



Original Article

Exudates used as medicine by the “caboclos river-dwellers” of the Unini River, AM, Brazil – classification based in their chemical composition



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ABSTRACT

Although the use of exudates in traditional medicine has been commonly observed during ethnopharmacological surveys, few records have been made concerning the scientific merits of these products. The aim of this study was to document ethnopharmacological data and to classify exudates used as medicine by the “caboclos” river-dwellers from the Unini River of Amazonas, Brazil, on chemical analyses basis. Using an ethnographic approach, indicated plants and their respective exudates were collected, identified and incorporated into herbarium of the National Institute of Amazonian Research. To classify these exudates, plant material was extracted using methanol, and obtained extracts were analyzed by Nuclear Magnetic Resonance and mass spectrometry aiming identification of main compounds. Fifteen exudates were indicated by “caboclos” river-dwellers as home remedies; among their therapeutic uses, inflammatory processes, culture-bound syndromes and respiratory diseases are most prominent. Based on their solubility and chemicals classes, fifteen exudates were classified into: latex (7), resins (5), sap (1), gum (1), oleoresin (1); and eleven of them have not been mentioned on pharmacological literature until this moment. The obtained results may contribute to chemical/pharmacological application of exudates from these species, several of which have been classically used in Brazilian folk medicine.

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Introduction

Although the use of exudates in traditional medicine has been commonly observed during ethnopharmacological surveys, few records have been made concerning the scientific merits of these products. In Brazil, the use of resin has been noted among the ethnic groups of Kapoor (Balée, 1994), Paumari (Prance et al., 1987) and Waimiri Atroari (Milliken et al., 1992). A possible explanation for the gap in records is the difficulty in identifying the exudates, since these exudates resemble one another in physical appearance. However, their characterization and means of distinction have been facilitated in recent years, as a result of technological developments in chemistry, molecular biology and microscopy. Water-soluble exudates include gums, which are composed of polysaccharides

and are secreted by wells; and saps, which consist of polysaccharides and amino acids, as described by Langenheim (2003). According to the same author, fat-soluble exudates include resins and oleoresins, which are composed of terpenoids and phenolic compounds secreted by resiniferous channels, cavities, trichomes and epidermal cells; oils are compounds of fatty acids and glycerol; and latex is a complex mixture of terpenoids, phenolic compounds, proteins and carbohydrates and it is secreted by laticifers.

Not only exudates are poorly studied from the ethnopharmacological standpoint, but, to the best of our knowledge, few pharmacological and chemical studies have been conducted on exudates. On the other hand, there are Amazonian cultures whose medicinal uses of exudates need to be identified and documented before they are lost due to the rapid introduction of synthetic medicines. Therefore, the aim of this study is to document ethnopharmacological data and classify, on the basis of chemical analysis, the exudates (as latex, resin, oleoresin and so on) used as medicine by “caboclos” river-dwellers from the Unini River of Amazonas, Brazil.

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Materials and methods

Ethnopharmacological data

The exudates analyzed in this study were indicated by twelve healers of “caboclos” river-dwellers living in two communities along the Unini River of Amazon, Brazil (Fig. 1), during 11 months of fieldwork, between April 2008 and January 2012 by one of the authors (JFLS). For local healing experts selection, a snow-ball sampling, as described by Bernard (1988), was performed by consultation of local inhabitants of riverine communities. Ethnographic techniques and methods were applied, including participant observation, field diaries, informal and unstructured interviews (Bernard, 1988; Foote-Whyte, 1990). During interviews, the following data sheets were administered: interviewee personal information, ethnopharmacological survey (ingredients, uses, parts used, mode of preparation, and contraindications of plants and animals used for therapeutic purposes) and plant collection (popular name, habit, time of flowering/fruitletting, organoleptic and morphological aspects) (Santos et al., 2012). The exudates indicated by interviewees and their respective vegetable materials were collected during fieldwork at Terra Nova (01°41' S, 61°49' W) and Tapiira (01°46' S, 62°13' W) communities (Fig. 1), they were identified by Mr. José Ramos, plant taxonomy technician, and incorporated into the herbarium of the National Institute of Amazonian Research. Prior to the field work, all necessary permits were obtained for the study, including a permit access to the Conservation Units, in order to ensure collection of samples, transport of biological material and access to associated traditional knowledge, and prior informed consent of informants (SISBIO No. 16805-2, CGEN/MMA No. 47/2009 and CEP-UNIFESP/EPM, No. 1354/08).

