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Antimalarial ethnopharmacology in the Brazilian Amazon

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ABSTRACT

The preoccupation to find new drugs for the treatment of malaria is increasing steadily due to the resistance of the parasite, which is a threat to disease control. The present study describes a literature review on the antimalarial ethnopharmacology (Anti-*Plasmodium falciparum - in vitro*) of the Brazilian Amazon plants. It was found a great diversity of plant species in the Brazilian Amazon with potential for research of new herbal and secondary metabolites with antiplasmodial action, in addition to treating other neglected parasitic diseases. However, for these studies is needed in addition to financial support, the interaction between different laboratories and research groups for the formation of multidisciplinary and interdisciplinary teams, which will enhance the research level in the region and increase the likelihood of new antimalarial drugs discovery.
Keywords: *Plasmodium falciparum*. Drug therapy. Ethnopharmacology.

INTRODUCTION

Malaria is an infectious and parasitic disease, not contagious, with episodes of acute manifestations and chronic evolution, which affects millions of people in tropical and subtropical regions of the world (Ferreira, 2005; Ferreira *et al*., 2012; WHO, 2014).

The etiological agents of malaria are protozoa of the phylum Protozoa, Sporozoea class, Plasmodiidae family and genus *Plasmodium*, of which there are five species with potential for human transmission: *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium malariae*, *Plasmodium ovale* and *Plasmodium knowlesi* (Sabbatani *et al*., 2009; Hellemond *et al*., 2009; Sá, 2011), occurring the majority in wild environment by the bite of the female mosquitoes of genus *Anopheles* (Mariath *et al*., 2009).

In Latin America, malaria is among the four major endemic diseases, mainly affecting people in poor countries of the American continent (Ferreira *et al*., 2012). In Brazil, 99% of the cases are concentrated in the Legal Amazon, where reported new cases are more than 170 thousand each year (Monteiro *et al*., 2013; Brasil & Daniel-Ribeiro, 2015). This higher incidence of the disease in the Amazon is owing to the fact that it is a region where conditions are favorable to the existence of the vector, due to lack of proper sanitation, disordered settlements and invasion of forests by human population (Costa *et al*., 2010). Besides, often reside in places of difficult access, where they are helpless in relation to basic health, having to look for alternative treatments in plant biodiversity for their illness. However, about 99% of the plants of this region have not yet proven their pharmacological effect and their active principles identified (Santos, 2009), which represents a major pharmacological and economic potential to be exploited (Cechinel-Filho & Rosendo, 1998; Fão *et al*., 2012).

This study aimed to perform a literature review describing the antimalarial ethnopharmacology (Anti-*Plasmodium falciparum – in vitro*) of plants in the Brazilian Amazon. The proposed study was due the preoccupation in search for new drugs for the treatment of malaria, due

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the drug resistance of the parasite, this being considered a threat to disease control (Villalobos *et al*., 1997), because the resistance of *P. falciparum* has been widely documented for various drugs in different countries (Dobenstyn *et al*., 1979; Alencar *et al*., 1997; Reyes *et al*., 1985; Fontanet *et al*., 1993; Villalobos *et al*., 1997; Sidhu *et al*., 2002; Chen *et al*., 2005; Pimentel *et al*., 2007; Mita & Tanabe, 2012; Bolzani & Bolzani, 2013; Ariey *et al*., 2014).

Antimalarial Drugs

Data in literature show that of 1,535 new drugs registered between 1975 and 2004 only 1% were developed to treat tropical diseases (Dias & Dessoy, 2009; Santos *et al*., 2012). The figures reveal a policy of exclusive research, in which only 10% of global spending on health research is spent on diseases that affect 90% of the global burden, the challenge therefore, is to provide alternatives to treatment in affected populations that, in most of cases, presents improperly (Sobrinho *et al*., 2007).

The malarial *Plasmodium* has a complicated life cycle, so malaria must be treated with drug combinations, as well as therapy must be acting in each phase of this cycle and certain criteria must be considered, such as the type of *Plasmodium*, the patient clinical classification and the group to which it is part. These aspects will determine the need for a different treatment for each situation (Osorio-de-Castro *et al*., 2011).

The first antimalarial drugs were created in the 1940s, being derived from natural products or synthetic compounds (Scalercio, 2010), having quinine the earliest medication used to treat malaria, which acts as an erythrocyte schizonticide with quick action, also acting on gametocytes of *P. vivax*, *P. ovale* and *P. malariae*, but having no action on tissue schizonts of *P. vivax* and *P. ovale* or gametocytes of *P. falciparum* (Gomes *et al*., 2011).

Quinine was discarded after the introduction of synthetic derivatives, being reintroduced when the emergence of resistant strains occurred and has been used for infections with *P. falciparum* resistant to chloroquine, as well as in the treatment of severe malaria, in which can also be used quinidine that proved to be more effective, but more toxic, than quinine (Silva *et al*., 2005).

Chloroquine has few adverse effects when used for chemoprophylaxis and was considered safe for pregnant women, however, when used at high doses in acute treatment, may occur nausea, vomiting, dizziness, blurred vision, headache, symptoms of urticarial and retinopathies (Cabral, 2010).

Due to the increasing resistance to antimalarial drugs such as chloroquine, quinine and mefloquine there was a rise in the number of cases in some tropical countries and this fact has been a threat to the local health system. Based on this assumption new drugs have been tested worldwide with the goal of which is preventing *P. falciparum*, resistance. Among these drugs, arthemether associated to lumefantrine was approved, for use in over 80 countries, causing no serious effects in 99% of patients who are carriers of malaria caused by *P. falciparum*, the other 1% had cough, diarrhea, vomiting and anemia (Pinheiro, 2008). Among the newer drugs for malaria control is artemisinin and its derivatives. They act quickly in the destruction of blood schizont preventing the formation of gametocytes, and such derivatives are generally used in combination with other long half-life drug, including mefloquine, piperaquine, amodiaquine, lumefantrine, forming a set of combination therapies established by Artemisinin Combined Therapy (ACT) (Teófilo, 2008).

Another drug therapy scheme used in several countries is the combination of sulfadoxine and pyrimethamine. However, the levels of resistance to this drug increased and are associated with mutations in two genes: DHPS and DHFR (Teófilo, 2008).

The mefloquine is another drug used to combat *P. falciparum* resistant to chloroquine. However, this drug has some side effects such as gastrointestinal complications, dizziness and psychological effects, and even these effects being temporary, its use is not recommended to treat patients with history of epilepsy or psychiatric disorders (França, 2008).

We can also cite derivatives of the phenanthrene, and amodiaquine, hydroxyl-chloroquine as drugs used for the treatment of malaria caused by *P. falciparum* strains resistant to chloroquine (CRS). However, they are less effective than drugs mentioned above and more toxic than chloroquine, wherein similar effects are also observed with halofantrine, besides the occurrence of cross-resistance to mefloquine (Franca, 2008).

