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

Viviane Lima Silva¹; Valéria Lima Silva²
¹Degree in Chemistry, Centro Universitário FIEO, UNIFIEO, Osasco/SP, Brasil.
¹vivianellyma956@gmail.com
²PhD Student in Biotechnology, Universidade Federal do Piauí, UFPI, Teresina/PI, Brasil.
²valeriafisiobr@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

ISSN: 2237-0722
Vol. 11 No. 4 (2021)
Received: 07.07.2021 – Accepted: 05.08.2021
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.
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 *Cladosporium herbarum*, *Aspergillus Niger*, *Penicilium chrysogenum*, *Cladosporium herbarum*, *Aspergillus Niger*, *Penicilium chrysogenum*, and *Penicilium chrysogenum*. 

Source: MARQUES et al., 1988.
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 Clasdoporum 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.
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.

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; POUPEI et al. 2016). | 5         |
| Biosynthetically Relevant Reactivity of Polyneuridine Aldehyde (TURPIN; POUPE; ERWAN, JULIAN 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.
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.

References

Annicchiarico, R. *et al.* Rivastigmine in Alzheimer’s disease: cognitive function and quality of life. *Therapeutics and Clinical Risk Management*, 2007. v. 3, n. 6, p. 1113–1123.

Antonaccio, L.D. *et al.* Polyneuridine, a new alkaloid from *Aspidosperma polyneuron* and some observations on mass spectra of indole alkaloids. *J. Am. Chem. Soc.* 1962, 84, 11, 2161–2169. Publication 1962. DOI: https://doi-org.ez17.periodicos.capes.gov.br/10.1021/ja00870a030.

Araújo, R.S., Pondé, M.P. Efficacy of Memantine in Alzheimer's Disease in its Moderate to Severe Stages. *Brazilian Journal of Psychiatry*, 55(2), 148 – 153, 2006.
Alzate-marin, Ana Lilia; Ferreira-ramos, Ronai; Guidugli, Marcela; Martinez, Carlos Alberto; Mestriner, Moacyr Antonio. Genetic diversity assessed in individuals of Aspidosperma polyneuron and Cariniana estrellensis used as seed donors in an forest gene bank. *BMC Proc.* 2011; 5(Suppl 7): P8. Published online 2011 Sep 13. doi: 10.1186/1753-6561-5-S7-P8

Barreiro, E.J.; Bolzani, V.D. Biodiversity: potential source for drug discovery. *New Chemistry*, 32(3), 679-688, 2009.

Castellani, R.J.; et al. *Alzheimer’s Disease*. 56, 484-546, 2010.

Celloto, Valéria R., Oliveira, Arildo J.B., Gonçalves, José E., Watanabe, Cecília S.F., Matioli, Graciete, Gonçalves, Regina A.C. Biosynthesis of Indole-3-Acetic Acid by New Klebsiella oxytoca Free and Immobilized Cells on Inorganic Matrices. *Scientific World Journal*, 2012; 2012: 495970. Published online 2012 May 1. doi: 10.1100/2012/495970.

Christopher, H. Extended-Release Physostigmine in Alzheimer’s Disease. *Arch. Gen. Psychiatry*, 57, 2000.

Coatti, Giuliana Castello; Marcarini, Juliana Cristina; Sartori, Daniele; Fidelis, Queli Cristina; Ferreira, Dalva Trevisan; Mantovani, Mário Sérgio. Cytotoxicity, genotoxicity and mechanism of action (via gene expression analysis) of the indole alkaloid aspidospermine (antiparasitic) extracted from Aspidosperma polyneuron in HepG2 cells. *Cytotechnology*, 2016 Aug; 68(4): 1161–1170. doi: 10.1007/s10616-015-9874-9

Ferreira, D.T. Evaluation of the antifungal activity of root, stem and leaf ethanol extracts of Aspidosperma polyneuron. In: Chemical Meeting of the South Region, 11, 2003. Pelotas. Abstracts: Pelotas, 2003.