Exudates extraction

Liquid exudates (latex, oleoresin and sap), were obtained from trunks of their respective trees by incisions utilizing machete or knife, depending on the thickness of the barks. A pointed metal canula was adapted in the trunk of each tree for collection of exudates.

The solids and semi-solids exudates (resin and gum, respectively), were stuck on tree trunks; therefore they were collected manually. All exudates were placed in amber glasses, properly labeled with date and numeric codes correlating them to the trees from which they were collected. These glasses were kept in a styrofoam box until they reach the laboratory where their extracts were prepared for chemical analysis. All exudates were dried after collection, before the preparation of the extracts.

Preparation of extracts and chemical analysis

Solubility of obtained exudates was evaluated using 10 mg of each plant material and 1 ml of H₂O or hexanes in a test-tube. Then, exudates were extracted using MeOH (50 ml of solvent to each 10 g of plant material) in a sonicated bath at room temperature during 20 min. After solvent evaporation under reduced pressure, obtained crude extracts were analyzed by ¹H and ¹³C NMR (nuclear magnetic resonance) spectroscopy in a Bruker Avance 300 spectrometer (300 MHz to ¹H and 75 MHz to ¹³C nuclei, respectively) using CDCl₃, CD₃OD, (CD₃)₂SO, (CD₃)₂O or D₂O as solvents and internal standard. Crude extracts were also analyzed by HPLC/ESIMS (liquid chromatography/electrospray ionization mass spectrometry) using a Bruker Daltonics equipment Esquire 3000 Plus. HPLC system was coupled with a Zorbax-C18 (250 mm × 4.6 mm, 3.55 μm, Agilent, USA) column at 40 °C. Solvents H₂O and acetonitrile (CH₃CN) were used, starting with 15% of CH₃CN (0–20 min), increasing to 100% (20–25 min), isocratic (5 min), and decreasing to 15% (30–32 min), and isocratic (3 min) at flow rate of 1 ml/min. Injection volume was 3 μl and UV detection at 352 nm and 280 nm. ESIMS spectra (low resolution) were recorded in full scan and product ion scan modes (argon CID). Ion source was set as follows: nebulizer gas = 3 l/min, desolvation gas = 15 l/min, DL = 150 °C, heat block = 300 °C and voltage = 3.5 kV. GC/EIMS (gas chromatography/low resolution electronic impact mass spectrometry) were measured in a Shimadzu GC-17A chromatograph equipped with a capillary column DB-5 (cross linked 5% phenyl in 95% silicone - 30 m, 0.32 mm, I.D., 0.25 μm film thickness) interfaced with a MS-QP-5050A mass spectrometer. Temperature programming was performed from 150 to

