



ELSEVIER

Contents lists available at ScienceDirect

Journal of Ethnopharmacology

journal homepage: www.elsevier.com/locate/jep

Antimalarial plants used by indigenous people of the Upper Rio Negro in Amazonas, Brazil



Carolina Weber Kffuri^{a,*}, Moisés Ahkató Lopes^b, Lin Chau Ming^a, Guillaume Odonne^c, Valdely Ferreira Kinupp^d

^a Universidade Estadual Paulista, Faculdade de Ciências Agrônômica de Botucatu, Departamento de Horticultura, Rua José Barbosa de Barros, 1780, 18.610-307 Botucatu, São Paulo, Brazil

^b Cunuri indigenous Community, São Gabriel da Cachoeira, Amazonas, Brazil

^c CNRS-Guyane(USR 3456), 2 avenue Gustave Charlery, 97300 Cayenne, French Guiana

^d Herbário EAFM, Instituto de Educação, Ciência e Tecnologia do Amazonas (IFAM), Manaus, Amazonas, Brazil

ARTICLE INFO

Article history:

Received 6 July 2015

Received in revised form

24 November 2015

Accepted 30 November 2015

Available online 2 December 2015

Keywords:

Ethnopharmacology

Amazonia

Malaria

*Aspidosperma schultesii**Ampelozizyphus amazonicus*

Medicinal plants

ABSTRACT

Ethnopharmacological relevance: This is the first intercultural report of antimalarial plants in this region. The aim of this study was to document the medicinal plants used against malaria by indigenous people in the Upper Rio Negro region and to review the literature on antimalarial activity and traditional use of the cited species.

Materials and methods: Participant observation, semi-structured interviews, and ethnobotanical walks were conducted with 89 informants in five indigenous communities between April 2010 and November 2013 to obtain information on the use of medicinal plants against malaria. We reviewed academic databases for papers published in scientific journals up to January 2014 in order to find works on ethnopharmacology, ethnobotany, and antimalarial activity of the species cited.

Results: Forty-six plant species belonging to 24 families are mentioned. Fabaceae (17.4%), Arecaceae (13.0%) and Euphorbiaceae (6.5%) account together for 36.9% of these species. Only seven plant species showed a relatively high consensus. Among the plant parts, barks (34.0%) and roots (28.0%) were the most widely used. Of the 46 species cited, 18 (39.1%) have already been studied for their antimalarial properties according to the literature, and 26 species (56.5%) have no laboratory essays on antimalarial activity.

Conclusions: Local traditional knowledge of the use of antimalarials is still widespread in indigenous communities of the Upper Rio Negro, where 46 plants species used against malaria were recorded. Our studies highlight promising new plants for future studies: *Glycidendron amazonicum*, *Heteropsis tenuispadix*, *Monopteryx uauçu*, *Phenakospermum guianensis*, *Pouteria ucuqui*, *Sagotia brachysepala* and notably *Aspidosperma schultesii*, *Ampelozizyphus amazonicus*, *Euterpe catinga*, *E. precatoria*, *Physalis angulata*, *Cocos nucifera* and *Swartzia argentea* with high-use consensus. Experimental validation of these remedies may help in developing new drugs for malaria.

© 2015 Elsevier Ireland Ltd. All rights reserved.

1. Introduction

Malaria, a major public health problem in the world, is complicated by the increased resistance of the parasite to antimalarial drugs. The search for safe, new, and effective chemical structures against the parasite has been undertaken in several countries. Today, 3.3 billion people, half of the world's population, are at risk for malaria, mainly in tropical and subtropical regions (WHO,

2014). In Brazil, 99.7% of malaria transmission is concentrated in the Amazon region, where it is considered the disease of greatest magnitude according to the Ministry of Health (2013), and numerous cases have been reported not far from the area of our fieldwork (Cabral et al., 2010). Owing to the region's remoteness and lack of resources, access to biomedicine and health centers is often limited in the Brazilian Amazon, whose inhabitants favor the use of medicinal plants. Some uses have already been documented for the riverine populations (Silva et al., 2007), the urban and rural people of the Rondônia and Pará states (Brandão et al., 1992a), and the neighboring state of Roraima by Yanomami Amerindians (Milliken and Albert, 1996), but based on our research, no single use reflects the diversity of cultures present in the area. Excepting

* Corresponding author.

E-mail address: carolkffuri@gmail.com (C.W. Kffuri).

¹ Phone number: +55 3799990614/+55 1438807126.

a major work by Milliken (1997) on antimalarial plants of Roraima more than 600 km to the west, our work is the first intercultural report of antimalarial plants in the municipality of São Gabriel da Cachoeira, Upper Rio Negro.

2. Material and methods

2.1. Study area

The municipality of São Gabriel da Cachoeira (Fig. 1) is located in the extreme Northwest of the Amazonas state within the largest rainforest on the planet, 852 km from the capital, Manaus. The annual rainfall ranges from 2500 to 3000 mm, and the annual average temperature is 26 °C, making it one of the wettest and least temperate regions in Amazonia (Radambrasil, 1976; Sombroek, 2001). It comprises extensive areas of elevated relief, tepuis, and isolated hills that emerge from a great plain. The vegetation in the Upper Rio Negro basin resembles a mosaic pattern: caatingas, campinaranas, wetlands, and dense montane and submontane forests (Rizzini, 1979). According to Oliveira and Nelson (2001), two characteristics of the flora stand out: the high biodiversity in a region of extremely poor soil and a large number of endemic species. The region of the Upper Rio Negro is also considered a major cultural area. It includes six approved indigenous lands, which are home to 23 ethnic groups who speak about 22 languages from five language families (Cabalzar and Ricardo, 2006). Because of this area's colonial history, people mainly live in multiethnic communities.

2.2. Research authorization

Research authorizations were obtained for access to traditional knowledge associated with genetic resources in Brazil as per the 2186-16 interim measure issued by the Brazilian Government Management Board of the Genetic Heritage (CGEN) (protocol number 02000.001373/2010-110), including authorization by the National Indigenous Foundation (FUNAI), the Foundation of Indigenous Organizations of Rio Negro (FOIRN), the local indigenous foundation, three local indigenous association. All of the residents of the communities studied gave their consent. The research began upon receiving the authorizations, which took three years.

2.3. Ethnobotanical survey

Observations of participants in the municipality of São Gabriel da Cachoeira lasted from the beginning of 2010 until mid-2012. The researchers lived in the city for nine months and took several trips to the city and communities. After authorization by CGEN, the fieldwork was conducted between early September 2013 and the end of November 2013, totaling over 91 days of continuous field effort. Surveys were conducted in five indigenous communities (Cunuri on the Uaupés River, Tapira Ponta on the Uaupés River, Ilha das Flores at the confluence of the Uaupés and the Negro River, Curicuriari at the confluence of the Curicuriari and Negro River, and São Jorge on the Curicuriari River, which is only accessible by boat). The communities are multiethnic and include native-born residents as well as those from various regions of the municipality, including the neighboring country of Colombia. Interviews were conducted with every community resident age 18 or older who had contracted malaria or treated someone who suffered from it (approximately 80% of the adult population). The semi-structured face-to-face interviews contained questions related to the sociocultural characteristics of respondents, plants used in their malaria treatment (excluding plants used for malaria-like symptoms such as fever, headache, and others caused by other

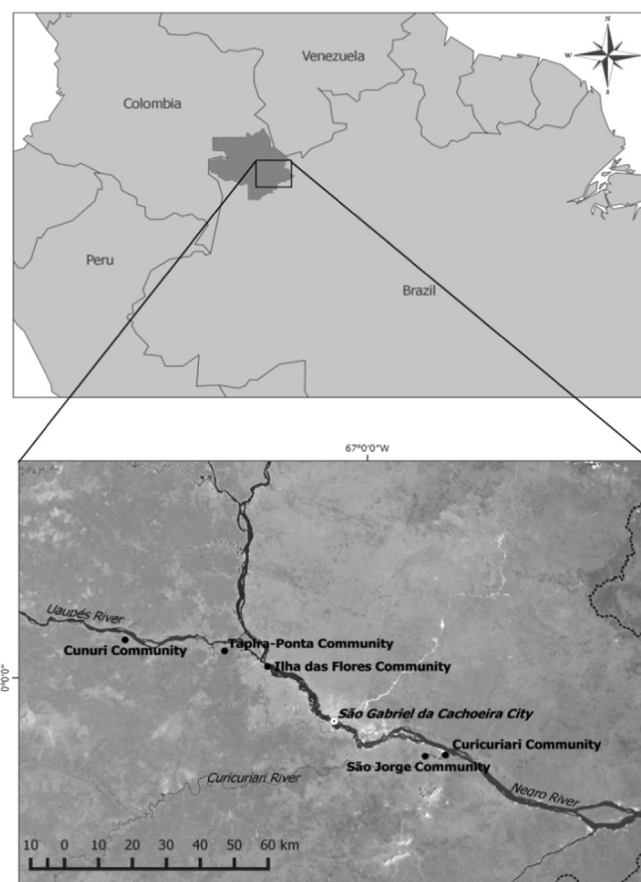


Fig. 1. Map of São Gabriel da Cachoeira and research area.

diseases) parts of the plants used, and preparation and dosage. The informants were asked how they were diagnosed and if they knew of plants to treat or prevent the disease. The common names of the plants were recorded in the language(s) of the respondent. Ethnobotanical walks were conducted to complement interviews and collect botanical material. The plants were picked up and photographed. Interviews and walks were aided by Moises Lopes Dias, a Tukano student and resident of the community of Cunuri. He helped with the collection of botanical material, filming, and translation and transcription of names from Tukano. He was paid for his work and is the co-author of this publication.

The plants were identified by specialists when necessary (Sr. José Ramos, Dr. Maria de Lourdes da Costa Soares Moraes and Dr. Michael Hopkins from Instituto Nacional de Pesquisas da Amazônia (INPA), and Dr. Vidal de Freitas Mansano from Instituto de Pesquisa do Jardim Botânico do Rio de Janeiro). The vouchers were included in the IFAM Herbarium - Campus Manaus (Herbarium EAFM). Names were checked with the List of Species of the Brazilian Flora, Rio de Janeiro Botanical Garden (<http://floradobrasil.jbrj.gov.br>).

2.4. Quantitative analyses

Relative Frequency of Citation (RFC)

This index was obtained by dividing the number of informants who mentioned using the plant species by the number of informants participating in the survey (N). It varies from 0, when nobody referred to the plant as useful, to 1, in the unlikely case that all the informants mentioned using the species (Tardío and Santayana 2008).

