CHAPTER 6

Development of Antimalarial and Antileishmanial Drugs from Amazonian Biodiversity

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Abstract: The search for therapeutic alternatives for the treatment of malaria and leishmaniasis is particularly important, given the increase in parasitic resistance to available drugs, as well as the high toxicity of those drugs. In this context, the Amazon region can make an important contribution through its high biodiversity of plants, many of which are informally used by local populations for the treatment of malaria, and leishmaniasis. This chapter aims to describe the main Amazonian species used to treat malaria and leishmaniasis in Brazilian folk medicine, relating ethnobotanical results to chemical studies, evaluation of activities, and toxicity. Different studies report the treatment of malaria with plants, with the most cited species being *Aspidosperma nitidum* Benth. (Apocynaceae); *Geissospermum sericeum* (Sagot.) Benth & Hook (Apocynaceae); *Euterpe precatoria* Mart. (Arecaceae); *Persea americana* Mill (Lauraceae); *Bertholletia excelsa* Bonpl (Lecythidaceae); *Portulaca pilosa* L. (Portulaceae); *Ampelozizyphus amazonicus* Ducke (Rhamnaceae). Additionally, traditional Amazonian populations use plants for the treatment of wounds, a clinical aspect associated with leishmaniasis, with the most cited genus being *Copaiba* and *Jatropha*. The antileishmanial activity of copaiba oil has been demonstrated, and it seems that this activity is related to terpenes. Another genus that deserves attention is *Musa*, used for the treatment of severe wounds. The leishmanicidal activity of triterpenes isolated from *Musa paradisiaca* and its anacardic acid and synthetic derivatives, which have been used against *Leishmania infantum chagasi*, was also tested. In summary, several isolated compounds of plants used in traditional Amazonian medicine are promising as antimalarial and antileishmanial drugs.

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INTRODUCTION

The recognition of the environmental limits of the modern development model has imposed the need for new forms of global governance upon the planetary environment, requiring proposals for sustainable development that oppose the worsening of environmental degradation and biodiversity loss [1].

In Brazil, the Amazon region and its people have been threatened by short-sighted, profit-driven economic interests, driving the increase in deforestation in an increasingly chaotic way. According to the Real-Time Legal Amazon Deforestation Detection System (DETER), deforestation alerts were recorded in an area of 4,219.3 square kilometers in 2018, and in 2019, 9,165.6 square kilometers of forest were deforested – more than double the area recorded in the previous year.

This accelerated deforestation will probably result in the extinction of many plant species, which will have negative impacts on the culture of the use of medicinal plants by the peoples of the Amazon. In 2005, it was estimated that about 180 indigenous peoples (approximately 208,000 individuals) lived in the Amazon, in addition to 357 remaining *quilombola* (maroon) communities and thousands of rubber tapper, riverside or babassu communities [2]. In fact, in addition to its biodiversity in terms of plant and animal species, due to the different ethnicities of its peoples, the Amazon also displays a wide spectrum of cultural diversity.

As a result of this fact, another important issue arises, which is the understanding of the process of occupation of the Amazon and the impact on the health of indigenous peoples and people who settled in the region. In this sense, this process stimulated the occurrence of several epidemics and created an asymmetry in the access to health services. For example, in metropolises, such as Belém and Manaus, health services are structured, while in remote locations within the forest, due to the great difficulty of access, the only therapeutic alternative available to treat diseases has often been the use of medicinal plants [3].

Among these diseases, malaria has been affecting the Amazonian people for centuries. A study conducted in 1885 showed that the Amazon was already plagued by the disease, and the possible explanation for this fact results from the intense migration that occurred to this region in the nineteenth century, resulting from rubber extraction activities and the construction of the Madeira-Mamoré railroad. In this scenario, many immigrants ended up dying from malaria – which

is considered the second major epidemic witnessed by Osvaldo Cruz and Carlos Chagas [4]. At the same time, as opposed to the high mortality experienced by immigrants, the riverside populations survived in this hostile environment due to their ancient knowledge of many native and exotic plant species to treat malaria and its symptoms, and this medicinal information was orally transmitted from one generation to another [5].

Deforestation in the Amazon is still a serious medical and public health problem, as it creates conditions for the development of several tropical endemic diseases, such as American Tegumentary Leishmaniasis (ATL). During deforestation, the rodent population migrates to other areas in search of natural shelters, and phlebotomic fauna, which previously engaged in hematophagy using these small mammals, begin to seek out humans for this purpose [6], thus transmitting the etiological agents of various diseases, such as malaria and leishmaniasis, among others. In this context, plant species that have historically been used in Amazonian folk medicine as healing agents and for wound treatment have shown promise for the treatment of tegumentary leishmaniasis.

This chapter aims to describe the main Amazonian species that are used in folk medicine for the treatment of malaria and leishmaniasis, relating ethnobotanical results to chemical studies, evaluation of activities, and toxicity. Initially, a search was performed for ethnobotanical studies available in different databases, and species with claims of use for malaria and leishmaniasis, for wound treatment, or as healing agents were selected.

Medicinal Plants used for the Treatment of Malaria and Leishmaniasis

Ethnobotanical studies have already been conducted in some regions of the Amazon, but in other regions, there is a lack of scientific studies aimed at describing the uses of plants for medicinal purposes. A range of factors contributes to create difficulties in conducting such studies, such as the large dimension of the territory of the Brazilian Amazon, and difficulties in moving across certain regions due to the lack of connecting roads, implying the need for air transport associated with river transport, which greatly increases the cost of a study. Another important factor is the reduced number of researchers in the ethnobotany field that reside in this region, in addition to scarce funding for these studies because of public policies related to research funding in Brazil.

Notwithstanding, among the studies already published, there are reports of popular use of plants for the treatment of malaria for more than 100 plant species of the region. The most cited families were Apocynaceae, Araceae, Arecaceae, Euphobiaceae, Fabaceae, Menispermaceae, Rhamnaceae and Simaroubacea. Table **1** summarizes the species that were mentioned in the available literature,

with the species with the highest number of citations being *Aspidosperma nitidum*; *Geissospermum sericeum*; *Euterpe precatoria*; *Persea americana; Bertholletia excelsa; Portulaca pilosa* and *Ampelozizyphus amazonicus*.

In addition to *A. nitidum* (Fig. **1**), antimalarial property has been attributed to *A. excelsum* [7, 8] (Table **1**), and the most recent botanical study considers the species *A. nitidum* a synonym of *A. excelsum* [9]. Other species of *Aspidosperma* are used for the treatment of malaria in the Amazon region [10 - 12] (Table **1**) and in other regions of Brazil [13, 14]. Another genus belonging to the family Apocynaceae, widely used in traditional Brazilian medicine for the treatment of malaria is *Geissospermum*, in particular the species *G. sericeum* [15 - 18] and *G. vellosii* [19, 20], both being used in the form of infusions of their barks for this medicinal purpose.

Fig. (1). *Aspidosperma nitidum* (courtesy of Dr. Pedro Pompei Filizzola Oliva and Museu Paraense Emilio Goeldi).

Euterpe precatoria (Fig. **2**), known in Brazil as *açaizeiro*, *açaí-do-amazonas* or *açaí-solitário*, is a species native to the Amazon, with great importance as an Amazonian food source and for popular medicine. In addition to the claim of use for the treatment of malaria [11, 12, 14] (Table **1**), this species is used to treat muscle pain, chest pain, snake bites, and in the treatment of flu, along with some very bizarre claims, such as for the hair to grow well and very black, and to prevent pregnant women from losing hair [21].

Likewise, several medicinal properties are attributed to *Persea americana* (Fig. **3**) - known as the avocado tree - from which teas and macerations are made from its leaves and seeds [22]. Ethnobotanical studies show that in Central America, the infusion of toasted leaves from *P. americana* is commonly used for malaria treatment [14].

Fig. (2). *Euterpe precatoria Mart.* (courtesy of Dr. Pedro Pompei Filizzola Oliva and Museu Paraense Emilio Goeldi).

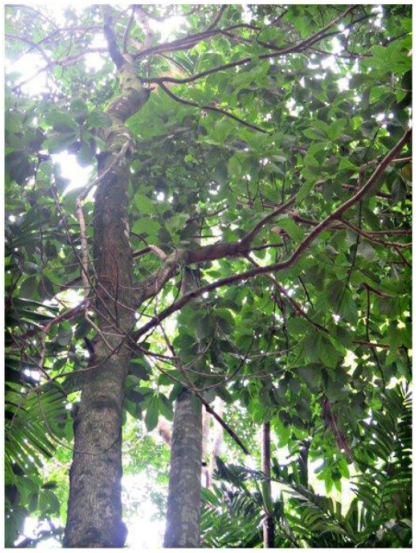

Fig. (3). *Persea americana* (courtesy of Dr. Pedro Pompei Filizzola Oliva and Museu Paraense Emilio Goeldi).

Bertholletia excelsa (Fig. **4**), known as the Brazil nut tree, is used to make tea and juices for topical use and macerations for internal use from its stem barks and fruits [22]. A study conducted in Acre reports the use of tea from this plant for the treatment of malaria [23], while in Manaus, the use of tea from the leaves has been reported [24]. In the Amazon region, decoctions of the bark of the species are also used for this purpose [14].

Fig. (4). *Bertholletia excelsa* Bonpl (courtesy of Ms. Paula Maria Correa de Oliveira and Dr. Marlia Regina Coelho Ferreira).

Ampelozizyphus amazonicus is popularly known as *saracuramirá* and is widely distributed throughout South America, being found in Amazonian territories of Brazil, Venezuela, Colombia, Peru, and Ecuador [25]. In the Amazon region,

decoction obtained from the root of *saracuramirá* is used in malaria prevention [26, 27] and treatment [28 - 30]. *In vivo* and *in vitro* antimalarial activity has already been demonstrated against the sporozoite form of *Plasmodium* [31], supporting the popular claim made for this species in the Amazon region.

Table 1. Ethnobotanical studies of plants popularly used for the treatment of malaria

Family	Species	References
Annonaceae	*Guatteria guianensis* (Aubl.)	Kffuri *et al.*, 2016 [11] Kffuri *et al.*, 2019 [12]
Apocynaceae	*Aspidosperma excelsum* Benth.	Vásquez *et al.*, 2014 [22]
	Aspidosperma nitidum Benth.	Altschul, 1973 [32] Brandão *et al.*, 2020 [33] Milliken & Albert, 1996 [34] Milliken, 1997 [18] Scudeller *et al.*, 2009 [35] Tomchinsky *et al.*, 2017 [14]
	Aspidosperma rigidum Rusby	Oliveira *et al.*, 2011 [10]
	Aspidosperma schultesii Woodson	Kffuri *et al.*, 2016 [11] Kffuri *et al.*, 2019 [12]
	Aspidosperma spp.	Killeen *et al.*, 1993 [36] Veiga & Scudeller, 2015 [13] Tomchinsky *et al.*, 2017 [14]
	Geissospermum argentum Woodson	Oliveira *et al.*, 2011 [10]
	Geissospermum sericeum Sagot	Le Cointe, 1947 [37] Correa, 1975 [15] Cruz & da Silva, 1979 [16] Balbach, 1980 [17] Milliken, 1997 [18]
	Himatanthus articulatus Vahl.	Milliken, 1997 [18]

