Research, Society and Development, v. 11, n. 9, e58311932389, 2022
(CC BY 4.0) | ISSN 2525-3409 | DOI: http://dx.doi.org/10.33448/rsd-v11i9.32389

Antimalarial activities of plants with medicinal potential: a systematic review of the literature

Atividades antimaláricas de plantas com potencial medicinal: uma revisão sistemática da literatura

Actividades antipalúdicas de plantas con potencial medicinal: una revisión sistemática de la literatura

Recebido: 01/07/2022 | Revisado: 10/07/2022 | Aceito: 12/07/2022 | Publicado: 19/07/2022

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Abstract

Objective: This is a qualitative study, whose objective was to investigate the scientific literature on plant species potentially active against *Plasmodium* sp. Method: This is a systematic literature review, which aimed to analyze the most recent articles published between the years 2005-2020 in the languages: English and Portuguese. The studies were chosen in an integrative way from the following databases: PubMed (National Library of Medicine), LILACS (Latin American and Caribbean Health Sciences Literature), Science Direct (Explore, scientific and medical) and SciELO (Scientific Electronic Library Online). Results and discussion: 115 species distributed in 50 botanical families were found in antiplasmodial inhibition studies, of which 66 different types of extracts showed action in eliminating these parasites, while 59 of these extracts were inactive. Of this total number, the most studied species belong to the Asteraceae and Fabaceae families. In addition, another 141 botanical species were cited in ethnobotanical surveys in different regions of the world. Aponynaceae and Lamiaceae were the most representative plant families among the studies focused on this topic. The data also allowed us to understand how popular knowledge can help to establish scientific discoveries about plants with antimalarial potential. In addition, environmental conditions were identified as determining factors for the production of chemical constituents in these plants. Conclusion: Efforts to identify plants with active potential in combating the parasite have increased significantly in recent years; however, it is important to emphasize that the preservation of biodiversity needs to be an important aspect of ethnobotanical research in order to guarantee the sustainable use of available resources.

Keywords: Medicinal plants; Herbal medicine; Malaria; Ethnobotany.

Resumo

Objetivo: Trata-se de um estudo qualitativo, cujo objetivo foi investigar a literatura científica sobre espécies vegetais potencialmente ativas contra *Plasmodium* sp. Método: Trata-se de uma revisão sistemática da literatura, no qual objetivou-se analisar os artigos mais recentes publicado entre os anos de 2005-2020 nos idiomas: inglês e português. Os estudos foram escolhidos de forma integrativa nas seguintes bases de dados: PubMed (National Library of Medicine), LILACS (Latin American and Caribbean Health Sciences Literature), Science Direct (Explore, scientific and medical) e SciELO (Scientific Electronic Library Online). Resultados e discussão: Foram encontradas 115 espécies distribuídas em 50 famílias botânicas em estudos de inibição antiplasmodial, das quais 66 diferentes tipos de extratos mostraram ação na eliminação desses parasitas, enquanto 59 desses extratos foram inativos. Deste número total, as

espécies mais estudadas pertencem às famílias Asteraceae e Fabaceae. Além disso, outras 141 espécies botânicas foram citadas em levantamentos etnobotânicos em diferentes regiões do mundo. Aponynaceae e Lamiaceae foram as famílias vegetais mais representativas entre os estudos voltados para este tema. Os dados também permitiram entender como o conhecimento popular pode ajudar a estabelecer descobertas científicas sobre plantas com potencial antimalárico. Além disso, as condições ambientais foram identificadas como fatores determinantes para a produção de constituintes químicos nessas plantas. Conclusão: Os esforços para identificar plantas com potencial ativo no combate ao parasita aumentaram significativamente nos últimos anos; no entanto, é importante ressaltar que a preservação da biodiversidade precisa ser um aspecto importante da pesquisa etnobotânica, a fim de garantir o uso sustentável dos recursos disponíveis.
Palavras-chave: Plantas medicinais; Fitoterapia; Malária; Etnobotânica.