2.5. Literature review

The literature was reviewed from scientific journals in academic databases (Google Scholar, Capes Portal, PubMed, JSTOR, EBSCO) of papers published up to January 2014 in order to find work on ethnopharmacology, ethnobotany, and antimalarial activity of the species cited as antimalarial in this research. The main keywords were: antiplasmodial activity, *Plasmodium*, malaria, and all accepted names and synonyms of the 46 species mentioned. For antimalarial activity, we researched articles from all regions of the planet. For references to ethnobotany and ethnopharmacology, papers were selected from countries that are part of the Pan Amazonia.

3. Results and discussion

3.1. Sociocultural characteristics of the informants

We interviewed 89 people in five indigenous communities. It is difficult to precisely quantify the total population because residents travel a lot, and changes in community composition occur constantly. We estimate that this number (89 people) is 80% of the adult population. Of the respondents, 49 are men (55.1%) and 40 are women (44.9%). They belong to 10 ethnic groups. The Tukano ethnic group is the most widely represented with 33.7% of respondents, followed by Dessana (19.1%), Baré (14.6%), Tariano (6.7%), Piratapuaia (4.5%), Arapaço (4.5%), Baniwa (3.3%), Hupda (3.3%), Curripaco (1.1%) and Bara (1.1%). Though most respondents spoke Portuguese, some spoke Spanish as well as 10 other indigenous languages. Most people interviewed spoke four or five languages. Popular names are in the Nheengatu and Tukano languages, which are understood and spoken by all respondents. The Nheengatu language (Tupi-Guarani family) was introduced into the region by European missionaries, whereas there was no previously Tupi language, originally spoken by other indigenous people of the Brazilian coast (Freire, 2004), and is the origin of many plant names in Portuguese, thus explaining the lexical similarities between the names cited in Nheengatu and in Portuguese. The average age of respondents was 46 and ranged from 22 to (approximately) 74.

3.2. The species used as antimalarial and general data on the species

3.2.1. Perception of the disease

According to the indigenous residents interviewed, the origins and transmission of malaria are diverse. Ninety-one percent (81/89) of the informants said that malaria is caused by the bite of a mosquito, a belief for which the government's anti-malaria interventions in the area might be responsible, though some informants also pointed to other causes of the disease. Traditional beliefs of malaria transmission were also voiced: the result of a poisoned arrow from a malevolent mythical being after disobeying the spirits, or the uprooting of the timbó vine (*Deguelia amazonica* Killip) and the waukú flower (*Monopteryx uauçu* Spruce ex Benth.) in the headwaters of rivers, which is subsequently drunk. It can also be contracted through dreams of a plant called umari (*Poraqueiba sericea* Tul.) and in places where there are "malaria pots," stagnant water wells on depressions in river rocks, also described by Buchillet (1995, 2000). Malaria is associated with *sopro*, a cultural disease caused by spiritual beings (WaiMahsã) "blown" by the shamans and only cured by *benzimento* (blessing) or by eating or drinking mosquito urine or eggs in water or food. They use the same word *wuhaké* (tukano) to refer to malaria and influenza, which references the initial fever of both diseases. Nonetheless, over a period of days, symptoms such as intermittent fever,

headache, joint pain, vomiting, and lack of appetite point to malaria, which they tend to diagnose accurately. The disease is perceived as dangerous and deadly if not treated in time. The majority of participants (67.4%; 60/89) said they prefer to use *remédio do branco* (white man's medicine), i.e., antimalarial tablets distributed by government health agencies. According to the informants, the use of medicinal plants occurs when there is no access to the pills distributed by the government: for example, on long trips, in gold mines, and when health service by government agents is delayed. Some participants (12.3%; 11/89) say they only use phytotherapy, while the rest (87.7%; 78/89) say that herbal remedies only work for a while, after which malaria comes back. Globally, most participants believe in the efficacy of medicinal plants but prefer to take the white man's medicine because it is easier to administer and works faster. Concomitant use was also reported (25.8%; 23/89), but this information is often not divulged because government health workers, arguing that the result would be a false negative due to decreased parasitaemia, do not administer the malaria test if the patient claims to have used a home remedy. Informants report that they prefer to be treated by government health workers in the community and go to the hospital in town only for very severe cases. They claim that the doctors do not have patience with them and fail to understand their perceptions of the causes and cures for the disease.

3.2.2. Medicinal plant species

Forty-six plant species belonging to 24 families were mentioned for the treatment of malaria (Table 1).

Among the species collected, three families are characterized by their species richness: Fabaceae (8 species/17.4%), Arecaceae (6 species/13.0%) and Euphorbiaceae (3 species/6.5%), which account together for 36.9% of the mentioned species.

The Fabaceae family represented the highest number of antimalarial plants in the Brazilian Amazonia, as observed by Brandão et al. (1992a), Santos et al. (2008) and Milliken and Albert (1997). Milliken and Albert (1997) claim that although this may be understood as an indicator for the most pharmacologically active families in the region, it probably reflects the size and diversity of these families, thus influencing their representativeness. This hypothesis is confirmed by Stropp et al. (2011) in the region, where the most abundant family identified in the white sand forests and upland was Fabaceae. The Arecaceae family, second on the list of species, is an abundant family in the area and throughout the humid tropics. The Euphorbiaceae family is also cited by Stropp et al. (2011) as the third most abundant in upland and white sand areas, and it is also the third highest in number of species cited in our study. The Asteraceae family appears first on the plant families list used as antimalarials in the work of Milliken (1997) and Oliveira et al. (2003) in the Brazilian Amazonia, but surprisingly, families renowned for their antimalarial metabolites, such as Asteraceae or Rubiaceae, are not highly cited.

The 46 species were classified into a) Amazonian native plants that occur exclusively in the Amazonian phytogeographic area, b) Brazilian plants that also occur in other Brazilian phytogeographic areas, and c) exotic, from other countries all over the world. More than half of the species used in the treatment of malaria are native to the Amazonian phytogeographical area (58.7%; 27/46), including four of the most cited species, 30.4% (14/46) are native to Brazil, and 10.9% (5/46) are exotic species. This high number of native species used can be explained by the excellent state of conservation of the area, the great distance from the larger cities, the difficulty of access, language barriers that hinder the entry of a greater number of exotic plants, and the knowledge and experience of the use of native species by indigenous people. This factor is even more important regarding the use of plants for a disease such as malaria and considered "new." It is the adaptation of local

Table 1
Plants used in the treatment of malaria. Local name: N (Nheengatu), T (Tukano), P (Portugues); Habit: T (tree), S (shrub), H (herbaceous), L (liana); Part used: R (root), B (bark), L (leaf), All (whole plant), S (seed), St (stem), E (exudate), H (heart of palm), F (fruit); Preparation method and use form: D (decoction), I (infusion), B (bath), R (roasted), M (maceration), N (*in natura*), E (enema), ST (steam bath). Endemic species: ES.