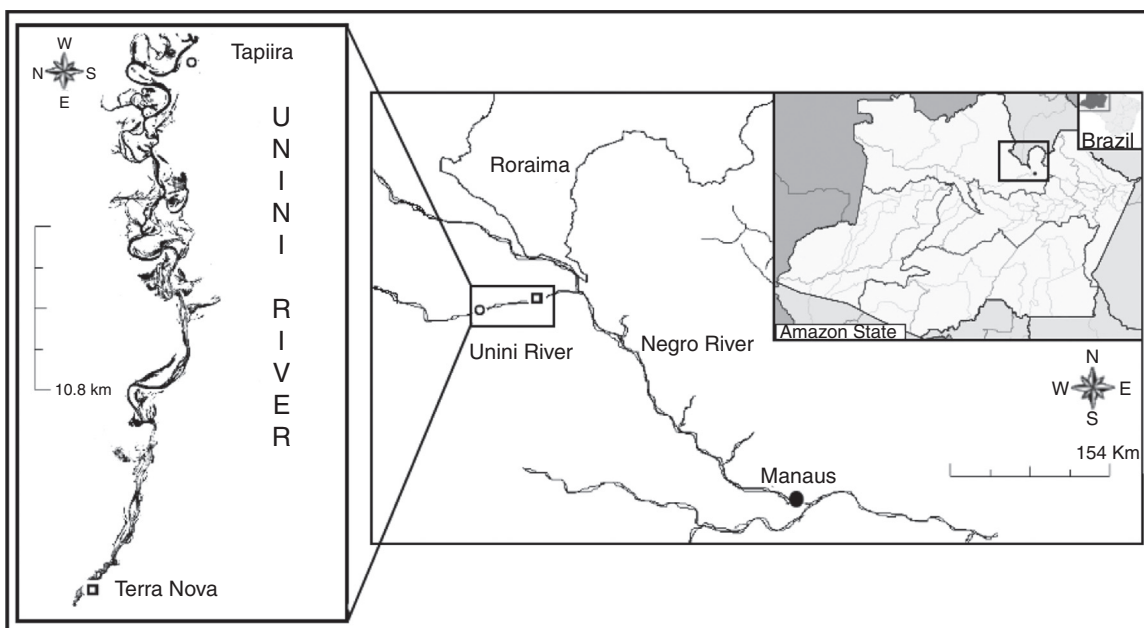


Figure 1. Unini River location in the Amazon forest biome, Amazon State – Brazil (map on the right). Location of two Unini River communities, where the exudates were collected during fieldwork: Terra Nova – 01°41' S, 61°49' W and Tapiira – 01°46' S, 62°13' W (left).

Source: *Vitoria Amazônica Foundation (2005)*.

300 °C at 15 °C/min, then isothermal at 300 °C for 5 min. Injector and detector temperatures were 150 °C and 320 °C, respectively, and helium was used as the carrier gas. Identification of compounds was conducted by analysis of individual NMR and MS spectra (low resolution). Obtained data were compared with those recorded to authentic samples (α - and β -amyrin, sitosterol, stigmasterol, quercetin, quercitrin, catechin, lupeol, friedelin, betulinic acid, copalic acid, oleanolic acid, ursolic acid, palmitic acid, brasiliensis acid and isobrasiliensis acid were available at our laboratory while lysin and tryptophan were obtained from Sigma–Aldrich) and/or with those available in the literature.

Bibliographic survey

From plant species identified, we searched scientific databases (Pubmed and Scopus June/2015) to determine whether their exudates had been targets of previous pharmacological studies.

Results

All the twelve interviewees (seven female and five male) were born in the Middle Negro River region and they are descended of inhabitants from Amazonas and Ceará States. They call themselves into following categories: knowledgeable of natural drugs (sic interviewees), healer (3), midwife (2) and ‘desmintidor’ (an expert in massage techniques for bone dislocation and muscle strain treatments) (1). They reported having learned the healing practices with parents, relatives, friends, neighbors, and often as a self-interest result, as it is the case of midwives and ‘desmintidores’ (Santos et al., 2012).

As showed on Box 1, “caboclos” river-dwellers indicated fifteen exudates. Members of the Burseraceae family were the most frequently identified, totaling four species. Their therapeutic uses were given as their local terms and they are signaled in italic throughout this paper. Among their therapeutic uses, *inflammation processes, culture-bound syndromes and respiratory diseases* are

Box 1: The 15 plant's exudates used as medicine by the 'caboclos' river-dwellers of the Unini River, AM; their pharmacological data present in scientific literature; their respective classifications based on our chemical analysis, and the main compounds identified.