Resumen

Objetivo: Este es un estudio cualitativo, cuyo objetivo fue investigar la literatura científica sobre especies de plantas potencialmente activas contra *Plasmodium* sp. Método: Se trata de una revisión sistemática de la literatura, que tuvo como objetivo analizar los artículos más recientes publicados entre los años 2005-2020 en los idiomas: inglés y portugués. Los estudios fueron seleccionados de manera integradora de las siguientes bases de datos: PubMed (Biblioteca Nacional de Medicina), LILACS (Literatura Latinoamericana y del Caribe en Ciencias de la Salud), Science Direct (Explore, científica y médica) y SciELO (Biblioteca Electrónica Científica en Línea). Resultados y discusión: En los estudios de inhibición antiplasmodial se encontraron 115 especies distribuidas en 50 familias botánicas, de las cuales 66 tipos diferentes de extractos mostraron acción en la eliminación de estos parásitos, mientras que 59 de estos extractos fueron inactivos. De este total, las especies más estudiadas pertenecen a las familias Asteraceae y Fabaceae. Además, otras 141 especies botánicas fueron citadas en estudios etnobotánicos en diferentes regiones del mundo. Aponynaceae y Lamiaceae fueron las familias de plantas más representativas entre los estudios enfocados en este tema. Los datos también permitieron comprender cómo el conocimiento popular puede ayudar a establecer descubrimientos científicos sobre plantas con potencial antipalúdico. Además, se identificaron las condiciones ambientales como determinantes para la producción de componentes químicos en estas plantas. Conclusión: Los esfuerzos para identificar plantas con potencial activo en el combate del parásito se han incrementado significativamente en los últimos años; sin embargo, es importante enfatizar que la preservación de la biodiversidad debe ser un aspecto importante de la investigación etnobotánica para garantizar el uso sostenible de los recursos disponibles.
Palabras clave: Plantas medicinales; Medicina herbaria; Malaria; Etnobotánica.

1. Introduction

Despite advances in malaria chemotherapy, the disease still remains a serious public health problem, especially in tropical and subtropical countries (Tajbakhsh et al., 2021). This parasitic disease is caused by the protozoan of the genus Plasmodium, which in turn is present in more than 90 countries in practically all continents of the world (Santos et al., 2021), it is estimated that only in the year 2020, were more than 200 million new cases were reported and more than 600 thousand people died due to the clinical complications of this disease. It should be noted that this increase is directly linked to the rise of the COVID-19 pandemic(World Health Organization – WHO, 2021).

According to data from the Organização Pan Americana de Saúde (2020), as the spread of COVID-19 increases, the situation in all areas at risk for malaria, especially rural ones, will become more critical, given the inconspicuousness of these populations and fragmentation in the healthcare system. How much will this impact active surveillance of the disease and how can we reduce these impacts which reinforce barriers to treatment, are still some of the challenges of this century (Sherrard-Smith et al., 2020).

Currently, five species are described as capable of infecting humans and causing the characteristic clinical picture of this pathology. Among these species, *Plasmodium vivax*, *Plasmodium falciparum*, *Plasmodium malariae*, *Plasmodium ovale*, *Plasmodium knowlesi* and more recently *Plasmodium simium* are described (Bassat et al., 2022; Brasil et al., 2017; Sabbatani et al., 2010).

Malaria has a major impact on peripheral communities in insalubrious localities, such as miners/excavators, riverside dwellers, indigenous villages, agricultural settlement projects, and squatters, who often engage in disorderly migration, favoring exposure to *Anopheles*. Patient care therefore becomes vulnerable since it depends on an effective and timely diagnosis and treatment. In addition, the phenomenon of drug resistance is a barrier to the elimination of this disease (Pluijm et al., 2021).

On the other hand, medicinal plants have historically been a means through which studies seek for antimalarial targets; for example, the discovery of quinine extracted from the bark of *Cinchona pubescecens*, artemisinin which was evaluated from extracts of *Artemisina annua* L., a traditional Chinese plant used to reduce fever (Bero et al., 2009; Tu, 2011). In this scenario, the search for compounds applicable towards the development of new drugs as alternatives to current antimalarial agents which are facing cases of resistance, remains important (Ménard et al., 2016; Leang et al., 2015; Pluijm et al., 2021).

From this perspective, the discovery of new antimalarials with action against different morphological stages of the parasite and with different mechanisms of action, becomes essential in the control and elimination of this disease (Tse et al., 2019). Thus, considering the lack of access to rapid treatment in some communities, over the decades, plants with medicinal potential have been used as an alternative means of treatment in these locations (Moraes et al., 2020; Martinez et al., 2020).

Considering the importance of adequate and effective treatments as a tool to contain episodes of malaria caused by *Plasmodium* spp, including the severe cases described in the study by Kotepui et al. (2020), the present study aimed to investigate in the scientific literature active and inactive medicinal plants against malaria parasites, emphasizing changes between different ecosystems.

2. Materials and Methods

The literature was reviewed in search of scientific articles reporting antispasmodics activities (IC_{50} or µg/mL) of plants with medicinal potential used around the world for the treatment of malaria.

