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 Picrondendraceae), 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.
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 16th, 17th and 18th 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 km² 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 (Amapa, Amazonas, Tocantins, Acre, and Rondonia), Northeast (Maranhao 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, chalice 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]](image-url)
Piranhea longepedunculata, Piranhea mexicana, Piranhea securinega, 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 (cocos 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 ± 0.02 grams [39] Fig. 2.

1.6 Phytochemical Properties

In bark and leaf extracts, the 28-hydroxyfriedel-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 α- and β-amirine, in addition steroids as β-sitosterol, stigmasterol, 7,4-dimethylmentofavone and 3'-O-methyl-loniflavone from P. trifoliata, which contributed to the first report of triterpenes (28-hydroxyfriedelan-3-one and 30-hydroxy-friedelan-3-one) and bioflavonoids (7,4-dimethylmentofavone 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, trifoliate leaves, long petiote. 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]
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.

### 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   | DCM and MeOH   | Anti malarial – in vitro  | IC<sub>50</sub> 5.8 μg/mL | Red blood cells infected by P. falciparum, clone W2, resistant to chloroquine [42] |
| 28-hydroxy-friedelan-3-one | L [41]     | DCM and MeOH   | *                        | --            | --                                                                                   |
| 30-hydroxy-friedelan-3-one lupeol | L [41] | DCM and MeOH   | *                        | --            | --                                                                                   |
| α-aminine                | L [41]      | DCM and MeOH   | *                        | --            | --                                                                                   |
| β-aminine                | L [41]      | DCM and MeOH   | *                        | --            | --                                                                                   |
| β-stitosterol            | L [41], B   | DCM and MeOH   | Antimalarial - in vitro  | IC<sub>50</sub> 5.8 μg/mL | Red blood cells infected by P. falciparum, clone W2, resistant to chloroquine [42] |
| Stigmasterol             | L [41], B   | DCM and MeOH   | Antimalarial - in vitro  | IC<sub>50</sub> 5.8 μg/mL | Red blood cells infected by P. falciparum, clone W2, resistant to chloroquine [42] |
| *                       | L [43]      | *              | Antioxidant – in vitro   | EC<sub>50</sub> 46.6 ± 0.6 | *                                                                                   |
| *                       | B [44]      | DCM and MeOH   | Antifungal – in vitro    | 0.25 mg/mL    | Candida albicans [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

