the role and action of the enzyme butyrylcholinesterase in the nervous system, as it is known that the enzyme systems are divided into two enzymatic pathways, that is, acetylcholinesterase acts on neurons and butyrylcholinesterase acts on glial cells, demonstrating thus the importance of the enzyme butyrylcholinesterase, which has the function of metabolizing acetylcholine, with rivastigmine and tacrine being the only drugs capable of inhibiting both acetylcholinesterase and butyrylcholinesterase (ANNICCHIARICO et al., 2007; MULLER, 2007).

3.4. Periodicals

We can observe in the graph below that few journals found in the Web of Science database have published on polyneuridine, making clear the existence of few studies and contributions on this indole alkaloid.

Figure 2 - Journals and the Number of Publications on the Polyneuridine Alkaloid

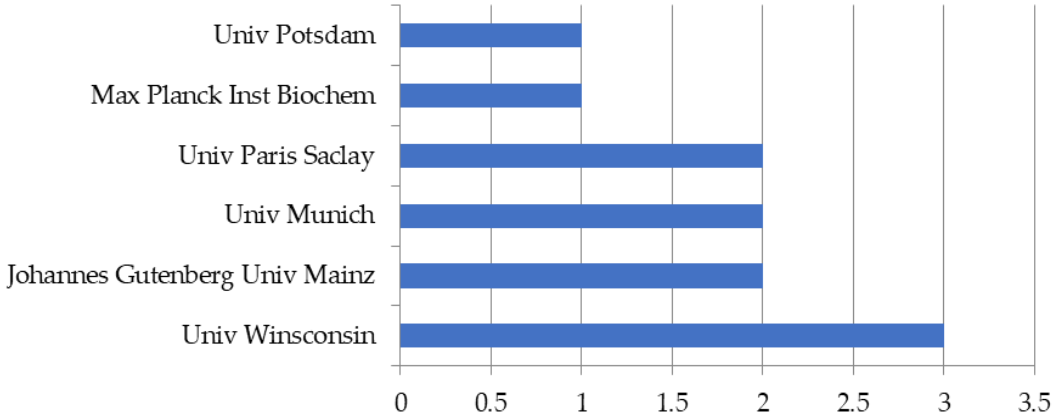


Source: Prepared by the authors with data from Web of Science (2021).

3.5. Research Institutions

The figure below shows the only institutions that developed scientific research on polyneuridine, where we can observe that all institutions are international and that some researches were carried out in partnership between research institutions as shown in the graph.

Figure 3 - Research institutions that have published on the polyneuridine alkaloid



Source: Prepared by the authors with data from Web of Science (2021).

3.6. Published Articles and Citations

The table below mentions the only articles on polyneuridine, with a moderate number of citations, found in the Web of Science database. When reading the research, one notices the lack of

works on the alkaloid under study in the context of physical-chemical characterization, pharmacological and biotechnological applicability.