Family	Species	References
Araceae	*Heteropsis* sp., *H. tenuispadix* G.S. Bunting	Frausin *et al.*, 2015 [38] Kffuri *et al.*, 2016 [11]
	Attalea maripa Aubl.	Kffuri *et al.*, 2016 [11] Kffuri *et al.*, 2019 [12]
	Euterpe catinga Wallace	Kffuri *et al.*, 2016 [11] Kffuri *et al.*, 2019 [12]
	Euterpe oleracea Mart.	Brandão *et al.*, 1992 [39] Vigneron *et al.*, 2005 [40] Tomchinsky *et al.*, 2017 [14]
	Euterpe precatoria Mart.	Deharo *et al.*, 2001 [41] Hidalgo, 2003 [42] Bertani *et al.*, 2005 [43] Balslev *et al.*, 2008 [44] Hajdu & Hohmann, 2012 [45] Vásquez *et al.*, 2014 [22] Frausin *et al.*, 2015 [38] Veiga & Scudeller, 2015 [13] Kffuri *et al.*, 2016 [11] Tomchinsky *et al.*, 2017 [14] Kffuri *et al.*, 2019 [12]
Arecaceae	*Iriartea deltoidea* Ruiz & Pav.	Kffuri *et al.*, 2016 [11] Kffuri *et al.*, 2019 [12]
	Vernonia condensata Baker	Milliken, 1997 [18] de Oliveira *et al.*, 2016 [46]
Bignoniaceae	*Jacaranda copaia* Aubl.	Kffuri *et al.*, 2016 [11] Kffuri *et al.*, 2019 [12]
Caricaceae	*Carica papaya* L.	Milliken, 1997 [18] de Oliveira *et al.*, 2016 [46]
Celastraceae	*Maytenus guianensis* Klotzch ex Reissek	Oliveira *et al.*, 2015 [47] Veiga & Scudeller, 2015 [13] Cajaiba *et al.*, 2016 [48]
Compositae	*Acanthospermum australe* Loefl.	Braga, 1960 [49] Correa, 1975 [15] Cruz & da Silva, 1979 [16]
Convolvulaceae	*Bonamia ferruginea* Choisy	Paes & Mendonça, 2008 [50] Veiga & Scudeller, 2015 [13]
Costaceae	*Costus spicatus* Jacq.	Hidalgo, 2003 [42] de Oliveira *et al.*, 2016 [46]
Cucurbitaceae	*Momordica charantia* L.	Milliken, 1997 [18] de Oliveira *et al.*, 2016 [46]

Family	Species	References
Euphorbiaceae	*Croton cajucara* Benth.	Milliken, 1997 [18] Veiga & Scudeller, 2015 [13]
	Jatropha gossypiifolia L.	Coutinho *et al.*, 2002 [51] Vásquez *et al.*, 2014 [22]
Fabaceae	*Hymenaea courbaril* L.	Oliveira *et al.*, 2015 [47] Vásquez *et al.*, 2014 [22]
	Monopteryx uaucu Spruce ex Benth.	Kffuri *et al.*, 2016 [11] Kffuri *et al.*, 2019 [12]
	Ormosia discolor Spruce ex Benth.	Kffuri *et al.*, 2016 [11] Kffuri *et al.*, 2019 [12]
	Swartzia argentea Spruce ex Benth.	Kffuri *et al.*, 2016 [11] Kffuri *et al.*, 2019 [12]
Lauraceae	*Persea americana* Mill.	Milliken, 1997 [18] Hidalgo, 2003 [42] Blair & Madrigal, 2005 [52] Coelho-Ferreira, 2009 [53] Oliveira, 2011 [10] Tomchinsky *et al.*, 2017 [14]
Lecythidaceae	*Bertholletia excelsa* Bonpl.	Brandão *et al.*, 1992 [39] Hidalgo, 2003 [42] Coelho-Ferreira, 2009 [53] Tomchinsky *et al.*, 2017 [14]
Menispermaceae	*Abuta* sp.	Frausin *et al.*, 2015 [38] Arevalo, 1994 [54]
Menispermaceae	*Cissampelos ovalifolia* DC.	Milliken, 1997 [18] de Oliveira *et al.*, 2016 [46]
Nyctaginaceae	*Boerhavia hirsuta* Willd.	Delorme & Miola, 1979 [55] Neves, 1980 [56]
Piperaceae	*Piper* sp., *Piper cernuum* Vell.	Kffuri *et al.*, 2016 [11]
Portulaceae	*Portulaca pilosa*	Neves, 1980 [56] da Silva *et al.*, 1998 [57] Souza, 2010 [58] Veiga & Scudeller, 2015 [13] Ferreira *et al.*, 2015 [23] Pinheiro, 2018 [24]

Family	Species	References
Rhamnaceae	*Ampelozizyphus amazonicus* Ducke	Neves, 1980 [56] Paulino-Filho, 1979 [59] Brandão *et al.*, 1992 [39] Milliken, 1997 [18] Hidalgo, 2003 [42] Oliveira *et al.*, 2011 [10] Vásquez *et al.*, 2014 [22] Kffuri *et al.*, 2016 [11] Tomchinsky *et al.*, 2017 [14] Kffuri *et al.*, 2019 [12]
Rubiaceae	*Sabicea amazonenses* Wernham	Kffuri *et al.*, 2016 [11] Kffuri *et al.*, 2019 [12]
Simaroubaceae	*Simaba cedron* Planch.	Altschul, 1973 [32] Oliveira *et al.*, 2011 [10] Frausin *et al.*, 2015 [38]
Strelitziaceae	*Phenakospermum guianensis* Rich.	Kffuri *et al.*, 2016 [11] Kffuri *et al.*, 2019 [12]
Verbenaceae	*Stachytarpheta cayennensis* Rich.	Milliken, 1997 [18] Oliveira *et al.*, 2003 [60]

Leishmaniasis is a parasitic disease caused by *Leishmania*, which infects the vertebrate host through the bite of female vectors of the genera *Lutzomyia* [61, 62]. Different studies conducted in the Amazon region have demonstrated the popular use of plants in the treatment of wounds and leishmaniasis. Table **2** summarizes the species cited in the studies conducted in the Amazon region.

Portulaca pilosa (Fig. **5**) and *Aspidosperma* (Fig. **1**) were also cited for the treatment of malaria and wound healing [22, 23, 63, 64] (Tables **1**-**2**, respectively). *Copaíba* oil, obtained from different species of *Copaifera* (Fig. **6**), is widely used for wound treatment and healing [65 - 67]; there have also been reports of the use of bark and leaves to produce the healing effect [68] (Table **2**).

Another genus with a popular claim of wound healing is *Jatropha* (Fig. **7**; Table **2**), and several studies have evaluated its healing effects [69 - 72]. In addition to medicinal use, this species has ornamental utility [73]. Preparations of *J. gossypiifolia* are also used in religious rituals [74, 75] and for the construction of living fences or hedges that are used against the spreading of fires [73, 76]. Other uses reported for this species include its insecticide action [77], and the use of seed oil in the preparation of paints, soaps, lubricants, and fuel for diesel engines and for lighting [73, 76].

Fig. (5). *Portulaca pilosa* (courtesy of Dr. Pedro Glecio Costa Lima and Dr. Marlia Regina Coelho Ferreira).

Fig. (6). *Copaifera reticulada* (courtesy of Dr. Pedro Pompei Filizzola Oliva and Museu Paraense Emilio Goeldi).

Fig. (7). *Jatropha curcas* (courtesy of Dr. Pedro Pompei Filizzola Oliva and Museu Paraense Emilio Goeldi).

Musa acuminata and *M. paradisiaca* (Fig. **8**) are species of banana trees that have several claims of popular use, including as a sedative for toothache, healing of surgical wounds from tooth extraction, gastric ulcers, hypoglycemia, as an antidote to snake bites, and diarrhea, among others [78]. The parts of the plant that can be used for medicinal purposes are flowers, roots, fruits, and latex, and are applied topically or internally.

Table 2. Ethnobotanical studies of plants used for the popular treatment of wounds and leishmaniasis

Family	Species	References
Anacardiaceae	*Schinus terebinthifolius* Raddi.	Silva *et al.*, 2011 [79]
Apocynaceae	*Aspidosperma excelsum* Benth	Vásquez *et al.*, 2014 [22]

Family	Species	References
Bignoniaceae	*Crescentia cujete* var.	Sarquis *et al.*, 2019 [80]
	Fridericia chica Bonpl.	Vásquez *et al.*, 2014 [22]
Boraginaceae	*Symphytum officinale* L.	Cajaiba *et al.*, 2016 [48]
Celastraceae	*Maytenus guianensis* Klotzch ex Reissek	de Oliveira *et al.*, 2015 [47] Veiga & Scudeller, 2015 [13] Cajaiba *et al.*, 2016 [48]
Chenopodiaceae	*Chenopodium ambrosioides* L.	Cajaiba *et al.*, 2016 [48] Scudeller *et al.*, 2009 [35]
Fabaceae	*Copaifera* sp.	Santana *et al.*, 2014 [66] Cavalcante *et al.*, 2017 [68]
	Copaifera langsdorffii	Cavalcante *et al.*, 2017 [68]
	Copaifera marti	Roman & Santos, 2006 [65]
	Copaifera pubiflora Benth.	Oliveira *et al.*, 2019 [67]
Euphorbiaceae	*Jatropha gossypiifolia* L.	Coutinho *et al.*, 2002 [51] Matos, 2004 [73] Aquino *et al.*, 2006 [69] Maia *et al.*, 2006 [70] Santos *et al.*, 2006 [71] Vale *et al.*, 2006 [72] Vásquez *et al.*, 2014 [22]
	Jatropha curcas L.	Vásquez *et al.*, 2014 [22] Leão *et al.*, 2007 [81]
Fabaceae	*Libidibia ferrea* Mart. ex Tul.	Sarquis *et al.*, 2019 [80]
	Manihot esculenta Crantz	Vásquez *et al.*, 2014 [22]
Lamiaceae	*Plectranthus barbatus* Andrews	Vásquez *et al.*, 2014 [22]
Meliaceae	*Carapa guianensis* Aubl.	Cajaiba *et al.*, 2016 [48]
Musaceae	*Musa acuminata* Colla	Vásquez *et al.*, 2014 [22]
	Musa paradisiaca L.	Vásquez *et al.*, 2014 [22]
Myrtacea	*Eugenia punicifolia* Kunth	Vásquez *et al.*, 2014 [22]
Plantaginacea	*Scoparia dulcis* L.	Vásquez *et al.*, 2014 [22]
Portulaceae	*Portulaca pilosa*	Da silva *et al.*, 1998 [57] Mors *et al.*, 2000 [82] Revilla, 2002 [83] Alves *et al.*, 2006 [84] Barata *et al.*, 2009 [85] Oak, 2015 [86] Fereira *et al.*, 2015 [23] Nunes, 2016 [63] Barros *et al.*, 2017 [64]

Family	Species	References
Simaroubaceae	*Quassia amara* L.	Botsaris, 2007 [87]
	Simarouba amara Aubl.	Botsaris, 2007 [87]

Fig. (8). *Musa parasidiaca* (courtesy of Dr. Pedro Pompei Filizzola Oliva and Museu Paraense Emilio Goeldi).

Chemical Studies and Evaluation of Biological Activities of Species that are more Frequently Cited in the Literature

Several studies have shown that different plant species are used in traditional medicine for the treatment of malaria and leishmaniasis. However, some species deserve special attention, and among these are *Portulaca pilosa*, *Aspidosperma* and Apocynaceae (*Geissospermum* and *Himatanthus*).

Phytochemical studies conducted from the ethanol extract of the aerial parts of *P. pilosa* show the isolation of diterpenes, such as pilosanone A and C (Fig. **9**) [88]. In another study, from the ethyl acetate fraction of the roots of *P. pilosa,* three clerodane diterpenes were isolated: pilosanol A, B and C (Fig. **9**) [89].

