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Bioactive profile of Aspidosperma pyrifolium Mart. & Zucc: An integrative review

Perfil bioativo de Aspidosperma pyrifolium Mart. & Zucc: Uma revisão integrativa

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ABSTRACT
The objective of this work was to evaluate the biological potential from *Aspidosperma pyrifolium* Mart. & Zucc presents, through reports found in the literature. For this, articles were evaluated using compatible descriptors with the objective. As a result, it was observed that many studies have found several biological activities associated with the species.

Keywords: Biotechnology, Medicinal plants, Pereiro.

RESUMO
O objetivo deste trabalho foi avaliar o potencial biológico de Aspidosperma pyrifolium Mart. & Zucc apresenta, por meio de relatos encontrados na literatura. Para isso, os artigos foram avaliados por meio de descritores compatíveis com o objetivo. Como resultado, observou-se que muitos estudos encontraram diversas atividades biológicas associadas à espécie.

Palavras-chave: Biotecnologia, Plantas medicinais, Pereiro.

1 INTRODUCTION

The potential of Brazil's flora has been highlighted in the scientific community, due to its relevance in discovering new substances for medicinal, biotechnological, and ecological use (MALAFAIA *et al.*, 2006; MONTES, 2009). Certainly, the interest in looking for new drugs from plant sources has increased thanks to secondary metabolites, such as flavonoids, tannins, alkaloids, glycosides, and terpenoids present in extracts and essential oils (ÖZÇELIK *et al.*, 2011; SAVOIA, 2012; KHAMENEH *et al.*, 2019).

Several botanical families can be explored to evaluate their medicinal properties and/or therapeutic validation (JOSELIN *et al.*, 2012). Among the species with biological potential, *Aspidosperma pyrifolium* stands out (SILVA *et al.*, 2004). This species is characteristic of the Caatinga region and has great resistance to drought. Also, it is widely used in folk medicine for its anti-inflammatory, analgesic, antipyretic, antimicrobial, and antitumor potential (SANTOS *et al.*, 2013; LIMA *et al.*, 2017).

Species of the genus *Aspidosperma* have biological activities related to indolic alkaloids. They are common secondary metabolic in species of the Apocynaceae Family, related to antiprotozoal activities such as aspidoscarpine, ramiflorin A and ramiflorin B

(CHIERRITO *et al.*, 2014). In addition to alkaloids, other classes of natural products are also found, such as flavonoids, saponins, and organic acids (SANTOS *et al.*, 2013).

The various therapeutic indications reported experimentally and proven from different parts of species of the genus *Aspidosperma* demonstrate their pharmacological importance. Representatives of this genus have therapeutic properties, so it is possible to notice that the species *A. pyrifolium* also has potential for the treatment of pathologies due to its ethnopharmacological indications. Therefore, the objective of this review is to reinforce the main bioactive characteristics found in this plant through reports in the literature.

2 METHODS

2.1 RESEARCH STRATEGY

This article is an integrative review characterized by grouping, analyzing, and synthesizing results on a given issue, in a systematic and orderly manner, to present, discuss and deepen the knowledge on the proposed thematic (MENDES; SILVEIRA; GALVÃO, 2008).

There were used articles published between 2000 and 2020. The researches were carried out in the main academic databases: PubMed, Web of Science, Scopus, Google Scholar, Virtual Health Library, LILACS, National Center for Biotechnology Information (NCBI), and Science Direct. There were selected about 23 articles, which were related to the following used descriptors: Pereiro, *Aspidosperma pyrifolium*, bioactivities. The research was conducted between March and July 2020.

2.2 ELIGIBILITY CRITERIA

The selection of the included studies was limited to researches that fit the inclusion criteria of (I) ethnopharmacological uses of *A. pyrifolium* in the past and clinical application, (II) pharmacological properties of *A. pyrifolium* in an animal or human model, in vitro or in vivo trial, and (III) no language restrictions and study design. Studies were excluded based on these criteria and did not fit the following items: (I) data extracted in an unreliable manner, (II) only summaries, (III) overlapping data sets, and (IV) theses, editorials, news or correspondence.