2.1 Search strategy and selection criteria

The study is a systematic and integrative review of the literature carried out in accordance with the study published by Tajbakhsh et al. (2021). A review of studies was carried out in PubMed (National Library of Medicine), LILACS (Latin American and Caribbean Health Sciences Literature), Science Direct (Explore, scientific and medical) databases and in the SciELO virtual library (Scientific Electronic Library Online).

Articles in both English and Portuguese were selected that had the descriptors MESCH/DECS and the following terms combined with the Boolean operators "AND" and "OR": "plant medicine malaria", "herbal malaria", "antimalarials vivax" and "ethnobotany *Plasmodium*".

Studies carried out between 2005 and 2020, the search was limited to studies published in English and Portuguese bthat were available in full and addressed this theme of medicinal plants, antimalarials and ethnobotanics, were selected.

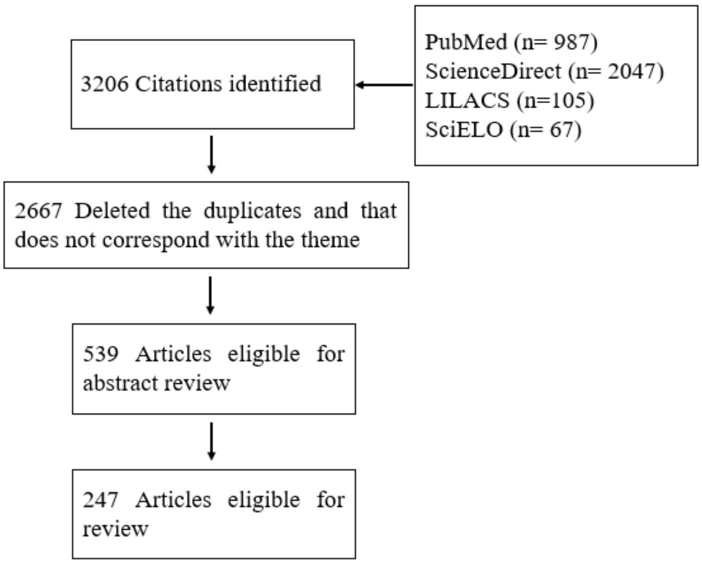
Project documents, reports, grey literature, papers presented at conferences, articles that overlap the theme, studies on *in vivo* tests with animals and those repeated in the databases were excluded. The titles and abstracts were subsequently examined by two reviewers, independently (parallel method) to identify articles reporting the antiplasmodial activity of potential medicinal plants.

For synthetic compounds, IC50 values $\leq$ 10 µM were considered potentially active compounds (Mahmoudi et al., 2006). Regarding compounds derived from plant extracts, the activity values considered active were $IC_{50} \leq 10$ µg/mL, and inactive $IC_{50} \geq 25$ µg/mL (Bagavan et al., 2013; Lima et al., 2015).

The following data were extracted from the selected articles by the reviewers: plant species, plant family, place of collection of plant, parts of the plant used, solvent used, isolated compounds. The entire selection process is presented in (Figure 1).

Data collection and analysis were performed by reading the titles and abstracts, choosing the complete texts based on the eligibility criteria, and extracting the data in a standardized Microsoft Office Excel® 2019 spreadsheet, tabulated in GraphPad Prisma Software (version 6).

Figure 1. Flowchart of the selection process for publications included in this review.



Source: Authors.

3. Results and Discussion

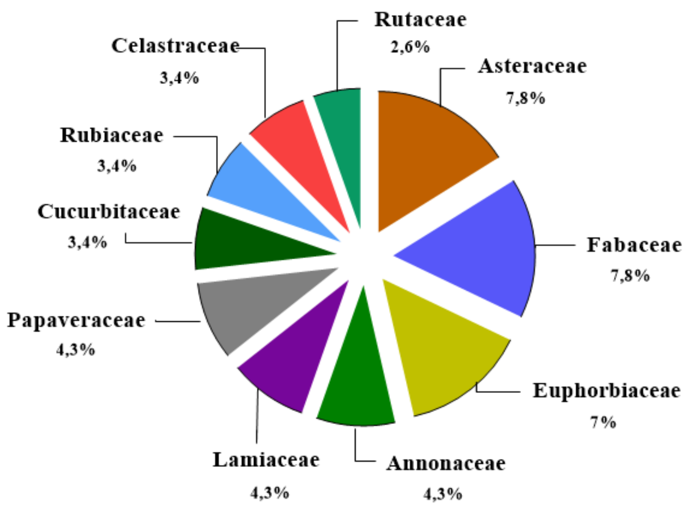
In carrying out this study, it was possible to identify relevant aspects of empirical knowledge and common sense in relation to the use of medicinal plants as antimalarials by populations in different regions of the world, after using the keywords.

