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## **Piranhea trifoliata an Amazonian Plant with Therapeutic Action: A Review**

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### **Authors' contributions**

*This work was carried out in collaboration among all authors. All authors equally worked during elaboration of manuscript, as in conceptualization, and writing (original draft preparation, review, and editing). Also, the authors read and approved the final manuscript.*

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### **ABSTRACT**

The use of medicinal plants reflects the reality of a part of human history. The Brazilian population with limited access to public health programs led to the development and conservation of ethnobotanical knowledge-rich information regarding medicinal plants. However, popular wisdom lacks systematization so that it can correctly use it. Herein we present the *Piranhea trifoliata* (family Picrondeaceae), an Amazonian plant with a wide variety of molecules with biological effects. The antimalarial effect was the dominant description observed in the studies used for this review, followed by antifungal and antioxidant actions. This review provides a synopsis of the recent literature exploring the extracts from *P. trifoliata* that could efficiently prevent pathologies associated with cellular maintenance mechanisms during malaria or fungal infection and oxidative stress.

**Keywords:** Amazonian extracts; *Piranhea trifoliata*; biological activity; medicinal plant.

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## 1. INTRODUCTION

### 1.1 Phytotherapy and historical aspects

For more than 9.000 years, Neolithic man used different ways to minimize pain, such as by plants, animal blood, cold, heat, and a psychic point of view through magic rites, spells, and communication with gods [1].

In clay plates found, with cuneiform inscriptions, the Sumerians people inhabited the regions near the Tigres and Euphrates River around 4.000 B.C. Used thyme, opium, licorice, and mustard as medicine. The Babylonians expanded the Sumerians list by adding saffron, coriander, cinnamon, garlic, and other herbs [2].

Ancient Egypt gave the world one of its first medical texts: Ebers Papyrus, named by the German Egyptologist Georg Ebers, in 1873, who bought a voluminous roll of papyrus about 20 meters long and was surprised by the translation. The papyrus admitted to be written 3.500 B.C. It is composed of a part related to the treatment of internal diseases and an extensive list of medicines containing about 800 recipes and more than 700 magic formulas to treat various ills where many of them use plants. The Egyptians were the first to register the specific dosage rules in administering each drug, giving birth to a medical prescription and respective dosage. This plants applicability was also used in embalming corpses [3].

The history goes that Emperor Huang Ti mentioned 252 plants in his "Canon of Herbs" (2.798 B.C.); Emperor Sheng-Nung was already experiencing the power of ginseng, which lived for 123 years [4]. However, the greeks, Hippocrates, and Galen were the undisputed models of subsequent medical traditions, which wrote the oldest treatise on the use of healing herbs dated from 300 B.C. and was written in Athens by Diocles of Carystus, a disciple of Aristotle. For posterity, consecrated the work of Pedanio Dioscorides, Greek from Asia Minor, who wrote his "From the medical question" between 50-68 A.D. In his five books, Dioscorides described the use of aromatic oils, medicinal plants (roots, seeds, herbs, shrubs, and sages), cereals, animals, wines, and minerals [5].

The consumption of medicinal plants in Brazil predates the arrival of the Portuguese in 1.500 A.C. Gradually, the colonizers assimilated the resources of indigenous medicine, incorporating

them into their pharmacopeia. Throughout the 16<sup>th</sup>, 17<sup>th</sup> and 18<sup>th</sup> centuries, products derived from Brazilian plant biodiversity were widely used in Europe, feeding an excellent commercial network [6].

In Brazil, five regions show an abundance of medicinal species: Amazon Forest, Atlantic Forest, Pantanal, Cerrado, and Caatinga. Some of these regions have medicinal plants indicated popularly, of which a chemical, pharmacological, or toxicological study has not yet been carried out [7]. According to the National Health Surveillance Agency (ANVISA) in Brazil, a medicinal plant is any plant or parts of it that contains the substances or classes of substances responsible for the therapeutic action [8]. In 2006, the Ministry of Health of Brazil started offering therapeutic and preventive options to users of the Unified Health System (SUS) of the Brazilian health system, including herbal medicines and medicinal plants [9].

