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Plants used by native Amazonian groups from the Nanay River (Peru) for the treatment of malaria

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ABSTRACT

Aim of the study: In order to evaluate the antimalarial potential of traditional remedies used in Peru, Indigenous and Mestizo populations from the river Nanay in Loreto were interviewed about traditional medication for the treatment of malaria.
Materials and methods: The survey took place on six villages and led to the collection of 59 plants. 35 hydro-alcoholic extractions were performed on the 21 most cited plants. The extracts were then tested for antiplasmodial activity *in vitro* on *Plasmodium falciparum* chloroquine resistant strain (FCR-3), and ferriprotoporphyrin inhibition test was also performed in order to assume pharmacological properties.
Results: Extracts from 9 plants on twenty-one tested (*Abuta rufescens*, *Ayapana lanceolata*, *Capsiandra angustifolia*, *Citrus limon*, *Citrus paradise*, *Minquartia guianensis*, *Potalia resinífera*, *Scoparia dulcis*, and *Physalis angulata*) displayed an interesting antiplasmodial activity (IC_{50} < 10 μg/ml) and 16 remedies were active on the ferriprotoporphyrin inhibition test.
Conclusions: The results give scientific validation to the traditional medical knowledge of the Amerindian and Mestizo populations from Loreto and exhibit a source of potentially active plants.

1. Introduction

Malaria still remains as one of the world's biggest killers with more than two million people dying from the disease each year. In this context, safe, effective and accessible new treatments are a matter of priority. Plant remedies seem to be the most convenient solution because of their accessibility and diversity in tropical regions. This study focused on the province of Loreto in Peruvian Amazonia, which is classified by the WHO as a grade III zone for its high frequency of chloroquine resistant malaria and which is the epicenter of this epidemic disease in Peru (75% of the national morbidity) (Chowell et al., 2009). The ethnopharmacological study was performed in six locations near the Nanay River, according to the population's ability to use medicinal plants and to the high incidence of the parasite. Therefore, the aim of this study was to gather ethnomedical data from Indigenous and Mestizo Amazonian groups living in the forest located near Iquitos, about their current traditional use of plants for the treatment of malaria (Fig. 1).

2. Materials and methods

2.1. Description of study area

The ethnopharmacological survey took place in six areas located on the banks of the Nanay River (Anguilla, Diamante azul, Manacamiri, Samito, Santa Maria del alto Nanay and Tarapoto). This river is a tributary of the Amazon River with its mouth situated on the eastern outskirts of Iquitos, capital of the department of Loreto. This town is located in the heart of the Peruvian rainforest and cannot be reached by road. Those areas are inhabited by various indigenous groups among which are members of the Zaparoan linguistic family (Iquito), Quechua speaking and Mestizo populations, which provide an important diversity of therapeutic process. The multi-ethnic configuration of the area has played a positive role in the transmission of knowledge and practice of medicinal plant therapy, including in some cases the propagation of medicinal plants by the way of mutual exchanges among native people. The historical background shows that important changes took place during the rubber boom era (1880–1914). The migrations of indigenous populations originating from other regions of the Amazon (Tigre, Chambira, Pinto Yacu and Napo) along the Nanay River had

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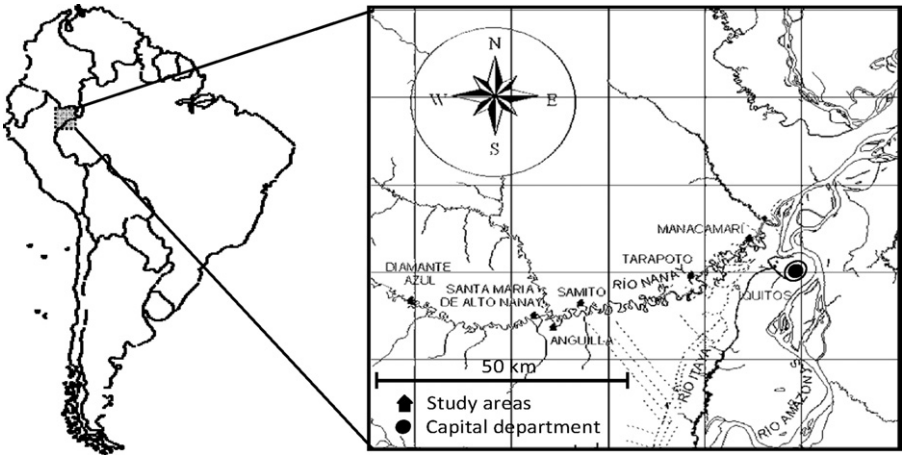

