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Review

Poincianella pyramidalis (Tul) L.P. Queiroz: A review on traditional uses, phytochemistry and biological-pharmacological activities

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ABSTRACT

Ethnopharmacological relevance: Poincianella pyramidalis (Tul.) LP Queiroz (Fabaceae) is an endemic tree in the Northeast of Brazil. Its flowers, leaves, stem bark and root have been used over the years to treat infections, abdominal pain, inflammation, diarrhea, heartburn, and dyspepsia.

Aim of the study: The present study is a critical assessment of the state-of-the-art concerning traditional uses, phytochemistry, pharmacology and toxicology of *P. pyramidalis* performed through the application of a robust research strategy to explore the therapeutic potential of *P. pyramidalis* extracts and isolated compounds for the treatment of human disorders.

Materials and methods: Information related to this review was systematically collected from scientific literature databases for *P. pyramidalis*, including papers and patents (PubMed, Science Direct, Scopus, Web of Science, Google scholar, INPI, WIPO, EPO and USPTO), published books (e.g. Plantas Forrageiras das Caatingas), dissertations and theses. Plant taxonomy has been confirmed in the "The Plant List" database (www.theplantlist.org).

Results: Phytochemical analysis of *P. pyramidalis* shows several constituents such as flavonoids, triterpenoids and phenylpropanoids. The extract and isolated constituents exhibited a wide range of *in vitro* and *in vivo* pharmacological effects including antimicrobial, antinociceptive, anti-inflammatory, gastroprotective and neuroprotective activities. In addition, toxicity studies showed that the administration of *P. pyramidalis* extract was safe in non-pregnant rats but displayed teratogenic effects in rats and goats. On the other hand, the search in patent databases reported a single filing, which highlights the disparity between a large number of published scientific articles versus the almost nonexistent filing of patents. This fact evidences a still little explored technological potential of the species.

Conclusion: P. pyramidalis represents an important therapeutic resource for the population from the Northeast of Brazil. Pharmacological studies confirmed the effectiveness of the extract or isolated compounds in the treatment of various pathologies traditionally treated with *P. pyramidalis.* The authors emphasize the need for in-depth research and future clinical trials in order to investigate the clinical efficacy and safety of *P. pyramidalis.*

1. Introduction

The genus *Poincianella* Britton & Rose belongs to the family Fabaceae, subfamily *Caesalpinioideae*, and has about 35 species with predominant occurrence in Central America and the Caribbean (Gagnon et al., 2013). In Brazil, this genus has seven species, five endemics (*Poincianella bracteosa* (Tul.) L.P. Queiroz, *P. gardneriana* (Benth.) L.P. Queiroz, *P. microphylla* (Mart. ex G.Don) L.P. Queiroz, *P. pluviosa* (DC.) L.P. Queiroz *and P. pyramidalis* (Tul.) L.P. Queiroz), with wide distribution, occurring in all phytogeographic domains. Among the aforementioned species, we highlight *Poincianella pyramidalis* (Tul.) L.P.

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Abbreviations

ASA	acetylsalicylic acid
ATCC	American Type Culture Collection
BDNF	Brain-derived neurotrophic factor
DPPH	2,2-diphenyl-1-picrylhydrazyl
EPO	European Patent Office
ER	estrogen receptor
GDNF	Glial cell-derived neurotrophic factor
IgA	immunoglobulin A
IL	interleukin
iNOS	inducible nitric oxide synthase
INPI	Instituto Nacional de Propriedade Industrial
L-NAME	Nω-Nitro-L-arginine methyl ester hydrochloride
MBC	minimum bactericidal concentration
MIC	minimum inhibitory concentration
MN	micronucleus
MPO	Myeloperoxidase
MRSA	Methicillin-resistant *Staphylococcus aureus*
MsrA	macrolide efflux protein
MSSA	Methicillin-sensitive *Staphylococcus aureus*
NCE	non-chromatic erythrocytes
NGF	Nerve growth factor
NO	nitric oxide
NorA	efflux protein for fluoroquinolones
NSAIDs	Non-steroidal anti-inflammatory drugs
NT-4	Neurotrophin-4
PAG	DL-propargylglycine
PCE	polychromatic erythrocyte
PD	Parkinson disease
PpyTI	trypsin inhibitor from *Poincianella pyramidalis* seeds
RES	reserpine
TE	time of exposure
TH	tyrosinehydroxylase
TNF-α	tumor necrosis factor α
USPTO	United States Patent and Trademark Office
WIPO	World Intellectual Property Organization

Queiroz, native and endemic from the Northeastern Brazil, occurring mainly in the Caatinga biome (Oliveira et al., 2016a, 2016b). Until recently, this species was known as *Caesalpinia pyramidalis* Tul., but due to a taxonomic update, the plant is now called *Poincianella pyramidalis* Tul. (Chaves et al., 2016).

Popularly known as “catingueira”, “catingueira-verdadeira”, "pau-de-rato" or "caatinga-de-porco", this bush, which grows preferentially in sandy soils, is of great importance to the local population (Maia-Silva et al., 2012). It is used for the most diverse purposes, where we can emphasize its use as fuel, raw material in construction, forage application and medicinal use (Chaves et al., 2016). In traditional medicine, its bark, leaves, flowers and roots are used in the form of decoction and infusion for the therapy of gastritis, colic, diarrhea, asthma, bronchitis, diabetes, inflammation, besides presenting healing activity (Albuquerque and Oliveira, 2007b; Cartaxo et al., 2010).

Chemically, *P. pyramidalis* stands out for the presence of steroids, phenolic acids, lignans, phenylpropanoids, tannins, flavonoids (especially biflavonoids) and fatty alcohols (Mendes et al., 2000; Bahia et al., 2005; Saraiva et al., 2012; Chaves et al., 2016; Oliveira et al., 2016a). This species has been submitted to biological assays that revealed its antimicrobial (Lima et al., 2006; Saraiva et al., 2012; Chaves et al., 2016), gastroprotective (Ribeiro et al., 2013; Diniz et al., 2015), anti-inflammatory and antinociceptive (Santos et al., 2011, 2013), anthelmintic (Borges-dos-Santos et al., 2012) and neuroprotective (Souza et al., 2018) properties.

The present study is a critical assessment of the state-of-the-art concerning the traditional uses, the phytochemistry, the pharmacology and the toxicology of *P. pyramidalis*. The article also aims to suggest further research strategies to facilitate the exploitation of the therapeutic potential of the plant products for the treatment of human disorders.

2. Methods

2.1. Search strategy

First, the plant name was authenticated using the International Plant Names Index (IPNI) and The Plant List (www.theplantlist.org). This bush was previously identified as *Caesalpinia pyramidalis* Tul., however recent taxonomic updates promoted a change in its nomenclature to *Poincianella pyramidalis* Tul. (de Moraes et al., 2020). Checking the correct nomenclature in the IPNI we verified that the current name of the plant is *Poincianella pyramidalis* (Tul.) LP Queiroz (urn: lsid: ipni.org: names: 77100753-1), but according to The Plant List, the name is under review, given the publication of Gagnon et al. (2016), which states that the species previously classified as *P. pyramidalis* would belong to the genus *Cenostigma*, being called *Cenostigma pyramidale* (Tul.) Gagnon & G.P. Lewis.

Electronic online databases such as PubMeD, Science Direct, Scopus, Web of Science and Google Scholar were used to collect information of *P. pyramidalis* published prior to December 2019. We use specific search terms such as "*Poincianella pyramidalis*"; "*Caesalpinia pyramidalis*"; "Traditional uses"; "Phytochemistry"; "Pharmacology" and "Toxicity" as keywords to gather relevant data. The following technology databases INPI, WIPO, EPO and USPTO were used with the before-mentioned keywords for patent research. Dissertations and theses were explored using Periódicos Capes Theses databases. Books were consulted.

