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Plants of the Araceae family for malaria and related diseases: a review

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RESUMO: Plantas da família Araceae para a malária e doenças relacionadas: uma revisão.

No presente trabalho realizamos uma revisão das espécies da família Araceae usadas para tratar malária e seus sintomas. O objetivo foi revelar o grande número de espécies da família usadas no mundo, assim como seu potencial como fontes de produtos naturais antimaláricos. Foram consultadas as plataformas de busca SciFinder Scholar, Scielo, PubMed, ScienceDirect e Google books. Encontramos quarenta e três registros de 36 espécies e 23 generos de Aráceas usadas para tratar malária e seus sintomas. Os generos neotropicais Philodendron Schott e Anthurium Schott foram os melhor representados, úteis para o tratamento da malária, febres, problemas hepáticos e dores de cabeça. Folhas e tubérculos foram as partes mais utilizadas, enquanto a decocção foi o método de preparo mais comum. Os extratos de espécies de Araceae inibem o crescimento in vitro do parasito da malária humana, Plasmodium falciparum Welch, e concentrações inibitórias medianas (CI_{so}) significativas foram relatadas para extratos de guaimbê-sulcado (Rhaphidophora decursiva (Roxb.) Schott), aninga (Montrichardia linifera (Arruda) Schott), Culcasia lancifolia N.E. Br. e anchomanes do mato (Anchomanes difformis (Blume) Engl.), demonstrando o potencial antimalárico e citotóxico de extratos e subfrações. No único relato sobre os componentes antimaláricos dessa família, a neolignana polisiforina e o benzoperóxido rafidecurperoxina apresentaram forte inibição das cepas D6 e W2 de Plasmodium falciparum in vitro (Cl_{ss} = 368-540 ng/mL). Nenhum estudo sobre a atividade antimalárica in vivo em modelo animal foi realizado com espécies da família Araceae. Mais trabalhos biomonitorados pela composição química sobre a atividade antimalárica in vitro, assim como estudos in vivo, são necessários para aprofundar os conhecimentos sobre potencial antimalárico da familia.

Palavras-chave: Anthurium, Philodendron, Rhaphidophora decursiva, Plasmodium falciparum, planta antimalárica.

ABSTRACT: In the current work we performed a review of the Araceae family species traditionally used to treat malaria and its symptoms. The aim is to reveal the large number of antimalarial Araceae species used worldwide and their great unexplored potential as sources of antimalarial natural products. The SciFinder Scholar, Scielo, PubMed, ScienceDirect and Google books search engines were consulted. Forty-three records of 36 species and 23 genera of Araceae used for malaria and symptoms treatment were found. The neotropical genera Philodendron Schott and Anthurium Schott were the best represented for the use in the treatment of malaria, fevers, liver problems and headaches. Leaves and tubers were the most used parts and decoction was the most common preparation method. The extracts of Araceae species inhibit the in vitro growth of the human malaria parasite, the Plasmodium falciparum Welch, and significant median inhibitory concentrations (IC_{so}) for extracts of guaimbê-sulcado (*Rhaphidophora decursiva* (Roxb.) Schott), aninga (Montrichardia linifera (Arruda) Schott), Culcasia lancifolia N.E. Br. and forest anchomanes (Anchomanes difformis (Blume) Engl.) have been reported demonstrating the antimalarial and cytotoxicity potential of the extracts and sub-fractions. In the only report about the antimalarial components of this family, the neolignan polysyphorin and the benzoperoxide rhaphidecurperoxin presented strong in vitro inhibition of the D6 and W2 strains of Plasmodium falciparum (IC₅₀ = 368-540 ng/mL). No live study about antimalarial activity in animal models has been conducted on a species of Araceae. More bioguided chemical composition studies about the *in vitro* and also the*in vivo* antimalarial activity of the Araceae are needed in order to enhance the knowledge about the antimalarial potential of this family.

Keywords: Anthurium, Philodendron, Rhaphidophora decursiva, Plasmodium falciparum, antimalarial plant.