Table 2 - Articles Published on Polyneuridine and the Number of Citations

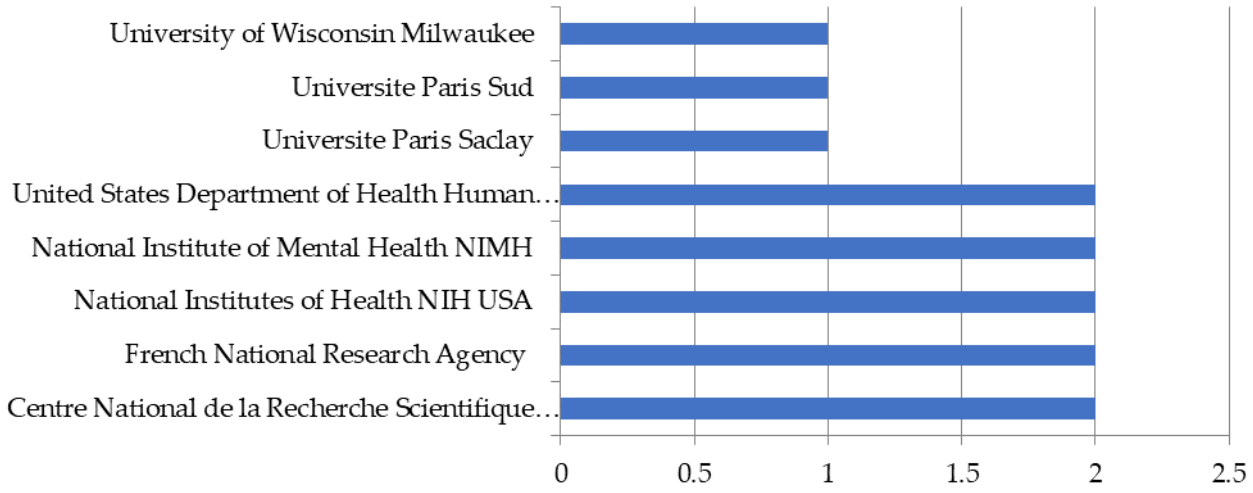
Title	Citations
Polyneuridine, a new alkaloid from aspidosperma polyneuron and some observations on mass spectra of indole alkaloids (ANTONACCIO; PEREIRA; GILBERT et al. 1962).	140
Degradation de la vincamedine et configuration absolue des alcaloides apparentes - vincamajine, akuammidine, polyneuridine, voachalotine et macusine a alcaloides des pervenches (JANOT; GOSSET; LEMEN et al., 1962).	39
Polyneuridine aldehyde esterase - an unusually specific enzyme involved in the biosynthesis of sarpagine type alkaloids (PFITZNER; STOCKIGT, 1983).	22
Characterization of polyneuridine aldehyde esterase, a key enzyme in the biosynthesis of sarpagine ajmaline type alkaloids (PFITZNER; STOCKIGT, 1983).	23
The gene encoding polyneuridine aldehyde esterase of monoterpenoid indole alkaloid biosynthesis in plants is an ortholog of the alpha/beta hydrolase super family (DOGRU; WARZECHA; SEIBEL et al., 2000).	54
Potential active-site residues in polyneuridine aldehyde esterase, a central enzyme of indole alkaloid biosynthesis, by modelling and site-directed mutagenesis (MATTERN-DOGRU; MA; HARTMANN et al. 2002).	14
Enantiospecific Total Synthesis of the Important Biogenetic Intermediates along the Ajmaline Pathway, (+)-Polyneuridine and (+)-Polyneuridine Aldehyde, as well as 16-Epivellosimine and Macusine A (YIN; KABIR; WANG et al. 2010).	40
First enantiospecific Total Synthesis of the Important Biogenetic Intermediates along the Ajmaline Pathway, (+)-Polyneuridine and (+)-Polyneuridine Aldehyde, as well as 16-epi-vellosimine and Macusine A (YIN; KABIR; WANG et al., 2010).	15
Polyneuridine aldehyde: structure, stability overviews and a plausible origin of flavopereirine (AHAMADA; BENAYAD; POUPON et al. 2016).	5
Biosynthetically Relevant Reactivity of Polyneuridine Aldehyde (TURPIN; POUPON; ERWAN, JULLIAN et al. 2020).	0

Source: Prepared by the authors with data from Web of Science (2021).

3.7. Funding Agencies

Research funding agencies interested in the polyneuridine alkaloid, according to the Web of Science database, are from the United States, Germany and France. Brazil has a vast territory that houses the main plant species that produce the polyneuridin alkaloid, the *Aspidosperma polyneuron* species, but no study on this alkaloid has been carried out in Brazil.

Figure 4 - Agencies and the Number of Funded Works



Source: Prepared by the authors with data from Web of Science (2021)

4. Conclusion

Due to the amount of published works, it is clear that studies in the literature about this alkaloid are scarce. Due to the chemical structure, discussed in this article, we can observe that the polyneuridine alkaloid should be studied in greater depth, as based on research and studies on the therapy of Alzheimer's disease, it is possible that this indole alkaloid is a promising drug to contribute in a way satisfactory as a potent cholinergic inhibitor. The need for studies on this alkaloid is urgent, especially as Brazil has the plant species that most produces the polyneuridine alkaloid, but unfortunately the plant species *Aspidosperma polyneuron*, according to the studies discussed here, is on the red line of extinction due to exploitation unbridled of its wood of great commercial value. It is concluded that if this exploration scenario continues, Brazil will lose a very important pharmacological genetic resource of its plant flora.

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