For the malaria control is necessary that new compounds and an effective vaccine are developed. Within this context research is being done based on empirical knowledge of traditional populations of the Brazilian Amazon region to search for new antimalarial drugs.

Antimalarial Ethnopharmacology

76 plant species of the Amazon were found with possible antimalarial activity, being distributed in 32 botanical families. Among the plants studied, 26 species belonging to 12 families, showed activity Anti-*Plasmodium falciparum in vitro*, by their crude extracts, fractions and isolated secondary metabolites, and 66 compounds were active against strains: 3D7, W2, FcB1, K1, Dd2, D2, D6, F32, FcM29 and Nigerian strains of *P. falciparum*.

Anti-P. falciparum activity of extracts and fractions
Chloroquine-sensitive strains

The *P. falciparum* 3D7 strain, which had its genome sequenced in 2002 (Gardner *et al*., 2002) is a chloroquine-sensitive strain (CSS), as well as D6 and F32 strains.

In the present study, 10 extracts and 2 fractions were found (with activity against 3D7 strain) prepared from 11 species belonging to five families, as can be seen in Table 1.

The samples that produced the best results were the *Maytenus guyanensis* (bast) hexane extract and the *A. rigidum* (stem) ethanol extract.

Table 1. Anti-*P. falciparum* activity (3D7 strain) of extracts and fractions of Amazonian plants (Brandão *et al*., 1997; Okunade & Lewis, 2004; Kvist *et al*., 2006; Dolabela, 2007; Mariath *et al*., 2009; Dolabela *et al*., 2008; Hurtado, 2013; Borges *et al*., 2013; De Paula, 2014).

Family	Specie	Sample	Antiplasmodial activity (µg/ml)
Apocynaceae	Aspidosperma rigidum	Stem(dichloromethane) Extract	1,0 ***
	Aspidosperma spruceanum	Stem(dichloromethane) Extract	6,0 ***
	Aspidosperma parvifolium	Bast (ethanol) Extract	20,5 **
	Aspidosperma cylindrocarpon	Core (ethanol) Extract	39,0 **
	Aspidosperma excelsum	Bast (ethanol) Extract	42,0 **
	Aspidosperma rigidum	Stem (ethanol) Extract	48,0 **
	Aspidosperma spruceanum	Stem (ethanol) Extract	100,0 *
Asteraceae	Bidens pilosa	Leaves and root (butanol) Fraction	50,0 **
Celastraceae	*Maytenus guyanensis*	Bast (hexano) Fraction	0,3 ***
Rutaceae	Esenbeckia febrifuga	Stem (ethanol) Extract	21,0 **
Verbenaceae	Lantana cujabensis	Leaves and root (ethanol) Extract	23,3 **

IC_{50}: Inhibitory concentration for 50% of the test population: low activity *(IC_{50}>100); moderate activity **(10<IC_{50}>100); high activity ***(IC_{50}≤10).

Activity against *P. falciparum* strains observed in studies using species of the genus *Maytenus*, where the aqueous and methanol extracts of *M. undata*, showed an IC50<10µg/ml, both for D6 (CSS) and W2 (CRS) (Muthaura *et al*., 2007). It is believed that the antiparasitic action of species of this genus is mainly due to the occurrence of friedelane triterpenes (Muhammad *et al*., 2000), like 3-oxo-friedelane, 3β-hydroxyfriedelane, 3-oxo-16β-hydroxyfriedelane that were isolated from *M. guyanensis* (Lima *et al*., 2013; Hurtado, 2013) and other species from the same genus (Nozaki *et al*., 1986).

The *A. rigidum* specie, belongs to Apocynaceae family, which is widely quoted in fever and malaria treatments (Brandão *et al*., 1992, Oliveira *et al*., 2011, Coutinho *et al*., 2013), also being cited with antibacterial action against *Escherichia coli* (Meneses-Pereira *et al*., 2006) and antileishmanial activity (Tanaka *et al*., 2007; Ferreira *et al*., 2004). The following alkaloids of genus Aspidosperma have been isolated: β- yohimbine (OH-17emβ), 10-methoxygeissoschizol, ramiflorines A and B (Marques *et al*., 1996; Oliveira *et al*., 2009) and isositsiriquina (Oliveira *et al*., 2001), which in combination or in isolation may be responsible for the antiparasitic action of the species.

The antiplasmodial action was assessed with the species *A. megalocarpon* and *A. oblongum*, against F32 and D6 strains, respectively. The methanol extract of *A. megalocarpon*, showed a moderate result, IC50=25,0µg/mL (Weniger *et al*., 2001), and high action against D2 (CRS), and for this species were also tested for antiplasmodial action these metabolites: aspidolimidine, aspidoalbine and fendlerine (Mitaine *et al*., 1998), The results and discussion of these metabolites are shown in the "Anti-*P. falciparum* activity of secondary metabolites" topic. The bast ethanol extract of *A. oblongum*, presented high antiplasmodial action with IC50=0,85µg/mL (Cabral *et al*., 1993). This species also presented the best results against the W2 strain, detailed in Table 2 and discussed in the following section.

Chloroquine-resistant strains

The W2 and FcB1 strains of *P. falciparum* (CRS), are used to search for effective drugs against resistant strains, especially chloroquine.

It was found 10 extracts and one fraction (with activity against W2 strain) prepared from nine species belonging to four plant families. Against the FcB1 strain, two extracts and twelve fractions were prepared from five species belonging to four plants species, as can be seen in Table 2.

The *A. oblongum* and A. spruceanum species, as well as the others of Apocynaceae family, presented mainly alkaloids among its secondary metabolites, and among these we may mention the *A. oblongum* species: 10-methoxy-17-epi alloyohimbine, 19,20-dehydro-P-yohimbie, 3,4-dehydro-β yohimbine, p-yohimbine oxindole, p-yohimbine pseudoindoxyle, pyohimbine N-oxide, 10-methoxy-P-yohimbine, 10-methoxy-a-yohimbine, 19,20-dehydro-a-yohimbine, aricine pseudoindoxyle, methoxy antirhine, 10- methoxy sitsirikine, tetradehydro-sitsirikine (Robert *et al*., 1983) and for A. spruceanum specie: spruceanumines A, spruceanumines B, aspidospermidine, demethoxypalosine, aspidocarpine , aspidolimine, fendlerine, aspidolimidine, obscurinervidine e obscurinervine (Oliveira *et al*., 2009). It is believed that the mixture of these metabolites are responsible for the antimalarial activity against W2 strain.

The best results against the FcB1 strain, were obtained from different fractions of C. sylvestris, which is characterized by the presence of substances of interest such as: coumarins, flavonoids, lignans and several diterpenes (Yamagushi *et al*., 2011). Beyond the antimalarial activity (Mesquita *et al*., 2007), also presents action against *Leishmania donovani* promastigotes, *Trypanosoma cruzi* amastigotes (Espíndola *et al*. 2004, Mesquita *et al*. 2005), *Aedes aegypti* larvae (Rodrigues *et al*., 2006) and antimicrobial action against fungi: *Aspergillus niger*, *Saccharomyces cerevisiae*, *Candida albicans*, *C. tropicalis* and bacteria: *Bacillus subtilis*, *B. cereus*, *Staphyloccoccus aureus*, *Enterococcus faecalis*, *Salmonella enteritidis* (Ferreira *et al*., 2011).

