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Pharmacological activities palmatine alkaloid compound isolated from *Guatteria friesiana* prospects for new drug development.

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Abstract

Medicinal plants have been used for thousands of years for the treatment of numerous diseases becoming an important source in the search for new drugs. Among the substances, palmatine, arising from natural sources, an alkaloid has been investigated with regard to their pharmacological actions and has demonstrated promising activity for the treatment of various diseases highlighting Alzheimer's disease (AD). The aim of this study was to verify the state of the art and technique on palmatine with emphasis on their pharmacological activity *in vitro*, *in vivo* and *ex vivo* which makes it promising in developing new drugs, primarily for the treatment of AD. 164 studies were found using the keywords "palmatine", "palmatine", "palmatine activity" and "activity palmatine". Patent deposit was not observed. The palmatine shown promising pharmacological activities, including: anti-inflammatory, anti-depressive, anti-pyretic, among others. Thus, it was observed that the alkaloid demonstrated some important pharmacological actions, including related to the therapy of neurodegenerative diseases.

Keywords: Human foetal skin, Burn model, Wound healing, Human peripheral blood mononuclear cells (hPBMCs), Matrix metalloproteinases (MMPs).

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Introduction

The medicinal plants have been used since the dawn of civilization for therapeutic purposes. The early civilizations have realized that some plants contain active principles that could be used for the treatment of diseases. Thus, nature has become a promising source of new substances for drug development [1-3].

Among the substances found in natural sources can highlight the palmatine an alkaloid and a major component of herbal preparations mainly used in tradicional medicine Chinese, Korean and Indian. The palmatine can be found in various medicinal plants such as Coptis chinensis, Rhizoma coptidis, Corydalis yanhusuo, Radix tinosporae, among others [4,5].

The palmatine (Figure 1) was isolated of the plant species *Guatteria friesiana*. This species is a small tree known as "envireira" or "envira" found the Brazilian and Colombian Amazon basin and used in traditional medicine for various purposes. Studies of extracts, fractions, essential oils and compounds isolated of *Guatteria friesiana* showed activities as antitumor, antimicrobial activities and action larvicide against larvae of *Aedes aegypti* [6-10].

The palmatine has presented certain pharmacological activities that may be related, for example, their ability to interact with proteins and nucleic acids, some of which are important in the treatment of neurodegenerative diseases [11,12].

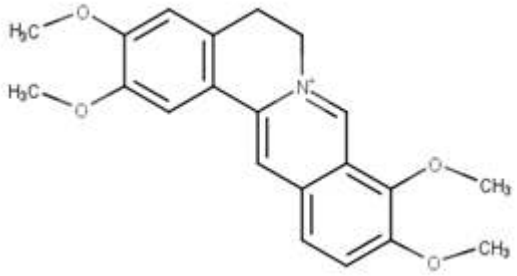

Figure 1. *Molecular structure of palmatine.*

Neurodegenerative diseases currently affecting millions of people and the incidence of new cases is mainly related to the increase in the aging population [13,14]. According to studies, the number of people affected by major neurodegenerative diseases will increase by 50% by 2030 [15]. Alzheimer's disease (AD) is a neurodegenerative disorder with cognitive and neuropsychiatric symptoms that triggers a progressive

disability both in memory and other cognitive functions [16,17]

The DA is an important public health problem, especially in countries where there is an increase in life expectancy, as well as affect functional and socially family and society [18,19].

Several studies are being conducted to evaluate the pharmacological activities associated with palmatine alkaloid, from *in vitro* assays to *in vivo* and *ex vivo* tests. Thus the aim of this review was to assess the state of the art and technique on palmatine with emphasis on their pharmacological activities evaluated *in vitro*, *in vivo* and *ex vivo*.

Materials and Methods

A literature about palmatine was performed through Science Direct, PubMed, LILACS, MEDLINE, Portal Capes, Web of Science, Scopus and Scielo databases. The key words used were: "palmatina", "palmatine", "atividade palmatina" and "activity palmatine". Articles published were selected during the period from 1993 to 2015. The selection of studies was based on analysis of titles and abstracts. A technological prospecting was performed in patents filed at the European Patent Office (EPO), Google patents, National Institute of Industrial Property (INPI), United States Patent and Trademark Office (USPTO) and World Intellectual Property Organization (WIPO). The period and the search terms were the same as for the scientific basis.

Results and Discussion

The search on a scientific basis using the keyword "palmatine" resulted in obtaining 164 studies, whereas no studies were found using the term "palmatina". For the term "atividade palmatina" were no studies in scientific bases and regarding the keyword "activity palmatine" were observed 51 studies as shown in Table 1. After analysis of titles and abstracts and elimination of repeated articles were selected 18 studies that directly evaluated the pharmacological activities of palmatine. There were no claims of patent applications in selected bases. The studies found were selected those that evaluated directly the activity of the alkaloid *in vitro*, *in vivo* and *ex vivo*.

Table 1. *Quantification of publishing on palmatine found in scientific database for each search descriptor.*

Databases	Keywords			
	Palmatine	Palmatina	Atividade palmatina	Activity palmatine
LILACS	0	0	0	0
MEDLINE	7	0	0	3
Portal da Capes	108	0	0	42
PubMed	0	0	0	0
SciELO	2	0	0	0
Science Direct	23	0	0	3
Scopus	7	0	0	0
Web of Science	17	0	0	3
Total publications	164	0	0	51

Pharmacological activities in in vitro assays

There are several types and methodologies of *in vitro* assays to prove or disprove pharmacological actions. Certain *in vitro* assays were performed with palmatine and some activities were attributed to the substance from these tests (Table 2).