Family	Scientific name/vernacular name (voucher)	Medicinal use (<i>local term</i>)	Pharmacological studies (plant part/exudate studied)	Exudates (solubility)	Main identified compounds*
Apocynaceae	<i>Couma macrocarpa</i> Barb. Rodr./leite-de-sorva (ER097)	<i>Weakness in the lung</i>	–	Latex (fat-soluble)	–
Araceae	<i>Philodendron solimoense</i> A.C.Sm./cipó-ambé (ER2000)	<i>Cataract</i>	–	Latex (fat-soluble) – alkylphenol, steroids Sap (water-soluble)	3-Octadecenyl-phenol, sitosterol, stigmasterol ^{a,b,d}
Bignoniaceae	<i>Tynanthus panurensis</i> (Bureau ex Baill.) Sandwith/cipó-cravo (ER2003)	<i>Improving memory and calming</i>	–	–	–
Burseraceae	<i>Protium amazonicum</i> (Cuatrec.) Daly/breu-branco (JFLS413)	<i>Headache, stroke and disease of the air</i>	–	Resin (fat-soluble) – triterpenes	α -Amyrin, β -amyrin ^{a,b,d}
	<i>Protium aracouchini</i> (Aubl.) Marchand/breu-preto (JFLS404)	<i>Headache, stroke and disease of the air</i>	–	Resin (fat-soluble) – triterpenes	α -Amyrin, β -amyrin ^{a,b,d}
	<i>Protium decandrum</i> (Aubl.) Marchand/chico-da-silva (JFLS421)	<i>Wounds</i>	–	Resin (fat-soluble) – flavonoid glycosides/triterpenes	α -Amyrin, β -amyrin, quercetin, quercitrin ^{a,b,c,d}
	<i>Protium heptaphyllum</i> (Aubl.) Marchand/breu-branco (JFLS458)	<i>Headache*, stroke*, disease of the air* and respiratory disease</i>	Analgesic – resin (Oliveira et al., 2005a); anxiolytic/anti-depressant – resin (Aragão et al., 2006); anti-inflammatory – resin (Oliveira et al., 2004)	Resin (fat-soluble) – triterpenes/polyphenolic	α -Amyrin, β -amyrin, quercetin, catechin ^{a,b,c,d}
Clusiaceae	<i>Calophyllum brasiliense</i> Cambess./jacareúba (JFLS513)	<i>Remove warts*</i>	Antiproliferative – stem bark (Jin et al., 2011)	Latex (fat-soluble) – phenolics	Brasiliensis acid, isobrasiliensis acid ^{a,c,d}
	<i>Vismia guianensis</i> (Aubl.) Choisy/lacre (JFLS359)	<i>Ringworm</i>	–	Latex (fat-soluble) – triterpenes	Lupeol, friedelin, betulinic acid ^{a,b,d}
Dilleniaceae	<i>Dolioscarpus</i> sp/cipó d'água (JFLS423)	<i>Stroke and disease of the air</i>	–	Latex (fat-soluble) – triterpene	betulinic acid ^{a,b,d}
Euphorbiaceae	<i>Hevea spruceana</i> (Benth.) Müll. Arg./seringa-barriguda (JFLS401)	<i>Fever</i>	–	Latex (fat-soluble) – triterpene	Lupeol ^{a,b,d}
Fabaceae s.l.	<i>Copaifera multijuga</i> Hayne/óleo-de-copaiba (JFLS403)	<i>Sore throat*, fever and flu</i>	Anti-inflammatory – oleoresin (Veiga-Junior et al., 2007); antinociceptive – oil (Gomes et al., 2007)	Oleoresin (fat-soluble) – diterpene	Copalic acid ^{a,d}
	<i>Hymenaea courbaril</i> L./jatobá-do-mato (JFLS424)	<i>Flu*, sore throat*, and cough</i>	Antiviral – no data found (Cecilio et al., 2012); anti-inflammatory – pericarp (Takagi et al., 2002)	Resin (fat-soluble) – diterpene	Kolavenic acid ^a
Lecythidaceae	<i>Bertolletia excelsa</i> Humb. & Bonpl./castanha-do-Pará (ER88)	<i>Hemorrhoids and diarrhea</i>	–	Gum (water-soluble) – aminoacids	Lysine, tryptophan ^{a,d}
Moraceae	<i>Brosimum parinarioides</i> Ducke/leite-do-Amapá (JFLS414)	<i>Tuberculosis, worm and weakness in the lung</i>	–	Latex (fat-soluble) – fatty acids, triterpenes	palmitic acid, lupeol, ursolic acid, oleanolic acid ^{a,b,d}

* The matches between uses proclaimed by the interviewees and pharmacological data.