Fig. 1. Location of study area in North Amazonian Peru in order to evaluate the antimalarial potential of traditional remedies (3°44′53″ South, 73°14′50″ West).

an impact on the demographic concentration in the area and the population's sensitivity to the disease. Amerindians have developed by themselves ways of curing malaria, taking advantage of their knowledge on biodiversity. The contact with western goods and medicines since the last century has not weakened the cultural transmission of knowledge related to the use of medicinal plants. Indeed nowadays, native communities from the area are involved in a project of protection of their own biodiversity and commercialization of medicinal plants extracts (Nanay Project, IIAP 2006), reinforcing the cultural value of phytotherapeutic knowledge.

2.2. Plant extracts and preparation

The dried and pulverized parts of the 21 most cited plants (250 g) were twice extracted at 30 °C with EtOH/H_2O (70/30) to obtain 35 representative extracts of common traditional preparations (decoction or maceration in water or alcohol). Plants were collected during summer (from December 2006 to March 2007).

2.3. Antiplasmodial screening

Parasites were cultured according to the method described by Benoit et al. (1995). Briefly, parasites (FCR-3 strain chloroquine-resistant with an IC_{50} of 152.2 ± 28.6 nM for the control chloroquine) were maintained on human red blood cells in RPMI 1640 medium (GIBCO) supplemented with 7.5% human serum and grown in a 5% CO_2 atmosphere. Cultures were synchronized every 48 h by 5% D-sorbitol lysis (Merck). The stock solutions of plant extracts were diluted in culture medium (10, 5, 1 and 0.1 μg/ml) and added to parasite culture. After 48 h of incubation, Giemsa-stained thick blood smears were prepared from each well and parasitemia was evaluated. The inhibitory concentrations of the parasites were calculated by regression analysis using Excel program.

2.4. FBIT testing

Ferriprotoporphyrin IX (FP) biomineralisation is a *Plasmodium* specific process of haeme detoxification in which FP derived from the digestion of ingested haemoglobin is converted to haemozoin (b-haematin). The inhibition of biomineralisation has been shown to be valuable for the detection of compounds with potential antimalarial activity. The procedure for Ferriprotoporphyrin Biomineralization Inhibition Test (FBIT) was realized according to the method described by Bourdy et al. (2004).

2.5. Chemical screening by thin-layer chromatography

The chromatograms of the active extracts were observed using specific spray reagents as described by Wagner and Bladt (1996).

2.6. Method of database preparation

The ethnopharmacological survey was partially undertaken during a long period (6 months overall between October 2006 and March 2007). Plants classified by indigenous or Mestizo people as curing "malaria" were selected for our study when they fitted several symptoms such as fever, shivering, headache, and feeling cold In other cases, malaria was known and recognized under the same term "malaria" (in Spanish) in the area where populations were informed by medical brigades of the state. Other informations on medicinal plants were asked such as the local name, the description of the part used as a remedy, the mode of preparation and the context of plant collection. One adult from each house was interviewed independently from the sex and a total of 266 persons were willing to share their knowledge on phytotherapy. The plants referred by the informants were then identified and deposited at the herbarium of the Universidad Nacional de la Amazonía Peruana (UNAP, Iquitos) and after identification, a second collection was realized in different reserves such as Allpahuayo-Mishana, Requena district, Pasaje Paujiles, Isula, Puerto Almendra and Ninarumi.