Medicinal plants were used by the Indigenous in their rituals of healing and worship, when the shaman, invoking and using various herbs, "cure" the sick. We emphasize that in Brazil, the use of medicinal plants was associated with the European colonizers' knowledge, allowing phytotherapy development [4]. Most of the community's medicinal plants are exotic, highlighting the need to enhance and rescue native flora species [10].

### 1.2 Amazonian Forest

The Amazon Forest is the largest tropical forest globally, covering about 8 million square kilometers of the woods with almost 16,000 trees that shelter approximately 10% of the world's biodiversity and 15% of the planet's freshwater [11]. However, it stands out among Brazilian biomes in terms of biodiversity. It occupies 60% of the national territory spans nine Brazilian federative units (Acre, Amapa, Amazonas, Maranhao, Mato Grosso, Para, Roraima, Rondonia, and Tocantins) Fig. 1. [12]. The floodplain in the Amazon covers 1,350.000 km<sup>2</sup> and suggested that more than five million square kilometers present several plant species, which were not studied phytochemically. Therefore, their potential therapeutics also remain hidden [13,14]. The igapo forests are flooded seasonally by rising water levels in rivers [15,16], which are rich in humic and fulvic acids and make the color of the water dark or crystalline, and another characteristic is related to the low sedimentation of organic compounds, resulting in poor in

nutrients [15,17]. The Amazonian floodplain is an ecosystem with forests periodically flooded by rivers of white or muddy water due to the clay particles and suspended sediments originating in the Andes, giving them a yellow-brown color determining soil fertility in these areas [18].

### 1.3 Family *Picrodendraceae* (Formerly *Euphorbiaceae*)

The *Picrodendraceae* family is small, having only 29 genera and 100 species [20], being native to tropical areas. However, it is a poorly studied family, even with its widespread medicinal use registered. *Picrodendraceae* found in the dry cerrado, dry forests, and the lowland forest, and its distribution is evident in the Southern hemisphere countries. The principal genera of the *Picrodendraceae* family are *Austrobuxus*, *Pseudanthus*, *Tetracoccus*, *Oldfieldia*, *Picrodendron*, and *Piranhea* [21].

The *Picrodendraceae* family species were part of the *Euphorbiaceae* family, considered one of the most complex and morphologically diverse taxonomic groups. Studies based on investigations into the anatomy of leaves and wood, and pollen structures, showed that the *Euphorbiaceae* family was not a monophyletic group [22]. Therefore, proposed some modifications in the *Euphorbiaceae* family organization, divided into three new families:

*Euphorbiaceae*, *Picrodendraceae*, and *Phyllanthaceae* [23,24]. The *Picrodendraceae* family presents the ovulated ovary loculi and the characteristic prickly pollen, which sets in apart. In the *Picrodendraceae* family, two genera (*Piranhea* Bail and *Podocalyx* Klotzch) are distributed in three Brazilian regions as in the Northern (Amapá, Amazonas, Tocantins, Acre, and Rorônia), Northeast (Maranhão and Bahia), and Center-West (Mato Grosso) [25,26]. Studies with some family species showed the class of terpenes as chemical constituents of the *Picrodendraceae* family, as in studies of the species *Androstachys* [27-29].

### 1.4 Genus *Piranhea*

The *Piranhea* genus is of native origin and it is not endemic, with geographical distribution occurs in the North, Northeast, Midwest, and Southeast of Brazil. Also, widely distributed in a different environment as caatinga, ciliary forest, igapo forest, and rainforest.

Plants of the genus *Piranhea* are shrubs or tree with particular botanical structures as simple trichome induction, peel usually exfoliating, three foliolate leaves, deciduous stipules, axillary inflorescences, spiciform staminate, racemic pistils or reduced to a single flower. The stamped pedicel flowers, calice imbricated with four or six sepals, free from each other, intertwined [30].