3 RESULTS AND DISCUSSIONS

3.1 BOTANICAL ASPECTS

3.1.1 Family Apocynaceae

Apocynaceae Family belongs to the division of Magnoliophytas, class of Magnoliopsida, and orde of Gentianales and has several species distributed in tropical and subtropical regions, reaching the temperate regions (BHADANE *et al.*, 2018). This family can be found in practically all biomes and corresponds to one of the ten largest families of angiosperms on the planet (PEREIRA; SIMÕES; SANTOS, 2016). There were already described 366 genera and about 5,100 species (ENDRESS; LIEDE-SCHUMANN; MEVE, 2014), among trees, shrubs, and vines (RAHMAWATI; HASANUDIN; NURMALIAH, 2016).

In Brazil, Apocynaceae corresponds to the tenth largest family of angiosperms. The family is recognized for having several distinct morphological characteristics and for the active compounds derived from its secondary metabolism, to which its medicinal properties are attributed (LIMA; SCARELI-SANTOS, 2016). The family is considered one of the largest providers of bioactive molecules with several substances isolated from its different species (LUZ *et al.*, 2014). Among the individuals belonging to this family, the genera that most stand out for their medicinal properties are *Catharanthus*, *Aspidosperma*, *Macrosiphonia*, *Mandevilla*, *Rauwolfia*, *Himatanthus*, *Plumeria*, and *Strophantus* (ASSIS JUNIOR *et al.*, 2013).

Chemically, Apocynaceae is characterized by the recurrent presence of alkaloids, which are used in the production of medicines. Also, it gives economic relevance to this family (REIS; POTIGUARA; REIS, 2013). In *Aspidosperma* species, for example, there is a predominance of structurally diverse indole alkaloids (PEREIRA *et al.*, 2007).

One of the main characteristics of alkaloids is their toxicity, and for decades they have been used in the production of poisons. Reports suggest that an ancient tribe that inhabited the Kenya region used arrows poisoned with *Strophanthus* (Apocynaceae) extract (NEPOVIMOVA; KUCA, 2018).

According to a survey carried out by Phumthum and Balslev (2020), when analyzing several studies covering 25 villages in Thailand, they found 185 reports of plants, which included 127 species distributed in 59 families, used in the treatment of different infectious diseases. In this survey, species of the Apocynaceae Family were the most used in the treatment of infections caused by protozoa. Another member of the family, *Alstonia scholaris* (L.) R. Br., is a tree widely used in the treatment of lung diseases (ZHAO *et al.*, 2020).

3.1.2 *Aspidosperma* Mart. & *Zucc* genus

The genus *Aspidosperma* Mart. is one of the most significant because it presents species that add economic and medicinal value (ENDRESS; LIEDE-SCHUMANN; MEVE, 2014). The genus has a Neotropical distribution, can be found in the Americas from Mexico to Argentina, and is among the most important within the family (ALMEIDA *et al.*, 2019). It presents 55 species already described, of which 41 occur in Brazil (MACHATE; ALVES; FARINACCIO, 2016), where its phytogeographic domain encompasses the Amazon, the Caatinga, the Cerrado, and the Atlantic Forest (KOCH *et al.*, 2015).

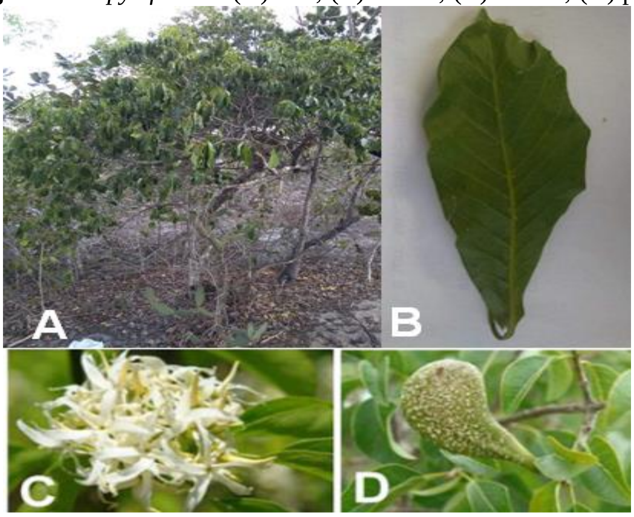
Regarding its medicinal properties, several species of the genus *Aspidosperma* are used in folk medicine against malaria, leishmaniasis, antimicrobial, anti-inflammatory, rheumatism, cancer, stomach diseases, diabetes, cholesterol, hypertension, and erectile dysfunction (OLIVEIRA *et al.*, 2009; LINO; GARROTE, 2005; CAMPOS *et al.*, 2006; BARBOSA *et al.*, 2010; MARCONDES *et al.*, 2010; CERAVOLO *et al.*, 2018). As mentioned above, most species of this genus are studied regarding their biological activities due to their medicinal actions (OLIVEIRA *et al.*, 2009). However, many species are toxic to man because they produce alkaloids and cardenolides, some possessing medicinal actions (COUTINHO; LOUZADA, 2018).