In *in vitro* assays that assess the ability of the substance to inhibit the enzyme acetylcholinesterase, one element for the treatment of Alzheimer's disease. Mak et al. [20] showed that the combination of palmatine and berberine resulted in inhibition synergistic *in vitro* of human recombinant AChE, the combination being a potential therapeutic strategy. Furthermore, it was observed sequestering capacity of ONOO- radicals, in other words, the antioxidant capacity with IC50 value of 28.70 micrometers [21]. The palmatine has also demonstrating other pharmacological actions such as the selective inhibition of prostate cancer cells and selective cytotoxic activity against cancer cell lines in the breast (MCF-7) and glioma cells (U251) [10,22]. Li et al. [23] suggested that some alkaloids, including the palmatine, would be responsible for the remarkable anti-inflammatory activity of Rhizoma coptidis.

Pharmacological activities in in vivo and ex vivo assays

Tests *in vivo* and *ex vivo* are widely used for the elucidation of pharmacological actions of numerous compounds. As well as *in vitro* tests, certain activities *in vivo* and *ex vivo* of palmatine have been proven in the literature (Table 3).

Ning et al. [24] evaluated the effect of palmatine isolated of *Coptis chinensis* in hamsters fed high fat diet. It was observed that the compound reduced the level of serum total cholesterol (TC), triglycerides (TG) and low density lipoprotein (LDL), as well as increased excretion of TC and total bile acids in animals.

Another study showed that the alkaloid had effect on motor activity and the concentration of monoamines in brain regions of rats. The substance increased the hypomotility induced by α-methyl-p-tyrosine, reserpine and 5-hydroxytryptophan and reduced hypermotility caused by L-DOPA with benserazide and p-chlorophenylalanine. The concentration of dopamine and homovanillic acid was significantly reduced in the cortex. In contrast the 5-HT levels in the cortex and 5-hydroxyindole acetic acid amounted [25].

In relation to Alzheimer's disease, certain behavioral tests and *ex vivo* tests are also suitable for evaluating the potential use of these compounds in the treatment of disease. The palmatine in doses 0.5 and 1 mg/kg, intraperitoneally, was assessed by the Morris maze test and it was found that the substance

significantly improved learning and memory of mice. Furthermore, the substance reversed amnesia caused by scopolamine and diazepam. In *ex vivo* tests found a reduction of acetylcholinesterase activity in the brains of animals [26].

Dhingra and Bhankher [27], demonstrated the alkaloid's ability to reduce mice immobility periolld, subject and not subject to unpredictable mild stress in the forced swimming test and the tail suspension, deducing an effect of antidepressant-like substance. The compound also significantly reversed the increased brain levels of catalase, lipid peroxidation, plasma nitrite and corticosteroid induced by stress.

Table 2. *Summary of studies of in vitro activities of palmatine.*

Specie	Part of plant	Type of extract/fraction	Purpose of the study	Results	References
-	-	-	To investigate the effect of palmatine on isometric strength in isolated strips of rat arteries	The palmatine relaxed dose-dependently the contractile response induced by phenylephrine	[28]
-	-	-	To observe the action of palmatine on chlorine colonic secretion (Cl-) in the colonic mucosa	The substance inhibits the secretion of Cl-activated by Ca2+ and AMPC	[29]
Enantia chlorantha	Bark	Methanol extract	To study the activity of the alkaloid front of Trypanosoma cruzi and Leishmania infantum	The compound exhibited significant inhibitory activity against both parasites	[30]
Coptis chinensis	-	-	To evaluate the effect of palmatine in relation to NS2B-NS3 protease of West Nile virus	The alkaloid was able to inhibit the protease activity without detectable cytotoxicity	[31]
Coptis chinensis	-	-	To study the effect of palmatine on the differentiation of osteoclasts	The palmatine showed inhibitory effect on differentiation and function of osteoclast	[32]
Coptis chinensis	Rhizome	Methanol extract (n-butanol fraction)	To investigate the effect of alkaloid isolated in adipocyte differentiation by measuring the accumulation of lipids and determine the gene expression levels of markers of adipocytes	The alkaloid, including palmatine, inhibit the accumulation of lipids in the cells and reduced the expression levels of various marker genes adipocytes	[33]
Legend: (-) not reported in the study					

Table 3. *Summary of studies of in vivo and ex vivo activities of palmatine.*

Specie	Part of plant	Type of extract/fraction	Purpose of the study	Results	References
Berberis spp.	Root	Alkaloid fraction	To study the effects of various alkaloids, including the palmatine in *in vivo* models	The palmatine showed anti-inflammatory, antinociceptive and antipyretic activity for certain routes of administration	[34]
Coptis chinensis	-	-	To evaluate the cytoprotective activity of the compound in fulminant hepatic failure induced by D-galactosamine (GalN)/lipopolysaccharide (LPS)	The alkaloid relieved liver injury induced GalN/LPS by modulating cytokine response and inhibition of apoptosis	[33]
Legend: (-) not reported in the study					

Conclusion

Through the survey it was observed that studies about the pharmacological and biological activities of palmatine are being carried out since 1993. During this period, they have been proven some important activities including anti-inflammatory, antiparasitic, antipyretic action, among others. However, there is a field for new research with the substance, which can be considered promising for use in various therapies.

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