In the PubMed data platform, 987 articles were found, but only 110 were selected according to the exclusion criteria. Similarly, 22 articles were selected from a total of 105 found in LILACS. In the SciELO database, 67 articles were found, but after applying the exclusion criteria, only 3 were in accordance with the objectives of this theme, and of the 2.047 articles found in the Science Direct database, 112 articles were selected. Ultimately, a total of 3.206 articles were found and only 247 were retained after analysis (Figure 1).

In this research, the evaluation of individual plant species was considered as an independent study, so it is common for an article to have more than one study depending on the number of plant species evaluated (Tajbakhsh et al., 2021).

In this study, 115 plant species were cited within studies aimed at inhibiting *P. falciparum*, which in turn are distributed among 50 botanical families (Table 1). When analyzing the literature, the most expressive families in relation to species were: Asteraceae, Fabaceae, Euphorbiaceae, Annonaceae, Lamiaceae, Papaveraceae, Cucurbitaceae, Rubiaceae, Rutaceae, and Celastraceae (Figure 2).

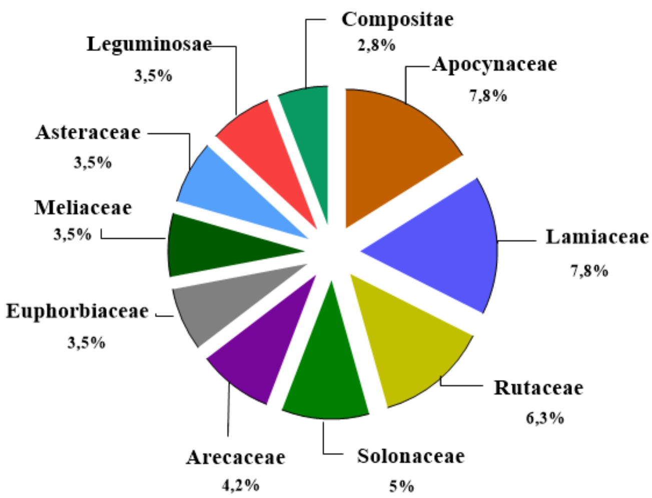
Figure 2. Number of botanical species most cited in *P. falciparum* inhibition studies.



Source: Authors.

As for the results obtained from the ethnobotanical surveys, 141 botanical species used for the treatment of malaria were found, distributed among 59 botanical families (Table 2), namely: Apocynaceae, Lamiaceae, Rutaceae, Solanaceae, Arecaceae, Asteraceae, Euphorbiaceae, Leguminosae, Meliaceae, and Anacardiaceae (Figure 3).

Figure 3. Number of botanical especies most cited in Surveys.



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The parts of the plants most used for the extraction of chemical constituents with a possible action on malaria parasites were: leaf, aerial part, root, stem and stem bark, of which 66 botanical extracts, extracted using a variety of methodologies, were active in inhibiting *P. falciparum*, and 59 extracts were inactive (Table 1). The most cited plant parts in ethnobotanical surveys for therapeutic preparations were leaves, roots, stem bark, aerial part and stem. (Table 2).

Finally, the countries that contain the most plants utilized in studies on *P. falciparum* inhibition belong to the African continent, especially to the countries of Cameroon and Kenya. The countries with the highest number of botanical species cited were Brazil and Kenya.

It is important to highlight that all the studies came from *in vitro* assays with *P. falciparum*. No studies related to *P. vivax* were found in the literature, since this species presents limitations when maintained in culture (Bermúdez et al., 2018).

Table 1. Medicinal plant species used in inhibition studies of *P. falciparum in vitro*.