Fig. 1. Territorial extension of Amazon forest. The Amazon forest covers nine of the twenty-seven federative units or states of Brazil [19]

*Piranhea longepedunculata*, *Piranhea mexicana*, *Piranhea securinaga*, and *Piranhea trifoliata* are known as genus *Piranhea* [26]. The phytochemical studies with *P. mexicana* showed isolated terpenes with biological properties as antimalarial, cytotoxic, and antiprotozoal [31-33]. However, the genus *Piranhea* shows as a promising source of terpenes and has chemotaxonomic potential. Still, few studies with species make a critical research line explored in the future [34], mainly *P. trifoliata*.

### 1.5 *Piranhea trifoliata*

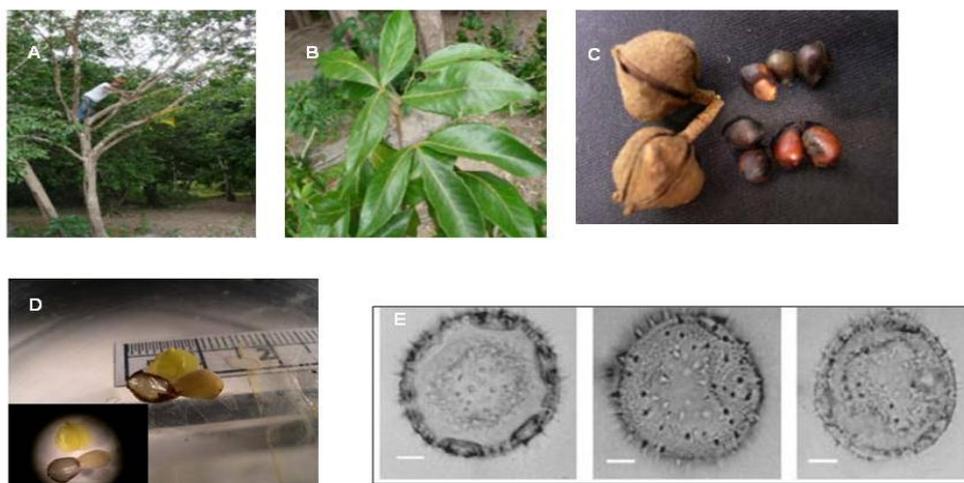
*Piranhea trifoliata* is a tree (up to 25 meters high) found in Venezuela, Bolivia, and Brazil. Distributed in areas of floodplains and igapos, and their woods is resistant to fungi and insects. The bark is used as a dressing for inflammations in the uterus in sitz baths and teas in malaria treatment [26,35,36].

Popularly, *P. trifoliata* is known as Piranheira because fruits and seeds feed piranhas and other fish [36]. Botanically, the bark is present in gray, roots are tabular, and phloem is orange with distinct growth rings. The flowers have white filaments with yellow stamens, and the pollens are characteristic of spines of the *Picrodendraceae* family [36,37]. The fruits are

triangular with 1-2 cm schizocarpaceous (cocas or mericarps) broken into coconuts at maturation, which present a firm texture and a fresh mass between 0.7 to 2.5 grams [38]. The seeds are oblong with an obovate outline, with endosperm and a straight embryo with flat cotyledons, when dry, the mass varies  $0.04$  to  $0.13 \pm 0.02$  grams [39] Fig. 2.

### 1.6 Phytochemical Properties

In bark and leaf extracts, the 28-hydroxy-friedelin-3-one triterpene and its isolated methanolic extracts showed antimalarial, antioxidant, and antibacterial activities [14,34]. Also, studies have demonstrated the isolation of friedelan-3-one, 28-hydroxy-friedelan-3-one, 30-hydroxy-friedelan-3-one, lupeol, the mixture of  $\alpha$ - and  $\beta$ -amirine, in addition steroids as  $\beta$ -sitosterol, stigmasterol, 7,4-dimethylamentofavone and 3'-O-methyl-loniflavone from *P. trifoliata*, which contributed to the first report of triterpenes (28-hydroxy-friedelan-3-one and 30-hydroxy-friedelan-3-one) and bioflavonoids (7,4-dimethylamentofavone and 3'-O-methyl-loniflavone) in the *Picrodendraceae* family [41]. There are few phytochemical studies with *P. trifoliata*; however, actual results demonstrated significant biological activities Table 1.