2.2. Study selection

The studies were carefully chosen based on these inclusion criteria: articles, books and patents, published in English and Portuguese, reporting pharmacological actions, toxicity, teratogenicity, phytochemistry or isolation of secondary metabolite and traditional uses of *P. pyramidalis* extracts and/or parts of the plant. Review articles, case reports, editorial/letters, conference proceedings or studies that do not discuss the above aspects of *P. pyramidalis* were not considered for this review. Included papers were evaluated by reading the title, abstract and full text.

2.3. Data extraction

The articles, book chapters and the patent were analyzed according to the part of the plant used in the test, the extractive process applied in the production of the extract, the isolated chemical compounds, the experimental models applied (*in vitro* or *in vivo*), the doses used and the pharmacological activities and/or toxicity found. The selected data were organized in tables and figures arranged throughout this paper.

3. Botanical characterization and distribution

P. pyramidalis is a shrub or grove of multiple trunks, with 1–6 m, with dense and open canopy, without thorns, with bark ranging from gray to brown, rigid, with smooth and rough parts, light gray and has numerous small and irregularly arranged (Silva et al., 2009). It has pinnate leaves, leathery, with 3 to 11 sessile to subsessile leaflets, pages opposite to

sub-opposites, with ± oblong to suborbicular shape; alternate. Terminal paniculate inflorescences, pyramidal, consisting of terminal racemes, multiflorous, ± corimbous at the apex; with oval-lanceolate bracts, acute to acuminate; articulated pedicel. Yellow flowers; oboval, elliptical, suborbicular to sub-rectangular petals; vexate petal with red-orange ribs. Legume oblong-oblanceolate, strongly compressed, apiculate and elastic dehiscence, polyspermic with 4–12 seeds (Queiroz et al., 2009). (Fig. 1). Commonly called Catingueira or Catinga-de-porco (Maia, 2004, 2012).

P. pyramidalis is a pioneer, heliophite, xerophytic plant, characteristic of the caatinga in the Northeast of Brazil, where it is endemic and widely distributed, but it is found in a disjoint way in the Amazon (Queiroz et al., 2009) and in the "restingas" in the coast of the Northeast of Brazil (Santos-Filho et al., 2011, 2013, 2015). It regenerates quickly after cutting, being one of the first to sprout after the beginning of the rains, reaching, after 30 days, abundant and abundant vegetation (Lorenzi, 2009).

4. Traditional uses

Poincianella pyramidalis (catingueira) is a species that represents an important source of income for the Northeast region of Brazil. The local population uses this plant for various purposes, such as the exploitation of the wood for the production of stakes and construction of clay houses or the application of firewood as an energy matrix (Maia, 2004). As forest contains high levels of cellulose and lignin it is considered a good source of energy, in addition to presenting an excellent yield in the production of charcoal (Medeiros Neto et al., 2014).

Other utilities for the economic exploitation of the plant are focused on the potential production of ethanol fuel and metallurgical coke (Silva et al., 2009), as well as its use in obtaining forage, since the referred species is deeply suitable for feeding small ruminant animals (Maia, 2004). The species is also appropriate for forest restoration of degraded areas (Lorenzi, 2009).

The medicinal use of catingueira by the Brazilian population is rather widespread and its empirical applicability has been reported over the years (Chaves et al., 2016). Several parts of *P. pyramidalis* have been used, in different preparations, to treat various pathologies (Table 1). The roots, stem bark, leaves and flowers are prepared by different methods, such as: maceration, infusion, decoction and syrup or juice, and are used to treat respiratory and gastrointestinal problems, inflammation, fever, pain, diabetes and as a scarring (Lima, 1996; Agra et al., 2007; Cartaxo et al., 2010; Albuquerque, 2006, 2007a; Oliveira et al., 2010). The most reported form of preparation for flowers is infusions and syrups, while leaves and roots are prepared in the form of infusion and decoction (Cartaxo et al., 2010; Lima, 1996; Albuquerque and Oliveira, 2007b; Almeida et al., 2006; Souza et al., 2011; Pereira Júnior et al., 2014).

5. Phytochemistry

In the last few decades, the phytochemistry studies have isolated and identified different types of chemical constituents in extracts from leaves, flowers, roots and bark of *P. pyramidalis*, including steroids, phenylpropanoids and flavonoids (Table 2) (Mendes et al., 2000; Bahia et al., 2005, 2010).

For example, Mendes et al. (2000) isolated two new glycosyl phenylpropanoid acids from dried leaves of *P. pyramidalis* using methanol as extractor solvent identifying them by liquid chromatography coupled mass spectrometry (LCMS) and nuclear magnetic resonance (NMR): 4-*O*-β-(2′,3′,4′,6′-tetraacetyl) glucopyranosyloxy-(*Z*) -7-hydroxycinnamic acid and **(1)**, 4-*O*-β-(2′,3′,4′,6′-tetraacetyl) glucopyranosyloxy-(*Z*)-8-hydroxycinnamic acid **(2)**, besides lupeol **(3)** and agathisflavone **(4)** (Mendes et al., 2000; Bahia et al., 2005; Oliveira, 2010; Borges-dos-Santos et al., 2012). After that, the chloroform extract of the leaves of *P. pyramidalis* showed a new biflavonoid named caesalflavone **(5)**, as well as podocarpusflavone A **(6)**, agathisflavone **(4),** kaempferol **(7)** and apigenin **(8)** (Bahia et al., 2005). The compounds amentoflavone **(9)**, 5'-hydroxyamentoflavone **(10)**, sequoiaflavone **(11)**, taxifolin **(12)**, loniflavone **(13)**, sitosterol **(14)**, were also found in the chloroform partition of methanol extract of leaves of this plant (Bahia et al., 2005, 2010).

The chromatographic fractionations performed on the methanolic extract of the roots allowed the isolation and elucidation by LCMS and

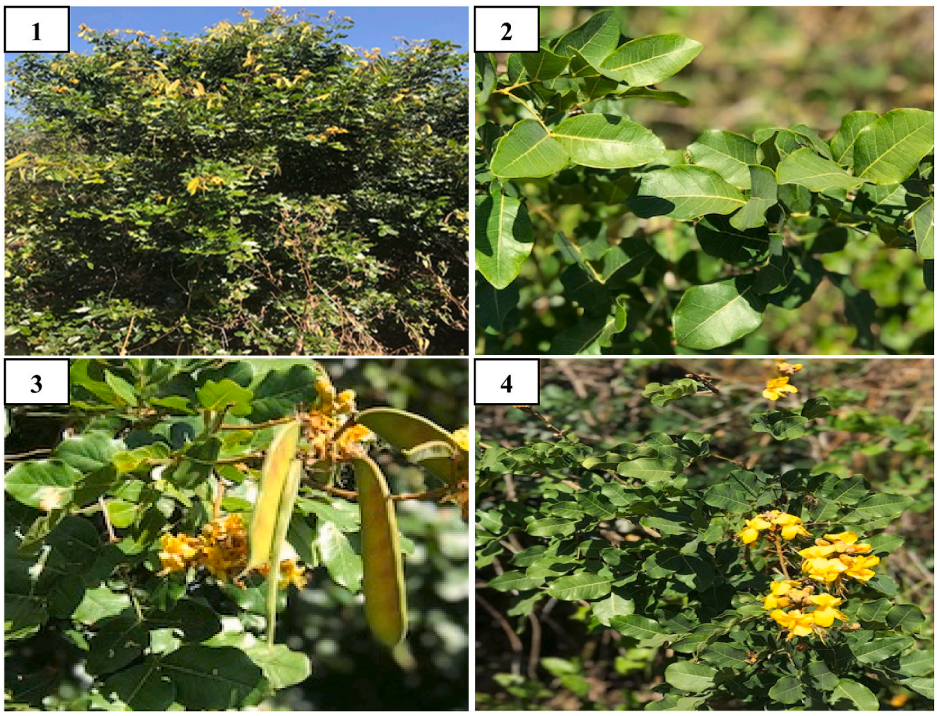

Fig. 1. *Poincianella pyramidalis* (1); leaves of *P. pyramidalis* (2); fruits of *P. pyramidalis* (3); flowers of *P. pyramidalis* (4).