Species and botanical family	Country	Part of the plant used	Extraction method	Inhibition results	References
(a) *Andrographis paniculata* Nees (b) *Dyschoriste perrottetii* O. Kuntze ACANTHACEAE	(a) India, (b) Burkina Faso	(a) Whole plant, (b) Aerial part	(a) MeOH, Combination (AP+HC+curcumin), (b) CH_2Cl_2, MeOH, H_2O	(a) Active, (b) Inactive	(a) Mishra et al. (2009); (b) Jansen et al. (2010)
(a) *Alstonia congensis* Engl. ALISMATACEAE	(a) -	(a) Root	(a) -	(a) Atcive	(a) Adams et al. (2011)
(a) *Achyranthes aspera* Duss AMARANTHACEAE	(a) Sri Lanka	(a) Stem, leaf, root	(a) EtOH	(a) Inactive	(a) Inbaneson, Ravikumar and Suganthi, (2012)
(a), (b), (c), (d) *Alchornea latifolia* Klotzsch (e) *Cananga odorata* (Lam.) Hook.f. & Thomson (f) *Polyalthia longifolia* (Sonn.) Thwaites (g) *Pseudomalmea boyacana* (J.F.Macbr.) Chatrou (h) *Rollinia pittieri* Saff. ANNONACEAE	(a), (b), (c), (d), (e) Cameroon, (f) Ghana, (g), (h) Colombia	(a) Stem, (b) Leaf, (c) Bough, (d) Bark, (e) Flowers, (f) Stem bark, (g) Leaf, bark, (h) Whole plant	(a), (b), (c), (d) EtOH (e) -, (f) EtOH, (g), (h) C_6H_{14}, $C_4H_8O_2$, MeOH	(a), (b), (c), (d), (e) Inactive, (f), (g), (h) Active	(a), (b), (c), (d), (e) Marie et al. (2018); (f) Gbedema et al. (2015); (g), (h) Osorio et al. (2007)
(a) *Ferula oopoda* Boiss. APIACEAE	(a) Iran	(a) Root	(a) MeOH	(a) Active	(a) Esmaeili et al. (2009)
(a) *Alstonia congensis* Engl. APOCYNACEAE	(a) Congo	(a) Root bark	(a) MeOH	(a) Active	(a) Cimanga et al. (2019)
(a) *Schefflera umbellifera* Baill. (b) *Seemannaralia gerrardii* R.Vig. ARALIACEAE	(a), (b) -	(a), (b) Leaf	(a), (b) MeOH	(a), (b) Inactive	(a), (b) De Villiers et al. (2010)
(a) *Vernonia amygdalina* Delile (b) *Baccharoides adoensis* (Sch.Bip. ex Walp.) H.Rob.	(a), (b), (c), (d) Uganda, (e) Burkina Faso, (f) Reunion island,	(a), (b) Leaf, (c) Aerial part, (d) Leaf, (e) Whole plant, (f) Leaf,	(a) Éter, MeOH, (b) C_6H_{14}, éter, CH_2Cl_2, MeOH, (c) C_6H_{14}, éter,	(a) Inactive, (b) Active, (c) Inactive, (d), (e) Active, (f), Active	(a), (b), (c) Obbo et al. (2019); (d) Adia et al. (2016); (e)Jansen et al.(2010); (f) Jonville et al. (2008);