Species of the genus *Aspidosperma* are recognized by the presence of indole alkaloids, an important secondary metabolite that is related to the defense of the plant against predators (ARAÚJO *et al*., 2018). Monoterpenic alkaloids, such as aspidofractinin, 15 demethoxypyrifoline, and N-formylaspidofractin, have already been identified in the plant (RIET-CORREA; MEDEIROS; SCHILD, 2012). Many of the alkaloids are related to pharmacological activities such as olivacine, guatambuina, and antitumoral compounds isolated from *A. olivaceum*, *A. australe*, and *A. longepetiolatum*.

3.1.3 *Aspidosperma pyrifolium* Mart. & Zucc species

Aspidosperma pyrifolium Mart. & Zucc. (figure 1) is a plant widely distributed in the Caatinga and can reach up to 8 meters in height (PESSINI *et al.*, 2012; CERAVOLO *et al.*, 2018). It is popularly known as Pereiro, Pereiro-branco, Pereiro-preto, Peroba-rosa and Pereiro-do-sertão. It is a native and non-endemic species found in several regions of the country, and its phytogeographic domain also extends to the Cerrado (FLORA DO BRASIL, 2020). Belonging to the Apocynaceae Family, *A. pyrifolium* is used in folk medicine and the wood industry, demonstrating its medicinal and commercial value. This species is used for different purposes, from wood for carpentry and coal to landscaping. Besides, it has ecological importance for being one of the most suitable plants for the recovery of degraded areas or in desertification processes. This use is due to its ability to adapt to these types of environments (SANTOS *et al.*, 2013; SOUSA *et al.*, 2014).

Figure 1: *A. pyrifolium*: (A) tree; (B) leaves; (C) flower; (D) pod.



Source: Barbosa, (2019); Riet-Correa; Medeiros; Schild, (2011).

It is a species that can survive in the most severe drought conditions, shallow and stony soils. Additionally, they manage to maintain their foliage even in prolonged periods of drought (AQUINO; FALCÃO; ALMEIDA-CORTEZ, 2017). *A. pyrifolium* represents one of the countless species of plants in the Caatinga with the highest Cultural Significance Index (CSI) that, in their majority, include native individuals and with medicinal importance (DARIO, 2018).

In some communities, stem-barks of *A. pyrifolium* are used to treat urinary inflammation and dermatitis (AGRA *et al.*, 2007). Their seeds have already shown anti-inflammatory activity in a model of Parkinson's disease (ARAÚJO *et al.*, 2018). It is reported in the literature and popular knowledge, mainly by animal breeders, that *A. pyrifolium* causes animal intoxication (SOUSA *et al.*, 2014) since they are consumed by cattle, goats, and horses during periods of drought (SILVA *et al.*, 2006; NETO; SAKAMOTO; SOTO-BLANCO, 2013). *A. pyrifolium* is also used in the treatment of ectoparasitic diseases in domestic animals (FERNANDES; BIZERRA, 2020).

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3.2 BIOLOGICAL ACTIVITIES

3.2.1 Antioxidant Activity

The antioxidant relationship found by several authors, it is shown in Table 1, where the synthesis of the results demonstrates the use of different parts of the species, such as leaves and seeds. The use of different antioxidant methodologies also contributed to the determination of a more complete antioxidant profile, where the main methodologies used were the lipid peroxidation assay, antioxidant capacity, evaluation of phenolic and flavonoid compounds, DPPH radical assay, and ABTS radical assay. The results found by each author varied according to the objective established in their research.

Araújo *et al.* (2018), for example, were able to verify the partial recovery of lipid peroxidation activity in their study model. Nunes *et al*. (2018), certain values for phenols and total flavonoids.

Table 1. Main antioxidant activities related to the type of extraction and the plant material used.