Family	Scientific name (voucher number)	Local name	Habit	Part used	Preparation method	UR ^a	RFC ^b	Origin
Annonaceae	<i>Annona mucosa</i> Jacq. (11399)	biribá (N)	T	R	D/ 1 cup 3x a day for 7 days	1/330	0.01	Brazil
Annonaceae	<i>Guatteria guianensis</i> (Aubl.) R.E.Fr. (11428)	envira-verde (N/P)	T	B	D/ 1 cup a day for 7 days	1/330	0.01	Amazonia
Apocynaceae	<i>Aspidosperma schultesii</i> Woodson (11402)	carapanauba (N) kome yahpuri (T)	T	B	D/ 1 cup 3x a day for adults and ¼ of a cup for children with sugar	80/330	0.89	Amazonia
Araceae	<i>Montrichardia arborescens</i> (L.) Schott (11414)	kahpó(T)	S	R	D/1 cup 3x a day for adults, 1 spoon for children 3xa day	1/330	0.01	Brazil
Araceae	<i>Heteropsis tenuispadix</i> G.S.Bunting (11419)	cipó-titica (N/P)	L	St	D/ 1 cup 3x a day	1/330	0.01	Amazonia
Arecaceae	<i>Euterpe catinga</i> Wallace (11400)	açaí-da- catinga(P) mihpi- tahtaboa-kasé (T)	T	R	M/ 1 cup 3x a day	61/330	0.68	Amazonia
Arecaceae	<i>Euterpe precatoria</i> Mart. (Nc)	açaí- do- mato(P)nuhka mihpi (T)	T	R / H	M/1 cup 3x a day	29/330	0.32	Amazonia
Arecaceae	<i>Cocos nucifera</i> L. (Nc)	coco (P)	T	F	D/ with coconut water, as much as you want for 7 days	11/330	0.12	Exotic
Arecaceae	<i>Attalea maripa</i> (Aubl.) Mart. (Nc)	inajá (N) ihki (T)	T	F	R/ drink ashes with warm water 1 cup 3x a day for 7 days	1/330	0.01	Amazonia
Arecaceae	<i>Astrocaryum aculeatum</i> G.Mey. (Nc)	tucumã (N) behta (T)	T	F	R/ drink ashes with warm water 1 cup 3x a day for 7 days	1/330	0.01	Brazil
Arecaceae	<i>Iriartea deltoidea</i> Ruiz & Pav. (Nc)	paxiuba (N/P)	T	L	D/ ½ cup 1x a Day and B.	1/330	0.01	Amazonia
Asteraceae	<i>Rolandra fruticosa</i> (L.) Kuntze (11405)	mata – pasto (P)	H	All	D/ 1 cup 3x a day	1/330	0.01	Brazil
Asteraceae	<i>Unxia camphorata</i> L.f. (11410)	são – João (P)	H	L	I/ 1 cup 3x a day and B.	1/330	0.01	Amazonia
Bromeliaceae	<i>Ananas</i> sp. (Nc)	abacaxi (N/P)	H	F	I/ of the grated fruit, 1 cup 3 x a day	1/330	0.01	Brazil
Bixaceae	<i>Bixa orellana</i> L. (Nc)	urucum (N/P) mohsã (T)	T	R	ST/ beneath the hammock, and D/for bath and drink 1 cup 3 a day	1/330	0.01	Brazil
Bignoniaceae	<i>Jacaranda copaia</i> (Aubl.) D.Don (11416)	pará-pará (N)	T	B	D/½ cup 3x a day and put three drops in the ear and B.	1/330	0.01	Amazonia
Bignoniaceae	<i>Tabebuia barbata</i> (E.Mey.) Sandwith (11417)	pau- de- arco (P) miraparaiwa (N) buhpo origu(T)	T	B	D/ ½ cup 3x a day	1/330	0.01	Brazil
Caricaceae	<i>Carica papaya</i> L. (11423)	mamoero (P)	T	R	M/ with the root of <i>E. precatoria</i> 3x a day	1/330	0.01	Brazil
Erythroxylaceae	<i>Erithroxylum coca</i> Lam. (11403)	ipadu (P)	H	L	D/ 1 cup 3x a day	1/330	0.01	Amazonia
Euphorbiaceae	<i>Sagotia brachysepala</i> (Müll.Arg.) Secco (11401)	farinha – seca (P)	T	B	D to bath at the time of fever	1/330	0.01	Amazonia
Euphorbiaceae	<i>Glycydendron amazonicum</i> Ducke (11413)	ka'su(T)	S	R/L	D/ 1 cup 1x a day	1/330	0.01	Amazonia
Euphorbiaceae	<i>Euphorbia prostrata</i> Aiton (11425)	bacurau (N)	H	All	D with the <i>E. precatoria</i> heart.1 cup 3x a day	1/330	0.01	Brazil
Fabaceae	<i>Monopteryx uauçu</i> Spruce ex Benth. (11404)	vacú (N) simiõgu (T)	T	B	D/ 1 cup take after malaria fever crisis and at bedtime	1/330	0.01	Amazonia
Fabaceae	<i>Swartzia</i> sp. 1 (11408)	cabari – de- folha-pequena (P)	T	B	D/ 1 cup 2x a day	1/330	0.01	Amazonia
Fabaceae	<i>Swartzia picta</i> Benth. (11407)	cabari- de folha– grande (P)	T	B	D/ 1 cup 2x a day	1/330	0.01	Amazonia
Fabaceae	<i>Swartzia argentea</i> Spruce ex Benth. (11409)	acuti –cabari (N) miõgu(T)	T	B	D/ ½ cup 3x a day	7/330	0.08	Amazonia
Fabaceae	<i>Deguelia amazonica</i> Killip (11415)	timbó (N)	L	L	ST/ 1 x a day at bedtime	1/330	0.01	Amazonia
Fabaceae	<i>Ormosia discolor</i> Spruce ex Benth. (Nc)	piisikanaperi(?)	T	S	D / 1spoon (2 ml) 3x a day	1/330	0.01	Amazonia
Fabaceae	<i>Libidibia ferrea</i> (Mart. ex Tul.) L.P. Queiroz (11427)	juçá (N)	T	B	D/ 1 cup a day	1/330	0.01	Brazil
Fabaceae	<i>Phanera splendens</i> (Kunth) Vaz (11429)	escada- de- jabuti (P)	L	St/E	D/ to bath 3x a day and N stem exudate <i>Ad libitum</i>	1/330	0.01	Brazil
Gentianaceae	<i>Tachia grandiflora</i> Maguire & Weaver (Nc)	canela- de- veado (P) yama puri (T)	S	R	I/1 cup 3x a day	1/330	0.01	Amazonia ES
Lauraceae	<i>Persea americana</i> Mill. (Nc)	abacate (P)	T	L	D/ 1 cup 3x a day	1/330	0.01	Exotic
Malpighiaceae	<i>Banisteriopsis caapi</i> (Spruce ex Griseb.) C.V. Morton (Nc)	cahpi(N, T)	S	B	I/ 1 cup 3x a day	1/330	0.01	Amazonia
Menispermaceae	<i>Abuta rufescens</i> Aubl. (11420)	waudá(T)	L	B	D/ 1 cup 3x a day	1/330	0.01	Amazonia
Menispermaceae	<i>Abuta grisebachii</i> Triana & Planch. (11411)	cipó- pacarão (?) mômôda(T)	L	B	D/ 1 cup 3x a day	1/330	0.01	Amazonia
Piperaceae	<i>Piper</i> sp. (11421)	coração (P)	H	R	M/ D 3x a day for 7 days	1/330	0.01	Amazonia
Poaceae	<i>Cymbopogon citratus</i> (DC.) Stapf (Nc)	capim-santo (P)	H	L	I/ <i>Ad libitum</i>	1/330	0.01	Exotic
Rhamnaceae	<i>Ampelozizyphus amazonicus</i> Ducke (11418)	saracura-mirã (N/P)	L	R/B	D or grating and stir the root in water to form a white foam which is removed 4 to 7 times.1 cup 3x a day for 15 days	79/330	0.88	Amazonia
Rubiaceae	<i>Genipa americana</i> L. (11406)	jenipapo (N/P) diawé (T)	T	B	D/ <i>Ad libitum</i>	1/330	0.01	Brazil
Rubiaceae	<i>Sabicea amazonenses</i> Wernham (11424)	buiuiu (N)	L	R	D/1 cup 3x a day	1/330	0.01	Amazonia
Rutaceae	<i>Citrus sinensis</i> (L.) Osbeck (Nc)	Laranja (P)	T	B	D/1 cup 3x a day	1/330	0.01	Exotic
Rutaceae	<i>Citrus</i> sp. (Nc)	limão (P)	T	R	D/1 cup 3x a day	1/330	0.01	Exotic
Sapotaceae	<i>Pouteria ucuqui</i> Pires & R.E. Schult. (11412)	ucuqui (N/P) puhpiágu (T)	T	B	D/½ cup 3x a day	1/330	0.01	Amazonia

Table 1 (continued)

Family	Scientific name (voucher number)	Local name	Habit used	Preparation method	UR ^a	RFC ^b	Origin
Solanaceae	<i>Physalis angulata</i> L. (11426)	camapu (N/P) pikasoró (T)	H	D to bath at the time of fever	30/330	0.33	Brazil
Solanaceae	<i>Solanum crinitum</i> Lam. (11422)	jurubeba (N/P)	H	D/ To clean the intestinal contents more 5 days and bath	1/330	0.01	Brazil
Strelitziaceae	<i>Phenakospermum guitanensis</i> (A.Rich.) Endl. exMiq. (11428)	sonoroça (N/P)	S	N/ Ad libitum	1/330	0.01	Amazonia

^a Number of specie use report (UR).

^b Relative frequency of citation (RFC).

flora to unknown diseases. On the other hand, it is interesting to note that one of the characteristics of local flora is the high endemism, and only one endemic plant was cited as antimalarial, *Tachia grandiflora* (Maguire and Weaver). The exotic species used are also widely cultivated, edible plants (*Cocos nucifera* L., *Persea americana* Mill., *Citrus* spp., *Cymbopogon citrates* (DC.) Stapf), as already observed by Bennett and Prance (2000).

Our study led to a total of 330 Use Reports (URs), but only seven plant species account for 290 URs, showing a relatively high consensus on a few plants, while the large majority of species (39/46) are only cited once. The most consensual ones are *Aspidosperma schultesii* Woodson (RFC=0.89), *Ampelozizyphus amazonicus* Ducke (RFC = 0.88), *Euterpe catinga* Wallace (RFC = 0.68), *Physalis angulata* L. (RFC=0.33), *Euterpe precatória* Mart. (RFC = 0.32), *Cocos nucifera* L. (RFC=0.12) and *Swartzia argentea* Spruce ex Benth (RFC=0.08). Excepting *S.argentea* and *E.catinga*, the two species restricted to the sandy soils of the area, the five others are widely used in various regions of the Amazonia for the treatment of malaria (Table 2). The consensus observed for these seven-most-cited species might indicate the presence of some key phytochemical ingredients in these plants. The wide range of species cited may be, on the other hand, a consequence of the focus on a particular disease, as observed in Odonne et al. (2011). Nevertheless, this fact might be explained by the cultural diversity or the mosaic of environments influencing people's knowledge. Moreover, informants say that some plants are only effective for certain people, usually those sharing the same blood type or siblings. Garnelo and Buchillet (2006) point out that therapeutic strategies, such as the use of medicinal plants in the Upper Rio Negro Baniwa, vary widely according to each patrisib and the distribution of residence microecosystems.

3.2.3. Plant parts

Among the plant parts, barks (34.0%; 17/50) and roots (28.0%; 14/50) were the most used, followed by leaves (14.0%; 7/50), fruits (8.0%; 4/50), whole plants (6.0%; 3/50), stems (4.3%; 2/50), exudates (4.0%; 2/50), and seeds (2.0%; 1/50).

The barks are widely used fresh and dried in Amazonia. According to respondents, the roots of plants growing in *chavascal* (permanently flooded vegetation) and *igapó* (seasonally flooded forest) do not have much medicinal power because they are constantly hydrated, which *diluem o remédio* (dilutes the medicine). Roots (28.0%; 14/50) used in the preparation of medicines to treat malaria are not as commonly used as leaves (Rodrigues, 2006; Odonne et al., 2013).

3.2.4. Preparation methods and posology

Most preparations are made by decoction (57.4%; 31/54), followed by bath (12.9%; 7/54), infusion (9.2%; 5/54), maceration (7.4%; 4/54), roast until ashes (3.7%; 2/54), *in natura* (3.7%; 2/54), steam bath (3.7%; 2/54), and enema (1.8; 1/54). The popularity of decoction, also found by Milliken (1997), Brandão et al. (1992a), and Vigneron et al. (2005), is probably due to the large number of barks and roots, suggesting an Amazonian pattern. The bath is the second-most-common form of preparation. For the bath, the entire body from head to foot is doused with water at the time of fever. In this study, as observed by Vigneron et al. (2005), or Houël et al. (2015), all of the plants used in the bath are also administered internally as tea. When this is done, the amount of tea consumed daily is much less than if it were only used internally. The only exception is *Sagotia brachysepala* (Müll.Arg.) Secco, for which decoction of bark is used in baths only at the time of fever, its intake being prohibited.

An enema is made with the decoction of *Solanum crinitum* Lam. roots, which are placed into a syringe and applied to the anus with the aim of clearing out the intestines. At the same time, the root

Table 2

Literature reports of traditional antimalarial uses and laboratory essays for the plants cited in the Upper Rio Negro region.