Table 1
Traditional uses of *Poincianella pyramidalis*.

Traditional medicinal uses	Traditional preparation and use procedures	Part of the plant	References
Aphrodisiac	A maceration of a handful in a liter of wine or "cachaça". It is drunk before the meals two times a day.	Stem-bark	Agra et al. (2007) Agra et al. (2008)
Against dysenteries, diarrheas and stomachache	A decoction of one part in two parts of water. It is drunk as tea until the symptoms disappear.	Stem-bark	Agra et al. (2007) Agra et al. (2008)
As an expectorant and used against bronchitis, coughs and respiratory infections,	A decoction with sugar as syrup. A spoonful of the syrup is drunk four to five times a day.	Stem-bark	Agra et al. (2007) Agra et al. (2008)
Catarrhal infections; diarrhea; disinterests.	NA	Leaves; flowers and bark	Lima (1996)
Cough, bronchitis, respiratory infection, influenza, asthma, gastritis, colic, fever, heartburn, flatulence, diarrhea, collision, injury, diabetes, aphrodisiac, stomachache, expectorant	NA	Stem; bark; flower; leaves; root.	Albuquerque et al. (2007a)
Influenza, stomachache, diarrhea, healing, hemostatic, expectorant, stomach problems, indigestion.	Decoction, leave soaking, juice or poultice. Drink or wash the affected site	Stem; bark; flower	Cartaxo et al. (2010)
Cough	Syrup. Drunk	Bark of the stem	Albuquerque (2006)
Diarreia; diabetes; inflamação em geral; gastrite.	Infusion; combined with alcoholic drink; juice. Oral ingestion	Stem bark	Oliveira et al. (2010)
The flu; cough; antiasthmatic	Infusion; combined with alcoholic drink; maceration. Oral ingestion.	Flower; bark	Marinho et al. (2011)
Anti-inflammatory; healing; prostate; the flu; rheumatism; digestive problems	Infusion; combined with alcoholic drink; syrup; fruit juice. Oral ingestion	Bark; fruit	Silva and Freire (2010)
The flu; expectorant; cough; congestion; diarrhea; bloody stools; gastritis, hepatitis; sexual impotence; urinary infections; rheumatism	NA	NA	Silva et al. (2010)
Abdominal pain; cough; coagulant; dysentery; inflammation of the prostate	Decoction	Stem bark; flower;	Pereira et al. (2014)
The flu; cough; inflammations in the body	Decoction; syrup. Oral ingestion	Bark; flower	Silva et al. (2015)
flatulence; indigestion	Decoction. Oral ingestion	Leaves; flower	Almeida et al. (2005) Almeida et al. (2006)
Diuretic; dyspeptic, digestive and antipyretic.	Infusion; decoction. Oral ingestion	Leaves	Bahia et al. (2005) Bahia et al. (2010)
Candidiasis	Infusion. Topical use.	Leaves	Cruz et al. (2007)
Cough; the flu		Leaves	
	Infusion. Oral ingestion		Ribeiro et al. (2014)
Expectorant; respiratory system disorder	Infusion; decoction; syrup. Oral ingestion 2 or 3 times a day	Leaves; flower	Lucena et al. (2018)
Anti-inflammatory; digestive system disorder	Infusion; decoction. Oral ingestion 2 or 3 times a day	Flower; bark; root	Lucena et al. (2018)
Hemostatic; circulatory system disorder	Bark powder. Apply the powder to the affected area and wait to stop the bleeding	Bark	Lucena et al. (2018)
Healing	Bark powder. Apply the powder to the affected area	Bark	Lucena et al. (2018)
Analgesic	Place the leaf under the tongue	Leaves	Lucena et al. (2018)

NA – Not available.

NMR of 3,3'-dimethoxy-4,4'-dihydroxyiellagic **(15)** and 3,3'-dimethoxy-4-hydroxyiellagic-4'-*O*-β-D-xylopyranoside **(16)**, lupeol **(3)** and the mixture of β-sitosterol/stigmasterol fatty acids **(17a/17b)**, in addition to a new biflavonoid, 7-hydroxy-4'-methoxyflavone-5α-2,4-dihydroxy-4'metoxidihidrochalcone **(18)**. In the hexane phase, acacetin **(19)** and (*E*) -8-hydroxy-3,5-dimethoxycoumaric acid were found **(20)** (Oliveira et al., 2016a).

Phytochemical investigations on the bark roots of this bush was performed from the extraction in methanol followed by partition in hexane, chloroform and ethyl acetate. This process led to the isolation of four new bioflavonoids by NMR techniques named (+)-5-hydroxy-7,4′-dimethoxyflavone-3α-2‴-hydroxy-4‴,4″-dimethoxydihydrochalcone **(21)**, (+)-5,7-dihydroxy-4′-methoxyflavone-3α-2‴-hydroxy-4‴,4″-dimethoxydihydrochalcone **(22)**, (−)-7-hydroxy-4′-methoxyflavone-3α-2‴,4‴-dihydroxy-4″-methoxydihydrochalcone **(23)**, (−)-7,4′-dihydroxy-flavanone-3,8-5″,6″,4″-trihydroxy-flavone **(24)**, and the previously identified compound 4,2′,4′,4″,2‴,4‴-hexahydroxy-3,5‴-bichalcone **(25)** (Oliveira et al., 2016b). The chemical structures of these compounds are shown in Fig. 2.

6. Biological activities

The popular use of plants has been an ally to aid research, being frequently used as a starting point for studies on various types of biological activities. Thus, information obtained from popular use is essential to support new studies focused on its effectiveness and identification of active constituents (Salehi et al., 2019a). Over the years, pharmacological studies have related the biological activities of *P. pyramidalis* and its chemical components, called bioactive (Table 2).

Although some studies report data on chemical antioxidant assays (for example, DPPH), these results are not included in this review, since this information is not considered pharmacologically relevant. Chemical antioxidant tests have been questioned for their inadequate transferability for clinical applications, and this requires clinical studies (HerbalEGram, 2018). In this section, the biological activities related to extracts and isolated compounds belonging to different pharmacogens of the species *P. pyramidalis* are briefly described.

6.1. Antibacterial activity

Research has shown the potential of plants to produce a variety of substances with intrinsic antimicrobial properties or as potentiators of other existing antibiotic substances, applied mainly against drug-resistant microorganisms (Ahmad and Beg, 2001; Luna et al., 2010;

Table 2
Chemical compounds isolated from *Poincianella pyramidalis*.