Author	Used part	Extract type	Assay	Results
Araújo *et al.* (2018)	Seed	Hexanic, ethanolic extracts, and fractions	LP	Partial recovery from lipid peroxidation
Nunes *et al.* (2018)	Bark	Ethanolic extract	1.9.2. Total phenols, flavonoids, and DPPH	22.54 ± 2.22 mg GAE / g 2.41 ± 0.07mg QE /g 132.24 ± 0.65 IC_{50} (µg / mL)
Aquino;Falcão; Almeida-Cortez (2017)	Leaves	Aqueous, hydroalcoholic and methanolic extracts	2.9.2. Total phenols	The rate of metabolites varies according to the collection area, period, and environmental preservation

Legend: GAE – Gallic Acid Equivalent; QE – Quercetin Equivalent; $IC_{50=}$ inhibitory concentration; DPPH - 2,2- difenil-1-picril-hidrazil; ABTS – 2,20 -azino-bis(3-ethylbenzthiazoline-6-sulphonic acid); LP – lipid peroxidation.

3.2.2 Cytotoxic and toxic activity

The cytotoxic profile (Table 2) of the species was traced through studies with several cell lines, including human monocytes, HeLa cells, and fibroblasts. The found results showed a cytotoxic variation. The study by Ceravolo *et al.* (2018), did not demonstrate cellular toxicity in any extract obtained from the species, which corroborates previous results by Lima *et al.* (2017), which showed a high degree of cell viability for all concentrations tested in 3T3 cell lines. However, studies with isolated metabolites of the species have shown significant cytotoxic activity, since they are in the class of alkaloids, which are known for their toxicity.

Mitaine-offer *et al.* (2002), showed in their study, that these metabolites showed toxicity to human NIH 3T3 cell lines (fibroblasts), which corroborated with later studies by Mustofa *et al.* (2006), who demonstrated the cytotoxic profile of vincadifformin and its derivatives isolated from the species *A. pyrifolium*. Lima and Soto-Blanco (2010), found that the leaf extract showed a toxicity for all tested models, where the effects varied according to the concentration used.

Table 2. Cytotoxic profile of the plant species.

Author	Used part	Extract type	Cell Type / Model	Results
Ceravolo *et al.* (2018)	Bark and stem ethyl acetate fractions	Ethanol extract (Soxhlet)	human hepatoma, monkey kidney cells or freshly isolated human monocytes from peripheral blood	None of the crude extracts or fractions were cytotoxic to normal monkey kidney cells or human hepatoma cell lines and human peripheral blood mononuclear cells
Lima *et al.* (2017)	Leaves	Aqueous extracts	3T3 cell lines	The degree of viability was high for all concentrations tested, except for the concentration of 1.75 mg / mL, after 72 h
Mustofa *et al.* (2006)	-	Isolated compounds	HeLa cells	In general, vincadifformin and its derivatives were more toxic after a 24-hour incubation (IC_{50} 16.3 – 96.8 µM) than after 72 h (IC_{50} 22.1 – 213.4 µM)
Mitaine-Offer *et al.* (2002)	-	Isolated compounds	NIH 3T3 human cell lines (fibroblasts)	Alkaloids found in *A. pyrifolium* showed cytotoxic activity

Lima, Soto-Blanco (2010)	Leaves	Ethanol extract	Intraperitoneal injection in animals, hemolytic activity, and *Artemia salina* toxicity test	In general, the extract showed a toxicity for all models tested, where the effects varied according to the concentration used

Legend: MTT = [3- (4,5-dimethylthiazol-2yl) -2,5-diphenyl tetrazolium bromide; HeLa cells = cervical cancer cell line; IC_{50} = inhibitory concentration.

3.2.3 Antimicrobial Activity

The antimicrobial profile (Table 3) of *A. pyrifolium* was determined by studies with different bacterial and fungal strains. Studies by Pessini *et al.* (2012), were also performed with fungal species, and the Minimum Inhibitory Concentration (MIC) varied between 100 and 500 µg/mL. Oliveira *et al.* (2009), determined an antimicrobial activity in concentrations higher than 1000 µg/mL for all tested strains. The studies carried out by Silva *et al.* (2016), and Silva *et al.* (2018), managed to find antimicrobial activities against several bacterial strains.

In activities analysis, it was observed the use of several parts of the plant. The bark was the most frequent. Besides, the use of hydroalcoholic extractive solutions and their fractions allowed a high amount of extracted metabolites and subsequent antimicrobial activity. The different methodologies used for the extraction may have been an important factor for some authors to find the desired activity. Evaluation of the tested strains allows us to understand the microbiological diversity used for the tests. All studies demonstrated high microbial activity for Gram-positive strains. For Gram-negative bacteria, the values of the inhibitory concentrations were higher or even non-existent.