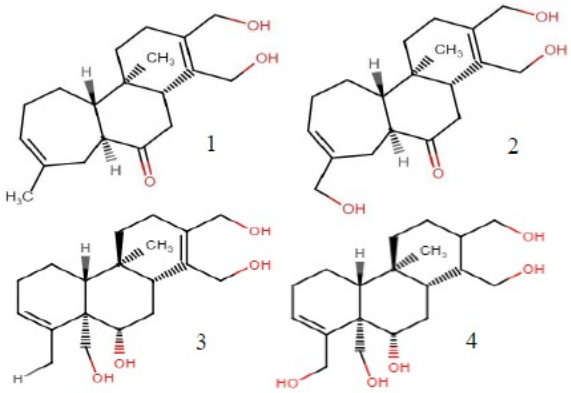

Fig. (9). Diterpenes isolated from *Portulaca pilosa*. ***Legend****: (1) Pilosanone A; (2) Pilosanone B; (3) Pilosanol A; (4) Pilosanol B.*

The ethanol extract obtained from the aerial parts of *P. pilosa* underwent a study *in vitro* against promastigote and amastigote forms of *Leishmania amazonensis*, but no promising activity has been demonstrated [90]. Another study evaluated the healing activity in surgical lesions of Wistar rats using gel and propylene glycol extracts from *P. pilosa* (150mg/kg), and the histological analysis of the lesions showed that the extract modulated the inflammatory response of the tissue, stimulated angiogenesis and fibroblast proliferation. In groups treated with *P. pilosa,* healing was better than the negative control, and a better pattern of organization of the epidermis and dermis was observed, in a mild inflammatory process, with fibroblast proliferation and increased collagen fiber formation. The topical anti-inflammatory activity is probably related to gallic acid, the phytochemical marker of this species [64].

An *in vitro* study carried out against *Plasmodium* showed that the ethanol extract obtained from aerial parts of *P. pilosa* was active and presented low cytotoxicity to macrophages, and high selectivity was observed. Further studies need to be conducted to verify antimalarial activity using *in vivo* models and to identify which compound is involved in this activity [33].

Another important species, *Aspidosperma nitidum (*synonym *A. excelsum)*, was subjected to chemical studies, and the following alkaloids were isolated: 11-methoxy tubotaiwine (Fig. **10**-1), compactinervine (Fig. **10**-2), N-acetyl aspidospermidine (Fig. **10**-3), O-desmethyl-aspidospermidine (Fig. **10**-4), aricine (Fig. **10**-5), yohimbine (Fig. 1**0**-6), tetrahydrosecamine (Fig. **10**-7), 16-desmethoxy-carboxyl-tetrahydrosecamine (Fig. **10**-8), didesmethoxy-carboxyl-tetrahydrosecamine (Fig. **10**-9), O-acetyl yohimbine (Fig. **10**-10) yohimbine, ocryl fuanine [91] (Fig. **10**-11), excelsinine [92] (Fig. **10**-12), 10-

methoxygeissoschizol (Fig. **10**-13), 10-methoxyyohimbine (Fig. **10**-14), and 10-methoxy-4-methylgeissoschizol [93] (Fig. **10**-15). O-acetyl yohimbine and 10-methoxycorynanthine (Fig. **10**-16) were isolated from the root bark of *A. excelsum* [94].

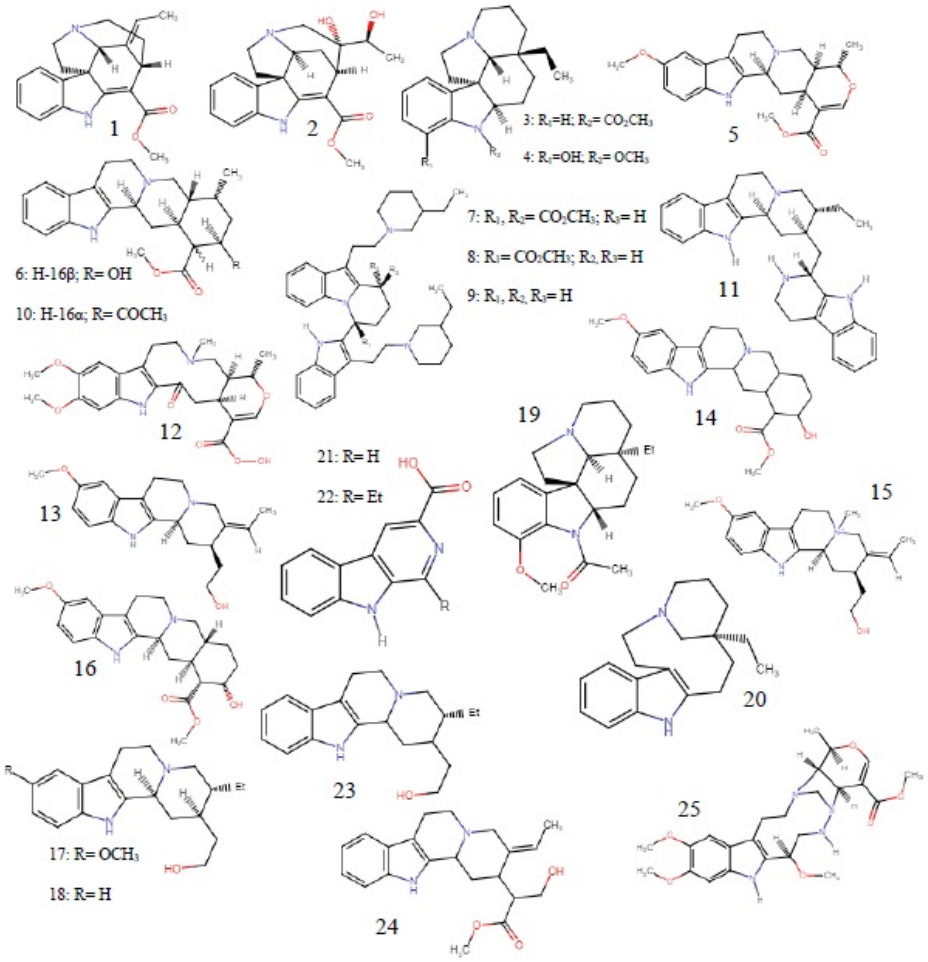

Fig. (10). Chemical structure of compounds occurring in *Aspidosperma excelsum* and *Aspidosperma nitidum.* **Legend:** 11-methoxytubotaiwine (1), compactinervine (2), N-acetyl aspidospermidine (3), O-desmethyl aspidospermidine (4), aricine (5), yohimbine (6), tetrahydrosecamine (7), 16-desmemethoxy-carboxyl-tetrahydrosecamine (8), didesmethoxy-carboxyl tetrahydrosecamine (9), O-acetyl yohimbine (10), ocryl fuanine (11), excelsinine (12), 10- methoxygeissoschizol (13), 10-methoxyyohimbine (14), 10-methoxy-4-methylgeissoschizol (15), 10-methoxycorynanthine (16), 10-methoxy-dihydro-corynantheol (17), corynantheol (18), aspidospermine (19), quebrachamine (20), carboxylic harman acid (21), 3-carboxylic ethylharman (22), dihydrocorynantheol (23), dehydrositsiriquine (24), and braznitidumine (25).

Other phytochemical studies of *A. nitidum* have also isolated 10-methoxy-

dihydro-corynantheol (Fig. **10**-17), corynantheol [95] (Fig. **10**-18), aspidospermine (Fig. **10**-19), quebrachamine (Fig. **10**-20), yohimbine [96] (Fig. **10**-6), carboxylic harman acid (Fig. **10**-21), 3- carboxylic ethylharman [97] (Fig. **10**-22), dihydrocorynantheol (Fig. **10**-23), dehydrositsiriquine [98] (Fig. **10**-24), and braznitidumine [98] (Fig. **10**-25).

The antiplasmodial activity of the ethanol extract obtained from the bark of *A. nitidum* proved to be active against clone of *Plasmodium falciparum* resistant to chloroquine and fractionation led to the obtainment of a more active fraction (fraction of alkaloids). In all doses used (125-500 mg/kg), on the 5th day of infection, a significant reduction in parasitemia was observed in mice infected with *Plasmodium berghei* [99].

In relation to leishmanicidal activity, the ethanol extract obtained from barks of *A. nitidum* proved to be active against promastigote forms of *L. amazonensis*, but the fraction of alkaloids seems to be less promising. This activity was suggested to be related to the synergism between alkaloids and other compounds presented in this species [100].

Another species widely used in the Brazilian Amazon is *Geissospermum sericeum*. In the phytochemical prospection of the ethanol extract obtained from *G. sericeum*, alkaloids, flavonoids, tannins and saponin were detected [101]. From the extracts obtained from the stem barks of *G. sericeum,* the following alkaloids were isolated: geissospermine [102] (Fig. **11**-1), geissoschizoline (Fig. **11**-2), geissoschizoline N4-oxide (Fig. **11**-3), 1,2 dihydrogeissoschizoline (Fig. **11**-4), and flavopereirine [103] (Fig. **11**-5).

The aqueous extract obtained from stem barks of *G. sericeum* proved inactive against *Plasmodium berghei* [104], but the hydromethanic extract and isolated alkaloids were active in an *in vitro* study against clones of *P. falciparum* resistant to chloroquine (K1), with the alkaloid flavopereirine being considered more promising [103]. Similarly, flavopereirine was very promising against *L. amazonensis*, as well as was the fraction of alkaloids [105].

Antimalarial and antileishmanial activities of *A. nitidum* and *G. sericeum* have been related to alkaloids. Some isolated alkaloids present in these species have already undergone *in vitro* studies to evaluate antiparasitic activities (Table **3**).

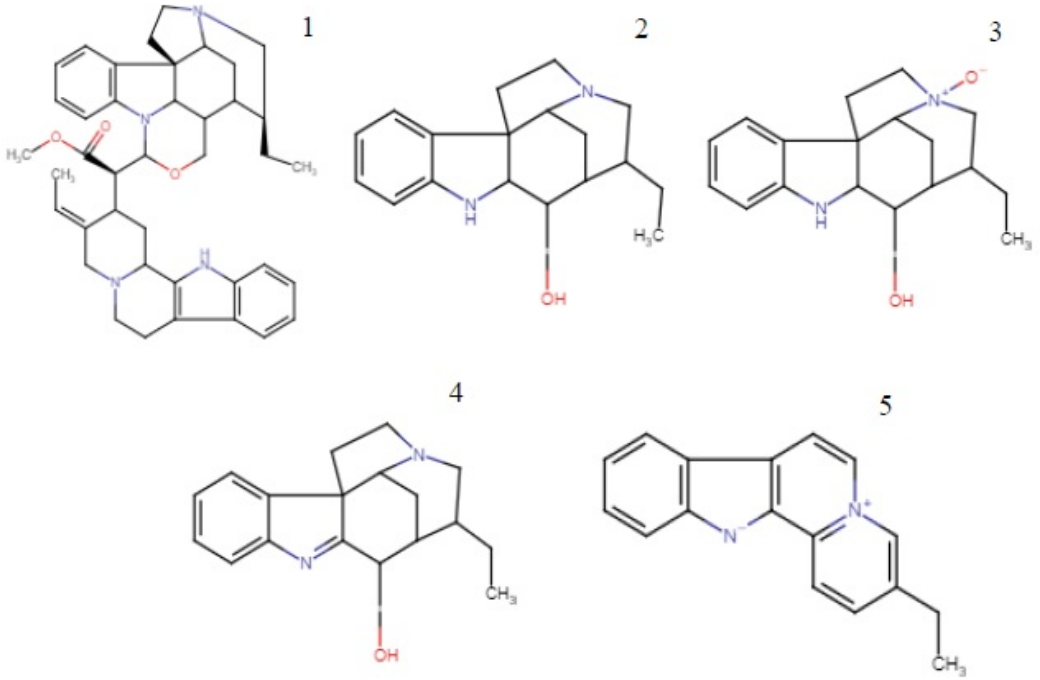

Fig. (11). Chemical structure of compounds isolated from *Geissospermum sericeum.*
Legend: geissospermine **(1)**, geissoschizoline **(2)**, geissoschizoline N4-oxide **(3)**; 1,2 dihydrogeissoschizoline **(4)**, and flavopereirine **(5)**.