**Fig. 2. Botanical aspects of *Piranhea trifoliata*. (A) Structure of branches connected to the trunk; (B) Compound, trifoliolate leaves, long petiole. Leaflets contain a yellow central vein located on the underside, slightly lobed edge [14]; (C) Main structures of the fruit and seeds [40]; (D) Seed size and cotyledon details [39]; (E) The pollen grains of *P. trifoliata* have very distinct morphological characteristics, they present the exine (outer layer) reticulated and with sharp spines of varying size, are pollen grains medium, isopolar, and radial symmetry [37]**

**Table 1. Bioactive compounds from *Piranhea trifoliata***

Bioactive compound	Plant organ	Extraction	Biological activity	Concentration	Animal or cell model
Friedelan-3-one	L [41], B [42]	DCM and MeOH [41,42]	Anti malarial – <i>in vitro</i> [42]	IC <sub>50</sub> 5.8 µg/mL [42]	Red blood cells infected by <i>P. falciparum</i> , clone W2, resistant to chloroquine [42]
28-hydroxy-friedelan-3-one	L [41]	DCM and MeOH [41]	*	--	--
30-hydroxy-friedelan-3-one	L [41]	DCM and MeOH [41]	*	--	--
lupeol	L [41]	DCM and MeOH [41]	*	--	--
α-amirine	L [41]	DCM and MeOH [41]	*	--	--
β-amirine	L [41]	DCM and MeOH [41]	*	--	--
β-stitosterol	L [41], B [42]	DCM and MeOH [41,42]	Antimalarial - <i>in vitro</i> [42]	IC <sub>50</sub> 5.8 µg/mL [42]	Red blood cells infected by <i>P. falciparum</i> , clone W2, resistant to chloroquine [42]
Stigmasterol	L [41], B [42]	DCM and MeOH [41,42]	Antimalarial - <i>in vitro</i> [42]	IC <sub>50</sub> 5.8 µg/mL [42]	Red blood cells infected by <i>P. falciparum</i> , clone W2, resistant to chloroquine [42]
*	L [43]	*	Antioxidant – <i>in vitro</i> [43]	EC <sub>50</sub> 46.6 ± 0.6 [43]	*
*	B [44]	DCM and MeOH [44]	Antifungal – <i>in vitro</i> [44]	0.25 mg/mL [44]	<i>Candida albicans</i> [44]

Legend: \* Not reported, -- Not done, L: leaves, B: branches, DCM: dichloromethane, MeOH: methanol, IC<sub>50</sub>, EC<sub>50</sub> (antioxidant activity) expressed as g DPPH/g dry material

Studies related to compounds with biological activities of extracts from *Piranhea trifoliata* were identified by searching electronic databases such as Pubmed, Scielo, ScienceDirect, and Web of Science, including publications in English, Spanish, and Portuguese. The studies eligible for this review included biological activities from *P. trifoliata* extracts. The terms used as an inclusion criterion were “*Piranhea* species,” “*Piranhea trifoliata*,” and “*Picrodendraceae* family”. In this review, we reached out to 44 publications, of which 15 papers were selected for biological activities of extracts from *P. trifoliata*. Most studies have shown antimalarial effects after searching on the database, but significant studies with antifungal and antioxidant compounds Table 1.

## 2. CONCLUSION

This review provides an overview of *P. trifoliata* from the Amazon region and some biological activities as antimalarial known by the local population. Recent studies with extracts of *P. trifoliata* described here have shown significant antifungal and antioxidant activities. Thus, studies should be considered the potential to prevent pathologies associated with cellular maintenance mechanisms during malaria or fungal infection and oxidative stress.

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### COMPETING INTERESTS

Authors have declared that no competing interests exist.

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