Other chloroquine-resistant strains were used, besides W2 and FcB1, such as: D2, Dd2, K1, FcM29 e

Table 2. Anti-*P. falciparum* activity (W2 and FcB1 strains) of extracts and fractions of Amazonian plants (Cabral *et al*., 1993; Sanaiotti *et al*., 1997; Miranda, 2000; Miranda & Absy, 2000; Okunade & Lewis, 2004; Carvalho, 2007; Dolabela, 2007; Mesquita *et al*., 2007; Dolabela *et al*., 2008; Mariath *et al*., 2009; Oliveira, 2012; De Paula, 2014; Meneguetti *et al*., 2014).

Family	Specie	Sample	Antiplasmodial activity (µg/ml)	
			W2	FcB1
Annonaceae	Xylopia aromática	Core of the root (hexane) Fraction	—	4,7 ***
	Xylopia aromática	Bark of the root (hexane) Fraction	—	6,8 ***
	Xylopia aromática	Bast (hexane) Fraction	—	15,3 **
	Aspidosperma macrocarpon	Bark of the root (ethanol) Extract	—	4,9 ***
Apocynaceae	Aspidosperma oblongum	Bast (ethanol) Extract	4,7 ***	—
	Aspidosperma spruceanum	Stem (dichloromethane) Extract	6,0 ***	—
	Aspidosperma rigidum	Stem (dichloromethane) Extract	19,7 **	—
	Aspidosperma parvifolium	Bast (ethanol) Extract	32,8 **	—
	Aspidosperma rigidum	Stem (ethanol) Extract	36,5 **	—
	Aspidosperma cylindrocarpon	Core (ethanol) Extract	44,0 **	—
	Aspidosperma spruceanum	Stem (ethanol) Extract	65,0 **	—
Bignoniaceae	Anemopaegma arvense	Root (hexane) Fraction	—	16,1 **
	Anemopaegma arvense	Leaf (hexane) Fraction	—	24,3 **
	Cybistax antisyphilitica	Core (hexane) Fraction	—	26,5 **
	Anemopaegma arvense	Bast (hexane) Fraction	—	27,6 **
Celastraceae	*Maytenus guyanensis*	Ethyl acetate (hexane) Fraction	56,6 **	—
Rutaceae	Esenbeckia febrífuga	Stem (ethanol) Extract	15,5 **	—
Salicaceae	Casearia sylvestris	Bast (hexane) Fraction	—	0,9 ***
	Casearia sylvestris	Bast (hexane) Fraction	—	1,0 ***
	Casearia sylvestris	Bark of the root (hexane) Fraction	—	1,2 ***
	Casearia sylvestris	Leaf (hexane) Fraction	—	1,3 ***
	Casearia sylvestris	Core of the root (hexane) Fraction	—	2,3 ***
	Casearia sylvestris	Bark of the root (ethanol) Extract	—	7,7 ***
Verbenaceae	Lantana cujabensis	Leaf and stem (ethanol) Extract	14,7 **	—

IC_{50}: Inhibitory concentration for 50% of the test population: low activity *(IC_{50}>100); moderate activity **(10<IC_{50}>100); high activity ***(IC_{50}≤10).

Nigerian Strains, in studies against *P. falciparum in vitro*. The results of extracts and fractions of Amazonian plants against these strains are shown in Table 3.

The plant species presenting high antiplasmodial activity were *A. megalocarpon* and *M. linifera*, both had some secondary metabolites tested, as described and discussed in the following topic. The leaves from *M. linifera* presented alkaloids and triterpenes, substances suggested as the responsible for the antiplasmodial activity (Basco *et al*., 1994; Costa *et al*., 2009).

Anti-P. falciparum activity of secondary metabolites

Importantly, both the above data, against CRS and CSS, were obtained from extracts and fractions, and these results can theoretically be potentiated with isolation of secondary metabolites of these plants. Some research groups are making efforts for the isolation of these substances in order to obtain a drug with enhanced antiplasmodial activity and less likely to cross-action interactions and toxic effects. On the other hand, there are some difficulties in working with these metabolites, like in obtaining the amount that often is insufficient for the *in vivo* tests, as well as performing the *in vitro* tests, due to the difficult solubility of these compounds, which often occurs fully on toxic solvents to the culture media.

Some results of secondary metabolites isolated from plants of the Brazilian Amazon are shown in Table 4 and Figure 1.

The most promising results were presented by the following metabolites: neosergeolide, aspidocarpine, elipticina, simalikalactone D and orinocinolide, isolated from the species: *Picrolemma sprucei, Aspidosperma desmanthum, Aspidosperma vargasii, Quassia amara and Simaba orinocensis* respectivily, all of them presenting action against CRS.

The neosergeolide, simalikalactone D and orinocinolide metabolites belongs to the triterpenes quassinoids group, which constitute a class of substances found almost exclusively in plants of Simaroubaceae family (Almeida *et al*., 2007).

The quassinoids are considered chemically triterpenes biodegradable with high standard oxygenation, presenting a wide range of biological activity (Polonsky & Fortschr, 1985), as: antiviral (Apers *et al*., 2002), anthelmintic (Nunomura *et al*., 2006) and antimalarial (Andrade-Neto, 2007), being these metabolites known by inhibiting growth of *P. falciparum in vitro* at nanomolar concentrations, having the IC50 three times lower than chloroquine and quinine on the inhibition of *P. falciparum* and five times lower against *P. berghei*. They also demonstrate better inhibition *in vivo* (rodents) than chloroquine and artemisinin. However, typically they induce toxicity due primarily to inhibition of protein synthesis (Fandeur *et al*., 1985; Kuo *et al*. 2004; Muhammad *et al*., 2004; Andrade-Neto, 2007; Silva *et al*., 2009).

The other two metabolites which had IC50 <0.1 µg/mL were alkaloid ellipticine and aspidocarpoine.