Table 3. Antimalarial and antileishmanial activities of alkaloids isolated from *Aspidosperma nitidum* and *Geissospermum sericeum*

Alkaloids	Antimalarial	Antileishmania	References
O-demethylaspidospermidine	Active against *P. falciparum* chloroquine-resistant	Active against *L. infantum* (CI_{50} = 7.7 0 µg/mL)	Reina *et al.*, 2012 [106]
Aricine	Active against *P. falciparum* chloroquine-resistant (IC_{50} 0.69 µM)	NE	Passemar *et al.*, 2011 [107]
Yohimbine	Active (W2, IC_{50} 14.35 ± 2.77)	NE	do Nascimento *et al.*, 2019 [108]
Aspidospermine	Active against *P. falciparum* chloroquine-resistant and -sensitive (IC_{50} 3.8 ± 0.7 and 4.6 ± 0.5 µM, respectively)	NE	Mitaine-Offer *et al.*, 2002 [109]
Quebrachamine	NE	NE	Saxton, 1996 [110]
Carboxylic harman acid	Inactive	NE	Coutinho *et al.*, 2013 [106]

Alkaloids	Antimalarial	Antileishmania	References
Braznitidumine	Active against *P. falciparum* (IC_{50} 8.3±1.6μg/mL)	NE	Coutinho *et al.*, 2013 [8]
Geissospermine	Active against *P. falciparum* (D10) sensitive to chloroquine (IC_{50} 5.02 ± 0.74 μM)	NE	Mbeunkui *et al.*, 2012 [19]
Geissoschizoline	Inactive	NE	Steele *et al.*, 2002 [103]
Geissoschizoline N4 -oxide	Inactive	NE	Steele *et al.*, 2002 [103]
1,2-de-hydrogeissoschizoline	Inactive against K1 and strains of *P. falciparum* T9-96 (IC_{50} 27.26 ± 10.9 and 35.37 ± 2.36 μM, respectively)	NE	Steele *et al.*, 2002 [103]
Flavopereirine	Active against *P. falciparum*	Active against *L. amazonensis*	Steele *et al.*, 2002 [103] Silva *et al.*, 2019 [105]

Legend: NE- unstudied; IC_{50}- inhibitory concentration 50%; Clones of *Plasmodium falciparum*: W2- resistant to chloroquine; K1- chloroquine resistant D10- chloroquine-sensitive; *L. infantum-Leishmania infantum.*

Nevertheless, it is observed that most antiparasitic studies of alkaloids isolated from *A. nitidum* and *G. sericeum* were evaluated only against malaria (Table **3**). Only O-demethylaspidospermidine and flavopereirine alkaloids were evaluated against *Leishmania*, where the former proved to be active against *L. chagasi* [106], and the latter against *L. amazonensis* [105].

As for antimalarial activity, it is observed that the alkaloids O-demethylaspidospermidine, aricine, yohimbine, aspidospermine, quebrachamine, braznitidumine, geissospermine, 1,2-de-hydrogeissoschizoline and flavopereirine were active against strains of *P. falciparum* in several studies [8, 19, 103, 106 - 109].

From the leaves of *Persea americana*, one previously undescribed flavonol glycoside (Fig. **12**-1) together with ten known flavonoids (Fig. **12**-2-11), four megastigmane glycosides (Fig. **12**-12–15) and two lignans (Fig. **12**-16–17) were isolated [111].

The aqueous extract of *P. americana* was active against clones of *P. falciparum* sensitive to chloroquine (3d7; IC_{50}= 9.93 ± 0.86 μg/mL) and chloroquine resistant (W2; IC_{50}= 34.20 ± 5.80 μg/mL), presenting high selectivity for clone 3d7 [112] (Selective Index >10.1). The methanol extract of *P. americana* leaves possesses significant antimalarial activity against *P. berghei*-infected mice ($p<0.05$). The

results also show that the extract exhibits excellent hematopoietic properties by reversing and restoring the altered plasmodium-induced changes and hematological indexes [113].

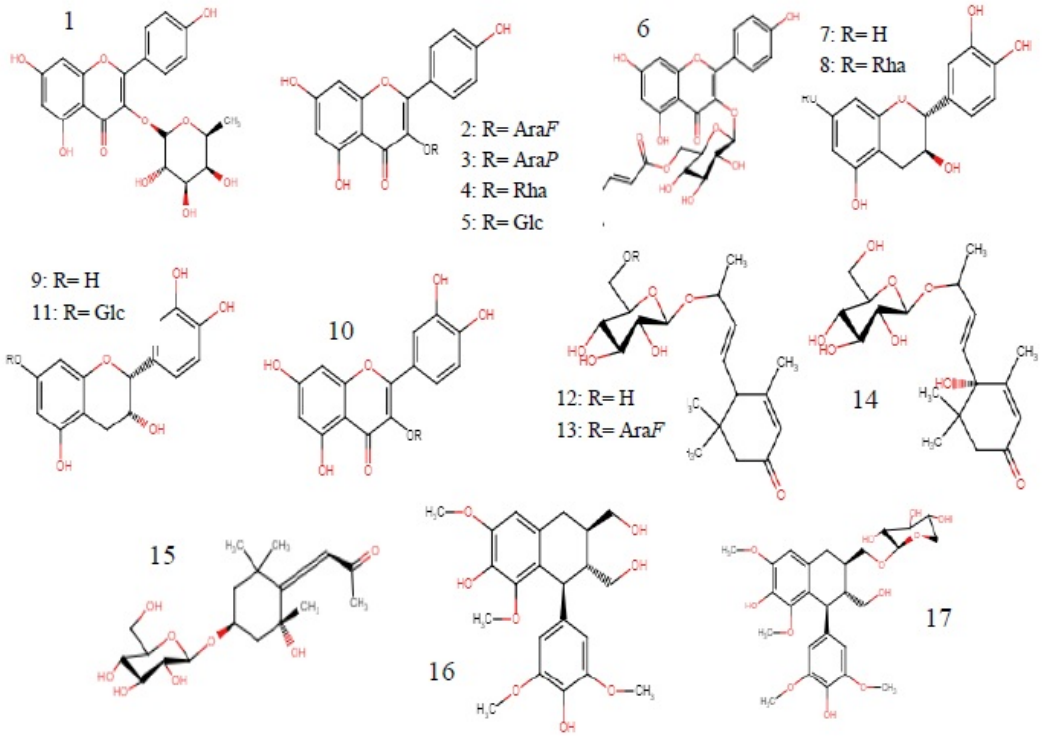

Fig. (12). Chemical structure of compounds isolated from *Persea americana.*
Legend: glycoside flavonol (1), juglanin (2), juglalin (3), afzelin (4) astragaline (5), trans-tiliroside (6), quercetin (7), quercitrin (8), catechin (9), epicatechin (10), senecin (11), (6R,9R)-3-oxo-alpha-ionol- 9-O-d-glucopyranoside (12), ficumegasoside (13), (6S,9R)-roseoside (14), icariside B1 (15), (+)-lyoniresinol (16), and (+)-isolariciresinol 9-O-D-xylopyranoside (17).

In relation to the isolated compounds of this species and its antiplasmodial activity, after extensive review, it was found that five isolated compounds were active *in vitro* against *P. falciparum* clones sensitive (D6) and resistant (W2) to chloroquine, based on the plasmodial LDH activity assay. The compound 2S4S-1,2,4-trihydroxyheptadec-16-ene was the most active against both plasmodium strains [114] (IC_{50} = 1.6 and 1.4 µg/mL for the D6 clone, respectively, and 2.1 and 1.4 µg/mL for the W2 clone, respectively.

Moreover, the dichloromethane extract obtained from fruits of the species *P. americana* showed moderate activity against promastigote forms of *Leishmania donovani.* However, the activity-guided fractionation of the above extract led to

the isolation of two acetogenins (5*E*,12*Z*,15*Z*)-2-hydroxy-4-oxohenicosa-5,-2,15-triene-5-1-yl acetate and (2*E*,5*E*,12*Z*,15*Z*)-1-hydroxyphone-2,5,12,15-tr-ene-4-one, which showed good antileishmanial activity [115]. From this species, compounds were isolated with several flexible hydrophobic ligands, geranylgeraniol and C17 fatty alcohol derivatives, which showed selective docking for *Trypanosoma cruzi* trypanothione reductase [116]. Thus, *P. americana* seems to be promising both as an antimalarial and antileishmanial agent, and perhaps acetogenins are involved in these activities.

Another species of great importance as a food source in the Amazon region and that is used in folk medicine is *Euterpe precatoria*. From the root powder and leaf splint, hexane, ethyl acetate, and methanolic extracts were obtained. From these extracts it was isolated β-sitosterol (Fig. **13**-1) and stigmasterol (Fig. **13**-2), stigmast-4-en-6b-ol-3-one (Fig. **13**-3), acid *P*-hydroxybenzoic (Fig. **13**-4), 3b-*O*-b-D- glucopyranosyl sitosterol (Fig. **13**-5), palmitate β -sitosterile (Fig. **13**-6), mixture of α- and β-amyrin (Fig. **13**-7 and **13**-8, respectively), and lupeol (Fig. **13**-9); friedelan-3-one (Fig. **13**-10); 28-hydroxy-friedelan-3-one (Fig. **13**-11), α and β D-glucose [117] (Fig. **13**-12 and **13**-13, respectively).

Indeed, various flavones, including homoorientin (Fig. **13**-14), orientin (Fig. **13**-15), taxifolin deoxyhexose, and isovitexin (Fig. **13**-16), various flavanol derivatives, including (+)-catechin (Fig. **13**-17), (−)-epicatechin (Fig. **13**-18), procyanidin dimers and trimers, and phenolic acids, including protocatechuic (Fig. **13**-19), *P*-hydroxybenzoic (Fig. **13**-20), vanillic (Fig. **13**-21), syringic (Fig. **13**-22), and ferulic acids (Fig. **13**-23) were identified in the juice obtained from the fruits of *E. precatoria* [118].

Nevertheless, in other studies, the compost dehydrodiconiferyl alcohol dibenzoate isolated of extract obtained from *E. precatoria* presented only modest antimalarial activity, displaying CI_{50}= 12 μM against clone 3d7 of *Plasmodium* [41, 119]. The *in vivo* activity in mice infected with *P. berghei* and treated with 100 to 500mg/kg was also investigated, with no promising results [41]. Notwithstanding, from *E. precatoria*, lignan dihydroconiferyl dibenzoate and *P*-hydroxybenzoic acid were also isolated, and the latter substance presented moderate antiplasmodial activity [119].

Hydroalcoholic extracts from *E. precatoria* obtained from leaves and stems were submitted to evaluation of leishmanicidal activity against amastigotes of *L. mexicana*, showing CI_{50}>10 μg/mL. In this same study, the antiplasmodial activity of the extracts was evaluated, with results similar to *Leishmania* [120] (IC_{50}>10 μg/mL). The anti-inflammatory [121] and antioxidant [117] effects of this species have already been evaluated; however, no study was found to evaluate its healing

potential. It is noteworthy that antimalarial properties have been attributed to this species, but this activity is quite modest [120], and this suggests that more than a direct antiplasmodial effect, it may act in reducing malaria symptoms and can prevent the worsening of the disease due to its antioxidant potential [122, 123].