N.	Part of the plant	Isolated chemical compound	Group	References
1	Leaves	4-*O*-β-(2′,3′,4′,6′-tetraacetyl) glucopyranosyloxy-(*Z*) -7-hydroxycinnamic acid	Glycosyl phenylpropenoid acid	Mendes et al. (2000)
2	Leaves	4-*O*-β-(2′,3′,4′,6′-tetraacetyl) glucopyranosyloxy-(*Z*) -8-hydroxycinnamic acid	Glycosyl phenylpropenoid acid	Mendes et al. (2000)
3	Leaves; root bark	Lupeol	Triterpene	Mendes et al. (2000), Bahia et al. (2005) Oliveira (2010) Borges-dos-Santos et al. (2012)
4	Leaves	Aghatisflavone	Biflavonoid	Mendes et al. (2000), Bahia et al. (2005), Oliveira (2010) Borges-dos-Santos et al. (2012)
5	Leaves	Caesalflavone	Biflavonoid	Bahia et al. (2005)
6	Leaves	Podocarpusflavone A	Biflavonoid	Bahia et al. (2005)
7	Leaves	kaempferol	Flavonoid	Bahia et al. (2005)
8	Leaves	Apigenin	Flavonoid	Bahia et al. (2005)
9	Leaves	Amentoflavone	Biflavonoid	Bahia et al. (2010)
10	Leaves	5- hydroxyamentoflavone	Biflavonoid	Bahia et al. (2010)
11	Leaves	Sequoiaflavone	Biflavonoid	Bahia et al. (2010)
12	Leaves	Taxifolin	Flavonone	Bahia et al. (2010)
13	Leaves	Loniflavone	Biflavonoid	Bahia et al. (2010)
14	Leaves	Sitosterol	Steroid	Bahia et al. (2010)
15	Root bark	3,3'-dimethoxy-4,4'-dihydroxyiellagic	Derivatives of ellagic acid	Oliveira et al. (2016a)
16	Root bark	3,3'-dimethoxy-4-hydroxyiellagic-4'-*O* -β-D-xylopyranoside	Derivatives of ellagic acid	Oliveira et al. (2016a)
17a	Flowers	β-sitosterol	Phytosterol	Oliveira et al. (2016a)
17b	Flowers	Stigmasterol	Steroid	Oliveira et al. (2016a)
18	Root bark	7-hydroxy-4'-methoxyflavone- 5α-2,4-dihydroxy-4'-metoxidihidrochalcone	Biflavonoid	Oliveira (2010)
19	Root bark	Acacetin	Flavonoid	Oliveira (2010)
20	Root bark	(*E*) -8-hydroxy-3,5-dimethoxycoumaric acid	Phenylpropanoid	Oliveira (2010)
21	Root bark	(+)-5-hydroxy-7,4′-dimethoxyflavone-3α-2‴-hydroxy-4‴,4″-dimethoxydihydrochalcone	Biflavonoid	Oliveira et al. (2016b)
22	Root bark	(+)-5,7-dihydroxy-4′-methoxyflavone-3α-2‴-hydroxy-4‴,4″-dimethoxydihydrochalcone	Biflavonoid	Oliveira et al. (2016b)
23	Root bark	(−) -7-hydroxy-4′-methoxyflavone-3α-2‴,4‴-dihydroxy-4″-methoxydihydrochalcone	Biflavonoid	Oliveira et al. (2016b)
24	Root bark	(−)-7,4′-dihydroxy-flavanone-3,8-5″,6″,4″-trihydroxy-flavone	Biflavonoid	Oliveira et al. (2016b)
25	Root bark	4,2′,4′,4″,2‴,4‴-hexahydroxy-3,5‴-bichalcone (rhuschalcone VI)	Biflavonoid	Oliveira et al. (2016b)

N. (number).

Sharifi-Rad et al., 2018a; https://www.ncbi.nlm.nih.gov/pubmed/?term=Salehi%20B%5BAuthor%5D&cauthor=true&cauthor_uid=30875872 Salehi et al., 2019b; https://www.ncbi.nlm.nih.gov/pubmed/?term=Salehi%20B%5BAuthor%5D&cauthor=true&cauthor_uid=30875872 Salehi et al., 2019c). Studies have reported the antimicrobial potential of *P. pyramidalis* extracts as a single therapy or as adjuvant (Lima et al., 2006; Alviano et al., 2008; Chaves et al., 2016, 2019).

The ethyl acetate phase of the ethanolic extract of the leaves and stem of *P. pyramidalis* showed antimicrobial activity against standard strains of *Staphylococcus aureus* by the disk diffusion method (13 μL of the extract impregnated in the paper disk), with a 10 mm inhibition halo. On the other hand, the same extract showed no activity against *E. coli* (Novaes et al., 2003). The ethanolic extract of the leaves of *P. pyramidalis* at a concentration of 100 μg/mL was classified as very active (without bacterial growth detected after an incubation time of 24 h) and active (showing bacterial growth at least 10 times less than that observed with negative control after an incubation time of 24 h) in combating strains of *Staphylococcus aureus*, resistant to drugs, which contains the gene for the efflux pump NorA (fluoroquinolones) and MsrA (macrolides), respectively (Lima et al., 2006). The acquired resistance of bacteria to antimicrobial drugs can be attributed to several mechanisms, among them, the involvement of efflux pumps (Kaatz et al., 2003). These results indicate that *P. pyramidalis* can enhance the activity of these antibiotics and act as adjuvant in the therapy of resistant pathogens. However, this study had no positive control, which impaired the ability to analyze the data critically.

Alviano et al. (2008) demonstrated the viability of aqueous extract of the leaves of *P. pyramidalis* for the treatment of oral diseases. In this study, the *in vitro* antimicrobial activity of the extract was evaluated against bacteria strains associated with periodontal disease: *Prevotella intermedia*, *Porphyromonas gingivalis, Fusobacterium nucleatum*, and cariogenic microorganisms: *Streptococcus mutans* and *Lactobacillus casei*. The results of the agar diffusion assay, show that the extract (20 mg/mL) has significant antimicrobial activity against all bacterial species tested (ATCC isolates), when compared with the positive control, Chlorhexidine® (40 mg/mL), and the minimum inhibitory concentration (MIC) varied between 1.0 mg/mL and 8.0 mg/mL. Also, after 2.5 h of incubation, we observed that *P. pyramidalis* aqueous extracts were able to kill 100% of the *P. gingivalis* and approximately 90% of the *P. intermedia,* respectively. Thus, we can say the extract can be used to inhibit oral microbial growth, representing great interest for future studies on the treatment of oral diseases.

Saraiva et al. (2012) evaluated the methanolic extracts, ethyl acetate and *n*-hexane fractions of different fresh parts of the plant, including: leaves, stem bark, root bark, flower, seeds and fruits of *P. pyramidalis*, against seventeen strains of multiresistant *Staphylococcus aureus* (MRSA), two strains of *S. aureus* MSSA and two standard strains, using the agar diffusion method (100 μL/mL of the extracts and 300 μg/mL for antibiotics) and MIC determination by the agar dilution method/Stears multi inoculator (31.5 μg/mL to 2000 μg/mL of the extracts). The root bark extract showed superior antimicrobial activity when compared with the other extracts, with MIC less than 0.5 mg/mL and the *n*-hexane fraction showed no activity. The results of bioautographies allowed visualizing six inhibition halos for the extracts in ethyl acetate from stem bark (in the order of 15, 16 and 18 mm) and three from leaves (in the order of 12 mm), which permits the authors to conclude that there are at least six plus three active compounds. *P. pyramidalis* extracts showed