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Table 3. Main antimicrobial activities.

Author	Used part	Extract type	Microorganisms	MIC valor (mg / mL)	MIC valor (µg / mL)	Results
Pessini *et al.* (2012)	Stem bark Root Bark Root Flowers Fruits	EtOH (Soxhlet)	*Staphylococcus aureus* ATCC *25923* *Bacillus subtilis* ATCC *6623* *Escherichia coli* ATCC *25922* *Pseudomonas aeruginosa* ATCC *15442* *Candida albicans* ATCC *10231* *Candida parapsilosis* ATCC *22019* *Candida tropicalis*		125 - >1000 >1000 >1000 500 500	No significant antimicrobial activity was found for the plant extracts and fractions on the tested bacteria and fungi
Oliveira *et al.* (2009)	Stem bark	Hydroethanolic, acid fraction and basic fraction	*E. coli* ATCC 25922 *P. aeruginosa* ATCC 27853 *B. subtilis* ATCC 6623 *S. aureus* ATCC 25923		>1000 >1000 >1000 >1000	*A. pyrifolium* was inactive against standard strains at concentrations > 1000 µg / mL
Silva *et al.* (2016)	Bark	Aqueous extract	*Acidovorax citrulli* *Pectobacterium carotovorum subsp. Carotovorum* *Ralstonia solanacearum* *Xanthomonas campestris pv.campestris*	12.5 25 12.5 25		All four tested bacterial strains were sensitive to the aqueous extract
Silva *et al.* (2018)	Bark	No extracts were made	*E. coli 25922* *P. aeruginosa 27853* *S. aureus 25923*	0.8 mm* - 1.0 mm*		The results confirm the producing potential of antimicrobial compounds by endophytic fungi

Legend: ATCC - American Type Culture Collection; MRSA - Methicillin resistant *S. aureus*; MIC - Minimum Inhibitory Concentration; EtOH-Ethanolic; MeOH- Methanolic;
* Growth-inhibited Halo activity.

3.2.4 Anti-inflammatory activity

The results of anti-inflammatory activities are shown in Table 4. Nogueira *et al.* (2014), found in their study that the residual aqueous fraction of the liquid-liquid partition of the ethanolic extract of *A. pyrifolium* seeds showed antinociceptive and anti-inflammatory activities in the formalin test, abdominal contortion induced by acetic acid and induced paw edema by carrageenan. The results by Lima *et al.* (2017), also showed that the extract and its bioactive molecules, specifically rutin, may have the potential anti-inflammatory application, which corroborates later with Araújo *et al.* (2018), who evidenced the anti-inflammatory effect of aqueous seed extract.

Table 4. Anti-inflammatory profile of the species.

Author	Used part	Extract type	Assay	Model	Results
Nogueira *et al.* (2014)	Seed	Maceration with hexane and fractions	Abdominal contortion, formalin test, and Paw edema	*In vivo*	Significant decrease in the number of abdominal contortions, antinociceptive and anti-inflammatory activity
Lima *et al.* (2017)	Leaves	Aqueous extract	Carrageenan-induced inflammation and poison-induced inflammation	*In vivo*	Extract and its bioactive molecules, specifically rutin, may have potential anti-inflammatory applications
Araújo *et al.* (2018)	Seed	Maceration with hexane and fractions	Intrastriatal and assessment of neuroinflammation	*In vivo*	The aqueous extract has anti-inflammatory properties

3.2.5 Neuroprotective activity

Araújo *et al.* (2018), showed that the APSE-Aq fraction isolated from *A. pyrifolium* seeds offers neuroprotection against Parkinson's disease in an animal model. This result is probably associated with its anti-inflammatory and antioxidant properties together. This study brings new possibilities for this theme since it demonstrates the neuroprotective power of this plant species in the face of a neurodegenerative disease that affects millions of people worldwide.

3.2. 6 Cardiovascular and hypotensive action

The characterization of the hypotensive potential and the properties that the plant species has on blood vessels was determined by Herculano *et al.* (2012). The authors observed the effects of intravenous administration of ethanolic bark extract. They produced dose-dependent hypotension and bradycardia in animals. The hypotensive response produced by the extract remained unchanged after the administration of the NG-nitro-L-arginine methyl ester of the Nitric Oxide Synthase inhibitor (NOS). The results obtained showed that the hypotension produced by the extract depends on the relaxing factors dependent on the endothelium, possibly prostacyclin, and that the hypotension induced by the extract does not involve the activation of the nitrous oxide mode.