3. Result and discussion

Primary tropical forest is generally considered for its high biodiversity and endemic species but the persons interviewed in this study were more using this area to take cuttings and use disturbed forest for the collect of remedies. All the more, disturbed habitats (mostly characterized by herbaceous, weedy, cultivated, and/or introduced species) still important areas to search for novel compounds in drug discovery because vegetal species were selected and tested by several generations of inhabitants whereas numerous of the active extracts or substances have not been yet indentified.

This survey led to the collection of 59 plants (belonging to 38 families) and 21 of the most cited ones were extracted; at least 8 plants displayed an interesting antiplasmodial activity (IC_{50} < 10 μg/ml). This demonstrates that the ethnopharmacological approach is a powerful tool to select plants among the countless possible candidates even if most of them are domesticated species. Moreover, it was the first time that such an important ethnopharmacological study on malaria was undertaken in those ethno-geographic areas near the Nanay River (266 persons were

Table 1
Plants used on the Nanay River against malaria with antiplasmodial or FBIT inhibition activities and chemical composition of the most cited ones.

Voucher number	Family Species (number of citations)	Part used (w/w, %)	Common name	Plasmodium IC50 (μg/ml)	IC50 FBIT (μg/ml)	Composition of extracts
	Amarantaceae					
036258	*Alternanthera brasiliana* (L.)	E.P. (4.6)	Lancetilla	>10	7.2	Fv, Cf. Cv, Sp, P, T, S
	Kuntze (12)	L.		–	–	–
	Anacardiaceae					
034216	*Anacardium occidentale* L. (1)	B.	Casho	–	–	–
033888	*Mangifera indica* L. (1)	B.	Mangua	–	–	–
034257	*Spondias mombin* L. (1)	B., L.	Ubos	–	–	–
	Apiaceae					
033895	*Eryngium foetidum* L. (20)	EP. (10.4)	Sacha culantro	>10	>10	–
036260	*Coriandrum sativum* L. (7)	E.P. (7.5)	Culantro	>10	4.7	Fv, Cf, Sp, P, S
		R., S.		–	–	–
	Apocynaceae					
034300	*Aspidosperma nitidum* Benth. (37)	B.	Remo caspi	–	–	–
	Arecaceae					