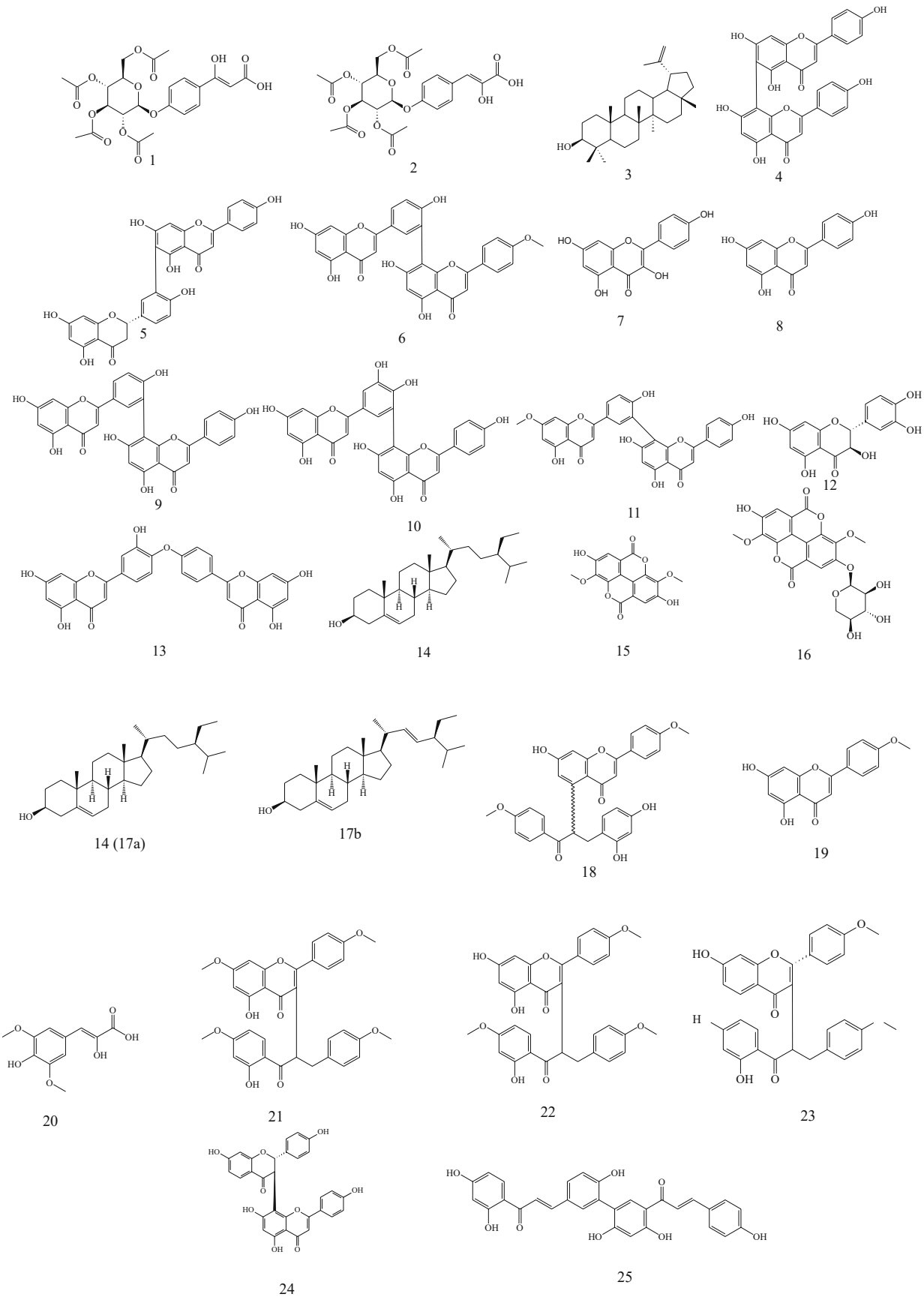

Fig. 2. Isolated substances from *P. pyramidalis*.

good antimicrobial activity against multidrug-resistant strains of *S. aureus*.

Ribeiro et al. (2013), considered the antimicrobial activity against *Helicobacter pylori* as weak. They evaluated the ethanolic extract of stem bark of *P. pyramidalis* (60 μg/mL to 10,000 μg/mL) using agar diffusion methods against *H. pylori*. The study showed that the extract generated inhibition halos of 12.0 ± 1.7 mm in the concentration of 10,000 μg/mL. On the other hand, tetracycline (30 μg/mL), used as a standard drug, presented inhibition halos of 40.0 ± 0.5 mm. For the microdilution test, the concentration of the extract used was 10,000 to 0.305 μg/mL of the ethanolic extract. The MIC and minimum bactericidal concentration (MBC) values obtained in the broth microdilution method of the ethanolic extract were 625 and 10,000 μg/mL, respectively.

Chaves et al. (2016), evaluated the intrinsic antimicrobial activity and the modulating action of bacterial resistance of extracts made with stem barks of *P. pyramidalis* against standard strains (ATCC) and clinical isolates of *E. coli*, *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*. The researchers used the microdilution method in the presence and absence of the extract (125 μg/mL) combined with synthetic antibiotics. The addition of the extract significantly increased the activity of different classes of antibiotics and reduced the MIC of multidrug-resistant strains. However, it did not produce significant intrinsic antimicrobial activity against multidrug-resistant strains with MIC> 1000 μg/mL.

Finally, Chaves et al. (2019) investigated the intrinsic and modulating antimicrobial activity of different classes of antibiotics with ethanolic extract produced with bark of P. *pyramidalis* against *Staphylococcus aureus*, *Streptococcus oralis* and *Streptococcus mutans*. The strains of *S. oralis* and *S. mutans* were susceptible to the extract at 500 μg/mL, while the multiresistant strains were susceptible to 1000 μg/mL. For *S. aureus*, the MIC values were the same for both strains (1000 μg/mL). On the other hand, catechin tested alone did not show significant MIC values (MIC > 1000 μg/mL). In addition, the extract of *P. pyramidalis*, when associated with different classes of antimicrobials, provided an enhancement of antimicrobial activity, significantly reducing its MICs, demonstrating good prospective use in antimicrobial therapy. When added to the culture medium at 125 μg/mL, the extract was able to significantly reduce the MIC values of ceftriaxone, cefepime and chloramphenicol against strains of *Streptococcus*. MIC values for gentamicin, ampicillin and oxacillin were significantly reduced in the assays with *S. aureus*. The combination of plant products with existing antibiotics appears to be an effective strategy for disrupting resistance mechanisms and increasing the antimicrobial effect.

The data presented in this topic show us that the extracts of *P. pyramidalis* have antimicrobial properties with both Gram-positive (ex: *Staphylococcus aureus*, *Streptococcus oralis* and *Streptococcus mutans*) and Gram-negative bacteria (ex: *Prevotella intermedia* and *Porphyromonas gingivalis*), proving to be a versatile agent. In general, the published studies indicate that *P. pyramidalis* extracts and fractions are a promising option in therapy to combat pathogenic microorganisms, especially in enhancing the effectiveness of existing antibiotics. However, adequate pharmacological models, consisting of *in vivo* studies, are necessary to confirm its antimicrobial potential or its modulating activity.

6.2. Antifungal activity

The use of medicinal plants to treat ringworm is a common practice in rural communities, but there are few studies of this activity for *P. pyramidalis* (Duarte et al., 2005; Cruz et al., 2007). It was demonstrated that the aqueous extract prepared with leaves of *P. pyramidalis* (1 mg/mL) according to popular usage (by infusion) showed significant antimicrobial activity against all species of fungi tested (*Trichophyton rubrum*, *Candida guilliermondii*, *Candida albicans, Cryptococcus neoformans* and *Fonsecaea pedrosoi*). The best activity of the extract was observed against *T. rubrum* and *C. guilliermondii* with MIC of 6.5 μg/ml (Cruz et al., 2007). The antifungal activity reported in this study supports the popular use of this plant in the treatment of some mycoses, corroborating the value of ethnopharmacological research in the selection of plant species bioactivities.

Later, Barbosa Junior et al. (2015) tested the activity of the aqueous extract of the leaves of *P. pyramidalis* obtained by infusion, in the concentrations of 4 mg/mL, 40 mg/mL and 100 mg/mL, by the disk diffusion method. As observed in the previously mentioned study, the plant extract showed antifungal action against clinical isolates of *C. neoformans* (inhibition halos in the order of 10 and 12 mm) (Barbosa Junior et al., 2015).

Despite the good results obtained, studies of the antifungal activity of the extract of *P. pyramidalis* are shown as preliminary data. These open great possibilities for further research on the evaluation of the activity of these extracts and its adverse effects that may occur. Another worrying factor is the dose, which can be potentially toxic in high concentration. Therefore, it is important to develop advanced models of antifungal potential, including resistant strains, adequate standards and statistical models to compare data. Thus, further studies of antifungal activity are needed to corroborate the antimycotic action of the tested plant species, in addition to a better understanding of its mechanism of action and safety.

6.3. Anthelmintic activity

The population of the Brazilian Northeast uses leaves of *P. pyramidalis* in the form of decoctions for the treatment of intestinal parasites. Interestingly, few studies report the anthelmintic effect of this species. The antiparasitic activity of the aqueous extract produced with leaves of *P. pyramidalis* was evaluated in goats naturally infected with gastrointestinal nematodes. The extract was administered to two groups of animals, at doses of 2.5 and 5 mg/kg, respectively. Stool and blood samples were collected regularly, to perform the fecal egg count and to determine the hematological and immunological parameters, to assess the antiparasitic activity of the extract. All groups treated with this extract had a positive reduction in egg count in feces from 54.61% (2.5 mg/kg) and 71.21% (5.0 mg/kg) suggesting a direct association of the extract activity in reducing the fertility of female parasites (Borges dos Santos et al., 2012).