Species	Ethnobotanical record in Pan- Amazonia	Antimalarial activity	Source
<i>Abuta rufescens</i> (Menispermaceae)	Milliken (1997), Kvist et al. (2006), Roumy et al. (2007), Ruiz et al. (2011)	Bark and leaves, in vitro, <i>P.falciparum</i> , IC ₅₀ =2.3 to 7.9 µg/mL. Bark, in vitro, <i>P. falciparum</i> (FCR3), 10 to 0.1 µg/ml, IC ₅₀ =5.9 and FBIT test 1.0 µg/ml.	Roumy et al. (2007) Ruiz et al. (2011)
<i>Ampelozizyphus amazonicus</i> (Rhamnaceae)	Santos et al. (2005), Luz (2001), Milliken (1997), Scudeller et al. (2009), Santos et al. (2012), Rodrigues (2006), Brandão et al. (1992a),	Roots, in vitro and in vivo <i>P. berghei</i> (ANKA), 100 to 400 mg/kg/day protection to mice from sporozoites, 100 and 50 µg/mL of extract inhibited in vitro <i>P. berghei</i> schizont development. Prophylactic. Bark, in vivo <i>P.chabaudi</i> , 10 mg/kg oral dose, act as an adaptogen by enhancing immune system function and could mitigate the inflammatory disorders.	Andrade-Neto et al. (2008) Peçanha et al. (2013)
<i>Banisteriopsis caapi</i> (Malpighiaceae)	Ruiz et al. (2011)	Leaves and stems, in vitro, <i>P. falciparum</i> (K1), 10 mg/mL.	Gachet and Schühly (2009) Ruiz et al. (2011)
<i>Bixa orellana</i> (Bixaceae)	Luz (2001), Brandão et al. (1992a), Milliken (1997), Bertani et al. (2005).	Bark, in vitro, <i>P. falciparum</i> (FCR3) 10, to 0.1 µg/ml, inactive. Seeds, in vitro, <i>P.falciparum</i> (GHANA), in vivo <i>P. berghei</i> (ANKA).the extract exhibited IC ₅₀ =11.6 µ/mL, 500 mg/kg dose caused parasitemia reduction of 50.3/5.8%.	Fernandez – Calienes et al. (2010)
<i>Carica papaya</i> (Caricaceae)	Brandão et al. (1992a), Milliken (1997), Ruiz et al. (2011), Valadeau et al. (2009)	Rind and pulp, in vitro, <i>P.falciparum</i> (FCK2). The pet. ether extract of the rind had the highest antimalarial activity of all the extracts tested (IC ₅₀ =15.19 µg/mL). Seeds, in vivo, <i>P. berghei</i> 50 to 200 mg/kg/day, showed a significant malaria parasitaemia suppressive activity ($P \leq 0.05$). Leaves, in vivo, <i>P.berghei</i> (NK65), 100 to 1000 mg/kg and in combination with artesunic acid. Alone have a very good activity, its combination with artesunic acid is antagonistic.	Bhat and Surolia (2001) Amazu et al. (2009) Onaku et al. (2001)
<i>Citrus sinensis</i> (Rutaceae)	Milliken (1997)	Pulp, in vitro, <i>P.falciparum</i> (MRC-2),125 to 1.9 µg/mL.	Venkatesalu et al., (2012)
<i>Cocos nucifera</i> (Arecaceae)	–	Fruit, in vitro, <i>P. falciparum</i> (FCK2) IC ₅₀ =51.1 (petroleum ester) and 53.6 µg/mL (MeOH). Flesh, in vivo <i>P. berghei</i> (NK65), 50 to 200 and 400 mg/kg, reduces the parasitemia by the 200 and 400 mg/kg doses. Husk fiber, in vivo <i>P. berghei</i> (NK65), in vitro <i>P. falciparum</i> (W2). Only ethyl acetate fraction was active against <i>P. falciparum</i> , IC ₅₀ = 10.94 µg/ml. And active in <i>mestiço</i> type hexane extract.	Bhat and Surolia (2001) Al-Adhroey et al. (2011) Adebayo et al. (2012, 2013)
<i>Cymbopogon citratus</i> (Poaceae)	Kvist et al. (2006), Ruiz et al. (2011), Odonne et al. (2013), Rodrigues (2006).	Leaves, in vitro <i>P. falciparum</i> (F32), <i>C.citratus</i> , were found to possess greater effects on the growth with 20 µg/ml giving 57.9%. Leaves volatile oil, in vivo, 62–87% suppression of <i>P. berghei</i> , 200–500 mg/kg/day). Leaves, 400 to 800 mg/kg, in vitro <i>P. falciparum</i> petroleum ether, ethyl acetate and methanol showed IC ₅₀ = 9.1, 12.1 and 15.9 µg/ml respectively and in vivo <i>P. berghei</i> (ANKA), 87.2% inhibition of parasites.	Bidla et al. (2004) Tchoumboungang et al. (2005) Melariri et al. (2011)
<i>Deguelia amazonica</i> (Fabaceae)	–	Stembark,100 mg/kg up to 1 g/kg and in vitro <i>P. falciparum</i> (Indo, F32 Tanzania). IC ₅₀ =3.2 (F32), 18 (Indo) µg/ml.	Muñoz et al. (2000)
<i>Euterpe precatoria</i> (Arecaceae)	Kvist et al. (2006), Bertani et al. (2005), Hajdu and Hohmann (2012), Ruiz et al (2011), Scudeller et al. (2009).	Buttress root, in vitro <i>P. falciparum</i> (D2, F32) and in vivo <i>P. berghei</i> . 100 up to 500 mg/kg. Root, in vitro <i>P. falciparum</i> (3D7), IC ₅₀ =12 µM.	Deharo et al. (2001) Jensen et al. (2002)
<i>Genipa americana</i> (Rubiaceae)	–	Leaves, in vitro <i>P. falciparum</i> (D2, F32) and in vivo <i>P. berghei</i> . 100 up to 500 mg/kg.	Deharo et al. (2001)
<i>Iriartea deltoidea</i> (Arecaceae)	–	Leaves, in vivo, <i>P. berghei</i> (NK65), 0.2 ml, IC ₅₀ =12 µg/ml.	Chinchilla-Carmona et al. (2011)
<i>Jacaranda copaia</i> (Bignoniaceae)	Valadeau et al. (2009), Cavalcante and Frikel (1973) (fever).	Leaves, in vitro <i>P. falciparum</i> (FCR3),IC ₅₀ =8.1–1.5 µg/ml.	Valadeau et al. (2009)
<i>Persea americana</i> (Lauraceae)	Milliken (1997), Coelho-Ferreira (2009), Ruiz et al. (2011).	Bark and leaves, in vitro, <i>P. falciparum</i> (FCR3) 10,5,1 and 0.1 µg/ml IC ₅₀ > 10 µg/ml. IC ₅₀ FBIT test > 10 µg/ml.	Ruiz et al. (2011)
<i>Phanera splendens</i> (Fabaceae)	Albert and Milliken, (2009).	Stembark, in vivo against <i>P. berghei</i> (NK65) and <i>P. vinckei</i> (279BY), 100 mg/kg up to 1 g/kg and in vitro <i>P. falciparum</i> (Indo, F32 Tanzania). IC ₅₀ = > 100 (F32), 28 (Indo) µg/ml, toxic (<i>P. vinckei</i>).	Muñoz et al. (2000)
<i>Physalis angulata</i> (Solanaceae)	Rodrigues (2006), Milliken (1997), Odonne et al. (2013), Kvist et al. (2006), Ruiz et al. (2011).	Whole plant, in vitro <i>P. falciparum</i> (FcB1),10 mg/ml, IC ₅₀ =7.9–0.7 µg/ml. Shoot, in vitro, <i>P. falciparum</i> (3D7), 100 to 12 µg/ml. Whole plant, in vitro <i>P.falciparum</i> (3D7, W2) from 200 to 0.09 µg/ml, and in vivo <i>P.berghei berghei</i> 300 mg/kg. in vitro <i>P. falciparum</i> (W2) IC ₅₀ =2.2–55 µM . Whole plant, in vitro <i>P. falciparum</i> (FCR3), 10,5,1 and 0.1 µg/ml IC ₅₀ =6.6 and FBIT test > 10 µg/ml.	Zirihhi et al. (2005) Kvist et al. (2006) Lusakibanza et al. (2010) Sa et al. (2011), Ruiz et al. (2011)
<i>Tachia grandiflora</i> (Gentianaceae)	Brandão et al. (1992a), Milliken (1997), Schultes and Raffauf (1990).	In vivo <i>P. berghei</i> , 100 to 1000 mg/kg/day. Inhibited 40% of parasites.	Carvalho and Krettli (1991)

Table 2 (continued)

Species	Ethnobotanical record in Pan- Amazonia	Antimalarial activity	Source
		Leaves and roots, in vitro <i>P.falciparum</i> (K1, W2), and in vivo <i>P. berghei</i> (NK65) 500 mg/kg/Day. Crude extracts were inactive in vitro, chloroform root and leaves IC ₅₀ = 10.5–35.8 µg/ml respectively and amplexine IC ₅₀ = 7.1 µg/ml are active in vitro.	Silva et al. (2013)

decoction is used in baths at the time of fever. The use of enemas is currently not very well documented in the Brazilian Amazonia.

A *suador* (steam bath) is made from the roots of *Bixa orellana* L. or leaves of *D.amazonica*, which are burned below the hammock of the patient, who is covered under a blanket.

Only two preparations are made from a mixture of plants: maceration of *Carica papaya* L. with *E. precatoria* roots and the decoction of *Euphorbia prostrata* Aiton with the palm of *E. precatoria*. Interestingly, all the mixtures cited include parts of *E. precatoria* in their preparations, suggesting a possible synergistic effect. According to Rasoanaivo et al. (2011), there is evidence for different types of positive interactions between components of medicinal plants used in the treatment of malaria. This species is often quoted in the literature for its use as an antimalarial in traditional medicine, but the laboratory work is inconclusive and only points to moderate antiplasmodial activity (Jensen et al., 2002). Albert and Milliken (2009) argue that most plants in Amerindian herbal medicine of Amazonia are used separately, and this seems to be a common pattern.

Concerning the posology, quantities may vary from half a cup (125 mL) to three cups (750 mL), but are always drunk three times a day. According to the interviewees, they are taken at a similar frequency as the antimalarial tablets, which seems to represent a hybrid of biomedical and traditional medicinal concepts. A reported problem regarding the dose is caused by the disappearance of symptoms in the second or third day of treatment, which makes patients feel they are cured. They no longer take the remedy, which increases the parasitaemia and subsequent symptoms.

Only one species, *A. amazonicus*, is used as a malaria preventive. Indigenous health workers prepare and distribute it to the community, not only as a malaria preventive, but also as a tonic and aphrodisiac.

3.3. Antimalarial activity and phytochemistry, a bibliographic review

After the literature review, the plants were divided into four categories.

Of the 46 species cited, 18 (39.1%; 18/46) have already been studied for their antimalarial properties according to the literature detailed in Table 2, and 26 species (56.5%; 26/46) have no laboratory essays about their antimalarial activity. The literature suggests antimalarial activity of different species in the same genus for 19 of our plants (41.3%; 19/46). Finally, no positive results against malaria parasites were found for two species (4.3% 2/46). The two species that have been identified at genus level only (*Swartzia* sp. and *Piper* sp.) were not included on that list.

3.3.1. Pharmacological and phytochemical data of the consensual antimalarial species

In the following section, we provide an in-depth phytochemical and pharmacological review of the seven consensual species cited in the Upper Rio Negro region.