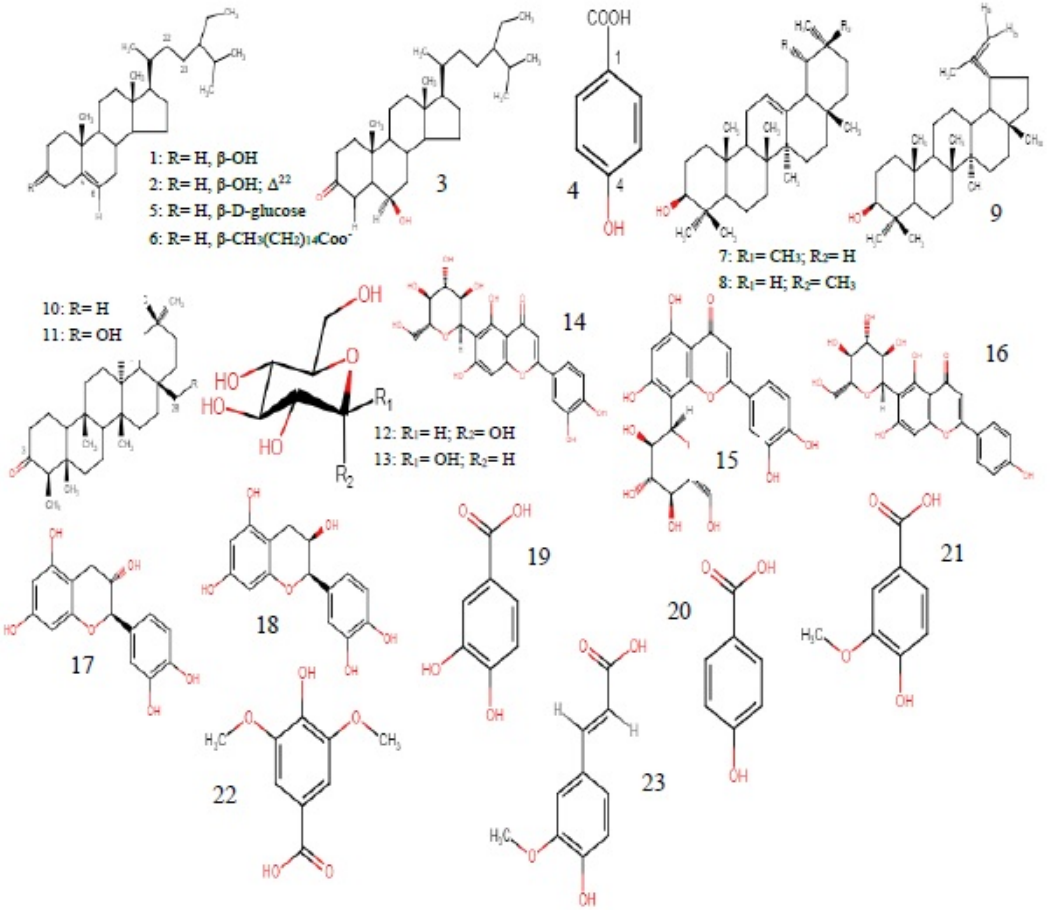

Fig. (13). Chemical structure of compounds isolated from *Euterpe precatoria.*
Legend: β-sitosterol (1) and stigmasterol (2), stigmast-4-en-6b-ol-3-one (3), acid *P*-hydroxybenzoic (4), 3b-*O*-b-D- glucopyranosyl sitosterol (5), palmitate β -sitosteril (6), mixture of α- and β -amyrin (7 and 8) and lupeol (9); friedelan-3-one (10); 28-hydroxy-friedelan-3-one (11), α and β D-glucose (12 and 13), homoorientin (14), orientin (15), isovitexin (16); (+)-catechin (17), (−)-epicatechin (18), protocatechuic (19), *P*-hydroxybenzoic (20), vanillic (21), syringic (22), and ferulic acids (23).

Another species often consumed as food by the Amazon population is *Bertholletia excelsa*, the brazilnut tree. Chemical study of extracts from this plant identified the following compounds: gallocatechin (Fig. **14**-1), gallic acid (Fig. **14**-2) and derivatives, protocatechuic acid (Fig. **14**-3), catechin (Fig. **14**-4),

protocateualdeyde, protocatechuic acid derivative (Fig. **14**-5), catechin derivative, vanillic acid (Fig. **14**-6) and derivatives, taxifolin (Fig. **14**-7) and derivatives, myricetin-3-o- rhamnoside (Fig. **14**-8), ellagic acid (Fig. **14**-9) and derivatives, and quercetin [124] (Fig. **14**-10).

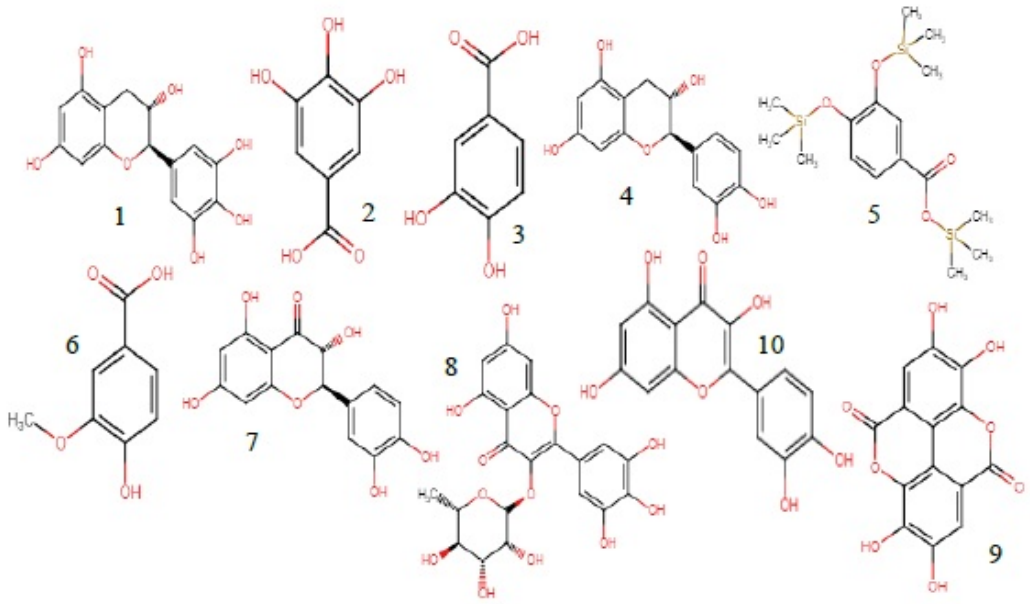

Fig. (14). Chemical structure of compounds isolated from *Bertholletia excelsa.*
Legend: gallocatechin (1), gallic acid (2), protocatechuic acid (3), catechin (4), protocatechuic acid derivative (5), vanillic acid (6), taxifolin (7), myricetin-3-o-rhamnoside (8), ellagic acid (9), and quercetin (10).

No studies of antiplasmodial activity of *B. excelsa* were found. Nevertheless, similar to *E. precatoria*, extracts obtained from the kernel and the brown skin that covers the nut of *B. excelsa* were submitted to the evaluation of antioxidant activity. Extracts obtained from the brown skin that covers the nut were more promising as antioxidants, and the activity is related to the higher content of phenolic compounds [124]. The evaluation of the impact of this antioxidant potential on the progression of malaria is important and may lead to the development of new therapeutic uses for this species.

Typically, studies assess the potential for secondary metabolites of plants; however, one study evaluated the antileishmanial potential of proteins from *B. excelsa* and showed that the DR2 fraction presented the strongest toxicity against *L. amazonensis*, causing 100% parasite elimination at 150 µg/mL. DR2 fraction toxic activity included membrane permeabilization, increased endogenous reactive oxygen species (ROS) production, and mitochondrial dysfunction [125].

From the extract of the roots of *Ampelozizyphus amazonicus,* triterpenic saponins-3–O-[β-D-glucopyranosyl(1-2) α-L-arabine-pyranosyl]-20-O-α-rhamnopy-anosyl-jujubogenine [39] (Fig. **15**-1), and L-ampelozigenin-15α-O-acetyl-3-O α-L-rhamnopyranosyl-(1-2)-β-D glucopyranoside [126] (Fig. **15**-2) were obtained. Additionally, 3-O-[β-D-glucopyranosyl-20-O-α-L rhamnopyranosyl-jujubogenine [127] (Fig. **15**-3) was isolated, as well as terpenoids such as ursolic acid (Fig. **15**-4); betulinic acid (Fig. **15**-5); lupenone (Fig. **15**-6); lupeol (Fig. **15**-7); betulin (Fig. **15**-8); 3β-hydroxylup-20(29)-ene-27,28-dioc acid (Fig. **15**-9); 2α,3β-dihydroxylup-20(29)-ene-27,28- dioic acid (Fig. **15**-10) and 3β,28-dihydroxy-l-p-20(29)-ene-27-oic acid (Fig. **15**-11). Steroids have also been isolated, such as stigmasterol (Fig. **15**-12), sitosterol (Fig. **15**-13), and campesterol [128] (Fig. **15**-14).

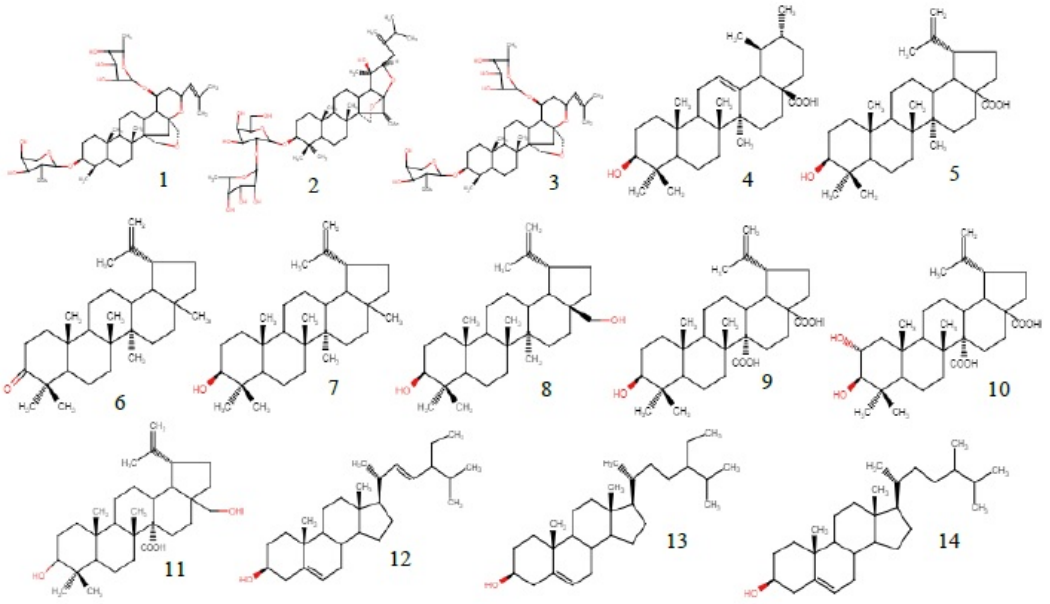

Fig. (15). Chemical structure of compounds isolated from *Ampelozizyphus amazonicus.*
Legend: triterpenic saponins: 3–O-[β-D-glucopyranosyl(1-2)α-L-arabine-pyranosyl]-20-O-α -rhamnopyranosyl-jujubogenine (1); L-ampelozigenin-15α-O-acetyl-3-O α-L-rhamnopyranosyl-(1-2)-β-D glucopyranoside (2); 3–O-[β-D-glicopyranosyl-20-O-α-L-rhamnopyranosyl-jujubogenine (3), ursolic acid (4), betulinic acid (5), lupenone (6), lupeol (7), betulin (8), 3β-hydroxylup-20(29)-ene-27, 28-dioic acid (9), 2α, 3β-hydroxylup-20(29)-ene-27,28-dioic acid (10), 3β, 28-hdihydroxi-lup-20(29)-ene-27,28-oic acid (11), stigmasterol (12), sitosterol (13), and campesterol (14).