The extract also led to an increase in the concentration of IgA, which may be involved in the generation of protective immunity. The IgA concentration of the group treated with the dose of 5.0 mg/kg was 488.69 ng/mL at the baseline moment, 517.12 ng/mL at 30 days and 483.51 ng/mL 60 days later. For the leukocyte count, no significant differences were observed in the values of eosinophils in the blood when compared to the negative (untreated animals) and positive control (Doromectin) (Borges dos Santos et al., 2012). Therefore, other experiments with different models of infected animals are essential to evaluate the best dose of the extract to be administered.

6.4. Gastroprotective activity

Plants and products derived from plants have been used popularly worldwide for the treatment of gastric diseases. *P. pyramidalis* has been widely used for the treatment of gastritis, heartburn, indigestion, stomach pain, stomach problems. Oral administration of ethanolic extract from the inner bark of the *P. pyramidalis* stem in rats at doses 30, 100 and 300 mg/kg reduced the ulcer injury index (18.20 ± 1.52; 11.90 ± 1.23; 0.92 ± 0.40), the total lesion area (45.47 ± 6.38; 36.41 ± 4.37; 0.93 ± 0.46) and increased the curative ratio (28 ± 4.09; 53.33 ± 3.32; 96.39 ± 1.56) compared to the vehicle group ($P < 0.01$) in ulcerative lesions induced by ethanol and non-steroidal anti-inflammatory drugs (NSAIDs) in a dose-dependent manner. The administration of *P. pyramidalis* extract also increased the mucus production significantly when compared to vehicle-treated animals (Ribeiro et al., 2013). These results indicate that the increase in the amount of mucus is a potential mechanism of action for the gastroprotective effect *P. pyramidalis* and

also favors the traditional use of the plant in the treatment of various gastrointestinal disorders.

In another study, with this extract in the same doses tested previously (30, 100 and 300 mg/kg), the authors determined the possible mechanisms of action of *P. pyramidalis* against gastric damage induced by ethanol. It was observed that the oral administration of the ethanolic extract produced with stem bark promoted inhibition in the total area of the lesion, in comparison with the vehicle group. Rats treated with extract and DL-Propargylglycine (PAG, a cystathionine-γ-lyase inhibitor) at the dose of 25 mg/kg showed more gastric lesions ($p < 0.05$), indicating a decrease in the gastroprotective effect of the compound tested. On the other hand, the intraperitoneal administration of N_w-nitro-l-arginine methyl ester hydrochloride (L-NAME, an inhibitor of nitric oxide synthase) at the dose of 70 mg/kg did not promote changes in the gastric effect of the extract, which suggests that the mechanism of action of the compound is not related to endogenous nitrous oxide (Diniz et al., 2015).

In the study, it was also observed that the amount of gastric mucosa mast cells of the animals treated with the extract reduced significantly. Immunohistochemistry and flow cytometry tests showed that the inflammatory cells of the ulcerated rodents administrated with the extract at a dose of 100 mg/kg displayed an upregulation of interleukin 4 (IL-4) expression and downregulation of inducible nitric oxide synthase (iNOS) expression. The results indicate that the ethanolic extract of *P. pyramidalis* stem bark caused dose-dependent gastroprotection on ethanol-induced stomach injuries in rats through mechanisms related with the interaction with endogenous hydrogen sulfide and a decrease of inflammation (Diniz et al., 2015).

6.5. Neuroprotective activity

Herbal products are valuable sources of substances with potential therapeutic value for neurodegenerative diseases such as Parkinson's disease (PD). The effect of the administration of a hydroalcoholic extract of *P. pyramidalis* produced with 90% ethanol (25 mg/kg/day; subcutaneous route; daily) in rodents was studied in the PD induced by the repeated dose of reserpine (0.1 mg/kg; subcutaneous route; every two days). Previous studies showed that repeated administration of 0.1 mg/kg of reserpine in rats induces progressive behavioral deficits that mimic PD symptoms in humans. Besides, this methodology promotes a reduction in the quantities of tyrosine hydroxylase in the brain of the animals, suggesting that the protocol of progressive Parkinsonism induction with reserpine may be useful in the study of neuroprotective agents for PD (Lins et al., 2017).

The treatment with reserpine (1 mg/kg) increased the number of empty chewing movements, protrusions of the tongue and the occurrence of rhythmic contractions of the animals' facial muscles. The administration of *P. pyramidalis* extract (25 mg/kg) reduced the motor deficit of the rodents. In addition, treatment with the extract delayed the onset of oral movements induced by reserpine. The authors suggest that the hydroalcoholic extract of *P. pyramidalis* may be an interesting adjuvant treatment of Parkinson's disease, since it may delay the onset of the neurodegenerative process of this disease (Lins et al., 2017). However, studies with other animal models, doses and routes of administration are needed to confirm these effects.

Additionally, to the effect of the crude extract, neuroprotective studies carried out with isolated phytochemicals also showed promising activities. For example, agathisflavone, a biflavonoid extracted from *P. pyramidalis*, promoted the generation of neurons in an *in vitro* experiment, using primary cultures of neurons and glial cells obtained from the cerebral cortex of newborn Wistar rats. Treatment with agathisflavone (10 μM) promoted a significant increase in the number of neuronal progenitors and mature neurons, without increasing astrocytes or microglia. To study the mechanism of action of agathisflavone's, pro-neuronal estrogen receptors (ERα and ERβ) were blocked, which produced an inhibition of the activity of this flavonoid, showing that the action of agastisflavone is directly related to these receptors (Souza et al., 2018).

Treatment with agathisflavone (0,1–10 μM) reduced the production of pro-inflammatory microglial cytokines (M1), which are associated with neurotoxicity, and increased the production of anti-inflammatory microglial cytokines (M2), which is linked to neuroprotection. This positive balance of cytokines resulted in a reduction in glutamate induced cell death. Agathisflavone also promoted an increase in neuroprotective trophic factors, such as BDNF, NGF, NT4 and GDNF (Souza et al., 2018).

The neuroprotective activity of the flavonoid was related to a greater expression of glutamate regulatory proteins in astrocytes. The results of this study demonstrate that agathisflavone, which acts *via* estrogenic signaling, provides the growth of neurons *in vitro* and improves the neuroprotective properties of microglia and astrocytes to decrease the effects of glutamate-mediated neurotoxicity (Souza et al., 2018).

6.6. Anti-inflammatory and antinociceptive activities

The demand for new molecules with effective anti-inflammatory and antinociceptive activity and with less adverse effects is continuous and necessary. Plants are constantly studied as potential sources of agents for this applicability since plant-based products usually have fewer side effects than NSAIDs, drugs of first choice for the treatment of inflammation and pain (Barragán-Zarate et al., 2020).

The ethanolic extract from the stem bark of the *P. pyramidalis* was used to treat pain and inflammation in rodents. The authors tested the extract in three animal models: (1) model of abdominal contortions caused by intraperitoneal injection of acetic acid in mice, (2) formalin test and (3) hot plate test in rats. The ethanolic extract at dose of 30 and 100 mg/kg, given orally, produced dose dependent inhibition of acetic acid-induced visceral pain (61.9 and 77.6%, respectively, $P < 0.001$). The ethanolic extract at the dose of 100 mg/kg caused significant inhibition of capsaicin nociception (40.1%, $P < 0.001$). Finally, the *P. pyramidalis* extract at the doses of 10, 30 and 100 mg/kg provoked a dose-dependent inhibition on glutamate induced pain (77.4%, $P < 0.001$). The antinociception caused by the ethanolic extract (30 mg/kg) in the abdominal constriction test was significantly attenuated ($P < 0.001$) by intraperitoneal treatment of mice with L-arginine (600 mg/kg). The antinociception promoted by the extract of *P. pyramidalis* is probably due to a decrease in the production of inflammatory mediators (Santos et al., 2011).