INTRODUCTION

Malaria is caused by protozoans of the genus *Plasmodium* that are transmitted to humans by the bite of infected, female *Anopheles* mosquitos. Malaria symptoms include fevers, headaches, vomiting and chills that appear 10-15 days after infection (WHO, 2014). Despite advances in its control and prevention in the past decade, malaria continues to be one of the world's major transmissible diseases. It is responsible for high mortality in tropical and sub-tropical regions of the planet (Muñoz et al., 2000; Adebayo & Krettli, 2011; Tsabang et al., 2011). Several factors contribute to the unacceptably high malaria morbidity and mortality rates. The major human malaria parasites Plasmodium falciparum Welch and P. vivax Grassi & Feletti are acquiring resistance to the most important drugs, the quinoline antimalarials and artemisinin derivatives. Also, many ecosystems favor the ready reproduction and propagation of malaria vectors: mosquitos of the genus Anopheles Meigen.

In tropical regions where malaria is endemic, alternative therapies based on traditionally used antimalarial plants are used (Milliken, 1997a; Willcox et al. 2004; Blair & Madrigal, 2005). New drugs introduced into the therapeutic arsenal are mostly derived from natural products (Newman & Cragg, 2012). Plants provide secondary metabolites that are useful for the treatment of protozoan diseases such as malaria (Pohlit et al., 2013), leishmaniasis, and African and American trypanosomiasis (Schmidt et al., 2012a; 2012b). In fact, traditionally-used antimalarial plants are the origin of the alkaloid quinine (isolated from species of Cinchona) and the sesquiterpene artemisinin (isolated from Artemisia annua L.) that gave rise last century to the synthetic quinoline antimalarials (chloroquine, etc.) and semi-synthetic artemisinin derivatives (sodium artesunate, etc.). These two classes are the basis of artemisinin-combined therapies (ACTs) now used worldwide. Plants also help combat malaria by providing mosquito repellent and insecticidal oils (citronella, neem, etc.), solvent extracts and isolated chemicals (chrysanthamic acid, nicotine, etc.) that have given rise to the pyrethroid, neonicotinoid and other insecticides and repellents (Pohlit et al., 2011a; 2011b).

The Araceae is one of the most botanically diverse families within the monocotolydons. It is

comprised of *ca*.105 genera and 3,300 species worldwide (Croat, 1983; Mayo et al., 1997; Croat, 1998; Ribeiro et al., 1999; Coelho, 2000; Vargas, 2002). The greatest diversity of its species is in tropical America (Croat, 1998). Brazil is among the countries having the largest variety of Araceae, numbering 30 genera and 700 species (Mayo et al.,1997).

Over 800 species of Araceae are of economic importance (ornamental, edible, medicinal). For example, about 10% of the world population consumes taro corms (rhizomes of Colocasia esculenta (L.) Schott), the most cultivated species of Araceae. It is a foodstuff and foodstock for animals (Pedralli, 2002). Most species of Araceae are ornamental plants the most important of which are from the genera Anthurium Schott, Philodendron Schott, Dieffenbachia Schott, Monstera Adams and Zantedeschia Spreng. (Pedralli, 2002). In the Amazon region, many species of Araceae are used for medicinal purposes, including the treatment of malaria and associated fevers and the most important species are from the genus *Philodendron* Schott (Milliken et al. 1997a, 1997b; Kvist et al., 2006; López et al., 2006). Species of Araceae traditionally used for malaria, fevers, headaches and liver disorders are reviewed. Relevant literature that reveals the antimalarial potential of extracts and isolated compounds, including median inhibitory concentrations (IC₅₀) against *Plasmodium falciparum*, are also reviewed.

SURVEY METHODS

This survey was performed mainly on the specialized literature published from July, 2010 until January, 2014, the first record on this topic was in 1977. Searches were performed in the Scifinder Scholar, Scielo, PubMed, Science Direct databases. In general, searches were performed using the terms Araceae antimalarial plants, Araceae fever, Araceae malaria and Araceae medicinal plants and library book collections and documents were used at the following institutions: HUAZ Herbarium of the University of Amazonia (Colombia) and the National Institute for Amazon Research (Manaus, Brazil). The data were compiled and organized in an Excel (Microsoft) spreadsheet containing information on

species name, regions where the plant is used, preparation methods, parts of the plants used and where available, information on chemical composition and pharmacological properties.

Species of araceae used in the treatment of malaria

Forty-three bibliographic sources were found on plants used to treat malaria and symptoms of malaria in the Araceae family. These works describe 38 species in 22 genera (Table 1). *Philodendron* Schott was the most cited genus with seven uses registered by communities in South American countries, including Brazil, Colombia, Equador, Peru and French Guyana (Figure 1). Antimalarial plants of the Araceae family are also found in Central America, Africa, Western Europe, Asia and Southeast Asia.