The infusion of roots of *Ampelozizyphus amazonicus* is used in Amazon folk medicine for malaria prevention [129], and the extract of *A. amazonicus* was active against sporozoites of *P. gallinaceum*, as well as during the early stages of the liver cycle [130]. Chloroform and aqueous extracts obtained from *A.*

amazonicus were also tested against *P. berghei* and were also active. Chloroform extract exhibited the highest antiplasmodial activity during the erythrocytic phase of *P. falciparum* and the fractionation of this extract led to the isolation and elucidation of pentacyclic triterpenes, lupeol, botulin, and betulinic acid, which showed high antiplasmodial activity [131].

Extracts from *A. amazonicus* were also tested against promastigote forms of the *Leishmania* species *L. amazonensis, L. braziliensis* and *L. donovani*. Ethanol extract was active against *L. braziliensis* and *L. donovani*, while dichloromethane extract was active only against *L. braziliensis* [132].

As stated earlier, *copaíba* oil (*Copaifera*) is used for wound treatment and as a healing agent. A comprehensive review of the chemical aspects and antileishmanial activity of this oil was conducted by Albuquerque *et al.*, (2017) [133]. Several sesquiterpenes and diterpenes were isolated from this oil (Table **4**; Figs. **16** and **17**, respectively).

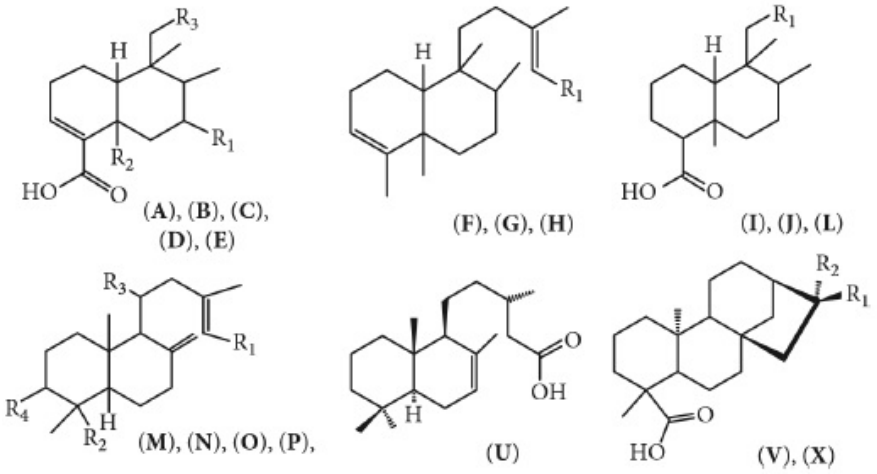

Fig. (16). Diterpenes found in *copaíba* oils [133].
Legend: (**A**) patagonic acid [R_1 = H; R_2= CH_3; R_3 = furanone]; (**B**) hardwickiic acid [R_1 = COOH; R_2 = H; R_3 = furan]; (**C**) 15,16-epoxy-7*β*-acetoxy-3,13(16),14-clerodatriene-18-oic acid [R_1 = H; R_2 = H; R_3 = furan]; (**D**) 7-hydroxyhardwickiic acid [R_1 = OH; R_2 = CH_3 R_3 = furan]; (**E**) clerodane-15,18-dioic acid [R_1 = H; R_2 = CH_3; R_3 = $CH(CH_3)CH_2COOCH_3$]; (**F**) 3,13-clerodadiene-15-oic acid [R_1 = COOH]; (**G**) colavenol [R_1 = CH_2OH, *trans* C_1, C_2]; (**H**) cis-colavenol [R_1 = CH_2OH *cis* C_1, C_2]; (**I**) 13-clerodane-15,16-olideo-18oic acid [R_1 = furanone]; (**J**) clerodane-15,18-dioic acid [R_1 = $CH_2(CH_3)CH_2CH_2COOH$]; (**L**) clorechinic acid [R_1 = furan]; (**M**) copaiferolic acid [R_1 = COOH; R_2 = OH; R_3 = H; R_4 = H]; (**N**) copaiferic acid, [R_1 = COOH; R_2 = CH_3; R_3 = H; R_4 = H]; (**O**) 8(17), 13-labdadiene-15-ol [R_1 = CH_2OH; R_2 = CH_3; R_3 = H; R_4 = H]; (**P**) 11-hydroxycopalic acid [R_1 = COOH; R_2 = CH_3; R_3 = OH; R_4 = H]; (**Q**) ent-3-hydroxy-labd 8(17),13-diene--5-oic acid [R_1 = COOH; R_2 = CH_3; R_3 = H; R_4 = OH]; (**R**) ent-agatic acid [R_1 = COOH R_2 = COOH R_3 = H R_4 = H]; (**S**) copalic acid [R_1 = COOH; R_2 = CH_3; R_3 = H; R_4 = H]; (**T**) 11-acetoxy-copalic acid [R_1 = COOH; R_2 = CH_3; R_3 = CO_2CH_3; R_4 = H]; (**U**) cativic acid; (**V**) ent-16(*β*)-cauranic-19-oic acid [R_1 = CH_3; R_2 = H]; (**X**) ent-caura-16-ene-19-oic acid [R_1 and R_2 = CH_2].

Table 4. Terpenes present in *Copaifera*

SESQUITERPENES	DITERPENES
	Clerodanes
Alloaromadendrene, ar-curcumene, *α*-bergamotene, *β*-bergamotene, ar-curcumene, bicyclogermacrene, *β*-bisabolene, *β*-bisabolol, cadalene, cadinene, *α*-cadinene, □-cadinene, *γ*-cadinene, *α*-cadinol, calamenene, caryophyllene, *β*-caryophyllene, *α*-caryophyllenol, cedrol, *α*-cedrene, cyperene, copaene, *α*-copaene, *β*-copaene, *γ*-elemene, *β*-farnesene, *trans*-*β*-farnesene, germacrene B, germacrene D, *α*-guaiene, *β*-guaiene, y-guaiene, guaiol, humulene, *α*-humulene, *β*-humulene, *γ*-humulene, ledol, longiciyclene, *α*-multijugenol, t-muurolol, *α*-muurolene, *γ*-muurolene, caryophyllene oxide, *α*-selinene	3,13-clerodadiene-15,16-olide-18-oic acid 3-clerodene-15,18-dioic acid 13-clerodene-15,16-olide-18-oic acid 3,13-clerodadiene-15-oic acid 3,13-clerodadien-15-ol ent-15,16-epoxy-7*β*-hydroxy-3,13(16),14-clerodatr-en-18-oic acid ent-(19a)-3,13-clerodadien-15-ol ent-neo-4(18), 13-clerodadien-15-ol clerodene-15,18-dioic acid ent-15,16-epoxy-13(16),14-clerodadien-18-oic acid ent-15,16-epoxy-3,13(16),14-clerodatrien-18-oic acid (+)-7*β*-Acetoxy-15,16-epoxy-3,13(16),14- clerodatrien-18-oic acid
	Labdanes
	ent-3-hydroxy-labda-8(17),13-dien-15-oic acid ent-8(17),13-labdadien-15,19-dioic acid ent-8(17)-labden-15-oic acid ent-8(17)-labden-15,18-dioic acid ent-15,16-epoxy-8(17),13(16),14-labdatrien-18-oic acid 18-hydroxy-8(17),13-labdadien-15-oic acid 8(17), 13E-labdadien-15-oic acid (13S)-7-labden-15-oic acid 3*β*-hydroxy-15,16-dinorlabda-8(17)-en-13-one 8(17),13-labdadien-15-ol