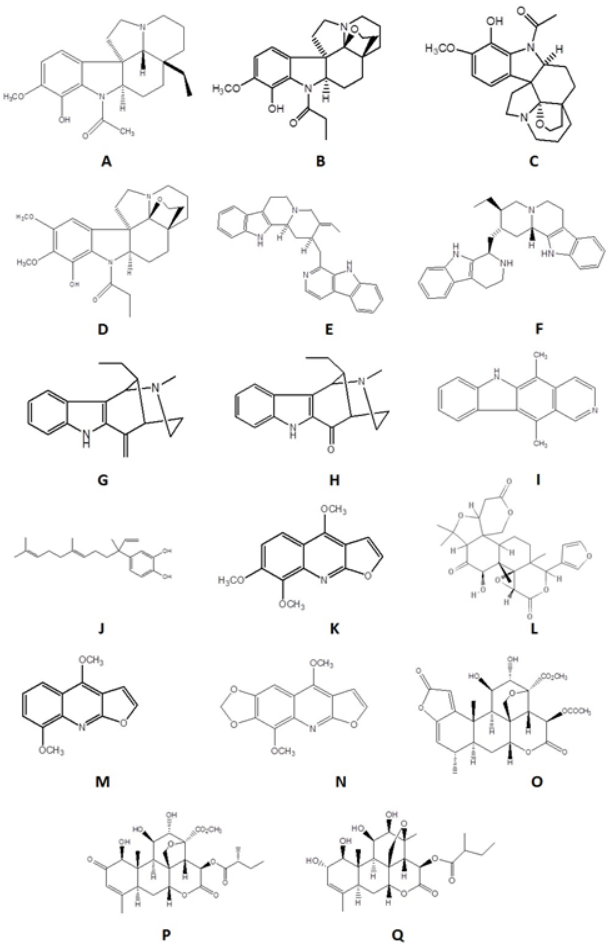

Figure 1. chemical structure of secondary compounds isolated from Amazonian plants with activity Anti-*P. falciparum*. A) Aspidocarpine; B) Fendlerine; C) Aspidolimidine; D) Aspidoalbine; E) Usambarensin; F) Ochrolifuanin A; G) Uleine; H) 20-epi-dasycarpidone; I) Ellipticine; J) 4-Nerolidylcatechol; L) Rutaevine; M) g-Fagarine; N) Flindersiamine; O) Neosergeolide; P) Simalikalactone D; Q) Orinocinolide.

The aspidocarpine and ellipticine metabolites, which are indolic alkaloids, exhibit a wide range of biological activities beyond antiplasmodial, antimicrobial, antibacterial and cytotoxic action, the latter being responsible for ellipticine to become one of the most studied indolic alkaloid eventually being used in clinical trials of cancer treatment (Mitaine *et al*., 1998; Pedersen *et al*., 2005; Endress *et al*., 2007).

The *M. linifera* and *A. oblongum* species have potentiated their results with the isolation of the metabolites 4-nerolidylcatechol, usambare and ochrolifuani, in where the best IC50 results of fractions and extracts ranged between 4,0-10µg/mL, while the isolated compounds IC50 ranged between 0,21 and 0,47µg/mL, both tested against CRS, showing the importance of the isolation of

Table 3. Anti-*P. falciparum* activity (D2, Dd2, K1 and Nigerian Strains) of extracts and fractions of Amazonian plants (Cabral *et al*., 1993; Mitaine *et al*., 1998; Weniger *et al*., 2001; Mitaine-Offer *et al*., 2002; Amarante *et al*., 2011; Silva *et al*., 2013; De Paula, 2014).

Family	Specie	Sample	Antiplasmodial activity (µg/ml)			
			D2	Dd2	K1	Nigerian Strains
Apocynaceae	Aspidosperma megalocarpon	Bast (methanol) Extract	8,0 ***	—	—	—
	Aspidosperma ulei	Bast (ethanol) Extract	—	—	17,6 **	—
	Aspidosperma megalocarpon	Bast (methanol) Extract	—	—	—	57,3 **
Araceae	Montrichardia linifera	Stem (diclhoromethane) Fraction	—	<10 ***	—	—
	Montrichardia linifera	Stem (methanol) Fraction	—	<10 ***	—	—
	Montrichardia linifera	Stem (ethanol) Extracto	—	10<CI50<100 **	—	—
	Montrichardia linifera	Stem (ethyl acetate) Fraction	—	10<CI50<100 **	—	—
	Montrichardia linifera	Stem (hexane) Extract	—	>100,0 *	—	—
	Montrichardia linifera	Stem (hexane) Fraction	—	>100,0 *	—	—
Gentianaceae	Tachia grandiflora	Root (Chloroform) Fraction	—	—	10,5 **	—
	Tachia grandiflora	Leaves (Chloroform) Fraction	—	—	35,8 **	—

IC_{50}: Inhibitory concentration for 50% of the test population: low activity *(IC_{50}>100); moderate activity **(10<IC_{50}>100); high activity ***(IC_{50}≤10).

substances to the search for new drugs. On the other hand *A. megalocarpon*, had its action reduced with the isolation of metabolites fendlerine, aspidolimidine e aspidoalbine, once its metanol extract showed an IC50=8,0µg/mL, and the isolated compound IC50 between 25,6 and 59,2µg/mL all tested against CRS, demonstrating that in this species the good activity of the extract may be related with the interaction between the different alkaloids or that the main antiplasmodial metabolite was not isolated and/or tested.

Besides the species with verified data of action against *P. falciparum* others are cited by traditional populations in antimalarial, antifever and antiparasitic, such as: Apocynaceae: *A. album, A. auriculatum, A. cuspa, A. discolor, A. sandwithianum, A. schultesii, A. tomentosum; Apocynaceae: Himatanthus sucuuba; Asteraceae: Ageratum conyzoides; Bixaceae: Bixa orellana; Clusiaceae: Mammea americana; Compositae: Acanthospermum australe, Pluchea sagitalis, Spilantes oleracea, Vernonia condensata; Convolvulaceae: Calycobolus sp; Euphorbiaceae: Croton cajucara, C. lechleri Euphorbia papillosa; Fabaceae: Bowdichia sp, Erythrina sp, Senna occidentalis, S. alata, S. spruceana; Guttiferae: Vismia japurensis; Labiatae: Leonotis nepetaefolia, Ocimum sp; Leguminosae: Bauhinia rutilans, Desmodium aakendens; Malpighiaceae: Banisteriopsis caapi, Malvaceae: Gossypium herbaceum, Sida spinosa; Meliaceae: Carapa guianensis; Menispermaceae: Abuta concolo, A. grandifolia; Moraceae: Ficus sp; Nyctaginaceae: Boerhavia hirsuta; Piperaceae: Piper glabratum, P. acutifolium, P. callosum; Pocynaceae: Geissospermum sericeum; Portulacaceae: Portulaca pilosa; Rhamnaceae: Ampelozizyphus amazonicus; Rubiaceae: Coutarea hexandra, Cinchona sp, Remijia sp, Psychotria viridis; Solanaceae: Physajis brasiliensis*. These species are indicated for antiplasmodial action studies of its extracts, fractions and isolates (Di Stasi, 2002; Lee & Coll, 2002; Andrade-Net *et al*., 2003; Barbosa *et al*., 2003; Quignard *et al*., 2003; Berg, 2010; Araújo Jr *et al*., 2007; Flores *et al*., 2008; Calderon *et al*., 2009; Fão *et al*., 2012; Bezerra *et al*., 2012).