3.3.1.1. *Aspidosperma schultesii* (RFC=0.89). From the interviewees' points of view, bark has two different characteristics: color, white or yellow, and the environment in which it occurs. In Igapó, the

bark is thinner and thought to be of lower quality because when the tree is submerged, water "dilutes the medicine." Upland, the bark is a little thicker and has a "good amount of medicine," the best quality with a thicker skin and "a larger amount of medicine" located on the mountaintop. Participants compare this species with chloroquine, primaquine and dipyrone because to them, the bitter taste is the same. Several species of *Aspidosperma* are cited in the literature for the treatment of malaria: *A. macrocarpon* Mart. (Mesquita et al., 2007), *A. excelsum* Benth., *A. rigidum* Rusby (Kvist et al., 2006), and *A. nitidum* Benth. ex Müll.Arg. (Ruiz et al., 2011). *A. nitidum* seems to be the most cited antimalarial species (Luz, 2001; Milliken and Albert, 1997; Brandão et al., 1992a; Scudeller et al., 2009; Milliken, 1997). *A. excelsum* and *A. marcgravianum* are less cited (Rodrigues, 2006; Santos et al., 2012; Milliken, 1997). Interestingly, the two *A. excelsum* and *A. nitidum* are now considered synonyms, *A. excelsum* being the accepted name (<http://www.tropicos.org/>). An unidentified *Aspidosperma* is used as an antimalarial in the neighboring region of Barcelos (Silva et al., 2007). *A.rigidum* is used to treat fever by the Indians of the Bolivian Amazonia (Hajdu and Hohmann, 2012).

The *Aspidosperma* genus is characterized by the occurrence of indole alkaloids, often considered chemical markers of the genus (Nunes et al., 1980). Several studies highlight the antimalarial activity of *Aspidosperma* genus (Torres et al., 2013; Henrique et al., 2010; Oliveira et al., 2010; Andrade-Neto et al., 2007; Dolabela et al., 2012), and antiplasmodial effects of *Aspidosperma* species are related to the presence of these alkaloids (Mitaine et al., 1996; Pereira et al., 2007). Three alkaloids (fendlerina, aspidoalbina and aspidolimidina) were isolated from the bark of *A. megalocarpon* and showed strong antimalarial activity in vitro (Mitaine et al., 1998), and according to Mitaine-Offer et al. (2002) various alkaloids of *Aspidosperma* are reasonable antiplasmodial agents. The study of *A.schultesii* bark extract by Reina et al. (2011) showed the presence of three alkaloids, and Mesia et al. (2012) later noted the presence of seven alkaloids.

3.3.1.2. *Ampelozizyphus amazonicus* (RFC= 0.88). It is used as both a preventive and curative medicine. According to the survey participants, there are two forms of *A. amazonicus*, a male and a female. In some communities, the male can only be used by men for the treatment of malaria, while the female can only be used by women. The difference lies in the root morphology. The male *saracura* has a root without secondary roots, whereas the female has secondary roots. The participants noted that the root of male *saracura* looks like a male phallus, and the root of the female *saracura* looks like a woman's pubic hair. They are used for energy and as preventive remedies for other diseases besides malaria.

Saponins have been isolated from their roots, also triterpenes melaleucic acid, betulinic acid, betulin and lupeol (Brandão et al., 1992b; Brandão et al., 1993). Ursolic acid, five lupane type triterpenes: betulin, betulinic acid, lupenone, 3 β -hydroxylup-20(29)-ene-27,28-dioic acid, and 2 α ,3 β -dihydroxylup-20(29)-ene-27,28-dioic acid, and three phytosteroids: stigmasterol, sitosterol and campesterol, have been isolated from stem extracts of *A. amazonicus* (Rosas et al., 2007). Silva et al. (2009) showed the presence of approximately 48% saponins in an aqueous extract from the roots

of the plant and high iron levels in vegetative organs of *A. amazonicus*, including the root bark.

As *A. amazonicus* showed no antimalarial activity (Brandão et al., 1985; Carvalho et al., 1991; Krettli et al., 2001), it was first supposed that its use might be related to a possible adaptogen and immunostimulant activity, given the presence of saponins and betulinic acid (Oliveira et al., 2011; Brandão et al., 1992b; Brandão et al., 1993). Nevertheless, Andrade- Neto et al. (2008) highlighted a good preventive use on chickens infected by *Plasmodium gallinaceum* and showed that an ethanol extract of the plant hampered *in vitro* and *in vivo* the development of *P. berghei* sporozoites in mice. They also proved a reduction in the number of infected liver cells and a smaller number of schizonts cells than in untreated mice. As the sporozoites are the form of contagion of the *Plasmodium*, this result confirmed the prophylactic activity of *A. amazonicus*. Possible interactions occur between saponins from “Indian beer” in: (i) the malaria primary liver forms, or (ii) the parasitophorous vacuole membrane, with consequent parasite destruction. Recently, the immunomodulatory and anti-inflammatory activities of an *A. amazonicus* extract was successfully explored (Peçanha et al., 2013). This work highlighted an increase in total serum IgM and IgG and a decrease in the percentage of splenic plasma cells (CD138+ cells) in *Plasmodium chabaudi*-infected mice treated by *A. amazonicus*.

3.3.1.3. *Euterpe catinga* (RFC= 0.68) and *Euterpe precatoria* (RFC= 0.32). According to informants, *E. caatinga* differs from other açai (*Euterpe* spp.) in its smaller and darker fruits and reddish petiole. *E. precatoria* and *E. oleracea* Mart. are often cited for their antimalarial use (Brandão et al., 1992a; Kvist et al., 2006; Ruiz et al., 2011). Although these species occur in the region, preference is given to the local *E. caatinga*. According to Mesa and Galeano (2013), the roots of *E. caatinga* are indicated as an antimalarial by the Tikuna Indians of Colombia. There are neither phytochemical studies of this species nor tests of their antimalarial activity, but some other species of the genus (mainly *E. precatoria*) have been studied further. *E. precatoria* is mainly used in mixtures. Its roots are macerated with *C. papaya*'s roots, or a piece of palm is cooked with *E. prostrata*. This plant is the most cited antimalarial in the Peruvian Amazonia, (Kvist et al., 2006) and is generally used in other parts of Amazonia (Bertani et al., 2005; Ruiz et al., 2011; Scudeller et al., 2009). Despite the intensive antimalarial use of *E. precatoria* roots in traditional medicine, only one study finds moderate antiplasmodial activity for lignan isolated from its roots (Jensen et al., 2002). Root, stem and leaf stalk of *E. precatoria* revealed the presence of cytotoxic triterpenes, sterols, lignans, flavonoids, coumarins, phenols and also p-hydroxybenzoic acid, cytotoxic triterpenes, and steroids (Harborne et al., 1994; Galotta and Boaventura, 2005; Galotta et al., 2008; Solis et al., 2010). The root shows a high concentration of phenolic compounds compared to the tea and wine (Solis et al., 2010) and high anti-free-radical potential on the root and petiole (Galotta et al., 2008).

3.3.1.4. *Physalis angulata* (RFC= 0.33). *P. angulata* is a widely used antimalarial in Amazonia (Rodrigues, 2006; Milliken, 1997; Odonne et al., 2013; Kvist et al., 2006; Ruiz et al., 2011). A review of molecules isolated from *P. angulata* is available (Rengifo and Vargas, 2013), citing notably flavonoids, tannins, terpenes and phenolic acids, alkaloids as physalins and whitanolides (Rengifo and Vargas, 2013; Lusakibanza et al., 2010). The methanol extract of *P. angulata* leaves demonstrated high activity against chloroquine-resistant and sensitive *P. falciparum* strains. Also, leaves of the aqueous and methanolic extract showed good inhibition of parasitaemia *in vivo* in mice infected by *Plasmodium berghei* (Lusakibanza et al., 2010; Ruiz et al., 2011; Ankrah et al., 2003). The antimalarial activity of isolated physalins from *P. angulata* was

investigated against chloroquine-resistant *P. falciparum* strains and show increased parasitemia and mortality in mice infected with *P. berghei*, whereas physalin 2 caused a reduction in parasitaemia. The exacerbation of infection *in vivo* treatment with physalin 3 is probably due to its potent immunosuppressive activity, which is not evident in physalin 2 (Sa et al., 2011). However, two studies found contradictory results, with weak or no antimalarial activity (Kvist et al., 2006; Zirihhi et al., 2005).

3.3.1.5. *Cocos nucifera* (RFC= 0.12). Coconut used to treat malaria is broken in half and placed in a pot with its water until boiling, and the bitter liquid is drunk for seven days. The coconut fiber, composed mainly of lignin and cellulose, is similar in chemical composition to wood. It is also a source of chemical compounds, particularly phenolic compounds. During the boiling process, organic substances such as pectin, tannins, and phenols are probably released into the water. The use of coconut fiber seems non-toxic for oral use (Alviano et al., 2004; Al-Adhroey et al., 2011). These results are consistent with those observed in popular use, during which the occurrence of adverse effects is unusual. Antiplasmodial activity is reported for the main polyphenolic components, particularly catechins (Al-Adhroey et al., 2011; Adebayo et al., 2012, 2013). Adebayo et al. (2012) showed a total absence of antimalarial activity in most of the tested varieties of *C. nucifera* and suggests that the popular use of the plant as a medicine should be restricted to the “right type.” The *in-vitro* evaluation of coconut fiber in antiplasmodial activity revealed that only the ethyl acetate fraction of the extract was active against *P. falciparum*, that the phytochemicals present in this fraction are alkaloids, tannins and flavonoids, and that there is no hepatotoxic potential nor predisposition to cardiovascular disease (Adebayo et al., 2013). The mesocarp extract of *C. nucifera* was evaluated *in vivo* against *P. berghei*, reducing significantly the parasitaemia, but not the survival time of infected mice (Al-Adhroey et al., 2011).

3.3.1.6. *Swartzia argentea* (RFC= 0.08). In the chemical analysis of *S. argentea*, eight metabolite classes were found within barks: catechin, flavanone, flavonol, condensed tannin, anthraquinone, resins and saponin (Barbosa et al., 2006). There was no work on the antimalarial activity of this species.

4. Conclusion

Local traditional knowledge of antimalarial plants is still widespread in indigenous communities of Upper Rio Negro, probably because of the high incidence of malaria in the region, the accessibility of the plants, and the difficulty of and delay in accessing the medicines distributed by the government. Forty-six plants species were identified, of which seven species present a good level of consensus, and among them, *A. schultesii*, *E. catinga*, *E. precatoria* and *S. argentea* have few or no studies dealing with their antimalarial activity. According to Krettli et al. (2001), the possibility of finding active molecules against plasmodium on selected plants through traditional knowledge is almost 2000% higher than that of randomly selected ones, and this paper references 26 plants that do not have any studies of their antimalarial activity. Our studies highlight the following species: *Glycidendron amazonicum*, *Heteropsis tenuispadix*, *Monopteryx uauacu*, *Phenakospermum guianensis*, *Pouteria ucuqui*, *Sagotia brachysepala* as interesting plants for future studies, because they are Amazonian species of widespread use but no studies. For 18 plant species, the traditional uses have been validated by phytochemical and modern pharmacological studies. Experimental validation of these remedies may help in developing new drugs for malaria and may eventually lead to more widespread use of traditional medicines in

local and cheaper health care systems that take into account the cultural aspects of disease healing. More than half of plants (58.7%) traditionally used against malaria are Amazonian native species, which highlights the importance of environmental protection and the territorial rights of indigenous people to ensure the supply of medicines.