(c) ***Stanleya pinnata*** **Britton** **(d)** ***Microglossa pyrifolia*** **(Lam.) O. Ktze** **(e)** ***Dicoma tomentosa*** **Cass.** **(f)** ***Psiadia arguta*** **Voigt** **(g)** ***Pluchea lanceolata*** **(DC.) C.B.Clarke** **(h)** ***Ageratum conyzoides*** **L.** **ASTERACEAE**	(g) India, (h) Kenya	(g) Aerial part, (h) Whole plant	(d) EtOAc, H_2O, MeOH, (e) CH_2Cl_2, MeOH, H_2O, (f) CH_2CL_2, MeOH, (g) MeOH, $CHCl_3$, $C_4H_8O_2$, BuOH, C_6H_{14}, (h) CH_2Cl_2,	(g), C_6H_{14}/ Active (h) Active	(g) Mohanty et al. (2013); (h) Owuor et al. (2012)
(a) ***Balanites aegyptiaca*** **Delile** **BALANITACEAE**	(a) Togo	(a) Aerial part	(a) -	(a) Inactive	(a) Karou et al. (2011)
(a) ***Buddleja salviifolia*** **(L.) Lam.** **(b)** ***Nuxia verticillata*** **Lam.** **BUDDLEJACEAE**	(a), (b) Reunion island	(a) Stem, leaf, (b) Leaf	(a) CH_2Cl_2, (b) CH_2Cl_2, MeOH	(a), (b) Inactive	(a) Jansen et al. (2010); (b) Jonville et al. (2008)
(a) ***Boswellia dalzielii*** **Hutch.** **BURSERACEAE**	(a) Burkina Faso	(a) Leaf	(a) CH_2Cl_2 , MeOH, H_2O	(a) Active	(a) Jansen et al. (2010)
(a) ***Buxus hyrcana*** **Pojark.** **BUXACEAE**	(a) Iran	(a) Root	(a) MeOH	(a) Active	(a) Esmaeili et al. (2009)
(a) ***Tamarindus indica*** **L.** **(b)** ***Cassia alata*** **L.** **CAESALPINIACEAE**	(a) Togo, (b) Burkina Faso	(a) - (b) Leaf	(a) CH_2Cl_2, EtOH, MeOH, (b) -	(a), (b) Active	(a) Koudouvo et al. (2011); (b) Traoré et al. (2008)
(a) ***Daniellia ogea*** **(Harms) Holland** **CAESALPINIOIDEAE**	(a) Nigeria	(a) Root	(a) EtOH	(a) Inactive	(a) Ezenyi et al. (2020)
(a) ***Warburgia stuhlmannii*** **Engl.** **(b)** ***Warburgia stuhlmannii*** **Engl.** **CANELLACEAE**	(a), (b) Kenya	(a), (b) Stem bark	(a), (b) MeOH, H_2O	(a), (b) Active	(a), (b) Muthaura et al. (2007)
(a) ***Carica papaya*** **L.** **CARICACEAE**	(a) Indonesia	(a) Leaf	(a) MeOH	(a) Active	(a) Julianti et al. (2013)
(a) ***Loeseneriella africana*** **N.Hallé** **(b)** ***Maytenus putterlickioides*** **(Loes.) Exell & Mendonça** **(c)** ***Maytenus undata*** **(Thunb.) Blakelock** **CELASTRACEAE**	(a) Burkina Faso, (b), (c) Kenya	(a) Leaf, (b) Stem root, (c) Leaf	(a) CH_2Cl_2, MeOH, H_2O, (b), (c) MeOH, H_2O	(a) Inactive, (b) Active, (c) Active	(a) Jansen et al. (2010); (b), (c) Muthaura et al. (2007)
(a) ***Psorospermum senegalense*** **Spach.** **CLUSIACEAE**	(a) Burkina Faso	(a) Leaf	(a) CH_2Cl_2, MeOH, H_2O	(a) Activo	(a) Jansen et al. (2010)