Ferreira-ramos, Ronai; Monteiro, Mariza; Zucchi, Maria Imaculada; Pinheiro, José Baldin; Martinez, Carlos Alberto; Mestriner, Moacyr Antonio; Alzate-marin, Ana Lilia. Twenty four microsatellite markers for Aspidosperma polyneuron (Apocynaceae), an endangered tree species. *BMC Proc.* 2011; 5(Suppl 7): P7. Published online 2011 Sep 13. doi:10.1186/1753-6561-5-S7-P7

Fonseca-santos, B. Nanotechnology-based drug delivery systems for the treatment of Alzheimer’s disease. *International Journal of Nanomedicine*, 2015. 10, 4981–5003. http://www.dovepress.com/permissions.php

Gonçalves, Endy-Ara Gouvea; Carmo, João dos Santos. Diagnosis of Alzheimer’s disease in the brazilian population: a literature review. *Journal of Health Psychology, Campo Grande*, 4(2), 170-176, 2012. http://pepsic.bvsalud.org/scielo.php?script=sci_arttext&pid=S2177093X2012000200010&lng=pt&nrm=iso

Granato, D. et al. Chemical and biological evaluation of rejects from the word industry. *Brazilian Archives of Biology and Technology*, 48, 237-41, 2005.

Guimarães, H.A.; Braz-filho, R; Vieira, I.J.C. 1H and 13C-NMR Data of the Simplest Plumeran Indole Alkaloids Isolated from Aspidosperma species. *Molecules*. 2012; 17(3): 3025-3043.

Higgins, Julian PT; Flicker, Leon. Lecithin for dementia and cognitive impairment. *Cochrane Systematic Reviews Database*, 4, 2000.

Holtzman, D.M. et al. Tau: from research to clinical development. *Alzheimer’s & Dementia: The Journal of the Alzheimer’s Association*, 2016. 12(10), 1033–1039.

http://www.sciencedirect.com/science/article/pii/S155252601630019X
Klein, Danieli Regina et al. General and silvicultura aspects of Cordia americana, Aspidosperma polyneuron, Toona ciliata e Khaya spp. Journal of Agricultural Sciences. 15(2) (2016). doi: https://doi.org/10.5965/223811711522016155

Knapp, M.J. A 30-week randomized controlled trial of high-dose tacrine in patients with Alzheimer’s disease. J. Am. Med. Assoc., 271, 992-998, 1994.

Marques, M.F.S. Contribution to the chemical study of the Aspidosperma genus: Aspidosperma ramiflorum Muell. Arg. Dissertation (Masters-Concentration Area in Organic Chemistry) - Department of Chemistry, State University of Campinas, Campinas, 1998.

Mazarotto, E.J., Poitevin, C.G., Carmo, A.L.M. Do; Santos, A.F. Dos; Tralamazza, V, Pimentel, I.C. Pathogenic Fusarium species complexes associated to seeds of indigenous Brazilian forest tree Aspidosperma polyneuron. European Journal of Plant Pathology, (IF 1.582) Pub Date: 2020-10-06, DOI: 10.1007/s10658-020-02120-8

Medeiros Filho, Francisco Carlos de. Study of acetylcholinesterase inhibition by molecular docking and mfcc: application in the treatment of Alzheimer. 2020. 147 fl. (Master's Dissertation in Natural Sciences and Biotechnology), Postgraduate Program in Natural Sciences and Biotechnology, Education and Health Center, Federal University Campina Grande - Cuité - Paraíba - Brazil, 2020.

Muller, T. Rivastigmine in the treatment of patients with Alzheimer’s disease. Neuropsychiatric Disease and Treatment, 2007. v. 3, n. 2, p. 211-218.

Prince, M. et al. World Alzheimer Report 2014. Dementia and risk reduction: an analysis of protective and modifiable factors. Alzheimer's Disease International, 1, 2014.

Rogers, S.L. et al. A 24-week, double-blind, placebo-controlled study of donepezil in patients with Alzheimer's disease. Neurology, 1998, 50.1: 136-145.

Sharma, K. Cholinesterase inhibitors as Alzheimer's therapeutics. Molecular medicine reports, 20.2(2019): 1479-1487.

Toublet, F.X. et al. Inhibiting Acetylcholinesterase to Activate Pleiotropic Prodrugs with Therapeutic Interest in Alzheimer’s Disease. Molecules 24.15(2019):2786.

Vale, L.A.C. Alzheimer's Disease Treatment. Dementia & Neuropsychologia, 5(suppl 1), 34-48, 2011.