FINAL CONSIDERATIONS

It was found a great diversity of plant species in the Brazilian Amazon with potential for research of new herbal and secondary metabolites with antiplasmodial action, in addition to treating other neglected parasitic diseases. This review demonstrated that future studies should be directed to species that present the quassinoids triterpene metabolites and indole alkaloids, that showed the best actions anti-*P. falciparum*. However, for these studies is necessary, in addition to financial support, the interaction between different laboratories and research groups for the formation of multidisciplinary and interdisciplinary teams, because this would increase the level of research and maximize the probability of discovery of new antimalarial drugs.

Table 4. Anti-*P. falciparum* activity (3D7, FcM29, K1, W2 and Nigerian Strains) of secondary compounds isolated from Amazonian plants (Amorim *et al*., 1986; Amorim *et al*., 1988; Mitaine *et al*., 1998; Mitaine-Offer *et al*., 2002; Muhammad *et al*., 2004; Dolabela, 2007; Almeida *et al*., 2007; Bertania *et al*., 2006; Andrade-Neto, 2007; Dolabela *et al*., 2008; Calderon *et al*., 2009; Passemar *et al*., 2011; De Paula, 2014; Chierrito *et al*., 2014).

Family	Specie	Sample	Atividade antiplasmódica (µg/ml)				
			3D7	FcM29	K1	W2	Nigerian Strains
Apocynaceae	Aspidosperma desmanthum	Aspidocarpine (Figure 1.A)	—	—	0,007 ***	—	—
	Aspidosperma megalocarpon	Fendlerine (Figure 1.B)	—	25,6 **	—	—	—
	Aspidosperma megalocarpon	Aspidolimidine (Figure 1.C)	—	—	—	—	28,0 **
	Aspidosperma megalocarpon	Aspidoalbine (Figure 1.D)	—	59,2 **	—	—	—
	Aspidosperma oblongum	Usambarensin (Figure 1.E)	—	0,23 ***	—	—	—
	Aspidosperma oblongum	Ochrolifuanin A (Figure 1.F)	—	0,47 ***	—	—	—
	Aspidosperma parvifolium	Uleine (Figure 1.G)	—	—	—	0,75 ***	—
	Aspidosperma parvifolium	Uleine (Figure 1.G)	11,9 **	—	—	—	—
	Aspidosperma ulei	20-epi-dasycarpidone (Figure 1.H)	—	—	—	4,5 ***	—
	Aspidosperma vargasii	Ellipticine (Figure 1.I)	—	—	—	0,018 ***	—
Piperaceae	Montrichardia linifera	4-Nerolidylcatechol (Figure 1.J)	—	—	0,21 ***	—	—
Rutaceae	Esenbeckia febrifuga	Skimmiamine (Figure 1.K)	—	—	—	75,3 **	—
	Esenbeckia febrifuga	Rutaevine (Figure 1.L)	—	—	—	>100,0 *	—
	Esenbeckia febrifuga	Rutaevine (Figure 1.L)	>100,0 *	—	—	—	—
	Esenbeckia febrifuga	g-Fagarine (Figure 1.M)	109,8 *	—	—	—	—
	Esenbeckia febrifuga	g-Fagarine (Figure 1.M)		—	—	157,2 *	—
	Esenbeckia febrifuga	Skimmiamine (Figure 1.K)	166,0 *	—	—	—	—
	Esenbeckia febrifuga	Flindersiamine (Figure 1.N)	265,6 *	—	——	—	—
	Esenbeckia febrifuga	Flindersiamine (Figure 1.N)	—	—	—	348,0 *	—
Simaroubaceae	Picrolemma sprucei	Neosergeolide (Figure 1.O)	—	—	0,001 ***	—	—
	Quassia amara	Simalikalactone D (Figure 1.P)	—	—	—	0,037 ***	—
	Simaba orinocensis	Orinocinolide (Figure 1.Q)	—	—	—	0,085 ***	—

IC_{50}: Inhibitory concentration for 50% of the test population: low activity *(IC_{50}>100); moderate activity **(10<IC_{50}>100); high activity ***(IC_{50}≤10).

RESUMO

Etnofarmacologia antimalárica na Amazônia Brasileira

Está cada vez maior a necessidade em se buscar novos fármacos para o tratamento da malária, principalmente devido à resistência do parasito, o que é uma ameaça ao controle da doença. O presente estudo descreve uma revisão bibliográfica sobre a etnofarmacologia antimalárica (Anti-*Plasmodium falciparum* - *in vitro*) de plantas da Amazônia brasileira. Constatou-se uma grande diversidade de espécies vegetais na Amazônia brasileira com potencial para a investigação de novos fitoterápicos e metabólitos secundários com ação antiplasmodial, além do tratamento de outras parasitoses negligenciadas. Porém, para a realização desses estudos são necessários além de apoio financeiro, a interação entre diferentes laboratórios e grupos de pesquisa para a formação de equipes multidisciplinares e interdisciplinares, o que irá potencializar o nível da pesquisa na região e aumentar a probabilidade de descoberta de novos fármacos antimaláricos.

Palavras-chave: *Plasmodium falciparum*. Quimioterapia. Etnofarmacologia

REFERENCES

Alencar FE, Cerutti CJ, Durlacher RR, Boulos M, Alves FP, Milhous W, Pang LW. Atovaquone and proguanil for the treatment of malaria in Brazil. J Infect Dis. 1997;175(6):1544-7.

Almeida MMB, Arriaga AMC, Santos AKL, Lemos TLG, Braz-Filho R, Vieira IJC. Ocorrência e atividade biológica de quassinóides da última década. Quim Nova. 2007;30(4):935-51.

Amarante CB, Müller AH, Póvoa MM, Dolabela MF. Estudo fitoquímico biomonitorado pelos ensaios de toxicidade frente à Artemia salina e de atividade antiplasmódica do caule de aninga (Montrichardia linifera). Acta Amaz. 2011;41(3):431-4.

Amorim CZ, Flores CA, Gomes BE, Marques AD, Cordeiro RSB. Screening for antimalarial activity in the genus Pothomorphe. J Ethnopharmacol. 1988;24:101-6.

Amorim CZ, Gomes BE, Flores CA, Cordeiro RSB. Antimalarial activity screening from plants of the genus Pothomorphe. Braz J Med Biol Res. 1986;19:569A.

Andrade-Neto VF, *et al*. *In vitro* inhibition of *Plasmodium falciparum* by substances isolated from Amazonian antimalarial plants. Mem Inst Oswaldo Cruz. 2007;102(3):359-65,

Andrade-Neto VF, Brandão MG, Stehmann JR, Oliveira LA, Krettli AU. Antimalarial activity of Cinchona-like plants used to treat fever and malaria in Brazil. J Ethnopharmacol. 2003;87(2-3):253-6.

Apers S, *et al*. Antiviral activity of simalikalactone D, a quassinoid from Quassia africana. Planta Med. 2002;68(1):20-4.

Araújo-Jr JX, Antheaume C, Trindade RCP, Schmitt M, Bourguignon JJ, Sant'Ana AEG. Isolation and characterisation of the monoterpenoid indole alkaloids of Aspidosperma pyrifolium. Phytochem Rev. 2007;6(1):183-8.