** Identification: ^aNMR, ^bGC/EIMS, ^cLC/ESIMS, ^dcomparison with authentic sample.

the most prominent. *Culture-bound syndromes* are listed as *derrame* (stroke) and *doença do ar* (air disease), which will be detailed below.

In regard to mode of preparation used for compounding exudates-containing medicines, most part of them are used *in natura* without passing through heat process. Some exceptions are: *Bertolletia excelsa* gum, used to prepare a tea by decoction; *Hymenaea courbaril* resin, used to prepare a syrup; and *Protium* resins are used for fumigation. This type of preparation method is more related to *culture-bound syndromes*, which is discussed below.

Administration route are varied, including oral, topic and inhalation. Topic use was observed in the case of warts removal by *Calophyllum brasiliense*. In this case it was also observed religious context on healing practice, since latex of this plant should be placed on for three followed Fridays while healer prays; on the last Friday the wart falls, according to what they explained and to our field observation. Latex produced by *Vismia guianensis* is also administered topically on micoses. Still, latex of *Philodendron solimoesense* is dropped directly into the eyes for cataract indication. Oral administration was observed for some latex, as the ones of *Brosimum parinarioides* and *Couma macrocarpa*. According to interviewees reports, they are considered as 'milk', because of its consistence and white color milk. Inhaling was observed only for resins, during fumigation process, described ahead.

Usually, doses are used as drops (considering latex, sap and oleoresins) or fresh pieces (resins and gums). However, doses used of these exudates on home-brewed remedies were not always clearly defined, and became even more subjective when used by fumigation, where many ingredients are carbonized in a clay pot with *Protium* resins – leaves, animals pieces, such as antlers, teeth, penis, birds' nests, among many others – along with charcoal. During this ritual, the child must be passed in cross through smoke produced by fumigation, three times a day, while praying. It is very common the use of prayers during various therapeutic practices observed, since religion is still Catholic in some communities. These practices are not observed anymore where religion has undergone change and became evangelical. This change triggered the breakup of some communities under study.

Based on solubility and chemical classes obtained during our chemical analyzes, fifteen exudates were classified into: latex (7 exudates), resins (5), sap (1), gum (1) and oleoresin (1). Eleven of them were not mentioned in pharmacological literature until now. **Box 1** shows family and scientific name/vernacular name of each plant analyzed, classification of exudates based on its solubility, main identified compounds, medicinal use by "caboclos" river-dwellers and pharmacological studies published related to these specific exudates.

To identify the main compounds of each obtained MeOH extract, they were individually analyzed by NMR and/or MS (LC/ESIMS or GC/EIMS) (**Box 1**). ^{13}C NMR spectra of extracts from *Protium* species as well as from *Hevea spruceana*, *Philodendron solimoesense*, *V. guianensis*, *Doliocarpus* sp. and *B. parinarioides* displayed more intense peaks of sp^2 carbons at δ 150/109, 145/122 and/or 139/124 characteristics of lupane, oleanane and ursane triterpenes skeleton (Olea and Roque, 1990). This analysis, in association with GC/EIMS data, afforded the identification of α - and β -amyrins, friedelin and lupeol as well as ursolic, oleanolic and betulinic acids. Additionally, ^1H NMR spectra of crude extracts from *Protium decandrum* and *Protium heptaphyllum* showed less intense signals at δ 6.2–8.0, suggesting the presence of phenolic derivatives. ^{13}C NMR associated to LC/ESIMS analysis of crude material afforded the identification of flavonoids quercetin, quercitrin and catechin. As crude MeOH extract from *C. brasiliense* showed to mainly composed, by ^1H NMR, of aliphatic/aromatic material, it was directly analyzed by LC/ESIMS. Using UV and MS data as well as co-injection using authentic samples, the identification of brasiliensic and iso-brasiliensic acids was possible. NMR (^1H and ^{13}C) spectral analysis