Acknowledgments

We thank the CNPq (National Council for Scientific and Technological Development) (555.669/2009-2), Capes/CsF (Coordination for the Improvement of Higher Education Personnel/Program Science without Borders) (201062/2012-7 author grant) and FAPESP (São Paulo Research Foundation) (2009/53638-7) for financial support. We are also grateful to IFAM – Campus São Gabriel da Cachoeira for logistical support and Foundation of Upper Rio Negro Indigenous Organizations (FOIRN).

References

- Adebayo, J.O., Santana, A.E.G., Krettli, A.U., 2012. Evaluation of the antiplasmodial and cytotoxicity potentials of husk fiber extracts from *Cocos nucifera*, a medicinal plant used in Nigeria to treat human malaria. *Hum. Exp. Toxicol.* 31 (3), 244–249. <http://dx.doi.org/10.1177/0960327111424298>.
- Adebayo, J.O., Balogun, E.A., Malomo, S.O., Soladoye, A.O., Olatunji, L.A., Kolawole, O.M., Oguntoye, O.S., Babatunde, A.S., Akinola, O.B., Aguiar, A.C.C., Andrade, I.M., Souza, N.B., Krettli, A.U., 2013. Antimalarial activity of *Cocos nucifera* husk fibre: further studies. *Evid.-Based Complement. Altern. Med.*, 2013. <http://dx.doi.org/10.1155/2013/742476>.
- Al-Adhroey, A.H., Nor, Z.M., Al-Mekhlafi, H.M., Amran, A.A., Mahmud, R., 2011. Evaluation of the use of *Cocos nucifera* as antimalarial remedy in Malaysian folk medicine. *J. Ethnopharmacol.* 134 (3), 988–991. <http://dx.doi.org/10.1016/j.jep.2011.01.026>.
- Albert, B., Milliken, W., 2009. Urihi - a: a terra-floresta Yanomami, first ed. Instituto Socioambiental, São Paulo.
- Alviano, D.S., Rodrigues, K.F., Leitão, S.G., Rodrigues, M.L., Matheus, M.E., Fernandes, P.D., Antonioli, A.R., Alviano, C.S., 2004. Antinociceptive and free radical scavenging activities of *Cocos nucifera* L.(Palmae)husk fiber aqueous extract. *J. Ethnopharmacol.* 92 (2), 269–273. <http://dx.doi.org/10.1016/j.jep.2004.03.013>.
- Amazu, L.U., Ebong, O.O., Azikiwe, C.C.A., Unekwe, P.C., Siminialayi, M.I., Nwosu, P.J.C., Ezeani, M.C., Obidiya, O.S., Ajugwo, A.O., 2009. Effects of the methanolic seeds extract of *Carica papaya* on *Plasmodium berghei* infected mice. *Asian Pac. J. Trop. Med.* 2 (3), 1–6.
- Andrade-Neto, V.F., Pohlit, A.M., Pinto, A.C.S., Silva, E.C.C., Nogueira, K.L., Melo, M.R., Henrique, M.C., Amorim, R.C.N., Silva, L.F.R., Costa, M.R.F., Nunomura, R.C.S., Nunomura, S.M., Alecrim, W.D., Alecrim, M.G.C., Chaves, F.C.M., Vieira, P.P.R., 2007. In vitro inhibition of *Plasmodium falciparum* by substances isolated from Amazonian antimalarial plants. *Mem. Inst. Oswaldo Cruz* 102 (3), 359–366. <http://dx.doi.org/10.1590/S0074-02762007000300016>.
- Andrade-Neto, V.F., Brandão, M.G.L., Nogueira, F., Rosário, V.E., Krettli, A.U., 2008. *Ampelozizyphus amazonicus* Ducke (Rhamnaceae), a medicinal plant used to prevent malaria in the Amazon Region, hampers the development of *Plasmodium bergheiporozoites*. *Int. J. Parasitol.* 38 (13), 1505–1511. <http://dx.doi.org/10.1016/j.ijpara.2008.05.007>.
- Ankrah, N.A., Nyarko, A.K., Addo, P.G., Ofosuhen, M., Dzokoto, C., Marley, E., Addae, M.M., Ekuban, F.A., 2003. Evaluation of efficacy and safety of a herbal medicine used for the treatment of malaria. *Phytother. Res.* 17 (6), 697–701. <http://dx.doi.org/10.1002/ptr.1196>.
- Barbosa, A.P., Palmeira, R.C.F., Nascimento, C.S., Feitosa, D.S., Cunha, M.S.C., 2006. Leguminosas Florestais da Amazônia Central: I. Prospecção de compostos presentes na casca de espécies arbóreas. *Rev. Fitos* 1 (3), 47–57.
- Bhat, G.P., Suroliya, N., 2001. In vitro antimalarial activity of extracts of three plants used in the traditional medicine of India. *Am. J. Trop. Med. Hyg.* 65 (4), 304–308.
- Bennett, B.C., Prance, G.T., 2000. Introduced plants in the indigenous pharmacopoeia of Northern South America. *Econ. Bot.* 54 (1), 90–102.
- Bertani, S., Bourdy, G., Landau, I., Robinson, J.C., Esterre, P., Deharo, E., 2005. Evaluation of French Guiana traditional antimalarial remedies. *J. Ethnopharmacol.* 98 (1), 45–54. <http://dx.doi.org/10.1016/j.jep.2004.12.020>.
- Bidla, G., Titanji, V., Joko, B., Ghazali, G., Bolad, A., Berzins, K., 2004. Antiplasmodial activity of seven plants used in African folk medicine. *Indian J. Pharmacol.* 36 (4), 245.
- Brandão, M.D.G.L., Botelho, M.D.G.A., Krettli, A.U., 1985. Quimioterapia experimental antimalárica com produtos naturais: I. Uma abordagem mais racional? *Ciênc. Cult.* 37 (7), 1152–1163.
- Brandão, M.G.L., Grandi, T.S.M., Rocha, E.M.M., Sawyer, D.R., Krettli, A.U., 1992a. Survey of medicinal plants used as antimalarials in the Amazon. *J. Ethnopharmacol.* 36 (2), 175–182. [http://dx.doi.org/10.1016/0378-8741\(92\)90018-M](http://dx.doi.org/10.1016/0378-8741(92)90018-M).
- Brandão, M.G.L., Lacaille-Dubois, M.A., Teixeira, M.A., Wagner, H., 1992b. Triterpene saponins from the roots of *Ampelozizyphus amazonicus*. *Phytochemistry* 31 (1), 352–354. [http://dx.doi.org/10.1016/0031-9422\(91\)83076-W](http://dx.doi.org/10.1016/0031-9422(91)83076-W).
- Brandão, M.G., Lacaille-Dubois, M.A., Teixeira, M.A., Wagner, H., 1993. A dammarane-type saponin from the roots of *Ampelozizyphus amazonicus*. *Phytochemistry* 34 (4), 1123–1127. [http://dx.doi.org/10.1016/S0031-9422\(00\)90728-3](http://dx.doi.org/10.1016/S0031-9422(00)90728-3).
- Buchillet, D., 1995. Perles de verre, parures de Blancs et « pots de paludisme ». Épidémiologie et représentations desana des maladies infectieuses (Haut Rio Negro, Brésil). *J. Soc. Am* 81 (1), 181–206. <http://dx.doi.org/10.3406/jsa.1995.1588>.
- Cabalzar, A., Ricardo, C.A., 2006. Mapa-livro povos indígenas do Rio Negro. São Paulo: ISA-Foirn.
- Cabral, A.C., Fé, N.F., Suárez-Mutis, M.C., Bóia, M.N., Carvalho-Costa, F.A., 2010. Increasing incidence of malaria in the Negro River basin, Brazilian Amazon. *Trans. R. Soc. Trop. Med. Hyg.* 104 (8), 556–562. <http://dx.doi.org/10.1016/j.trstmh.2010.03.008>.
- Carvalho, L.H., Krettli, A.U., 1991. Antimalarial chemotherapy with natural products and chemically defined molecules. *Memó. Inst. Oswaldo Cruz* 86, 181–184. <http://dx.doi.org/10.1590/S0074-02761991000600041>.
- Carvalho, L.H., Brandão, M.G., Santos-Filho, D., Lopes, J.L., Krettli, A.U., 1991. Antimalarial activity of crude extracts from Brazilian plants studied in vivo in *Plasmodium berghei*-infected mice and in vitro against *Plasmodium falciparum* in culture. *Braz. J. Med. Biol. Res.* 24 (11), 1113–1123.
- Cavalcante, P.B., Frikel, P., 1973. A Famacopéia Tiryó: estudo étno-botânico, first ed. Museu Paraense Emílio Goeldi, Belém.
- Chinchilla-Carmona, M., Valerio-Campos, I., Sanchez-Porras, R., Mora-Chaves, V., Bagnarello-Madrigal, V., Martínez-Esquivel, L., Gonzalez-Paniagua, A., Vanegas, J.C., 2011. Evaluación in vivo de la actividad antimalárica de 25 plantas provenientes de una Reserva de Conservación Biológica de Costa Rica. *Rev. Chil. Hist. Nat.* 84 (1), 115–123. <http://dx.doi.org/10.4067/S0716-078X2011000100009>.
- Coelho-Ferreira, M., 2009. Medicinal knowledge and plant utilization in an Amazonian coastal community of Marudá, Pará State (Brazil). *J. Ethnopharmacol.* 126 (1), 159–175. <http://dx.doi.org/10.1016/j.jep.2009.07.016>.
- Deharo, E., Bourdy, G., Quenevo, C., Munoz, V., Ruiz, G., Sauvain, M., 2001. A search for natural bioactive compounds in Bolivia through a multidisciplinary approach. Part V. Evaluation of the antimalarial activity of plants used by the Tacana Indians. *J. Ethnopharmacol.* 77 (1), 91–98. [http://dx.doi.org/10.1016/S0378-8741\(01\)00270-7](http://dx.doi.org/10.1016/S0378-8741(01)00270-7).
- Dolabela, M.F., Oliveira, S.G., Peres, J.M., Nascimento, J., Póvoa, M.M., Oliveira, A.B., 2012. In vitro antimalarial activity of six *Aspidosperma* species from the state of Minas Gerais (Brazil). *An. Acad. Bras. Ciênc.* 84 (4), 899–910. <http://dx.doi.org/10.1590/S0001-37652012000400005>.
- Fernández-Calienes, V.A., Mendiola, M.J., Acuña, R.D., Scull, L.R., Gutiérrez, G.Y., 2010. Antimalarial activity of hydroalcoholic extract from *Bixa orellana* L. *Rev. Cubana Med. Trop.* 63 (2), 181–185.
- Freire, J.R.B. (2004). Rio Babel – a história social das línguas na Amazônia, first ed. EDURJ, Rio de Janeiro.
- Gachet, M.S., Schühly, W., 2009. Jacaranda—an ethnopharmacological and phytochemical review. *J. Ethnopharmacol.* 121 (1), 14–27. <http://dx.doi.org/10.1016/j.jep.2008.10.015>.
- Galotta, A.L.Q.A., Boaventura, M.A.D., 2005. Chemical constituents from roots and leaf stalks of açai (*Euterpe precatoria* Mart., Arecaceae). *Quím. Nova* 28 (4), 610–613. <http://dx.doi.org/10.1590/S0100-40422008000600028>.
- Galotta, A.L.Q.A., Boaventura, M.A.D., Lima, L.A., 2008. Antioxidant and cytotoxic activities of açai (*Euterpe precatoria* Mart.). *Quím. Nova* 31 (6), 1427–1430. <http://dx.doi.org/10.1590/S0100-40422008000600028>.
- Garnelo, L., Buchillet, D., 2006. Taxonomias das doenças entre os índios Baniwa (arawak) e desana (tukano oriental) do alto rio negro (Brasil). *Horiz. Antropol.* 12 (26), 231–260.
- Hajdu, Z., Hohmann, J., 2012. An ethnopharmacological survey of the traditional medicine utilized in the community of Porvenir, Bajo Paraguá Indian Reservation, Bolivia. *J. Ethnopharmacol.* 139 (3), 838–857. <http://dx.doi.org/10.1016/j.jep.2011.12.029>.
- Harborne, J.B., Saito, N., Detoni, C.H., 1994. Anthocyanins of *Cephaelis*, *Cynomorium*, *Euterpe*, *Lavatera* and *Pinanga*. *Biochem. Syst. Ecol.* 22 (8), 835–836. [http://dx.doi.org/10.1016/0305-1978\(94\)90088-4](http://dx.doi.org/10.1016/0305-1978(94)90088-4).
- Henrique, M.C., Nunomura, S.M., Pohlit, A.M., 2010. Indole alkaloids from the bark of *Aspidosperma vargasii* and *A. desmanthum*. *Quím. Nova* 33 (2), 284–287. <http://dx.doi.org/10.1590/S0100-40422010000200010>.
- Houël, E., Fleury, M., Odonne, G., Nardella, F., Bourdy, G., Vonthron-Sénécheau, C., Villa, P., Obrecht, A., Eparvier, V., Deharo, E., Stien, D., 2015. Antiplasmodial and anti-inflammatory effects of an antimalarial remedy from the Wayana Amerindians, French Guiana: Takamalaimé (*Psidiumacutangulum* Mart. ex DC., Myrtaceae). *J. Ethnopharmacol.* 166, 279–285. <http://dx.doi.org/10.1016/j.jep.2015.03.015>.
- Jensen, J.F., Kvist, L.P., Christensen, S.B., 2002. An Antiplasmodial Lignan from *Euterpe precatoria*. *J. Nat. Prod.* 65 (12), 1915–1917. <http://dx.doi.org/10.1021/np020264u>.
- Krettli, A.U., Andrade-Neto, V.F., Brandão, M.D.G.L., Ferrari, W., 2001. The search for new antimalarial drugs from plants used to treat fever and malaria or plants randomly selected: a review. *Mem Inst. Oswaldo Cruz* 96 (8), 1033–1042. <http://dx.doi.org/10.1590/S0074-02762001000800002>.
- Kvist, L.P., Christensen, S.B., Rasmussen, H.B., Mejia, K., Gonzalez, A., 2006. Identification and evaluation of Peruvian plants used to treat malaria and