The intraplantar injection of the formalin solution produced nociceptive behavior in the first and second phases (neurogenic and inflammatory, respectively). *P. pyramidalis* extract produced a significant inhibition of neurogenic markers induced by formalin (45.5, 31.9 and 42.0% at 100, 200 and 400 mg/kg, respectively) and inflammatory markers (92.8, 81.0 and 93.0% at 100, 200 and 400 mg/kg, respectively) in the same way as the positive controls morphine (10 mg/kg) and ASA (300 mg/kg). This result suggests that *P. pyramidalis* extract has anti-inflammatory and antinociceptive activity, and the inhibition presented in the first phase suggests an interruption in the production or release of central neurotransmitters. Another interesting result of the study was the production of a significant antinociceptive effect of the pretreatment with the extract, given the exposure to the thermal stimulus. In addition, the single oral treatment with the extract at a dose of 400 mg/kg reduced the edema induced by carrageenan in a similar way to the inhibition caused by the dexamethasone control (2 mg/kg) (Santos et al., 2011). The antinociceptive and anti-inflammatory effect of *P. pyramidalis* extract in rodent supports the use of this plant in the treatment of various inflammatory diseases for which it has traditionally been used.

The ethanolic extract of the stem bark of *P. pyramidalis* was tested in mice orally, at doses of 10, 30 and 100 mg/kg, using three behavioral models of nociception: model of abdominal contortions caused by intraperitoneal injection of acetic acid, capsaicin-induced nociception

and glutamate-induced nociception. In the analysis, the extract at doses of 30 and 100 mg/kg produced dose-dependent inhibition of visceral pain induced by acetic acid (61.9 and 77.6% respectively). On the other hand, the neurogenic pain caused by capsaicin was reduced by pre-treatment with the extract at 100 mg/kg (40.1%). In addition, oral administration of the extract in the three tested doses produced marked and dose-dependent attenuation of glutamate-induced nociception (23.8, 49.2 and 72.9%, respectively, $p < 0.01$) (Santos et al., 2013). The authors suggest that the ethanolic extract of the species produced dose-related antinociception in pain models, supporting the folk's use of the plant to treat various painful processes.

Santana et al. (2012) studied the activity of the ethanolic extract of the stem bark of *P. pyramidalis* on acute pancreatitis provoked by obstruction of the common bile duct in rodents. The rats were pre-treated with the extract at doses of 100, 200 and 400 mg/kg 1 h before the induction of pancreatitis. Then, the researchers observed the following variables: inflammation/oxidation (myeloperoxidase action and malondialdehyde production in lung and pancreas, blood leukocytes quantity and serum nitrate/nitrite), enzymes (serum amylase and lipase measures) and nociception (abdominal hyperalgesia). The extract administration (100, 200 or 400 mg/kg) was capable of decrease serum amylase and lipase after 6 or 24 h of the pancreatitis induction, analogously to the drug chosen as positive control (dexamethasone, 10 mg/kg), demonstrating that the extract is a promising strategy for the treatment of the disease.

P. pyramidalis ethanolic extract treatment at the doses of 100–400 mg/kg reduced the myeloperoxidase (MPO) effect in pancreas after 6 or 24 h of pancreatitis promotion. Lung damage is an important aggravation of pancreatitis (McKay and Butter, 2003; Wang et al., 2009). The extract administration decreased the infiltration of pulmonary neutrophils. Additionally, the increase in leukocytes was also attenuated by the extract (100–400 mg/kg). In conclusion, the authors demonstrated that the extract reduces inflammation, lipoperoxidation and pain found in acute pancreatitis (Santana et al., 2012).

Finally, a study carried out with Wistar rats with cyclophosphamide-induced hemorrhagic cystitis, showed that pretreatment with doses ranging from 100-400 mg/kg of ethanolic extract from the stem bark of *P. pyramidalis* reduces urinary bladder damage. Treatment with the extract did not alter the urinary bladder edema, but it did cause a significant reduction in myeloperoxidase (Moraes et al., 2013).

Analyzing the studies described here, we can say that all tests for anti-inflammatory and antinociceptive activity were performed with the ethanolic extract from the stem bark of *P. pyramidalis*. The ethanolic extract showed antinociceptive and anti-inflammatory activity in animal models (ex: abdominal contortion caused by acetic acid injection, formalin test, hot plate test and glutamate-induced nociception), probably due to a decrease in the synthesis of inflammation mediators. The extract also proved to be useful in the treatment of pancreatitis and hemorrhagic cystitis. These data support the use of *P. pyramidalis* in the treatment of various inflammatory processes in popular medicine over the years.

6.7. Toxicity, teratogenic effects, and cytotoxicity

The evaluation of the possible toxic effects of a plant is a fundamental aspect of its characterization, since the absence of toxicity, or fatal adverse effects of its extracts or isolated compounds is often more important than its therapeutic potential (Sharifi-Rad et al., 2017, 2018b; Salehi et al., 2019d, 2020). Although several pharmacological activities have been reported for *P. pyramidalis*, supporting its extensive historical use as a medicinal plant, the evaluation of its toxicity and safety should be better explored, as it is still insufficient.

The ethanolic extract of the stem bark of *P. pyramidalis* showed high toxicity when submitted to the toxicological bioassay with *Artemia salina* Leach (Luna et al., 2005). On the other hand, the aqueous extract of the leaves of *P. pyramidalis*, in increasing doses of 1–5 g/kg, administered orally in mice, presented low acute toxicity (Cruz et al., 2007).

Alviano et al. (2008) determined the acute toxicity of the aqueous extract of the leaves of this plant, in rodents, through the oral administration of doses varying between 1 and 5 g/kg. In the study, treated animals showed no behavioral changes and the administration of the extract did not show a lethal effect in any of the tested doses. The extract showed low toxicity and the LD_{50} was 2 g/kg (Alviano et al., 2008). Later, Chaves et al. (2016), tested the acute toxicity of the hydroalcoholic extract of the stem bark of *P. pyramidalis* (administered orally) in rodents at a dose of 2 g/kg and no death was observed in any animal or a change in behavior.

In order to study the toxicity of compounds isolated from *P. pyramidalis*, Andrade et al. (2019) investigated the toxicological effects of agathisflavone in mice. Animals were divided into three groups: the first was treated with vehicle (control group), the second was treated with agathisflavone at the dose of 300 mg/kg and the third received agathisflavone at the dose of 2000 mg/kg. Agathisflavone and the vehicle were administered via oral only once, and mice were kept under observation for 14 days. During this period, food and water consumption, urination and fecal excretion were monitored by using metabolic cages. In addition, the general behavior of animals was monitored (Hippocratic screening) and biochemical, hematological, anatomical, and histopathological parameters were analyzed.

Agathisflavone did not cause any behavioral changes in mice at the doses tested. Therefore, no alteration was observed in biochemical and hematologic functions or in the anatomical and histopathological parameters. No weight variations were observed in the animals and no deaths were reported. All things considered, this non-clinical toxicological study revealed that agathisflavone has a median lethal dose 50% (LD_{50}) larger than 2000 mg/kg (Andrade et al., 2019).

Reis et al. (2016), studied possible effects of *P. pyramidalis* on congenital malformations and reproductive losses of goats in the Northeastern region of Brazil. Two groups of eight goats each were used in the experiment. Animals from Group 1 were fed with fresh leaves of *P. pyramidalis*, as the only forage source, during the reproductive cycle and gestation. Animals from Group 2 (control) were fed with Cynodon dactylon (Tifton).

Five goats from Group 1 aborted and the fetuses exhibited micrognathia. The other goats ($n = 3$) had six goatlings: 50% were born normal and 50% had bone malformations in the head, sternum, spine, ribs and limbs. Among the malformations, it was possible to observe arthrogryposis, scoliosis, micrognathia, in addition to hypoplasia of the pulmonary lobes. In the control group, the goats had no abortion episodes and none of the thirteen goatlings showed abnormalities. These results confirm the pre-existing suspicions that the fresh leaves of *P. pyramidalis* cause congenital malformations and other reproductive losses in goats (Reis et al., 2016).