026315	*Euterpe precatoria* C. Martius (C.)	R. (4.2)	Huasaí	>10	7.9	Fv, Cf, Cv, L, Tn, S
033549	*Oenocarpus bataua* Mart. (2)	S.	Ungurahui	–	–	–
		F.		–	–	–
036688	*Cocos nucifera* L. (3)	F.	Coco	–	–	–
	Asteraceae					
036259	*Ayapana lanceolata* R. M. King & H. Rob. (7)	L. (18.4)	Caguena	8.2	>10	Fv, Cf, Cv, P, S, Cr
036421	*Tagetes erecta* L. (2)	L.	Rosa sisa	–	–	–
	Bignoniaceae					
033852	*Crescentia cujete* L. (14)	L.	Huingo	–	–	–
035204	*Mansoa alliacea* (Lamarck) A. H.	L. (14.9)	Ajo sacha	>10	2.0	A, Fv, Cf, Cv, Sp, P, S
	Gentry (10)	R. (8.3)		>10	>10	–
		B. (9.6)		>10	>10	–
		E.P. (6.8)		–	–	–
	Bixaceae					
033676	*Bixa orellana* L. (2)	L.	Achiote	–	–	–
	Bombacaceae					
033496	*Ceiba pentandra* (L.) Gaertn (1)	B.	Lupuna	–	–	–
	Caricaceae					
033863	*Carica papaya* L. (1)	S.	Papaya	–	–	–
	Celastraceae					
033887	*Maytenus macrocarpa* (Ruíz &. Pavr) Briq. (2)	B.	Chuchuhuasi	–	–	–
	Euphorbiaceae					
033349	*Alchornea triplinervia* (Spreng.) Müll. Arg.	B.	Zancudo caspi	–	–	–
026397	*Phyllantus niruri* L.	R.	Chanca piedra	–	–	–
033699	*Jatropha gossypifolia* L.	L.	Algodón	–	–	–
	Fabaceae					
035336	*Senna reticulata* (Willd.) H. Irwin & Barneby (16)	B. (18.2)	Retama	>10	8.4	Fv, L, Q, P
		I. (6.4)		>10	2.1	Fv, Cf, Cv, L, Q, P
		R. (5.3)		>10	4.7	Fv, Cf, L, Q, P
		E.P. (10.6)				
024405	*Hymenea courbaril* L. (1)	B.	Azúcar huayo	–	–	–
	Lauraceae					–
033683	*Persea americana* Mill. (1)	L.	Palta	–	–	–
		B.(12.6)	Retama	>10	>10	Fv, Cf, Cv, L, Tn, T
	Lecythidaceae					
033652	*Grias newberthii* J.F. Macbr (1)	F. (16.4)		>10	2.1	
033949	*Couroupita guianensis* Aubl. (1)	R. (7.9)		>10	>10	Fv, Cf, L, P, S
	Leguminosae					
030024	*Capsiandra angustifolia* Spring ex Benth (5)	B. (8.2)	Huacapurana	8.8	6.9	–
	Liliaceae					
029078	*Allium sativum* L. (1)	R.	Ajos	–	–	–
	Loganiaceae					
033688	*Potalia resinifera* Mart. (6)	B. (6.8)	Sacha curarina	6.2	>10	Fv, Cf, Cv, L, Tn, T
		L. (12.3)		>10	>10	–
		R. (7.4)		8.3	>10	Fv, Cf, L, P, S
	Malpighiaceae					
033892	*Banisteriopsis caapi* (Spruce ex Grises) Morton (1)	B.	Ayahuasca	–	–	–
	Malvaceae					
033871	*Malachra alceifolia* Jacq. (61)	L. (20.3)	Malva	>10	>10	–