(a) ***Warburgia stuhlmannii*** **Engl.** **COCHLOSPERMACEAE**	(a) Burkina Faso	(a) Rhizome	(a) -	(a) Active	(a) Traoré et al. 2008)
(a) ***Terminalia catappa*** **L.** **(b)** ***Terminalia bentzoe*** **L.** **(c)** ***Terminalia mantaly*** **H.Perrier** **COMBRETACEAE**	(a) Cameroon, (b) Reunion island, (c) Cameroon	(a), (b) Leaf, (c) Leaf, bark	(a) -, (b) MeOH, CH_2Cl_2, (c) -	(a) Active, (b) Inactive, (c) Active	(a), (c) Marie et al. (2018); (b) Jonville et al., 2008)
(a) ***Cornus florida*** **Hook.** **CORNACEAE**	(a) U.S.A	(a) Bark, fruit, Leaf	(a) EtOH	(a) Inactive	(a) Graziose et al. (2012)
(a) ***Momordica foetida*** **Schumach** **(b)** ***Momordica foetida*** **Schumach** **(c)** ***Momordica balsamina*** **L.** **(d)** ***Momordica charantia*** **L.** **CUCURBITACEAE**	(a), (b) Uganda, (c) Nigeria, (d) India	(a) Leaf, root, (b) Leaf, (c) -, (d) Leaf	(a) C_6H_{14}, ether, CH_2Cl_2 (b) EtOAc, H_2O, MeOH, (c) -, (d) $C_4H_8O_2$	(a) Inactive, (b) H_2O/ Active, (c), (d) Active	(a) Obbo et al, (2019); (b) Adia et al., (2016); Benoit-Vical et al.,(2006); (d) Kamaraj et al. (2012)
(a) ***Bergia suffruticosa*** **Fenzl** **ELATINACEAE**	(a) Burkina Faso	(a) Whole plant	(a) CH_2Cl_2 , MeOH, H_2O	(a) Active	(a) Jansen et al. (2010)
(a), (b), (c), (d) ***Annona senegalensis*** **Pers.** **(e), (f), (g)** ***Drypetes principum*** **Hutch.** **(h)** ***Phyllanthus amarus*** **Schumach. & Thonn.** **(i)** ***Phyllanthus amarus*** **Schumach. & Thonn.** **(j)** ***Phyllanthus amarus*** **Schumach. & Thonn.** **(k)** ***Acalypha indica*** **L.** **(l)** ***Jatropha glandulifera*** **Roxb.** **(m)** ***Jatropha gossypiifolia*** **L.** **EUPHORBIACEAE**	(a), (b), (c), (d), (e), (f), (g) Cameroon, (h) India (i) Burkina Faso (j), (k), (l) Sri Lanka, (m) Burkina Faso	(a) Stem, (b) Leaf, (c) Bough, (d) Bark, (e) Stem, (f) Leaf, (g) Bough, (h) Leaf, (i) Whole plant, (j) Leaf, root, stem, (k), (l) Stem, leaf, root, (m) Leaf	(a), (b), (c), (d) Hydroethanol, EtOH, (e), (f), (g) EtOH, (h) MeOH (i) - (j), (k), (l) EtOH, (m) CH_2Cl_2, MeOH, H_2O	(a), (b), (c), (d) Inactive, (e), (f), (g) Active, (h), (i) Active, (j) Inactive, (k), (l), (m) Active	(a), (b), (c), (d), (e), (f), (g) Marie et al. (2018); (h) Kamaraj et al. (2012) (i) Traoré et al. (2008); (j), (k), (l) Inbaneson, Ravikumar and Suganthi, (2012); (m) Jansen et al. (2010)
(a), (b), (c) ***Senna alata*** **(L.) Roxb.** **(d)** ***Glycine max*** **(L.) Merr.** **(e)** ***Gliricidia sepium Kunth*** **(f)** ***Erythrina abyssinica Lam.*** **(g)** ***Copaifera reticulata*** **Ducke** **(h)** ***Cajanus caja*** **(L.) Millsp.** **(i)** ***Cassia siamea*** **L.** **(j)** ***Glycyrrhiza glabra*** **L.** **(k)** ***Bauhinia rufescens*** **Lam.**	(a), (b), (c) Cameroon, (d), (e) Colombia, (f) Uganda, (g) Brazil, (h), (i) Nigeria, (j) Iran (k) Burkina Faso	(a) Stem, (b) Leaf, (c) Bough, (d) Seed, (e) Leaf, Stalk, (f) Seed, (g) -, (h) Leaf, (i) Stem bark, (j) Aerial part, (k) Leaf	(a), (b), (c) EtOH, (d) H_2O, MeOH, (e) $C_4H_8O_2$, (f) éter, CH_2Cl_2, MeOH (g), (h), (i) -, (j) MeOH, (k) CH_2Cl_2, MeOH, H_2O	(a), (b), (c) Inactive, (d) Active, (e), (f) Inactive, (g), (h), (i), (j) Active, (k) Inactive	(a), (b), (c) Marie et al. (2018); (d) Nyandwaro et al. (2020); (e) Vargas-Sinisterra et al. (2018); (f) Obbo et al. (2019); (g) Souza et al. (2017); (h), (i) Ajaiyeoba et al.(2008); (j) Esmaeili et al. (2009); (k) Jansen et al. (2010)