of Fabaceae plants (*Copaifera multijuga* and *H. courbaril*) crude extracts suggested the predominance of diterpene acids due the presence of several peaks at δ 106–165 (sp^2 carbons) and at approximately δ 172 (COOH). The comparison of reported data to copalic and kolavenic acids (Marchesini et al., 2009), allowed the identification of these diterpenes. The ^1H NMR spectrum of MeOH extract from *B. excelsa* suggested the occurrence of aminoacids as main constituents. Using NMR data obtained for authentic samples, the identification of lysine and tryptophan was possible. The identification of steroids sitosterol and stigmasterol in the crude MeOH extract from *P. solimoesense* was conducted by analysis of ^1H NMR spectrum due the characteristic peaks at δ 0.7 (s), 5.4 (br d) and 3.5 (m). Aiming confirmation, part of this material was dissolved in MeOH:H₂O 2:1 and partitioned with hexane. The organic phase was analyzed by ^{13}C NMR and GC/EIMS confirming the occurrence of detected steroids as well as 3-octadecenyphenol.

Discussion

Based on the solubility and chemical classes found in each of the fifteen exudates analyzed, and comparing them to the chemical evidence presented by Langenheim (2003), we classified them into: latex, resins, sap, gum, and oleoresin, as shown in **Box 1**. Our classification was corroborated by some existing studies from botanical anatomy and morphology which confirm the presence of resins and/or resiniferous channels in *Protium* species, such as *P. amazonicum*, *P. aracouchini*, *P. decandrum*, *P. heptaphyllum* (Rüdiger et al., 2007; Daly et al., 2011), *C. multijuga* (Milani et al., 2012) and *H. courbaril* (Cunningham et al., 1974); and laticifers in *C. macrocarpa* (Williams, 1962), *C. brasiliense* (Cabral, 2011) and *B. parinarioides* (Jacomassi et al., 2007).

As shown in **Box 1**, among the fifteen exudates, four have been described in previous pharmacological studies and they have presented correspondence between at least one local medicine use and the observed effect published on scientific literature. Moreover, it is noteworthy that pharmacological studies of literature were conducted with plants exudates. An exception was the antiviral citation for *H. courbaril* by Cecílio et al. (2012), which the investigated part of the plant was not mentioned. These four species are highlighted below.

The 'breu-branco' – 'pitch-white' (*P. heptaphyllum* (Aubl.) Marchand) is used by diverse cultures for treatment of headache, inflammation, as expectorant, insect repellent and for respiratory disease (Branch and Silva, 1983; Marques et al., 2010). In this study, this was one of the most cited plant by the interviewees; its resins, burned and smelled, are mainly used for the treatment of headache, *derrame* (stroke), *doença do ar* (disease of the air) and respiratory disease and it showed to be composed by triterpenes (α - and β -amirin) as well as poliphenolic derivatives (quercetin and catechin). The first three therapeutic uses were confirmed in pharmacological studies: analgesic (Oliveira et al., 2005a) and anxiolytic (Aragão et al., 2006), since analgesic can be related to headache, and anxiolytic to both disorders: *derrame* (stroke) and *doença do ar* (disease of the air). *P. heptaphyllum* also possesses gastroprotective and anti-inflammatory effects (Oliveira et al., 2004); and their triterpenes (α - and β -amirin) have a hepatoprotective potential (Oliveira et al., 2005b). Also, da Silva et al. (2013) described an antimicrobial activity of the essential oil of 'black breu' (*Protium* spp.). According to our fieldwork observations, and as we previously discussed (Santos et al., 2012), *doença do ar* (disease of the air) and *derrame* (stroke) are the same disease, the first terminology is adopted when the patients are children, and the second for adults. They are diseases whose symptoms could be associated to anxiety and seem to be part of the culture-bound syndromes discussed by Bourbonnais-Spear et al. (2007).