Twenty-one species of Araceae are specifically used to treat malaria and many are from South America. Thus, the aerial part of folha cheirosa, yeuri cumare (Anthurium oxycarpum Poepp.) is used by the Tacana Amerindians of Bolivia (Deharo et al., 2001) and macerates and decoctions of cipo de tara or tracua (Philodendron cf. linnaei Kunth) are indicated by the Tirios Amerindians of Suriname (Lopéz et al., 2006). Also, taioba (Xanthosoma sagittifolium (L.) Schott) is a widely cultivated tuber that is a foodstuff and foodstock for animals (Aiyeloja & Bello, 2006) and is used as an antimalarial along the Manso River in Minas Gerais, Brazil (Reskalla, 2001). In northern Brazil, an antimalarial aerial root infusion of a species of Philodendron is prepared by the native Watorik Yanomami (Milliken 1997a). In Togo, Africa, whole plant decoctions of tonflo (Pistia stratiotes L.) are used as antimalarials (Kyei et al., 2012).

Araceae species for fevers, headaches and other symptoms of malaria

Several plants have uses both in the treatment of malaria and also in the treatment of the symptoms of malaria. Thus, whole plant decoctions of *P. stratiotes* are used in Togo to treat fevers and malaria infections (Lahitte et al., 1998; Kyei et al., 2012).

Some species of Araceae are not used specifically to treat malaria, but are used to treat symptoms often associated with malaria such as fevers and headaches. So, the indigenous Wayãpi in French Guyana treat fevers with a decoction of Tapi`Ykũ (*Philodendron linnaei* Kunth) (Grenand et al., 1987). Similarly, the Tukano of southeast Colombia treat headaches by placing fresh inflorescences of madona lily (*Spathiphyllum floribundum* (Linden & André) N.E. Br.) on the sick person´s forehead (Croat, 1994). *Culcasia lancifolia*

N.E. Br. has been used by traditional healers to treat headaches, fevers and vomiting (Lekana-Douki et al., 2011).

Traditional methods of preparation of remedies

Decoction was the method of preparation most cited for antimalarial remedies based on species of Araceae. Leaves and the tubercules were the parts most often cited. Few details on the method of preparation are included in many reports (Table 1). Some methods of preparation and treatments are, however, especially interesting. Three slices of hoa pouk, also called habarala (Alocasia macrorrhizos (L.) G. Don) are boiled with 3 pieces of sugar cane and 7 unpolished rice grains in the Province of Khammouane, Laos. A non-malarious person who drinks the decoction is said to become itchy wheras someone with malaria is said to feel good and is then expected to continue treatment with the decoction (Shirayama et al., 2006). On the Pacific Coast of Colombia, the leaves of mano, also known as guaco de mata or tres dedos (Anthurium cf. tridigitatum Engl.) are macerated and rubbed on the body as a rheumatic treatment for malaria (Blair & Madrigal, 2005). Similarly, the Achuar Jívaro of Peru apply hot leaves of a species of *Monstera* on the skin to relieve liver pain (Lewis et al., 1977; cited in Croat, 1994).

Therapeutic preparations often involve species from Araceae and other families. Corazón de Jesús or Jesus's heart (*Caladium bicolor* Vent.) leaves are boiled in 1 L of water until half the volume evaporates and then lemon (*Citrus* × *Iimon* (L.) Osbeck) is added. The resulting liquid is allowed to sit to catch the morning dew and consumed on an empty stomach for 9 consecutive mornings in the treatment of inflamed liver (Blair & Madrigal, 2005).

Distribution of araceae species used in the treatment of malaria and related symptoms

Species of Araceae are used for the treatment of malaria and its symptoms throughout the tropical regions of the world (Figure 1). Poverty and lack of access to health services in many countries make these plants an important alternative for the treatment of malaria. Reports from the African nations of Ivory Coast, Kenya, Benin, Gabon and Togo have revealed eight antimalarial species belonging to the genera Amorphophallus Blume ex Decne, Anchomanes Schott, Culcasia P. Beauv., Homalomena Schott, Pistia L. and Pothos L. In the Amazon region, the largest numbers of Araceae species are used as antimalarials. The neotropical genera Philodendron Schott and Anthurium Schott are used by these Amerindian ethnic groups: Yanomami (Brazil), Tirios (Suriname), Wayapi (French Guyana), Makuna and Miraña (Colombia)

TABLE 1. Species of the Araceae family used in the treatment of malaria and malaria symptoms.