Ariey F, *et al*. A molecular marker of artemisinin-resistant *Plasmodium falciparum* malaria. Nature. 2014;505(7481):50-5.

Barbosa WLR, Tavares ICC, Soares DC. Alcalóides de Aspidosperma auriculatum Standl. Braz J Pharmacogn. 2003;13(supl.1):6-8.

Basco LK, *et al*. *In vitro* activities of furoquinoline and acridone alkaloids against *Plasmodium falciparum*. Antimicrob Agents Ch. 1994;38(5):1169-71.

Berg MEVD. Plantas medicinais na Amazônia: contribuição ao seu conhecimento sistemático. 3 ed. Museu Paraense Emílio Goeldi, 2010.

Bertania S, *et al*. Simalikalactone D is responsible for the antimalarial properties of an Amazonian traditional remedy made with Quassia amara L. (Simaroubaceae). J Ethnopharmacol. 2006;108(1);155-7.

Bezerra WS, Meneguetti DUO, Camargo LMA. A Busca de fármacos para tratamento da Tripanossomíase Americana: 103 anos de negligência. Rev Saúde. 2012;38(1):09-20.

Bolzani MS, Bolzani VS. Do Peru à Java: A trajetória da quinina ao longo dos séculos. [Internet]. [Accessed in 01/10/2013]. Available in <http://www.sbq.org.br/filiais/adm/Upload/subconteudo/pdf/Historias_Interessantes_de_Produtos_Naturais04.pdf>.

Borges CC, Matos TF, Moreira J, Rossato AE, Zanette VC, Amaral PA. Bidens pilosa L. (Asteraceae): traditional use in a community of southern Brazil. Rev Bras Plantas Med. 2013;15(1):34-40.

Brandão MGL, Grandi TSM, Rocha EMM, Sawyer DR, Krettli AU. Survey of medicinal plants used as antimalarials in the Amazon. J Ethnopharmacol. 1992;36(2):175-82.

Brandão MGL, Krettli AU, Soares LSR, Nery CGC, Marinuzzi HC. Antimalarial activity of extracts and fractions from Bidens pilosa and other Bidens species (Asteraceae) correlated with the presence of acetylene and flavonoid compounds. J Ethnopharmacol. 1997;57:131-8.

Brasil P, Daniel-Ribeiro CT. Malária: número de casos cai no Brasil, mas ainda chega a 300 mil ao ano. [Internet]. [Accessed in 20/03/2015]. Available in <http://www6.ens*P*.fiocruz.br/visa/?q=node/2083>.

Cabral JA, McChesney JD, Milhous WK. A new antimalarial quassinoid from Simaba guianensis. J Nat Prod. 1993;56(11):1954-61.

Cabral MA. Anotações em farmacologia e farmácia clínica. [Internet]. [Accessed in 01/10/2013]. Available in: <http://farmacolog.dominiotemporario.com/doc/Anotacoes_em_Farmacologia.pdf>.

Calderon LA, *et al*. Amazonian biodiversity: a view of drug development for Leishmaniasis and malaria. J Braz Chem Soc. 2009;20(6):1011-23.

Carvalho PER. Cafezeiro-do-Mato. Embrapa Circular Técnica. 2007;138.

Cechinel FV, Rosendo AY. Estratégias para a obtenção de compostos farmacologicamente ativos a partir de plantas medicinais. Conceitos sobre modificação estrutural para otimização da atividade. Quim Nova. 1998;21(1):99-105.

Chen N, *et al*. Origin and dissemination of chloroquine-resistant *Plasmodium falciparum* with mutant pfcrt alleles in the Philippines. Antimicrob Agents Chemother. 2005;49(5):2102-5.

Chierrito TPC, *et al*. Anti-malarial activity of indole alkaloids isolated from Aspidosperma olivaceum. Malar J. 2014; 13:142.

Costa ESS, Dolabela MF, Póvoa M, Oliveira DJ, Müller AH. Estudos farmacognósticos, fitoquímicos, atividade

antiplasmódica e toxicidade em Artemia salina de extrato etanólico de folhas de Montrichardia linifera (Arruda) Schott, Araceae. Rev bras farmacogn. 2009;9(4):834-8.

Costa AP, *et al*. Diagnóstico tardio de malária em área endêmica de dengue na extra-Amazônia Brasileira: experiência recente de uma unidade sentinela no estado do Rio de Janeiro. Rev Soc Bras Med Tro*P.* 2010;43(5):571-4.

Coutinho JP, *et al*. Aspidosperma (Apocynaceae) plant cytotoxicity and activity towards malaria parasites. Part I: Aspidosperma nitidum (Benth) used as a remedy to treat fever and malaria in the Amazon. Mem Inst Oswaldo Cruz. 2013;108(8): 974-82.

De-Paula RC, Dolabela MF, De-Oliveira AB. Aspidosperma Species as Sources of Antimalarials. Part III. A Review of Traditional Use and Antimalarial Activity. Planta Med. 2014;80(5):378-86.

Di-Stasi LC. Plantas medicinais na Amazônia e na Mata Atlântica. 2 ed. Unesp, 2002.

Dias LC, Dessoy MA. Quimioterapia da doença de chagas: estado da arte e perspectivas no desenvolvimento de novos fármacos. Quím Nova. 2009;32(9):2444-57.

Dobenstyn FB, Phintuyothin P, Noeypatimanondh S, Teerakiarkamjorn S. Single dose therapy of falciparum malaria with mefloquine and pyrimethamine-sulfadoxine. Bull World Health Organ. 1979;57(2):275-8.

Dolabela MF, *et al*. *In vitro* antiplasmodial activity of extract and constituents from Esenbeckia febrifuga, a plant traditionally used to treat malaria in the Brazilian Amazon. Phytomedicine. 2008;15(5):367-72.

Dolabela MF. Atividade antiplasmódica e citotoxicidade de Esenbeckia febrifuga (A.ST-HIL) Juss. ex Mart. (Rutaceae) e de espécies do gênero Aspidosperma (Apocynaceae). [Dissertation]. Universidade Federal de Minas Gerais, Brasil, 2007.

Endress ME, Bruyns PV. A revised classification of the Apocynaceae S.L. The Bot Rev. 2000;66(1):1-46.

Espíndola LS, *et al*. Trypanocidal activity of a newditerpene from Casearia sylvestris Var. Lingua. Planta Med. 2004;70(11):1093-5.

Fandeur T, Moretti C, Polonsky J. *In vitro* and *in vivo* assessment of the antimalarial activity of sergeolide. Planta Med. 1985;51:20-3.

Fao F, Zan RA, Brondani FMM, Ramos LJ, Meneguetti DUO. Análise do potencial mutagênico da seiva da casca de Croton lechleri (Mull. Arg), no estado de Rondônia, Amazônia Ocidental. SaBios. 2012;7(1):91-8.

Ferreira MS. Malária. In: Focaccia R. Tratado de Infectologia. Atheneu, 2005;1589-1632.