- leishmaniasis. *J. Ethnopharmacol.* 106 (3), 390–402. <http://dx.doi.org/10.1016/j.jep.2006.01.020>.
- Luz, F.J.F., 2001. Plantas medicinais de uso popular em Boa Vista, Roraima, Brasil. *Hortic. Bras.* 19 (1), 88–96.
- Lusakibanza, M., Mesia, G., Tona, G., Karemere, S., Lukuka, A., Tits, M., Angenot, L., Frederich, M., 2010. In vitro and in vivo antimalarial and cytotoxic activity of five plants used in congolesse traditional medicine. *J. Ethnopharmacol.* 129 (3), 398–402. <http://dx.doi.org/10.1016/j.jep.2010.04.007>.
- Melariri, P., Campbell, W., Etusim, P., Smith, P., 2011. In vitro and in vivo anti-plasmodial activities of extracts of *Cymbopogon citratus* Staph and *Vernonia amygdalina* Delile leaves. *J. Nat. Prod.* 4, 164–172.
- Mesa, L., Galeano, G., 2013. Usos de las palmas en la Amazonia Colombiana. *Caldasia* 35 (2), 351–369.
- Mesía, L.R., Mesía, W.R., Rios, J.M.R., Atilés, M.R., Coloma, A.G., Alberto, R., 2012. Búsqueda de principios activos antiparasitarios en plantas de uso tradicional de la amazonia peruana. Especial énfasis en alcaloides indólicos. *Cienc. Amazon.* (Iquitos 2) (2), 116–123.
- Mesquita, M.L., Grellier, P., Mambu, L., De Paula, J.E., Espindola, L.S., 2007. In vitro antiplasmodial activity of Brazilian Cerrado plants used as traditional remedies. *J. Ethnopharmacol.* 110 (1), 165–170. <http://dx.doi.org/10.1016/j.jep.2006.09.015>.
- Milliken, W., Albert, B., 1996. The use of medicinal plants by the Yanomami Indians of Brazil. *Econ. Bot.* 50 (1), 10–25. <http://dx.doi.org/10.1007/BF02862108>.
- Milliken W. and Albert B. 1997. The use of medicinal plants by the Yanomami Indians of Brazil, Part II. *Econ Bot* 51: 264–278.
- Milliken, W., 1997. Traditional anti-malarial medicine in Roraima, Brazil. *Econ. Bot.* 51 (3), 212–237.
- Ministry of Health. 2013. Ministério da Saúde, Secretaria de Vigilância em Saúde. Boletim Epidemiológico de Malária (Internet). Brasília: Secretaria de Vigilância em Saúde. Ministério da Saúde; 2013. Available at: (http://bvsms.saude.gov.br/bvs/periodicos/boletim_epidemiologico_numero_1_2013.pdf).
- Mitaine, A.C., Mesbah, K., Richard, B., Petermann, C., Arrazola, S., Moretti, C., Zechés-Hanrot, M., Men-Olivier, L.L., 1996. Alkaloids from *Aspidosperma* species from Bolivia. *Planta Med.* 62 (5), 458–461.
- Mitaine, A.C., Weninger, B., Sauvain, M., Lucumi, E., Aragón, R., Zechés-Hanrot, M., 1998. Indole alkaloid from the trunk bark of *Aspidosperma megalocarpon*. *Planta Med.* 64, 487. <http://dx.doi.org/10.1055/s-2006-957496>.
- Mitaine-Offier, A.C., Sauvain, M., Valentin, A., Callapa, J., Mallié, M., Zèches-Hanrot, M., 2002. Antiplasmodial activity of *Aspidosperma indole* alkaloids. *Phytomedicine* 9 (2), 142–145. <http://dx.doi.org/10.1078/0944-7113-00094>.
- Muñoz, V., Sauvain, M., Bourdy, G., Arrázola, S., Callapa, J., Ruiz, G., Choque, J., Deharo, E., 2000. A search for natural bioactive compounds in Bolivia through a multidisciplinary approach: Part III. Evaluation of the antimalarial activity of plants used by Alteños Indians. *J. Ethnopharmacol.* 71 (1), 123–131. [http://dx.doi.org/10.1016/S0378-8741\(99\)00191-9](http://dx.doi.org/10.1016/S0378-8741(99)00191-9).
- Nunes, D.S., Koike, L., Reis, F., de, A.M., Taveira, J.J., 2010. New indol alkaloids from *Aspidosperma pruinosum*. *Cienc. Cult.* 32 (7), 466.
- Odonne, G., Valadeau, C., Alban-Castillo, J., Stien, D., Sauvain, M., Bourdy, G., 2013. Medical ethnobotany of the Chayahuita of the *Paranapura basin* (Peruvian Amazon). *J. Ethnopharmacol.* 146 (1), 127–153. <http://dx.doi.org/10.1016/j.jep.2012.12.014>.
- Odonne, G., Berger, F., Stien, D., Grenand, P., Bourdy, G., 2011. Treatment of leishmaniasis in the Oyapock basin (French Guiana): A K.A.P. survey and analysis of the evolution of phytotherapy knowledge amongst Wayãpi Indians. *J. Ethnopharmacol.* 137, pp. 1228–1239. <http://dx.doi.org/10.1016/j.jep.2011.07.044>.
- Oliveira, A.A., Nelson, B.W., 2001. Floristic relationships of terra firme forests in the Brazilian Amazon. *For. Ecol. Manag.* 146 (1), 169–179. [http://dx.doi.org/10.1016/S0378-1127\(00\)00458-8](http://dx.doi.org/10.1016/S0378-1127(00)00458-8).
- Oliveira, F.Q., Junqueira, R.G., Stehmann, J.R., Brandão, M.G.L., 2003. Potencial das plantas medicinais como fonte de novos antimaláricos: espécies indicadas na bibliografia etnomédica brasileira. *Rev. Bras. Plantas Med.* 5 (2), 23–31.
- Oliveira, A.B., Dolabela, M.F., Póvoa, M.M., Santos, C.A.M., de Pilla Varottil, F., 2010. Antimalarial activity of ulein and proof of its action on the *Plasmodium falciparum* digestive vacuole. *Malar. J.* 9 (2), 09. <http://dx.doi.org/10.1186/1475-2875-9-S2-09>.
- Oliveira, D.R.D., Alma, C., Leitão, G.G., Castro, N.G., Santos, J.P.D., Leitão, S.G., 2011. Estudo etnofarmacognóstico da saracuramirã (*Ampelozizyphus amazonicus* Ducke), uma planta medicinal usada por comunidades quilombolas do Município de Oriximiná-PA, Brasil. *Acta Amaz.* 41, 383–392.
- Onaku, L.O., Attama, A.A., Okore, V.C., Tijana, A.Y., Ngene, A.A., 2001. Antagonistic antimalarial properties of pawpaw leaf aqueous extract in combination with artesunic acid in *Plasmodium berghei*-infected mice. *J. Vector Borne Dis.* 48, 96–100.
- Peçanha, L.M.T., Fernandes, P.D., Simen, T.J.M., Oliveira, D.R.D., Finotelli, P.V., Pereira, M.V.A., Barboza, F.F., Almeida, T.S., Carvalhal, S., Pierucci, A.P.T.R., Leitão, G.G., Rastrelli, L., Piccinelli, A.L., Leitão, S.G., 2013. Immunobiologic and anti-inflammatory properties of a bark extract from *Ampelozizyphus amazonicus* Ducke. *Biomed. Res. Int.* 2013, 1–11.
- Pereira, M.D.M., Jácome, R.L.R.P., Alcântara, A.D.C., Alves, R.B., Raslan, D.S., 2007. Alcalóides indólicos isolados de espécies do gênero *Aspidosperma* (Apocynaceae). *Quim. Nova* 30, 970–983.
- Radambrasil. 1976. Ministério das Minas e Energia, Departamento Nacional de Produção Mineral, Rio de Janeiro.
- Rasoanaivo, P., Wright, C.W., Willcox, M.L., Gilbert, B., 2011. Whole plant extracts versus single compounds for the treatment of malaria: synergy and positive interactions. *Malar. J.* 10 (11), 4. <http://dx.doi.org/10.1186/1475-2875-10-S1-54>.
- Reina, M., Ruiz-Mesia, W., Ruiz-Mesia, L., Martínez-Díaz, R., González-Coloma, A., 2011. Indole alkaloids from *Aspidosperma rigidum* and *A. schultesii* and their antiparasitic effects. *Z. Naturforschung* 66 (5–6), 225–234. <http://dx.doi.org/10.1515/znc-2011-5-605>.
- Rengifo, S.E., Vargas, A.G., 2013. *Physalis angulata* L.(Bolsa Mullaca): a review of its traditional uses, chemistry and pharmacology. *Bol. Latinoam. Del. Caribe Plantas Med. Aromat.* 12 (5), 431–445.