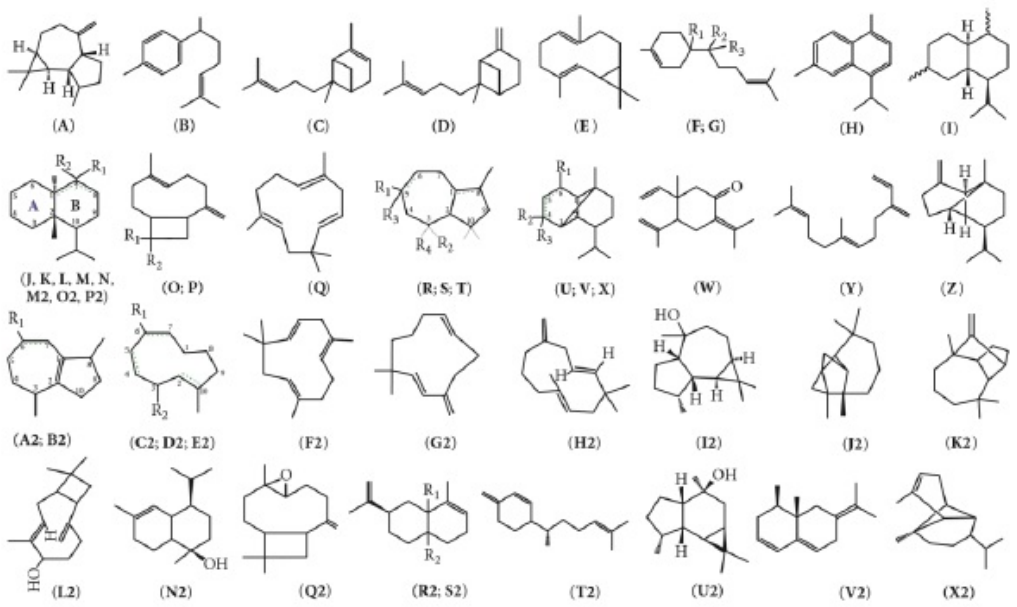

Fig. (17). Sesquiterpenes found in copaiba oils (ALBUQUERQUE *et al.*, 2017) [133].
Legend: A) alloaromadendrene; (**B**) ar-curcumene; (**C**) *α*-bergamotene; (**D**) *β*-bergamotene; (**E**) bicyclogermacrene; (**F**) *β*-bisabolene [R_1 = H, R_2 and R_3 = CH_2]; (**G**) *β*-bisabolol [R_1 = OH, R_2 = CH_3, R_3 = H]; (**H**) cadalene; (**I**) cadinene; (**J**) *α*-cadinene [R_1 = CH_3; R_2 = not; C_7 = C_8; A = 4- CH_3-hexcycl-3-ene]; (**K**) *γ*-cadinene [R_1 and R_2 = CH_2; C_7 = C_8; A = 4- CH_3-hexcycl-3ene]; (**L**) □-cadinene [R_1 = CH_3; R_2 = not; C_1 = C_7; A- CH_3 -hexcycl- 3-ene]; (**M**) *α*-cadinol [R_1 = H; R_2 = OH; A = 4- CH_3 -hexcycl-3-ene]; (**N**) calamenene [R_1 = H; R_2 = CH_3; A = benzene]; (**O**) caryophyllene [R_1 = CH_3, R_2 = CH_3, *cis*]; (**P**) *β*-caryophyllene [R_1 = CH_3; R_2 = CH_3, *trans*]; (**Q**) *α*-caryophyllenol; (**R**) cedrol [R_1 = H; R_2 = CH_3; R_3 = OH; R_4 = CH_3; C_1, C_4 = CH_2]; (**S**) *α*-cedrene [R_1 = CH_3; R_2 = CH_3; R_3 = not; R_4 = CH_3; C_1, C_4 = CH_2; C_5 = C_6]; (**T**) cyperene [R_1 = H; R_2 = CH_3; R_3 = H; R_4 = C_2, $C_6CH_2(CH_3)_2$]; (**U**) copaene; (**V**) *α*-copaene; (**X**) *β*-copaene; (**W**) *γ*-elemene; (**Y**) *β*-farnesene; (**Z**) trans-*β*-farnesene; (**A2**) germacrene B [R_1 = CH_3; R_2 = $C(CH_3)_2$; C_6 = C_7; C_2 = C_{10}]; (**B2**) germacrene D [R_1 = CH_2; C_4 = C_5; C_9 = C_{10}]; (**C2**) *α*-guaiene [R_1 = $C(CH_2)CH_3$]; (**D2**) *β*-guaiene [R_1 = $(CH_3)_2$]; (**E2**) *γ* -guaiene [R_1 = $CH(CH_3)_2$; C_6 = C_7]; (**F2**) humulene; (**G2**) *α*-humulene; (**H2**) *β*-humulene; (**I2**) ledol; (**J2**) longicyclene; (**K2**) longifolene; (**L2**) longipinene; (**M2**) *α*-multijugenol [R_1 = H; R_2 = OH; A = 4- CH_3 - hexcycl-3-ene]; (**N2**) t-muurolol; (**O2**) a-muurolene [R_1 = CH_3; R_2 = not; C_7 = C_8; A = 4-Me-hexcyc--3-ene]; (**P2**): *γ*-muurolene [R_1 + R_2 = CH_2; A = 4- CH_3-hexcycl-3-ene]; (**Q2**): caryophyllene oxide; (**R2**) *α*-selinene [R_1 = H; R_2 = CH_3*cis*]; (**S2**) *β*-selinene [R_1 = H; R_2 = CH_3*trans*]; (**T2**) *β*-sesquiphellandrene; (**U2**) viridiflorol; (**V2**) *β*-vetivenene; (**X2**) *α*-ylangene.

Most studies evaluating antileishmanial activity of *Copaifera* sp. were carried out against strains of *L. amazonensis,* but there is a lack of studies evaluating their activities against intracellular forms of the parasite (amastigote; Table **5**).

The oil of *C. reticulata* displayed activity against the two evolutionary forms of *Leishmania* (promastigote and amastigote) and against two strains: *L. amazonensis* and *L. chagasi* [134, 135] (Table **5**). For the amastigote forms of *L. chagasi*, the oil of *C. reticulata* showed higher activity [135] (CI_{50}= 0.52 μg/mL), while for *L. amazonensis* it showed greater activity against promastigote forms

[134] (CI_{50}= 5.0 μg/mL). The leishmanicidal activity of this species may have been influenced by the chemical composition of the oil. Phytochemical studies carried out from *C. reticulata* demonstrate that this is mainly composed of sesquiterpenes and, among the major constituents, *β*-caryophyllene, trans-*α*-*β*-bergamotene, and bisabolene [136].

Oils obtained from *Copaifera marti, C. cearensis, C. paupera, C. langsdorffii, C. multijuga,* and *C. lucens* have been evaluated primarily against promastigote forms of *L. amazonensis* and all of them showed activity [134] CI_{50}= 10–22 μg/mL), with the only exception being the oil obtained from *Copaifera paupera* [137] (Table **5**). Substances isolated from copaíba oils showed greater activity against amastigote forms of *L. amazonensis*, except for hydroxycopalic acid (Table **5**).

Unlike studies against leishmania, only a few studies show the antimalarial activity of *Copaifera.* In this sense, dichloromethane extract obtained from *Copaifera religiosa* showed promising antiplasmodial activity against strains of *Plasmodium falciparum*, with IC_{50} = 13.4 ± 3.6 μg/mL and 8.5 ± 4.7 μg/mL against chloroquine-sensitive and chloroquine-resistant strains, respectively (Table **5**). However, the methanol extract of *C. religiosa* showed no antiplasmodial activity [138] (CI_{50} = 500.7 ± 16.4 μg/ml and 480.9 ± 34.2 μg/mL for chloroquine-sensitive and resistant strains, respectively).

Additionally, the resin oil of *C. reticulata* containing the sesquiterpenes *β*-caryophyllene (41.7%) and *β*-bisabolene (18.6%) was active against strains of *P. falciparum* [139] (sensitive and resistant to chloroquine; IC_{50} = 1.66 and 2.54 μg/mL, respectively).

Table 5. Antileishmanial and antiplasmodial activity of *Copaifera* and terpenes isolated in this genus.

Species or terpenes isolated	Samples	Antileishmanial activity (IC_{50} μg/mL)		Antiplasmodial activity (IC_{50} μg/mL)		Reference
		Promastigote	Amastigote	Sensitive to chloroquine	Chloroquine resistant	
P. falciparum						
Copaifera religiosa	Dichloromethane	-	-	13.4 ± 3.6 8	8.5 ± 4.7	Lekana-Douki *et al.*, 2011 [138]
Copaifera religiosa	Methanol	-	-	500.7 ± 16.4	480.9 ± 34.2	Lekana-Douki *et al.*, 2011 [138]

Species or terpenes isolated	Samples	Antileishmanial activity (IC_{50} µg/mL)		Antiplasmodial activity (IC_{50} µg/mL)		Reference
		Promastigote	Amastigote	Sensitive to chloroquine	Chloroquine resistant	
Copaifera reticulata	Resin Oil	-	-	1.66	2.54	De Souza *et al.*, 2017 [139]
L. chagasi						
Copaifera reticulata	Oil	7.88	0.52	-		Rondon *et al.*, 2012 [135]
L. amazonensis						
Copaifera reticulata	Oil	5.0 ± 0.8	20.0	-		Santos *et al.*, 2008 [134]
Copaifera marti	Oil	14.0 ± 0.9	-	-		Santos *et al.*, 2008 [134]
Copaifera cearensis	Oil	18.0 ± 0.0	-	-		Santos *et al.* 2008 [134]
Copaifera paupera	Oil	11.0 ± 0.4	-	-		Santos *et al.*, 2008 [134]
Copaifera langsdorffii	Oil	20.0 ± 0.8	-	-		Santos *et al.*, 2008 [134]
Copaifera officinalis	Oil	20.0 ± 0.4	-	-		Santos *et al.*, 2008 [134]
Copaifera multijuga	Oil	10.0 ± 0.8	-	-		Santos *et al.*, 2008 [134]
Copaifera lucens	Oil	20.0 ± 0.9	-	-		Santos *et al.*, 2008 [134]
Copaifera paupera	Oil	>100	>100	-		Estevez *et al.*, 2007 [137]
Kaurenoic acid	-	28.0 ± 0.7	3.5 ± 0.5	-		Santos *et al.*, 2013 [140]
Hydroxycopalic acid	-	2.5 ± 0.4	18.0 ± 1.5	-		Santos *et al.*, 2013 [140]
Polyalthic acid	-	35.0 ± 2.0	15.0 ± 1.0	-		Santos *et al.*, 2013 [140]
Pinifolic acid	-	70.0 ± 8.0	4.0 ± 0.4	-		Santos *et al.*, 2013 [140]
Caryophyllene oxide	-	-	2.9	-		Soares *et al.*, 2013 [141]
Sesquiterpenes	-	-	2.3	-		Soares *et al.*, 2013 [141]

Species or terpenes isolated	Samples	Antileishmanial activity (IC_{50} µg/mL)		Antiplasmodial activity (IC_{50} µg/mL)		Reference
		Promastigote	Amastigote	Sensitive to chloroquine	Chloroquine resistant	
Amphotericin B	-	0.06 ± 0.0	0.23 ± 0.0	-		Santos *et al.*, 2013 [140]

In the Amazon, the population attributes healing action to the genus *Jatropha*. The alcoholic extract of *J. gossypiifolia* was tested on colonic anastomosis in rats, and only a weak effect was observed in the final stage of healing, but there was a decrease in the inflammation process [142]. In the healing of gastrorrhaphy in rats, a result similar to that of the previous study was seen, with reduction of acute inflammation. Nevertheless, there were no statistical differences compared to the control group [72]. In a third study, similar results were obtained, that is, when evaluating the healing activity of this species in skin wounds in rats, reduced healing potential was obtained [71].

Additionally, some studies attributed antiplasmodial activity to this species. In a study conducted by ONYEGBULE *et al.* (2019) [143] in which the *in vivo* antiplasmodial activity of the ethanol extract from leaves and fractions of *J. gossypiifolia* was evaluated in mice infected with *P. berghei*, it was demonstrated that the fractions of the leaf extract exhibited moderate prophylactic and curative activities, with the ethyl acetate fraction inducing the best antimalarial activity.

MARIZ *et al.* (2010) [144] performed a review intitled "The therapeutic possibilities and toxicological risk of *J. gossypiifolia* L". (Table **6** and Fig. **18**) summarize the compounds already isolated from the species, along with fatty acids that were isolated from the seeds and other metabolites that were found in different parts of the plant and in different types of extracts.

Table 6. Compounds isolated from *Jatropha gossypiifolia*

Class	Vegetable part	Compounds	References
Fatty acids	Seeds	Araquidic acid, Araquidonic acid, Behenic acid, Caprilic acid, Estearic acid, Lignoceric acid, Linoleic acid, Myristic acid, Oleic acid, Palmitic acid, Palmitoleic acid, Ricinoleic acid, Vernolic acid	Ogbobe & Akano, 1993 [145] Prasad *et al.*, 1993 [146] Matos, 2004 [73] Hosamani & Katagi, 2008 [147]

Class	Vegetable part	Compounds	References
Alkaloids	Leaves, roots, seeds, and latex	Jatrophine	Morton, 1968 [148] Gupta *et al.*, 1979 [149] Ogbobe & Akano, 1993 [145] Matos, 2004 [73]
Coumarins	Stem, roots, and the whole plant	Cleomiscosin A; 7,8-dihydroxi-6-methoxy-coumarin; Propacin	Das *et al.*, 2003 [150] Das & Kashinatan, 1997 [151]
Diterpenes	Roots, leaves, and the whole plant	Jatropholone A; 2α-OH-Jatrophobon 2β-OH-Jatrophobon 2β-OH-5,6-Isojatropone; Jatrophone; Jatropholone B; Jatrophenone	Adesina, 1982 [152] Taylor *et al.*, 1983 [153] Das & Kashinatan, 1997 [151] Ravindranath *et al.* 2003 [154] Matos, 2004 [73]
Flavonoids	Leaves, roots, stem, seeds, and the whole plant	Apigenin; Ferulic acid; 2,3-bis- (hydroxymethyl)-6,7-methylenedioxy-1-(3'4'-dimethoxyphenyl)-naphthalene; Dihydroprasantaline; Gadaine; Gossypidiene; Gossypifane; Isogadaine, Isovitexin, Vitexin	Subramanian *et al.* 1971 [155] Banerji *et al.* 1984 [156] Das *et al.* 1996[a] [157] Das *et al.*, 1996[b] [158] Das & Das, 1995 [159] Das & Kashinatan, 1997 [151] Das & Anjani, 1999 [160] Matos, 2004 [73]

Class	Vegetable part	Compounds	References
Lignans	Stem, roots, seeds, and whole plant	Jatrodiene; Jatrophan; Jatrophatrione; Lignan aril naphthalene; 2-Piperonilideno3-veritril-3R-ybutyrolactone; Prasantaline; Tetradecyl ferulate (Tetradecyl (E)- ferulate)	Das & Kashinatham, 1997 [151] Kavitha *et al.*, 1999 [161] Chatterjee *et al.*, 1988 [162] Matos, 2004 [73] Das & Banerji, 1988 [163]

To date, no study has specifically evaluated the effect of extracts from *J. gossypiifolia* on the wound healing process caused by *Leishmania*, but studies of its metabolites (alkaloids and phenolic compounds) have shown that they participate in the protective antioxidant activity of higher organisms, as well as in the inhibition of the enzyme acetylcholinesterase, which causes damage to the membranes of *Leishmania* [164]. Thus, it is possible that the species also presents leishmanicidal properties, as suggested in a previous study by CHAN-BACAB and PEÑA-RODRIGUÉZ (2001) [165].