It was also observed that resins of other species of the same genus, *P. aracouchini* (Aubl.) and *P. amazonicum* (Cuatrec.) can also be used to treat *headache*, *derrame* (*stroke*) and *doença do ar* (*disease of the air*), in form of cigarettes.

Latex of 'jacaréuba' (*C. brasiliense* Cambess.) is indicated to *remove warts* in local medicine and it has been the target of several pharmacological studies, which have confirmed its anti-proliferative effect on mantle cell lymphoma (Jin et al., 2011), antifungal (Reyes-Chilpa et al., 1997), anti-ulcer (Lemos et al., 2012) and trypanocidal activities (Rea et al., 2013). These biological activities could be related to the presence of coumarins, chromenes, xanthenes and triterpenes, since these compounds were found as main constituents of resin (Noldin et al., 2006).

The oleoresin of 'copaiba' (*C. multijuga* Hayne) is used for the treatment of *sore throat*, *fever* and *flu*. It is a versatile specie among interviewees, its exudate is used to prepare a syrup with other plant species, and in severe cases of throat inflammation it is recommended to put a few drops *in natura* on affected site. In surveys conducted in Amazon region, it was observed similar uses for copaiba (Branch and Silva, 1983; Balée, 1994; Pinto and Maduro, 2003; Shanley and Rosa, 2005; Rodrigues, 2006). Some studies have evaluated its anti-inflammatory effects (Veiga-Junior et al., 2007), anti-oedematogenic properties (Veiga-Junior et al., 2006), antinociceptive (Gomes et al., 2007), antineoplastic (Gomes et al., 2008) and antimicrobial activities (Santos et al., 2008). The use for *sore throat* showed some similarity with investigated effects/actions, demonstrating concordance between popular knowledge and academic science.

The 'jatobá-do-mato' (*H. courbaril*) is a well-known plant in the Amazon as well as in other Brazilian biomes, and it is frequently cited to cure respiratory diseases in ethnopharmacological surveys (Oliveira et al., 2011). Among the "caboclos" river-dwellers living along the Unini River, resin of this plant is used to treat *flu*, *sore throat*, and *cough*. Cecílio et al. (2012) demonstrated its antiviral activity, while its anti-inflammatory effect was reported by Takagi et al. (2002). The latter may be related to *sore throat* indication. Both studies utilized EtOH extracts, from leaves and pericarps of the plant, respectively. These activities could be associated to the presence of kolavenic acid, a clerodane type diterpene, found as the main derivative of the plant material. This diterpene revealed antimicrobial (Faizi et al., 2008) and antifungal (Salah et al., 2003) activities.

The major contribution of this study lies on exudates registration by ethnopharmacology, especially those eleven that have not been investigated by pharmacology yet. Based on wealth of data collected in Amazon region – and considering the fact that various Brazilian biomes also have exudates-producing plants – we believe that a greater effort should be done by researchers of ethnoscience areas in order to register these uses.

Conclusion

Exudates are promising plant materials which could be used in drug discovery due to accumulation of several metabolites. Although these materials have been only sparingly investigated by pharmacological studies, the results reported in this work may contribute to chemical/pharmacological knowledge of these plant species, many of which have been used in classical Brazilian folk medicine.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Authors' contributions

ER has idealized, oriented, collected some of the exudates, and coordinated the study. JHGL was responsible for chemical analysis. JLS performed part of the fieldwork and data collection. JT, PBY e FC contributed to discussions, map elaboration, review, formatting and standardization of manuscript. All authors have read final manuscript and they have approved submission.

Conflicts of interest

The authors declare no conflicts of interest.

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