- Rizzini, C.T., 1979. Tratado de Fitogeografia do Brasil. Aspectos ecológicos. Hucitec/Edusp, São Paulo.
- Rodrigues, E., 2006. Plants and animals utilized as medicines in the Jaú National Park (JNP), Brazilian Amazon. *Phytother. Res.* 20 (5), 378–391. <http://dx.doi.org/10.1002/ptr.1866>.
- Rosas, L.V., Cordeiro, M.S.C., Campos, F.R., Nascimento, S.K.R., Januário, A.H., França, S.C., Nomizo, A., Toldo, M.P.A., Albuquerque, S., Pereira, P.S., 2007. In vitro evaluation of the cytotoxic and trypanocidal activities of *Ampelozizyphus amazonicus* (Rhamnaceae). *Braz. J. Med. Biol. Res.* 40 (5), 663–670. <http://dx.doi.org/10.1590/S0100-879X2007000500009>.
- Roumy, V., Garcia-Pizango, G., Gutierrez-Choquevilca, A.L., Ruiz, L., Jullian, V., Winterton, P., Fabris, N., Mouris, C., Valentin, A., 2007. Amazonian plants from Peru used by Quechua and Mestizo to treat malaria with evaluation of their activity. *J. Ethnopharmacol.* 112 (3), 482–489. <http://dx.doi.org/10.1016/j.jep.2007.04.009>.
- Ruiz, L., Ruiz, L., Maco, M., Cobos, M., Gutierrez-Choquevilca, A.L., Roumy, V., 2011. Plants used by native Amazonian groups from the Nanay River (Peru) for the treatment of malaria. *J. Ethnopharmacol.* 133 (2), 917–921. <http://dx.doi.org/10.1016/j.jep.2010.10.039>.
- Sa, M.S., de Menezes, M.N., Krettli, A.U., Ribeiro, I.M., Tomassini, T.C., Ribeiro dos Santos, R., Azevedo, W.F., Soares, M.B., 2011. Antimalarial activity of physalins B, D, F, and G. *J. Nat. Prod.* 74 (10), 2269–2272. <http://dx.doi.org/10.1021/np200260f>.
- Santos, A.M.S., Kahwage, C.C., Ferreira, M.R.C., Sampaio, N.A., 2005. Medicinas Tradicionais no Vale do Rio Negro (Amazonas, Brasil). Observações sobre Etnofarmacologia e o Uso da Planta Saracura-Mirã (*Ampelozizyphus amazonicus*): Atividade Farmacológica e/ou Eficácia Simbólica. *Bol. Mus. Para. Emílio Goeldi: Sér. Ciênc. Hum.* 1, 137–147.
- Santos, M.R.A.D., Lima, M.R., Ferreira, M.G.R., 2008. Uso de plantas medicinais pela população de Ariquemes, Rondônia. *Hortic. Bras.* 26 (2), 244–250.
- Santos, J.D.F.L., Pagani, E., Ramos, J., Rodrigues, E., 2012. Observations on the therapeutic practices of riverine communities of the Unini River, AM, Brazil. *J. Ethnopharmacol.* 142 (2), 503–515. <http://dx.doi.org/10.1016/j.jep.2012.05.027>.
- Schultes, R.E., Raffauf, R.F. 1990. The Healing Forest: Medicinal and Toxic Plants of the Northwest Amazonia. Dioscorides Press, Oregon, United States.
- Scudeller, V.V., Veiga, J.B.D., Araújo-Jorge, L.H.D., 2009. Etnoconhecimento de plantas de uso medicinal nas comunidades São João do Tupé e Central (Reserva de Desenvolvimento Sustentável do Tupé). *Biotupé: Meio Físico, Diversidade Biológica e Sociocultural do Baixo Rio Negro, Amazon. Cent.* 2 (15), 185–199.
- Silva, A.L., Tamashiro, J., Begossi, A., 2007. Ethnobotany of riverine populations from the rio negro, amazonia (Brazil). *J. Ethnobiol.* 27 (1), 46–72.
- Silva, J.A., Correa, G.M., Carvalho, R., Costa, R.A., Pinheiro, M.L., Araujo, L.M., Amaral, A.F., 2009. Analyses of *Ampelozizyphus amazonicus*, a plant used in folk medicine of the Amazon Region. *Pharmacogn. Mag.* 5 (17), 75.
- Silva, L.F.R., Lima, E.S., Vasconcellos, M.C., Aranha, E.S.P., Costa, D.S., Santos, E.V.M., Morais, S.K.R., Alecrim, M.G.C., Nunomura, S.M., Struwe, L., Andrade-Neto, V.F., Pohlit, A.M., 2013. In vitro and in vivo antimalarial activity and cytotoxicity of extracts, fractions and a substance isolated from the Amazonian plant *Tachia Gd.* (Gentianaceae). *Mem. Inst. Oswaldo Cruz* 108 (4), 501–507. [http://dx.doi.org/10.2993/0278-0771\(2007\)27 \[46:EORPFT\]2.0.CO;2](http://dx.doi.org/10.2993/0278-0771(2007)27 [46:EORPFT]2.0.CO;2).
- Solis, V.S., Lujan, M.M., Vela, J.E. 2010. Evaluación antioxidante y caracterización química de las especies *Euterpe oleracea* y *E. precatoria*. Programa de Investigación en Biodiversidad Amazónica. Instituto de Investigaciones de la Amazonia Peruana. Available in: (<http://190.187.112.90/cdpublicaciones2011/documentos/pdf/piba/pu1>).pdf Accessed in: 18/02/2014.
- Sombroek, W., 2001. Spatial and temporal patterns of Amazon rainfall: consequences for the planning of agricultural occupation and the protection of primary forests. *AMBIO: J. Hum. Environ.* 30 (7), 388–396. <http://dx.doi.org/10.1579/0044-7447-30.7.388>.
- Stropp, J., Sleen, P.V.D., Assunção, P.A., Silva, A.L.D., Steege, H.T., 2011. Tree communities of white-sand and terra-firme forests of the upper Rio Negro. *Acta Amazon.* 41 (4), 521–544. <http://dx.doi.org/10.1590/S0044-59672011000400010>.
- Tardío, J., Santayana, M.P., 2008. Cultural importance indices: a comparative analysis based on the useful wild plants of Southern Cantabria (Northern Spain) 1. *Econ. Bot.* 62 (1), 24–39.
- Tchoumboungang, F., Zollo, P.H., Dagne, E., Mekonnen, Y., 2005. In vivo antimalarial activity of essential oils from *Cymbopogon citratus* and *Ocimum gratissimum* on mice infected with *Plasmodium berghei*. *Planta Medica* 71 (1), 20–23. <http://dx.doi.org/10.1055/s-2005-837745>.
- Torres, Z.E., Silveira, E.R., Rocha e Silva, L.F., Lima, E.S., de Vasconcellos, M.C., de Andrade Uchoa, D.E., Pohlit, A.M., 2013. Chemical composition of *Aspidosperma ulei* Markgr. and antiplasmodial activity of selected indole alkaloids. *Molecules* 18 (6), 6281–6297. <http://dx.doi.org/10.3390/molecules18066281>.
- Valadeau, C., Pabon, A., Deharo, E., Albán-Castillo, J., Estévez, Y., Lores, F., Rojas, R., Gamboa, D., Sauvain, M., Castillo, D., Bourdy, G., 2009. Medicinal plants from the Yanessa (Peru): evaluation of the leishmanicidal and antimalarial activity of selected extracts. *J. Ethnopharmacol.* 123 (3), 413–422. <http://dx.doi.org/10.1016/j.jep.2009.03.041>.

- Venkatesalu, V., Gopalan, N., Pillai, C.R., Singh, V., Chandrasekaran, M., Senthilumar, A., Chandramouli, N., 2012. In vitro anti-plasmodial activity of some traditionally used medicinal plants against *Plasmodium falciparum*. Parasitol. Res. 111 (1), 497–501. <http://dx.doi.org/10.1007/s00436-012-2834-9>.
- Vigneron, M., Deparis, X., Deharo, E., Bourdy, G., 2005. Antimalarial remedies in French Guiana: a knowledge attitudes and practices study. J. Ethnopharmacol. 98 (3), 351–360. <http://dx.doi.org/10.1016/j.jep.2005.01.049>.
- World Health Organization (WHO). 2014. World Malaria Report 2014. Geneva, 227p.
- Zirihi, G.N., Mambu, L., Guédé-Guina, F., Bodo, B., Grellier, P., 2005. In vitro anti-plasmodial activity and cytotoxicity of 33 West African plants used for treatment of malaria. J. Ethnopharmacol. 98 (3), 281–285. <http://dx.doi.org/10.1016/j.jep.2005.01.004>.