Table 1 (*Continued*)

Voucher number	Family Species (number of citations)	Part used (w/w, %)	Common name	Plasmodium IC50 (μg/ml)	IC50 FBIT (μg/ml)	Revealed compounds
	Melastomataceae					
024096	*Clidemia hirta* (L.) D. Don (1)	E.P.	Mullaca morada	–	–	–
	Menispermaceae					
035471	*Abuta rufescens* Aubl. (6)	B. (7.8)	Abuta	5.9	1.0	A, Fv, Cf, L, P, T, S
	Moracaceae					
033854	*Ficus insipida* Will. Subsp. (1)	Rs.	Ojé	–	–	–
035211	*Brosimun rubescens* Taub. (1)	B.	Pali sangre	–	–	–
	Myrtaceae					
23694	*Myrciaria dubia* (Kunth) Mc Vaugh. (5)	F. (20.3)	Camu	>10	1.0	Fv, Cv, L, Tn, T
		L. (14.8)	camu	>10	4.1	Fv, L, Sp, Tn, S
		S. (9.5)		>10	4.7	Fv, Cv, L, Tn, T
035790	*Psidium guajava* L. (2)	L.	Guaba	–	–	–
	Olacaceae					
023028	*Minquartia guianensis* Aubl. (3)	B. (8.5)	Huacapú	4.2	>10	Fv, L, Tn, T
	Piperaceae					
034356	*Piper peltatum* L. (1)	L.	Santa maria	–	–	–
	Poaceae					
033669	*Cymbopogon citratus* (DC.) Stapf. (9)	E.P. (11.6)	Hierba luisa	>10	>10	–
		L.		–	–	–
036625	*Saccharum officinarum* L. (1)	St.	Caña	–	–	–
	Phytolacaceae					
035371	*Petiveria alliacea* L. (9)	L. (9.7)	Mucura	>10	3.8	Fv, Sp, S
	Rubiaceae					
036281	*Coffea arabica* L. (3)	L.	Café	–	–	–
033858	*Uncaria guianensis* (Aublet) Gmel. (1)	B.	Uña de gato	–	–	–
	Rutaceae					
033894	*Citrus limon* (L.) Burman f. (18)	F. (18.6)	Limón	4.9	>10	Fv, Cf, L, Q, P
		R. (6.2)		>10	>10	–
		S., B.				
033873	*Citrus paradisi* Macfaden (82)	F. (17.3)	Toronja	4.0	>10	Fv, Cf, Cv, L, P
		L. (12.5)		>10	7.2	Fv, F, S
		R. (6.8)		>10	1.2	A, Fv, Cf, Cv, L, P
		S., B.		>10	>10	–
033853	*Citrus medica* L. (1)	L.	Cidra	–	–	–
	Scrophulariaceae					
033869	*Scoparia dulcis* L. (4)	E.P. (8.3)	Ñucño pichana	6.6	>10	Fv, Cv, Sp, Tn, S, Cr
		L.		–	–	–
	Solanaceae					
033573	*Physalis angulata* L. (9)	E.P. (5.7)	Bolsa mullaca	4.6	>10	A, Fv, Cv, Sp, P, S,Cr
		R.		–	–	–
035791	*Cestrum megalophyllum* Dunal (3)	L.	Hierba santa	>10	>10	–
033886	*Brunfelsia grandiflora* D.Don (2)	R.	Sanango	–	–	–
	Sapotaceae					
033389	*Pouteria caimito* (Ruíz & Pav) Radlk. (3)	L.	Caimito	–	–	–
	Sterculiaceae					
035785	*Theobroma bicolor* Humbl. & Bonpl. (3)	B.	Cacao	–	–	–
	Urticaceae					
033692	*Laportea aestuan* (L.) Chef. (2)	R.	Ishanga	–	–	–
		L., St.		–	–	–
	Verbenaceae					
033890	*Verbena litoralis* H. B. K. (6)	L. (11.6)	Verbena negra	>10	>10	–
033876	*Stachytarpheta straminea* Moldenke. (1)	L.	Sacha verbena	–	–	–
	Zingiberaceae					
033876	*Curcuma longa* L. (2)	R.	Guisador	–	–	–
		L.		–	–	–
033675	*Costus arabicus* L. (2)	St.	Caña agre	–	–	–
	Alpinia nutans Rosc. (1)	L.	Canelilla	–	–	–
Control	**Chloroquine**			0.06 (0.2 μM)	8.9 (28 μM)	

interviewed). In the following discussion, we present the plants extracts tested on *Plasmodium falciparum in vitro*. We have also studied the chemical composition of the antiplasmodial extracts and evaluated their inhibition of biomineralization of Ferriprotoporphyrin IX (FP) *in vitro*. In fact, biomineralization is a *Plasmodium* specific process in which FP (that is lethal for the parasite) is derived from the digestion of haemoglobin that is converted to haemozoin, and can explain drugs pharmacological properties. The analysis of