Species	Local name	People, Region where used	Use	Part used	Preparation	Source
Alocasia macrorrhizos (L.) G. Don (APGIII 2009) [Name cited: Alocasia macrorrhiza (L.) Schott]	Habarala; Hoa Pouk	Sri Lanka; Bourapar District, Khammouane Province LAO	Malaria	Tuber	Boil 3 slices with 3 parts sugar cane and 7 whole grains of rice, drink.	Edirisinghe, 1999; Shirayama et al., 2006
Amorphophallus bequaertii De Wilde	Mbandakabiri, Ikomalyakabiri	Africa	Malaria, fever	Tuber	Place fresh tuber in hot water, filter, use filtrate for rectal injection	Tshibangu et al., 2002
Anchomanes difformis(Blume) Engl.	forest anchomanes	Benin, Côte d'Ivoire	Malaria, analgesic	Leaves, Rhizomes/ Roots	-	Adjano cited in Bero et al., 2009; Almeida et al., 2001; Atindehou et al., 2004
Anthurium sp.		Ingano Macoa Amerindians, Mocoa, Putumayo, Colombia	Fever sores	Sap	Caustic sap is applied directly on fever sores	Schultes & Raffauf, 1990
Anthurium uleanum Engl.		Secoya Amerindians, Amazonia	Headaches	Roots	Decoction	Schultes & Raffauf, 1990 (based on Vickers 220); Croat, 1994
Anthurium oxycarpum Poeppig	folha cheirosa; yeuri cumare	Indigenous Tacana, Bolivia	Malaria	Aerial parts	-	Deharo et al., 2001
Anthurium cf. tridigitatum	Mano, guaco de mata, tres dedos, corrientoso, deshinchador	Costa pacífica, Colombia	Rheumatic pain caused by malaria	Leaves	Macerated leaves rubbed over whole body	Blair & Madrigal, 2005
Arisaema triphyllum (L.) Schott	-	Menomini and Iroquois tribes	Headaches	-	-	Croat, 1994
Arum maculatum L.	Wild arum	Europe	Malaria	-	-	Zwinger, 1696, cited by Adams, 2011
Caladium bicolor Vent.	Pana, corazón de Jesús	Costa pacífica, Colombia	Swollen liver, liver tonic	Leaves	Boil 5-6 leaves in 1 L of water until ½ volume evaporated. Add lemon, allow to sit in morning dew. Drink 9 mornings before eating	Blair & Madrigal, 2005
Colocasia affinis Schott		Eastern Himalayan India	Febrifuge	Leaves		Prakash, 2005
Colocasia esculenta (L.) Schott	Taro (saru)	Brazil	Malaria		-	Pravakar- Padhial, 2011

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TABLE 1. Species of the Araceae family used in the treatment of malaria and malaria symptoms.

continuação... Culcasia lancifolia Lekana-Douki, Kele, Gabon Fever N.E. Br. et al., 2011 Leaves, Cyrtosperma flowers, roots/ India Headaches Gosling, 2001 johnstonii N.E. Br. rhizome or whole plant Loreto, Perú Kvist et al., 2006 Dieffenbachia sp. Patiquina Malaria Leaves Homalomena Heated, propingna Muruts, Sabah, [presumably Nyato Chills placed on Kulip, 2003 Malaysia forehead Homalomena propinqua Schott] Splenomegaly, Homalomena rubra Leaman et al., Lung bala Kenya malaria, Roots Decoction Hassk. 1995 rubefacient Lasia spinosa (L.) Vietnam Malaria Whole plant Tran et al., 2003 Thwaites Hot leaves applied to skin Lewis et Achuar Jívaro, Liver pain over the liver al..1977. cited Monstera sp. Leaves Peru to alleviate by Croat, 1994 pain Monstera deliciosa Brandão et al., Brazil Malaria Liebm. 1985 Hot leaves applied to skin Lewis et al., Achuar Jívaro, Monstera spruceana 1977 cited by Liver Leaves over the liver (Schott) Engl. Peru Croat, 1994 to alleviate pain Infusion of Indigenous Watorik aromatic, Milliken, 1997a Malaria Philodendron sp. Roots Yanomami, Brazil aerial roots. oral Marles et Philodendron sp. Quichua, Ecuador Hepatitis al.,1988 Taracua; bejuco agraz, meonomisi Softer pendant (Makuna), Brazil, Colombia vines are Philodendron cf. pijimacu (Yukuna); (Indigenous macerated López et al. deflexum Poepp. ex Roots huncageme Fever Makuna), Ecuador, and drunk in 2006 Schott (Huaorani), u'cu cold water for Peru (Secoya), ya'i fever (Siona); chuhudaek, itininga, pantorrilla Cold poultice of the plant Philodendron placed over Lewis et al., Liver pain fragantissimum **Tropical Americas** Leaves the liver, for 1977, cited by relief Croat, 1994 (Hook.) Kunth pain. Leaves may also be heated

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TABLE 1. Species of the Araceae family used in the treatment of malaria and malaria symptoms.