Another genus that deserves attention is *Musa*, used for the treatment of severe wounds among Amazon peoples. From peeled fruits of *M. paradisiaca*, two acyl steryl glycosides, sitoindoside-III and sitoindoside-IV, and two steryl glycosides, sitosterol gentiobioside and sitosterol myo-inosityl- β-D-glucoside were isolated [166] (Fig. **19**). The tetracyclic triterpene isolated from the flowers of *M. paradisiaca* was determined as (24R)-4α,14α.24-trimethyl-5α-cholesta-8,2-(27)-dien-3β-ol [167], and the leishmanicidal activity of the triterpenes isolated from *M. paradisiaca* and the anacardic acid and synthetic derivatives against *Leishmania infantum chagasi* were also tested. It was identified that, except for cycloeucalone, all other compounds (31-norcyclolauddeone, stigmasterol, β-sitosterol and 24-methylene-cycloartanol) from the fruit peel were active against the promastigote form. On the other hand, against the amastigote forms, all other compounds, including anacardic acid, were active, except for 31-norcyclocondeone [168].

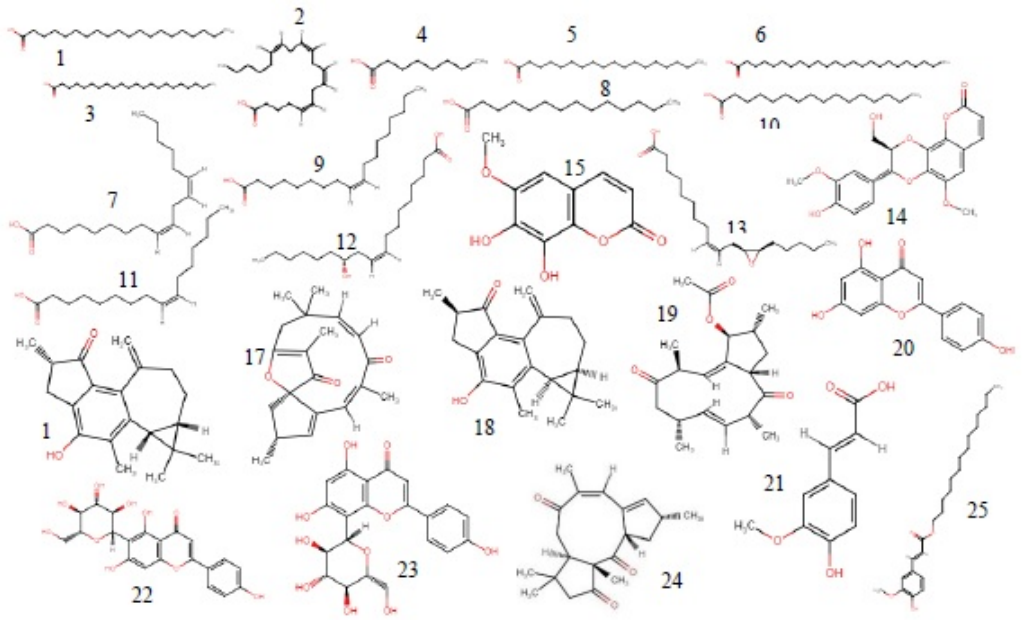

Fig. (18). Chemical structure of compounds isolated from *Jatropha gossypiifolia.*
Legend: arachidic acid (1), araquidonic acid (2), behenic acid (3), caprilic acid (4), estearic acid (5), lignoceric acid (6), linoleic acid (7), myristic acid (8), oleic acid (9), palmitic acid, (10), palmitoleic acid (11), ricinoleic acid (12), vernolic acid (13), cleomiscosin a (14), 7,8-dihydroxi-6- methoxy-coumarin (15), jatropholone a (16), jatrophone (17), jatropholone b (18), jatrophenone (19), apigenin (20), ferulic acid (21), isovitexin (22), vitexin (23), jatrophatrione (24), and tetradecyl ferulate (25).

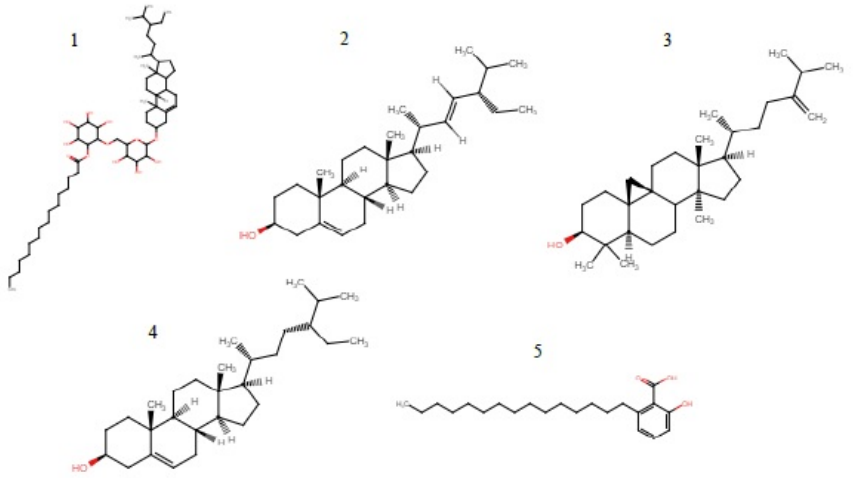

Fig. (19). Chemical structure of compounds isolated from *Musa paradisiaca.*
Legend: sitoindoside-IV (1), stigmasterol (2), 24-methylene-cycloartanol (3), β-sitosterol (4), anacardic acid (5).

In summary, some plant species seem to be more promising for malaria, and others for leishmania. Notwithstanding, some species seem to be very promising both for the treatment of malaria and leishmaniasis and these are widely used in folk medicine by Amazonian communities, *i.e.*, species of *Copaifera* and *Aspidosperma nitidum*. The antiparasitic activity of *A. nitidum* is probably related to its alkaloids [169], while the activity of *Copaifera* is related to terpenes (Table **7**). It is emphasized that there are other species used by Amazonian communities for the treatment of malaria, including *G. sericeum* and *A. excelsum*, that also produce alkaloids, and these are responsible for the antiparasitic activity [103, 170].

Table 7. Analysis of whether the species is promising for antimalarial or antileishmanial activities and the possible activity marker

Species	Antimalarial	Antileishmanial	Marker	References
Portulaca pilosa	Promising	Promising as a healing agent	NC	Brandão *et al.*, 2020 [169]
Aspidosperma nitidum	Promising	Promising	Tannins, flavonoids, alkaloids, triterpenoids and saponins	Komlaga *et al.*, 2015 [112] Kenechukwu, 2020 [113]
Persea americana	Promising	Extract with moderate activity; Acetogenins were active	5E,12Z,15Z)-2-hydroxy-4-oxohenicosa-5,12,15-triene-1-yl acetate and (2E,5E,12Z,15Z)-1-hydroxyhenicosa-2,5,12-15-triene-4-one	Dharmaratne *et al.*, 2012 [115]
Euterpe precatoria	Modest antiparasitic activity	Modest leishmanicidal activity	β-sitosterol and stigmasterol, stigmast-4-en-6b-ol-3-one, p-hydroxybenzoic acid, 3b-O-b-D- glucopyranosyltestosterol, palmitate β-sitosteryl, mixture of α- and β-amyrin and lupeol; friedelan-3-ona; 28-hydroxy-friedelan-3-ona	Galotta & Boaventura, 2005 [117]
Bertholletia excelsa	NC	Promising	Protein	Fardin *et al.*, 2016 [125]
Ampelozizyphus amazonicus	Promising	Promising	Quercetin 3,3'-dimethyl ether 7-0-α-L-rhamnopyran-syl-(1→6)-β-D-glucopyranose; Quercetin 3,3'-dimethyl ether 7-0-β-D-glucopyranose;	Krettli *et al.*, 2001 [130] do Carmo *et al.*, 2015 [131] Rojas *et al.*, 2009 [132]
Copaifera sp.	Promising	Promising	Rutin, quercetin-3-O-alpha-L rhamnopyranoside, canferol 3-O-alpha-L rhamnopyranoside, quercetin, canferol, abergamotene, α-himachalene, β-selinene, β-caryofilenol, abiotic, daniellic, lambertinnic, labd-7-en-15-oic, isopimaric acids; kaur16-en18-oic, 9.10-Dimethil-1.2 benzanthracene, 3-O-alpha rhamnopyranosil-quercetin, 3-O-alpha rhamnopyranosil-canferol and canferol	Santana *et al.*, 2014 [66] Cavalcante *et al.*, 2017 [68] de Souza *et al.*, 2017 [139]

Species	Antimalarial	Antileishmanial	Marker	References
Jatropha gossypiifolia	Modest antiplasmodial activity	Leishmanicidal effect	Alkaloids (jatrophan glycoside), steroids (β-sitosterol), triterpenoids, saponins and phenolic compounds.	Onyegbule *et al.*, 2019 [143] Martins *et al.*, 2018 [164] Chan-Bacab & Peña-Rodriguéz, 2001 [165]
Musa paradisiaca	Modest antiplasmodial activity	Leishmanicidal effect	gentilebioside sitosterol; myo-inosityl-β-D-glucoside sitosterol; (24R)-4α,14α,24-trimethyl-5α-cholesta-8,2-(27)-dien-3β-ol; stigmasterol; β-sitosterol; cycloeucaleone; 31-norcyclolaudeone; 24-methylene-cycloartanol, anacardic acid	Ghosal, 1985 [166] Dutta *et al.*, 1983 [167] Silva *et al.*, 2014 [168] Bagavan *et al.*, 2011 [171]

NC- not yet known.

CONCLUSION

Different species are used by the Amazon population for the treatment of malaria and leishmaniasis. It is observed that species that have alkaloids, such as *G. sericeum, A. nitidum,* and *A. excelsum*, were shown to be promising as antimalarial and antileishmanial agents, and these activities were related to alkaloids. It is emphasized that the antimalarial drug quinine was isolated from a medicinal plant and this reinforces the hypothesis that compounds obtained from these species may be promising for the treatment of both diseases.

In the case of *Portulaca pilosa*, which contains diterpenes, studies have confirmed their antimalarial potential. Moreover, leishmaniasis can be characterized by wounds that are difficult to heal and the use of *P. pilosa* may contribute to the healing process, although it does not seem to have a direct effect against the parasite.

Undoubtedly, copaíba oil seems to be the most promising for the treatment of leishmaniasis since it displays an antiparasitic and healing effect. Another promising species is *Persea americana,* and it seems that acetogenins are the constituents responsible for the leishmanicidal effect. However, it is emphasized that the acetogenin content of these plants, in general, is extremely low and the synthesis is also overly complex. All other species seem to be less promising as antimalarials and leishmanicidal agents.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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