our biological results and a precise bibliographic study of all the plants permitted a biological evaluation of the phytotherapeutic knowledge of the Nanay River inhabitants. 59 different species were reported. The evaluation of antiplasmodial activity *in vitro* (in our study or previously described in the literature) revealed that among the 49 tested plants only 23 (39%) of them were inactive against *Plasmodium falciparum in vitro* (*Alternanthera brasiliana*, *Banisteriopsis caapi*, *Bixa orellana*, *Brosimum rubescens*, *Brunfelsia grandiflora*, *Carica papaya*, *Cestrum megalophyllum*, *Cocos nucifera*, *Costus arabicus*, *Couroupita guianensis*, *Ficus insipida*, *Hymenea courbaril*, *Jatropha gossypifolia*, *Laportea aestuan*, *Malachra alceifolia*, *Mangifera Indica*, *Persea americana*, *Pouteria caimito*, *Saccharum officinarum*, *Senna reticulata*, *Tagetes erecta*, *Theobroma bicolor*, and *Verbena litoralis*) (Renapurkar and Sutar, 1989; Misra et al., 1991; Muñoz et al., 2000; Zirihi et al., 2005; Calderon et al., 2006; De Mesquita et al., 2007; and Table 1). Nonetheless, it is important to remind that nonactivity of plant extracts *in vitro* must not be interpreted as *in vivo* inactivity against malaria for different reasons, as the biological and phytochemical limits of the test (due to biodistribution and extraction process), or because of the nonevaluated effects of the remedies (symptomatic medicine or drug effects depending from the cultural construction of the efficacy of the remedy, etc.). We also noticed that 10 cited species (17%) still untested for their antiplasmodial potential activity (*Alpinia nutans*, *Anacardium occidentale*, *Aspidosperma nitidum*, *Alchornea triplinervia, Clidemia hirta, Coffea arabica*, *Crescentia cujete*, *Oenocarpus bataua*, *Stachytarpheta straminea*, and *Uncaria guianensis*). Concerning the 26 species (44%) which extracts displayed an inhibitory activity on *P. falciparum* ($4 \leq IC_{50} \leq 40\ \mu g/ml$), as described in the literature or in Table 1, the ability to inhibit the haem biocrystallization was evaluated for 10 of them and 8 were characterized by an $IC_{50} < 10\ \mu g/ml$. Although FBIT assays have a lower specificity and a higher sensibility than the assay on *P. falciparum*, we can assume that those 8 plants contain compounds able to inhibit the parasite by disturbing FP biocrystallization as it had been proved for *Cinchona officinalis*.

Among the plants tested in our study or mentioned in other publications, the following ones displayed an activity on *Plasmodium falciparum*: *Abuta rufescens*, *Allium sativum* (Coppi et al., 2006), *Ceiba pentandra* (Tran et al., 2003), *Citrus medica*, *Curcuma longa* (Rasmussen et al., 2000), *Cymbopogon citratus*, *Erymgium foetidum*, *Euterpe precatoria*, *Grias newberthii*, *Mansoa alliacea* (Valadeau et al., 2009), *Minquartia guianensis*, *Piper peltatum*, *Potalia resinifera* (Weniger et al., 2001), *Phyllantus niruri*, *Physalis angulata* (Tona et al., 1999), *Psidium guajava* (Titanji et al., 2008), *Scoparia dulcis*, *Spondias mombin* (Diallo et al., 2007; Gutierrez Yapu et al., 2008), and the species with both inhibitory activity on *P. falciparum* and FBIT are: *Ayapana lanceolata*, *Capsiandra angustifolia*, *Citrus limon*, *Citrus paradisi*, *Coriandrum sativum* (Sathiyamoorthy et al., 1999), *Maytenus macrocarpa* (Bourdy et al., 2004; Kvist et al., 2006), *Myrciaria Dubia* and *Petiviera alliacea*.

12 species were tested *in vitro* for the first time in this study on *P. falciparum* or FBIT.

Half of the plants reported in this study have an antiplasmodial activity but few of them had ever been studied for their chemical composition. Hence, further investigations are anticipated for isolation and identification of antiplasmodial compounds as well as *in vitro* evaluation of the 10 species that have never been tested on *P. falciparum.*

The results provided by this ethnopharmacological survey showed the pharmacological efficacy and the diversity of the phytotherapeutic knowledge from the inhabitants of the Nanay River and permitted to select new kind of plants that will be studied for their antimalarial potentiality. The rich diversity of botanical families or species traditionally used by the population of the Nanay River reveals the dynamic transmission of ethnomedical knowledge between Amerindian and Mestizo cultures, both proving a constant interest in traditional phytotherapeutic remedies.

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