### 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.

REFERENCES

1. Pérez-Cajaraville J, Abejón D, Ortiz JR, Pérez JR. El dolor y su tratamiento através de la historia. Revista De La Sociedad Española Del Dolor. 2005;16(6):373-384. Available:http://scielo.isciii.es/scielo.php?script=sci_arttext&pid=S1134-80462005000600007
2. Marins A. Secrets and virtues of medicinal plants – reader's digest, first ed. Reader's Digest; 1999.
3. Korczovei SRM, Romagnolo MB. Medicinal plants: Valuing and preserving popular knowledge associated with scientific knowledge. The Challenges of the Public School in Paraná from the Perspective of the PDE Teacher, first ed.; 2013. Available:http://www.diaadiaeducacao.pr.gov.br/portals/cadernospde/pdebusca/producoes_pde/2013/2013_uem_cien_artigo_silvia_raquel_martini_korczovei.pdf
4. Braga CM. History of the use of medicinal plants; 2011. Available:https://bdm.unb.br/bitstream/10483/1856/1/2011_CarladeMoraisBraga.pdf
5. Collins M. Medieval herbalists: The illustrative traditions. The British Library/University of Toronto Press; 2000.
6. Rocha FAG, Araújo MFF, Costa NDL, Silva RP. The therapeutic use of flora in world history. Holos. 2015;49-61. DOI: https://doi.org/10.15628/holos.2015.2492
7. Almeida MZ. Medicinal plants, third ed. EDUFBA; 2011;221.
8. Brazil. Ministry of health: National health surveillance agency. Resolution – RDC n. 10, March 9th, Brasilia; 2010. Available:http://bvsms.saude.gov.br/bvs/saudelegis/anvisa/2010/res0010_09_03_2010.html
9. Brazil. Ministry of state for health. Office of the ministry. Ordinance n. May 3rd, Brasilia, 2006;971. Available:https://bvsms.saude.gov.br/bvs/saudelegis/gm/2006/prt0971_03_05_2006.html
10. Brito SF, Evangelista AWL. Medicinal plants used in the community of campo preto, Armeiroz, Ceará. Revista Verde. 2020;15(4):434-441. Available:https://www.gvaa.com.br/revista/index.php/RVADS/article/view/8170
11. Steege HT, Vaessen RW, Cárdenas-López D, Sabatier D, Antonelli A, De Oliveira SM, Pitman NCA, Jorgensen PM, Salomão RP. The discovery of the amazonian tree flora with an updated checklist of all known tree taxa. Scientific Reports. 2016;6:1-15. DOI: https://doi.org/10.1038/srep29549
12. Borges SH, Durigan CCI, Pinheiro MR. Windows for biodiversity in the Jaú national park: A strategy for studying biodiversity in the amazon. 2004;273.
13. Junk WJ. Wetlands of tropical South America, in: D. Higham, S. Hejny, D. Sykyjova (Eds.). Wetlands in the Amazon floodplain. Hidrobiologia, Bucuresti. 1993:155-162.
14. Jeffreys MF. Chemical study and biodiversity of Piranhea triofoliata (Picrodendraceae). 2011;123.
15. Julião GR. Wealth and abundance of galling insects associated with the canopy of terra firme, lowland and igapó forests of central America. 2007;158.
16. Ayres JM. The lowland forests of mamirauá. Mamirauá Studies, Sociedade Civil Mamirauá. 1993;10(1):73-84.
17. Prance GT. Notes on the vegetation of amazonas III. The Terminology of Amazonian forest Types Subject to Inundation, Brittonia. 1979;3:26-38.
18. Sioli H. The amazon – limnology and landscape ecology of a mighty tropical river and its basin. Junk, Dordrecht; 1984.
19. Tyukavina A, Hansen MC, Potapov PV, Stehman SV, Smith-Rodriguez K, Okpa C, et al. Types and rates of forest disturbance in Brazilian legal amazon, 2000-2013. Science Advances. 2017;3:1601047. DOI: https://doi.org/10.1126/sciadv.1601047
20. Sutter DM, Forster PI, Endress PK. Female flowers and systematic position of Picrodendraceae (Euphorbiaceae s.l, Malpighiales). Plant Systematics and Evolution. 2006;261:187-215. DOI: https://doi.org/10.1007/s00606-006-0414-0
21. MOBOT (Missouri Botanical Garden); 2020.
22. Wurdack KJ, Hoffmann P, Samuel R, Debruin A, Vanderbank M, Chase MW. Molecular phylogenetic analysis of \textit{Phyllanthaceae} (Phyllanthoideae pro sensu lato) using plastid rbcL DNA. American Journal of Botany. 2004;91:1882-1900. DOI: http://dx.doi.org/10.1590/1809-4392201504572

23. Chase MW, Zmarztz S, Ledó MD, Wurdack KJ, Swesen SM, Fay MF. When in doubt, put it in Flacourtiaceae: A molecular phylogenetic analysis based on plastid rbcL DNA sequences. Kew Bulletin. 2002;57:141-181. DOI: https://doi.org/10.2307/4110825

24. APG II. An update of the phylogeny group classification for the orders and families of flowering plants: APG II. Botanical Journal of the Linnean Society. 2003;141:399-436.

25. Hiura AL. \textit{Euphorbiaceae} sensu stricto, \textit{Phyllanthaceae}, \textit{Picrodendraceae}, and \textit{Putranjivaceae} from the experimental field of embrapa, Eastern Amazon. 2011;112.

26. Secco R, Cordeiro I. \textit{Picrodendraceae}: In: List of species of flora of Brazil. Botanical Garden of Rio de Janeiro; 2014.