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Philodendron cf. linnaei Kunth	Cipo de tara, tracua; bejuco quemador; orejita de venado, ellapapar	Brazil, Colombia, Peru, Suriname (indigenous Tirios)	Malaria	Whole plant	Decoction of macerated plant for washings	López et al., 2006
	Tapi`Ykũ	Wayapi, French Guiana	Fever associated with tabu	Leaves	Decoction for external washings	Grenand et al., 1987
Philodendron cf. uleanum Engl.	-	Miraña, Colombia	Malaria, fever	-	Infusion	Schultes & Raffauf, 1994
Pinellia ternata (Thunb.) Ten. ex Breitenb.	-	-	Intense fever	Rhizome	In mixture with <i>Artemisia</i> annua	Willcox et al., 2004
Pistia stratiotes L.	Tonflo	Maritime Region, Togo	Malaria	Whole plant	Decoction, taken orally	Koudouvo et al., 2011
Pothos ovatifolius Engl.	Aka malung	Kenya	Splenomegaly, malaria	Leaves	Poultice	Leaman et al., 1995
Rhaphidophora decursiva (Roxb.) Schott	- Guaimbê-sulcado	Brazil	Malaria	-	-	Zhang et al., 2001
Rhaphidophora pertusa (Roxb.) Schott		Manokwari, (West Papua Province), Merdey, Wasior, Indonesia	Liver diseases	Leaves	-	Lense, 2011
Scindapsus officinalis (Roxb.) Schott	Takbir gach	Bangladesh	Fever, pain	Leaves	Powdered leaves are drunk for 21 days	Rahmatullah et al., 2009
Spathiphyllum floribundum (Linden & André) N.E. Br.	Madonna Lily	Indigenous Tukano and Gwanano (near the Papurf River), Southeast Colombia	Headaches	Fresh inflorescences	Placed directly on forehead	Croat, 1994
Symplocarpus foetidus (L.) W. Salisb.	-	Micmac Indians	Headaches	Leaves	Inhalation of volatile oils from ground leaves	Lewis & Elvin 1977, cited by Croat, 1994
Xanthosoma atrovirens K. Koch & C.D. Bouché	-	-	For swollen liver after bouts of swamp or malaria fever	Leaves	Fresh leaves applied to body	Peckolt, 1893 and Uphof, 1959, cited by Croat, 1994.
Xanthosoma sagittifolium (L.) Schott	Taioba, taiá	Rio Manso-MG, Brazil	Malaria	-	-	Reskalla, 2001, cited by Pedralli, 2002
Xanthosoma undipes (K. Koch & C.D. Bouché) K. Koch	Tall elephant's ear	Costa Rica	Malaria	-	-	Chinchilla- Carmona et al., 2011

and Secoya and Tacana, and by African descendants (Pacific Coast, Colombia). Interestingly, no genus of antimalarial Araceae was reportedly used on both the African and American Continents thus providing evidence for the local distribution of the species used.

Antiplasmodial activity and toxicity of species of araceae

Extracts of plants of the Araceae exhibit antimalarial potential and also cytotoxicity. The hexane and ethanol extracts of the stems of the aquatic plant aninga (*Montrichardia linifera* (Arruda) Schott) were inactive *in vitro* against *P. falciparum* Dd2 strain. However, the dichloromethane fraction of the ethanol extract exhibited high antiplasmodial activity ($IC_{50} < 10 \mu g/mL$) and toxicity to the brine shrimp species *Artemia salina* (Amarante et al., 2011). *M. linifera* from Belém, Brazil exhibited leaf ethanol extracts with no toxicity to *A. salina* ($DL_{50} > 500 \mu g/mL$) and moderate inhibition of *P. falciparum* W2 strain ($IC_{50} = 11.7 \mu g/mL$) (Costa et al., 2009).