Ferreira PMP, *et al*. Folk uses and pharmacological properties of Casearia sylvestris: a medicinal review. An Acad Bras Ciênc. 2011;83(4):1373-84.

Ferreira GM, Zan RA, Ramos LJ, Souza RAA, Meneguetti DUO. Panorama Epidemiológico da Malária no Município de Ariquemes, Rondônia, Amazônia Ocidental: Um Inquérito de Seis Anos (2005 a 2010). Rev Reci. 2012;2(4):128-32.

Ferreira ICP, *et al*. Anti-leishmanial activity of alkaloidal extract from Aspidosperma ramiflorum. Mem Inst Oswaldo Cruz. 2004;99(3):325-7.

Flores N, *et al*. Benzoic acid derivatives from Piper species and their antiparasitic activity. J Nat Prod. 2008;71(9):1538-43.

Fontanet AL, *et al*. High prevalence of mefloquine-resistant falciparum malaria in Eastern Thailand. Bull World Health Organ. 1993;71(3-4):377-83.

França TCC, Santos MG, Figueroa-Villar, JD. Malária: aspectos históricos e quimioterapia. Quím Nova. 2008;31(5):1271-8.

Gardner MJ, *et al*. Genome sequence of the human malaria parasite *Plasmodium falciparum*. Nature. 2002;419(6906):498-511.

Gomes AP, *et al*. Malária grave por *Plasmodium falciparum*. Rev Bras Ter Intensiva. 2011;23(3):358-69.

Hélio AF, João FJ, Roger S. Resistência do *Plasmodium falciparum* ao fansidar, quinina e tetraciclina. Rev Saúde Pública. 1982;16(5):299-302.

Hellemond, *et al*. Human *Plasmodium knowlesi* infection detected by rapid diagnostic tests for malaria. 2009;15(9):1478-80.

Hurtado FB. Contribuição ao estudo fotoquímico e atividade biológico da entrecasca de *Maytenus* guianensis klotzsch ex Reissek (Celastraceae). [Doctor´s Theses]. Universidade Federal de Rondônia, Brasil, 2013.

Kuo PC, Damu AG, Lee KH, Wu TS. Cytotoxic and antimalarial constituents from roots of Eurycoma longifolia. Bioorg Med Chem. 2004;12(3):537-44.

Kvist LP, Christensen SB, Rasmussen HB, Mejia K, Gonzalez A. Identification and evaluation of Peruvian plants used to treat malaria and leishmaniasis. J Ethnopharmacol. 2006;106(3):390-402.

Lee MR, Coll JR. Plants against malaria. Part 1: Cinchona or the Peruvian bark. Physicians Edinb. 2002;32(3):189-96.

Lima RA, Hurtado FB, Silva GVJ, Militão JSLT, Facundo VA. Triterpenos friedelanos isolados do eluato hexânico da entrecasca de *Maytenus* guianensis (Celastraceae). In 64º Congresso Brasileiro de Botânica, 2013.

Mariath IR, *et al*. Plants of the American continent with antimalarial activity. Rev Bras Farmacogn. 2009;19(1a):158-91.

Marques MFS, *et al*. Indole alkaloid from Aspidosperma ramiflorum. Phytochemistry. 1996;41(3):963-7.

Meneguetti DUO, *et al*. Atividade antiplasmodial da fração (acetato de etila) obtidos da entrecasca de *Maytenus guyanensis* Klotzsch ex Reissek (Celastraceae), xixuá amazônico. In 50º Congresso da Sociedade Brasileira de Medicina Tropical, 2014.

Meneses-Pereira M, Alcântara AFC, Pilo-Veloso D, Raslan DS. NMR structural analysis of braznitidumine: a new indole alkaloid with 1,2,9-triazabicyclo [7.2.1] system, isolated from Aspidosperma nitidum (Apocynaceae). J Braz Chem Soc. 2006;17(7):1274-80.

Mesquita M, *et al*. Antileishmanial and trypanocidal activity of Brazilian Cerrado plants. Mem Inst Oswaldo Cruz. 2005;100(7):783-7.

Mesquita ML, Grellier P, Mambu L, de Paula JE, Espindola LS. *In vitro* antiplasmodial activity of Brazilian Cerrado plants used as traditional remedies. J Ethnopharmacol. 2007;110(1):165-70.

Miranda IS. Análise florística e estrutural da vegetação lenhosa do Rio Comemoração, Pimenta Bueno, Rondônia, Brasil. Acta Amaz. 2000;30(3):393-422.

Miranda IS, Absy ML. Fisionomia das Savanas de Roraima, Brasil. Acta Amaz. 2000;30(3):423-440.

Mita T, Tanabe K. Evolution of *Plasmodium falciparum* drug resistance: implications for the development and containment of artemisinin resistance. Jpn J Infect Dis. 2012;65(6):465-75.

Mitaine AC, Weniger B, SauvainM, Lucumi E, Aragon R, Zeches-Hanrot M. Indole alkaloids from the trunk bark of Aspidosperma megalocarpon. Planta Med. 1998;64(5):487.

Mitaine-Offer AC, Sauvain M, Valentin A, Callapa J, Mallie M, Zeches-Hanrot M. Antiplasmodial activity of Aspidosperma indole alkaloids. Phytomedicine; 2002;9(2):142-5.

Monteiro MRCC, Fernandes SC, Ribeiro MC. Aspectos clínicos e epidemiológicos da malária em um hospital universitário de Belém, Estado do Pará, Brasil. Rev Pan-Amaz Saude. 2013;4(2):33-43.

Muhammad I, *et al*. Bioactive 12- oleanene triterpene and secotriterpene acids from *Maytenus* undata. J Nat Prod. 2000;63(5):605-10.

Muhammad I, *et al*. A new antimalarial quassinoid from Simaba orinocensis. J Nat Prod. 2004;67(5):772-7.

Muthaura CN, *et al*. Antimalarial activity of some plants traditionally used in treatment of malaria in Kwale district of Kenya. J Ethnopharmacol. 2007;25;112(3):545-51.

Nozaki H, *et al*. Antintumor triterpenes of *Maytenus* diversifolia . Phytochemistry. 1986;25(2):479-85.

Nunomura RCS, *et al*. *In vitro* studies of the anthelmintic activity of Picrolemma sprucei Hook. f. (Simaroubaceae). Acta Amaz. 2006;36(3):327-30.

Okunade AL, Lewis WH. Oleanene constituents of Lantana cujabensis. Fitoterapia. 2004;75(3-4):327-31.

Oliveira DR, Costa A, Leitão GG, Castro NG, dos Santos JP, Leitão SG. Estudo etnofarmacognóstico da saracuramirá (Ampelozizyphus amazonicus Ducke), uma planta medicinal usada por comunidades quilombolas do Município de Oriximiná-PA, Brasil. Acta Amaz. 2011;41(3):383-92.

Oliveira VB, Freitas MSM, Mathias L, Braz-Filho R, Vieira IJC. Atividade biológica e alcalóides indólicos do gênero Aspidosperma (Apocynaceae): uma revisão. Rev Bras Plantas Med. 2009;11(1):92-9.