Similarly, pregnant rats (*Rattus norvegicus*) fed with a diet containing 10% dry leaves of *P. pyramidalis* for 15 days showed a reduction in the number and size of the fetuses, in addition to placental lesions. It is worth mentioning that the administration of *P. pyramidalis* in pregnant rats was responsible for impaired fetal development, skeletal anomalies in the fetuses and prenatal mortality (Câmara et al., 2017).

Embryonic death, abortions, malformations and premature births of weak and unviable lambs, were observed in the study carried out by Lopes et al. (2017), confirming the embryotoxic, abortive and teratogenic properties of *P. pyramidalis* in sheep. The dried plant caused reproductive changes in forage concentrations of 20% and 40% (Lopes et al., 2017).

The occurrence of experimental poisoning in sheep by *P. pyramidalis* has also been reported by Correia et al. (2017). In this work, the species proved to be an important cause of malformation in the head and limbs of the lambs, besides provoking abortion and perinatal mortality. It could also be observed that the severity of *P. pyramidalis* lesions is dose-dependent because in the groups with the highest dose ingestion (feeding consisting 100% from *P. pyramidalis*) the malformations were

more severe and they had earlier abortion. It is important to note that all doses studied (50%, 80% and 100% of feeding consisting of *P. pyramidalis*) were able to cause congenital malformation in lambs (Correia et al., 2017).

Santos et al. (2018), demonstrated that *P. pyramidalis* affects reproduction in goats, causing embryonic losses and abortions. The dry plant induced abortions in late stages of pregnancy in goats fed with 20% of dry forage and the green plant (*ad libitum*) induced late embryonic mortality during organogenesis and early abortion. The higher intake of the green plant (100% of the roughage *ad libitum*) increased the number of abortions in relation to the dry plant (80% of forages). The drying process may have led to a partial loss of toxicity. However, it is clear that the dry plant was still toxic and its consumption by goats during the dry season would cause reproductive losses. The authors did not report embryonic malformations in this trial.

In vitro cytotoxic studies supported the antiproliferative activity of this plant against several cell lines. Hydroalcoholic extract of *P. pyramidalis* bark with different concentrations (100, 200 and 500 mg/kg) showed significant cytotoxic and genotoxic activity through the micronucleus (MN) frequency assay in polychromatic/non-chromatic erythrocytes (PCE/NCE) of the peripheral blood and bone marrow of mice after 24, 48 and 168 h of treatment. Genotoxicity is revealed by a growth in the frequency of MN, while cytotoxicity is suggested by a decrease in PCE. Peripheral blood cytotoxicity was detected at the two highest concentrations of the extract (200 and 500 mg/kg) and at the exposure time (ET) of 48 and 168 h. The extract also promoted mutagenic effects at the concentration of 100 mg/kg in the ET of 72 and 168 h. In slides prepared with bone marrow, the extract showed a cytotoxic effect in the highest concentration in the ET of 168 h. No mutagenic effects were observed in bone marrow assays (Chaves et al., 2019).

6.8. Insecticidal activity

The insecticidal potential of *P. pyramidalis* seeds was tested by Guimarães et al. (2015). A new inhibitor of the I03 family (Kunitz inhibitor) was purified and characterized from seeds of *P. pyramidalis* (PpyTI). PpyTI is a single-head inhibitor with high affinity for trypsin enzymes and moderate affinity for chymotrypsin. Its potential was evaluated in the control of *Anagasta kuehniella*, an insect that feeds on grains and storage flour, through bioassays and biochemical analyzes. The larvae were chronically fed with an artificial diet containing 0.25% and 1% PpyTI (w/w). Larvae fed with 1% PpyTI showed a marked reduction in survival (70%) and average weight (80%). To elucidate the mechanism of action of PpyTI in the digestive process of *A. kuehniella* biochemical tests were carried out. Larvae with 0.25% PpyTI showed a reduction in trypsin and chymotrypsin activity by 30% and 10%, respectively. Detailed studies must be developed to assess the occurrence of possible adaptive responses, such as the synthesis of new resistant enzymes (Guimarães et al., 2015).

Similarly, pollen from *P. pyramidalis* added to basal foods at the levels of 2.5, 5.0 and 10.0% (w/w) has been proven to be toxic to bees (*Apis melífera*), causing death of these organisms (Melo et al., 2013). Although *P. pyramidalis* shows good insecticidal activity in these two models, different genera of insects should be investigated, since the insect genera are diverse with complex genetic makeup.

7. Patents

Technological Prospecting is an efficient approach to outline future scientific and technological developments (Amparo et al., 2012). It is important to associate scientific reviews and technological documents and build connections that benefit industrial-market development (Pereira et al., 2014).

Searching for "*Caesalpinia pyramidalis*" on title and summary from EPO, USPTO, WIPO and INPI patent databases do not generate any result, suggesting the inexistence of deposited documents. Searching for "*Poincianella pyramidalis*" using the title and summary fields from EPO, USPTO, WIPO and INPI patent databases we found only one result for WIPO and INPI. These results draw attention to the databases with only one deposit made. This lack of patents can be interpreted as an alert to the scientific community emphasizing on the need for new research and development of products related to the plant species *P. pyramidalis*.

The patent present in both database is from Brazil (BR 10 2016 008585 3 A2) and describes a technological route, referring to an *in vitro* germination and multiplication protocol for Leguminosae (Fabaceae) plants, especially *P. pyramidalis*, with better parameters to raise the concentration of agathisflavone and amentoflavone biflavonoids, which have cytotoxic activity. This invention is also referred to as a method for isolated acquisition of active compounds, a composition for chemotherapeutic treatment for cancer in animals and humans. Consequently, this patent corroborates the articles to develop methods of extraction, chemical composition or biological active of the plant species.

8. Conclusion

P. pyramidalis is a plant widely used in traditional medicine in the Northeast of Brazil. Twenty-five compounds were isolated and identified from this plant, among them: flavonoids, phenylpropanoid, triterpenes, steroids, phytosterols, derivatives of ellagic acid and glycosyl phenylpropenoid acids. According to the records of this review, *P. pyramidalis* has been popularly used in the treatment of several pathologies such as respiratory and gastrointestinal diseases, diabetes, fever, colic and inflammation in general. In order to justify the popular use, pharmacological investigations of extracts and isolated compounds from *P. pyramidalis* were carried out *in vitro* and *in vivo,* that demonstrated several biological properties such as antibacterial, antifungal, anthelmintic, anti-inflammatory, antinociceptive, neuroprotective and gastroprotective activity.

Despite advances in the understanding of phytochemistry and biological activities of the plant species, the scientific literature should seek to understand some crucial gaps. In some cases, the pharmacological activity of *P. pyramidalis* is present only at doses that may be too high for clinical use. Although some experimental studies have shown that the administration of *P. pyramidalis* is non-toxic, there are reports of cytotoxicity and teratogenicity of the species. Future studies should evaluate possible adverse effects and the toxicity of *P. pyramidalis* extracts and their bioactive constituents when used in a subchronic and chronic way since only acute toxicity tests were performed. In addition, clinical trials should be carried out to evaluate the safety and clinical efficacy of *P. pyrmidalis* in humans.

In summary, we can say that although *P. pyramidalis* proves to be a promising alternative for the treatment of various pathologies, further studies are needed that address the routes of absorption, distribution, metabolism and excretion of active extracts and constituents to better understand the underlying mechanisms of its various biological activities.

Authors contribution

L. Sousa wrote and revised the manuscript; B. Santos and I. Lima collected and tabulated the articles used as references; A. Santana and F. Santos-Filho helped us with the botanical part of the study; M. Medeiros and L. Nunes extracted and analyzed the data; L. Moreno remodelled the paper.

Declaration of competing interest

The authors declare that there are no conflicts of interest.

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