3.2.7 Photoprotective activity

The photoprotective profile of *A. pyrifolium* was established by Nunes *et al.* (2018). They evaluated the ethanolic extract at characteristic peaks in the region of UVB rays. In this study, the sun protection factor equivalent to 8.83 was found, indicating the plant species as a promising source in the development of new products with various therapeutic classes associated with oxidative stress and skincare.

3.2.8 Antiplasmodial activity

The antiplasmodial potential of *A. pyrifolium* was determined by Ceravolo *et al.* (2018). The antimalarial activity of the ethanolic extract of the root bark, root, and selected fractions, which showed activity in vitro, were tested in mice with an infection induced by *Plasmodium berghei.* The results of the study demonstrated that oral administration (100 mg/kg) of the root extract reduced parasitemia by *P. berghei*. The reduction was 75% on the fifth day of administration. This reduction was 79% when the animals were treated with the crude extract of the root bark. This study is of great importance since it paves the way for the development of new therapeutic substances to combat neglected diseases that affect millions of people worldwide.

3.2.9 Insecticidal activity

Trindade *et al.* (2008), evaluated the insecticidal activity of the ethanolic extracts of the stem bark, fruit, root and the subfractions of *A. pyrifolium* on cabbage moth (*Plutella xylostella*). The results showed that the stem bark extract was more lethal and its aqueous subfraction rich in alkaloids, caused 100% larval mortality at 4 mg L^{-1}. The authors associated the insecticidal activity with the presence of the indole monoterpenoid alkaloids aspidofractinin, 15 demetoxypyrifoline and *N*-formilaspidofractinine.

3.2.10 Phytochemical composition

The diversity of bioactivities found for this species can be justified by the phytochemical composition that it presents, where many authors have managed to define the profile of substances with activities of biotechnological interest. The correlation established between all the activities previously demonstrated and the phytochemical profile corroborates with the adaptive advantages that this species has for surviving in environments of difficult survival. Thus, these advantages confer to the species potential to be used in sectors of clinical, pharmaceutical, cosmetic, and social interest.

The investigation of the phytochemical profile of this species was established using several quantitative and qualitative methodologies. The synthesis of the results is described in Table 5. It was observed that depending on the type of extraction, chromatographic technique, and used part, the plant has different compounds that allow for varied bioactivity.

Table 5. Phytochemical profile of the species.

Author	Used part	Technique	Extract type	Components founds
Nogueira *et al.* (2014)	Seed	TLC and NMR	Ethanolic	(-) - (3 *S* , 7 *S* , 21 *R*) - *rel* - (3α *H*) -15 (14 → 3) -abeo-2 , 16,17,20,6,7-hexa-hidro-15 *H* , 8- *H* , 16a, 20a-etano-1 *H* -indolizine [3,1- *cd*] carbazole, besides six other Plumeran alkaloids
Lima *et al. (*2017)	Leaves	HPLC-DAD and LC-DAD-MS	Aqueous extract	Rutin and phenolic compounds
Ceravolo *et al.* (2018)	Stem-bark and ethyl acetate fractions from the stem extract	1.9.2. LC–MS/ MS	EtOH (Soxhlet)	Bisindole alkaloid Leucoridine B and unidentified compound with molecular formula $C_{41}H_{46}N_4O_2$
Araújo *et al.* (2007)	Stem-bark	TLC and MNR	Ethanolic, methanolic and fractions	Alkaloids aspidofractinine (1), 15- demethoxypyrifoline (3), and N-formylaspidofractinine (2)

Legend: TLC = Thin Layer Chromatography; HPLC-DAD = Qualitative High Performance Liquid Chromatography coupled with Diode Matrix analysis; LC-DAD-MS = Liquid Chromatography coupled to Mass Spectrometry with Diode array detection analysis; LC-MS/MS = *Liquid Chromatography Tandem Mass Spectrometry;* NMR = Nuclear Magnetic Resonance; EtOH = Ethanol extract.

4 CONCLUSION

The studies found demonstrate the biotechnological profile of the plant species *A. pyrifolium*. Also, its use in various activities of pharmacological interest. Further studies will be necessary to evaluate the other characteristics and biological activities of the species. However, the present work summarized the main activities found revealing the medicinal value and the biological importance that *A. pyrifolium* represents.

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