Oliveira AJB, Koike L, Reis FAM, Shepherd SLK. Callus culture of Aspidosperma ramiflorum Muell. Arg.: growth and alkaloid production. Acta Scient. 2001;23(2):609-12.

Oliveira VB. Potencial dos frutos de Xylopia aromática (Lam.) Mart. (Annonaceae) no tratamento de alterações metabólicas, induzidas por dieta em camundongos balb/c. [Dissertation]. Universidade Federal de Minas Gerais, Brasil, 2012.

Oliveira VB, *et al*. Spruceanumines A and B, novel plumeran indole alkaloids from Aspidosperma spruceanum (Apocynaceae). J Braz Chem Soc. 2009;20(4):753-9.

Osorio-De-Castro CGS, *et al*. Conhecimentos, práticas e percepções de profissionais de saúde sobre o tratamento de malária não complicada. em municípios de alto risco da Amazônia Legal. Ciênc Saúde Coletiva. 2011;16(1):1445-56.

Passemar C, *et al*. Indole and aminoimidazole moieties appear as key structural units in antiplasmodial molecules. Phytomedicine 2011;18(13):1118-25.

Pedersen JM, Bowman WR, Elsegood MRJ, Fletcher AJ, Lovell PJJ. Synthesis of Ellipticine: A Radical Cascade Protocol to Aryl- and Heteroaryl-Annulated[b]carbazoles. Org. Chem. 2005;70(25):10615-8.

Pimentel LF, *et al*. Nanotecnologia farmacêutica aplicada ao tratamento da malária. Braz Jour Pharmaceutical Sciences. 2007;43(4):503-14.

Pinheiro PNQ, *et al*. Aspectos farmacológicos do antimalárico lumefantrina. Rev Para Med. 2013;27(1):3532.

Polonsky J, Fortschr. Quassinoid bitter principles II. Chem Org Nat. 1985;47:221-64.

Pereira MM, Jácome RLRP, Alcântara AFC, Alves RB, Raslan DS. Alcalóides indólicos isolados de espécies do gênero Aspidosperma (Apocynaceae). Quim Nova. 2007;30(4):970-83.

Quignard ELJ, *et al*. Screening of plants found in Amazonas state for lethality towards brine shrimp Artemia franciscana. Acta Amaz. 2003;33(1):93-104.

Reyes S, Passos ADC, Osanai CH. Resistência *in vivo* do *P. falciparum* às 4-aminoquinoleínas e à associação

sulfadoxina-pirimetamina. I. Estudo de Porto Velho, Rondônia. Rev Soc Bras Med Tro*P.* 1985;18(3):175-81.

Robert GMT, Ahond A, Poupat C, Potier P, Jacquemin H, Kan SK. Aspidosperma de Guyane: alcaloides des graines de Aspidosperma oblongum. J Nat Prod. 1983;46(5):708-22.

Rodrigues AMS, De-Paula JE, Degallier N, Molez JF, Espíndola LS. Larvicidal activity of some Cerrado plant extracts against *Aedes aegypti*. J Am Mosq Control Assoc. 2006;22(2):314-7.

Sá MS. Avaliação da atividade antimalárica de substâncias obtidas de espécies vegetais nativas ou endêmicas do semi-árido brasileiro e derivados sintéticos. [Doctor's Theses]. Fundação Oswaldo Cruz - Salvador, Brasil, 2011.

Sabbatani S, Fiorino S, Manfredi R. Malária por *Plasmodium knowlesi* no Sudeste Asiático e na América: casos importados podem representar um alerta de saúde: *Plasmodium knowlesi* como o quinto parasita da malária. AVFT. 2009;28(2):48-50.

Sanaiotti TM, Bridgewater S, Ratter JA. A floristic study of the savana vegetation of the state of Amapá, Brazil, and suggestions for its conservation. Bol Mus Para Emílio Goeldi. 1997;13(1):3-29.

Santos FLA, *et al*. Pesquisa, desenvolvimento e inovação para controle das doenças negligenciadas. Rev Ciênc Farm Básica Apl. 2012;33(1):37-47.

Santos FS. As plantas Brasileiras, os jesuítas e os indígenas do Brasil: história e ciência na triaga brasílica (séc. XVII-XVIII). Casa do Novo Autor, 2009.

Scalercio SRRA. Estudo teórico do mecanismo redox de derivados quinolínicos na atividade antimalárica. [Dissertation]. Universidade Federal do Pará, 2010.

Sidhu AB, Verdier-Pinard D, Fidock DA. Chloroquine resistance in *Plasmodium falciparum* malaria parasites conferred by pfcrt mutations. Science. 2002;298(5591):210-3.

Silva ECC, *et al*. Biological activity of neosergeolide and isobrucein B (and two semi-synthetic derivatives) isolated from the Amazonian medicinal plant Picrolemma sprucei (Simaroubaceae). Mem Inst Oswaldo Cruz. 2009;104(1):48-56.

Silva LFR, *et al*. *In vitro* and *in vivo* antimalarial activity and cytotoxicity of extracts, fractions and a substance isolated from the Amazonian plant Tachia grandiflora (Gentianaceae). Mem Inst Oswaldo Cruz. 2013;108(4):501-7.

Silva THA, *et al*. Estudo de modelagem molecular de complexos ferriprotoporfirina-IX e quinolinocarbinolaminas antimaláricas: proposta de um farmacóforo. Quím Nova. 2005;28(2):244-9.

Sobrinho JL, Medeiros FPM, La Roca MF, Silva KR, Lima LNA, Neto PJR. Delineamento de alternativas terapêuticas para o tratamento da doença de Chagas. Rev Patol Tro*P.* 2007;36(2):103-18.

Tanaka JCA, *et al*. Antileishmanial activity of indole alkaloids from Aspidosperma ramiflorum. Phytomedicine. 2007;16(6):377-80.

Teófilo VHM. Estudo da resistência aos antimaláricos sulfadoxina e pirimetamina em *Plasmodium falciparum* nas ilhas de São Tomé e Príncipe: origem das mutações pontuais nos genes DHFR e DHPS. [Dissertation]. Universidade de Lisboa, 2008.

Villalobos SJ, Camargo LMA, Braga MFV, Medeiros MPS, Macêdo VO. Avaliação da eficácia do artesunato associado à tetraciclina na terapêutica da malária falciparum. Rev Soc Bras Med Tro*P.* 1997;30(3):215-22.

Weniger B, *et al*. Antiprotozoal activities of Colombian plants. J Ethnopharmacol. 2001;78(2-3):193-200.

WHO. World Malaria Report. World Health Organization, 2014.

Yamagushi MQ, Gusman GS, Vestena S. Efeito alelopático de extratos aquosos de Eucalyptus globulus Labill. e de Casearia sylvestris Sw. sobre espécies cultivadas. Semina: Ci Agrárias. 2011;32(4):1361-74.

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