27. Piacenza LPL, Pegel KH, Phillips L, Waight ES. Beyerane diterpenes: Structure and reactivity of the a-ketol ent-3b-hydroxybeyer-15-ene-2,12-dione, its corresponding diosphenol, and synthesis of the isomeric a-keto acetates. Journal of the Chemical Society. 1979;1004-1012. DOI:https://doi.org/10.1039/P19790001004

28. Piacenza LPL, Pegel KH, Laing M, Waight ES, Weeks CM, Gorstallman CP. A new atisane diterpene: Ent-16α-hydroxyatis-13-en-3-one from 80 \textit{Androstachys johnsonii} prain. Journal of the Chemical Society. 1985;703-709. DOI: https://doi.org/10.1039/P19850000703

29. Grace MH, Jin Y, Wilson GR, Coastes RM. Structures, biogenetic relationships, and cytotoxicity of pimarane-derived diterpenes from \textit{Petalostigma pubescens}. Phytochemistry. 2006;67:1708-1715. DOI: https://doi.org/10.1016/j.phytochem.2005.09.026.

30. Silva OLM, Cordeiro I. \textit{Picrodendraceae} in flora of Brazil; 2020. Available: http://reflora.jbrj.gov.br/reflora/floradobrasil/FB38585.

31. Kaur K, Jain M, Kaur T, Jain T. Review antimalarials from nature. Bioorganic and Medicinal Chemistry. 2009;17(9):3229-3256. DOI: https://doi.org/10.1016/j.bmc.2009.02.050.

32. Castañeda PMR, Alma B, Garcia E, Chávez D, Mata R. Secondary metabolites from the sten bark \textit{Celaenodendron mexicanum}. Journal of Natural Products. 1993;56(9):1575-1579. DOI: https://doi.org/10.1021/np50099a017

33. Camacho MDR, Phillipson JD, Croft SL, Solis PN, Marshall SJ, Ghazanfar SA. Screening of plant extracts for antiprotozoal and cytotoxic activities. Journal of Ethnopharmacology. 2003;89:185-191. DOI: https://doi.org/10.1016/s0378-8741(03)00269-1.

34. Pedroza LS. Chemical study and evaluation of the biological activities of the branches of \textit{Pirania trifoliata} Baill (Picrodendraceae). 2014:82.

35. Worbes M, Klinger H, Revilla JD, Martins C. On dynamics, floristic subdivision and geographical distribution of várzea forest in central amazonia. Journal of Vegetation Science. 1992;3:553-564. DOI: https://doi.org/10.2307/3235812.

36. Filho EMC. Plant the xingu and araguaia trees. 2012;218.

37. Moura CO, Absy ML, Santos FAR, Marques-Souza AC. Pollen morphology of lowland and igapó species from central amazonia. Acta Amazonica. 2004;34:15-19. DOI: http://dx.doi.org/10.1590/S0044-5967200400100003.

38. Barroso GM, Morim MP, Peixoto A, Ichaso CLF. Fruits and seeds: Morphology applied to dicotyledonous systematics. 1999:443.

39. Conserva AS. Seed germination, emergence and recruitment of seedlings of ten tree species in the floodplains of the amanã and mamirauá sustainable development reserves. Central Amazonia. 2007;153.

40. Wittman F, Schongart J, Montero JC, Motzer T, Junk WJ, Piedade MTF, et al. Tree species composition and diversity gradients in white-water forests across the amazon basic. Journal of Biogeography. 2006;33:1334-1347. DOI: https://doi.org/10.1111/j.1365-2699.2006.01495.x.
41. Jeffreys MF, Nunes CV. Triterpenes of leaves from *Piranhea trifoliata* (*Picrodendraceae*). Acta Amazonica. 2016;46(2):189-194. DOI: http://dx.doi.org/10.1590/1809-4392201504572

42. Pedroza LS, Salazar MGM, Osorio MIC, Fachin-Espinar MT, Paula RC, Nascimento MFA, et al. Chemical study and antimalarial activity evaluation of branches of *Piranhea trifoliata*. Revista Fitos. 2020 14(4):476-491. DOI: http://dx.doi.org/10.32712/2446-4775.2020.905

43. Santana WEL, Nunes CV, Moya HD. Antioxidant activity and polyphenol content of some Brazilian medicinal plants exploiting the formation of the Fe(II)/2,2'-bipyridine complexes. Natural Product Communications. 2015;10(11):1821-1824.

44. Rodrigues K, Ramos DF, Carrion LL, Cursino LMC, Jeffreys MF, Pedroza LS, et al. Antifungal activity of Brazilian amazon plants extracts against some species of *Candida* spp. *International Journal of Phytopharmacology*. 2014;5(6):445-453.

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