In other work, dichloromethane root extracts of *Culcasia lancifolia* inhibited the growth of FCB and W2 strains of *P. falciparum* ($IC_{50} = 8.9$ and

10.0 μ g/mL, respectively) and exhibited toxicity to MRC-5 cells. The root methanol extract exhibited moderate antiplasmodial activity (IC₅₀ = 25.0 and 16.0 μ g/mL against FCB and W2 strains of *P. falciparum*, respectively) (Lekana-Douki et al., 2011). Root extracts of forest anchomanes (*Anchomanes difformis* (Blume) Engl.) failed to inhibit (IC₅₀ > 100 μ g/mL) the 3D7 strain of *P. falciparum* and were cytotoxic (Bero et al. 2009).

Water and ethanol extracts of the leaves of water lettuce (*Pistia stratiotes* L.) were apparently well-tolerated and exhibited antiarthritic and antipyretic effects in formalin-induced arthritis and LPS-induced fever in Sprague-Dawley rats (Kyei et al., 2012). On the other hand, the sap of *Caladium bicolor* is toxic and can even produce asphyxia (Flores et al. 2001). Isolation of the antiplasmodial and cytotoxic components from the extracts of plants of the Araceae is necessary for a better understanding of the medicinal potential of this family.

Chemistry of antimalarial species of araceae

Oxalic acid is frequently deposited as

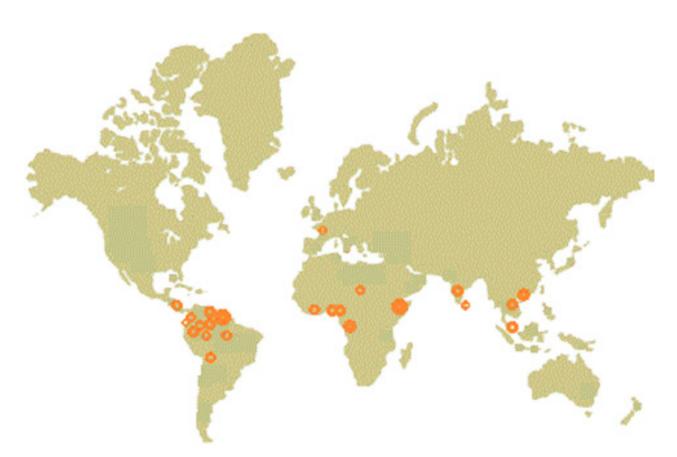


FIGURE 1. World locations where species of Araceae are used to treat malaria and its symptoms. Note: An orange colored point indicates where an Araceae species has been reported as being used to treat malaria or its symptoms. This maps was generated based on the countries represented in Table 1.

crystals of calcium oxalate (Figure 2) in plants of the Araceae and is responsible for the toxicity of some genera (e.g. Dieffenbachia Schott). A large variety of anthocyanines have been identified in the flowers, fruit, leaves and leaf stems of 59 species of Araceae (Williams et al., 1981). The most commonly occurring pigment in these species was cyanidin 3-O-rutinoside, however, pelargonidin 3-rutinoside is also regularly found in the Araceae.

Leaves and branches of guaimbê-sulcado (Rhaphidophora decursiva (Roxb.) Schott) were extracted with methanol. The dry extract was defatted with hexanes. The chloroform soluble fraction of this extract was evaporated and chromatographed on silica gel using an acetone-chloroform gradient. Further normal phase, flash or reverse-phase chromatographies on the resulting fractions provided 14 compounds. Six of these compounds exhibited in vitro antiplasmodial activity (Zhang et al., 2001). The most active against P. falciparum D6 and W2 strains were the neolignan threo-polysyphorin (IC_{so}= 404 and 368 ng/mL, respectively; Figure 2) and the benzoperoxide rhaphidecurperoxin (IC_{50} = 540 and 420 ng/mL, respectively; Figure 2). The neolignans rhaphidecursinol A and B and lignans grandisin and epigrandisin were less active. To our knowledge, the above is the only report on antimalarial components from the Araceae.

FINAL REMARKS

A number of South American Araceae species are traditionally used in the treatment of malaria and its symptoms. Despite the *in vitro* inhibitory activity of extracts, fractions and isolated constituents against the human malaria parasite *Plasmodium falciparum* we found no *in vivo* antimalarial study in animal models for this family. Studies on the *in vitro* and *in vivo* antimalarial activity are needed to further explore the antimalarial potential of the Araceae.

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FIGURE 2. Antiplasmodial chemical constituents of Rhaphidophora decursiva.

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