FABACEAE					
(a) *Aphloia theiformis* Benn. **FLACOURTIACEAE**	(a) Reunion island	(a) Leaf	(a) CH_2Cl_2, MeOH	(a) Active	(a) Jonville et al. (2008)
(a) *Erodium oxyrrhnchum* M. Bieb. **GERANIACEAE**	(a) Iran	(a) Aerial part	(a) MeOH	(a) Active	(a) Esmaeili et al. (2009)
(a) *Andropogon schirensis* Hochst. **GRAMINACEAE**	(a) Nigeria	(a) Root	(a) EtOH	(a) Inactive	(a) Ezenyi et al. (2020)
(a) *Icacina trichanta* Oliv. **ICACINACEAE**	(a) Nigeria	(a) Leaf	(a) EtOH	(a) Inactive	(a) Ezenyi et al. (2020)
(a), (b), (c) *Ocimum gratissimum* Forssk. **(d) *Clerodendrum rotundifolium* Oliv.** **(e) *Leucas aspera* Link** **(f) *Ocimum kilimandscharicum* Gürke** **(g) *Plectranthus barbatus* Andrews** **LAMIACEAE**	(a), (b), (c) Cameroon, (d) Uganda, (e) India, (f), (g) Kenya	(a) Stem, (b) Leaf, (c) Root, (d), (e) Leaf, (f) Leaf, bough, (g) Leaf, peduncle	(a), $C_4H_8O_2$, MeOH (b) $C_4H_8O_2$, MeOH (c) $C_4H_8O_2$, MeOH, (d) EtOAc, H_2O, MeOH, (e) $C_4H_8O_2$, (f), (g) CH_2Cl_2	(a), (b), (c) Inactive, (d), (e), (f) Active, (g) Inactive	(a), (b), (c) Marie et al. 2018); (d) Adia et al. (2016); (e) Kamaraj et al. (2012); (f), (g) Owuor et al. (2012)
(a) *Albezia gummifera* C.A.Sm. **LEGUMINOSAE**	(a) Kenya	(a) Root bark	(a) MeOH	(a) Inactive	(a) Rukunga et al.(2007)
(a) *Punica granatum* L. **LYTHRACEAE**	(a) India	(a) Fruit peel	(a) MeOH	(a) Inactive	(a) Dell'Agli et al. (2009)
(a) *Khaya anthotheca* C.DC. **(b) *Entandrophragma utile* Sprague** **MELIACAE**	(a), (b) Uganda	(a), (b) Seed	(a) C_6H_{14}, éter, CH_2Cl_2, MeOH, H_2O, (b) éter, CH_2Cl_2, MeOH	(a), (b) Inactive	(a), (b) Obbo et al. (2019)
(a) *Chasmanthera dependens* Hochst. **(b) *Albertisia delagoensis* (N.E.Br.) Forman** **(c) *Triclisia sacleuxii* Diels** **MENISPERMACEAE**	(a) Nigeria, (b) South Africa, (c) Tanzania	(a) Stem bark (b) Leaf, rhizome, (c) Root	(a) EtOH, (b) MeOH, (c) EtOH	(a) Inactive, (b), (c) Active	(a) Ezenyi et al. (2020); (b) De Wet, et al. (2007); (c) Murebwayire et al. (2009)
(a), (b), (c), (d) (e) *Ficus benjamina* (Miq.) Corner **(f) *Ficus exasperata* Vahl** **(g) *Ficus thonningii* Blume** **MORACEAE**	(a), (b), (c), (d), (e), (f) Cameroon, (g) Burkina Faso	(a) Fruit, (b) Leaf, (c) Stem, (d) Bark, (e) Stem, (f), (g) Leaf	(a), (b), (c), (d), (e), (f) Hydroethanol, (g) CH_2Cl_2, MeOH, H_2O	(a), (b), (c), (d), (e), (f), (g) Inactive	(a), (b), (c), (d), (e), (f) Marie et al. (2018); (g) Jansen et al. (2010)

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(a) *Callistemon citrinus Skeels* **(b) *Myrtus communis* L.** **MYRTACEAE**	(a) Cameroon (b) Iran	(a) Leaf (b) Aerial part	(a) $C_4H_8O_2$, MeOH, (b) MeOH	(a), (b) Active	(a) Larayetan et al. (2019); (b) Naghibi et al. (2013)
(a) *Opilia celtidifolia* Endl. ex Walp. **OPILIACEAE**	(a) Togo	(a) -	(a) CH_2Cl_2, EtOH, MeOH	(a) Inactive	(a) Koudouvo et al. (2011)
(a) *Fumaria cilicica* Hausskn. **(b) *Fumaria densiflora* DC.** **(c) *Fumaria Kralikii* Jord.** **(d) *Fumaria parviflora* Lam.** **(e) *Fumaria rostellata* Knaf** **PAPAVERACEAE**	(a), (b), (c), (d), (e) -	(a), (b), (c), (d), (e) Aerial part	(a), (b), (c), (d), (e) EtOH	(a) Inactive, (b), (c) Active, (d) Inactive, (e) Active	(a), (b), (c), (d), (e) Orhan, Ozturk and Sener, (2015)
(a) *Flueggea virosa* Wall. **PHYLLANTHACEAE**	(a) Kenya	(a) Leaf	(a) MeOH	(a) Active	(a) Muthaura et al. (2007)
(a) *Piper tricuspe* C.DC. **(b) *Piper nigrum* L.** **PIPERACEAE**	(a) Colombia, (b) India	(a) Leaf, Stalk, (b) Seed	(a) EtOH, (b) $C_4H_8O_2$	(a) Inactive (b) Active	(a) Vargas-Sinisterra et al. (2018); (b) Kamaraj et al. (2012)
(a) *Plantago major* L. **PLANTAGINACEAE**	(a) Colombia	(a) Leaf, stalk	(a) EtOH	(a) Inactive	(a) Vargas-Sinisterra et al. (2018)
(a) *Crossopteryx febrifuga* Benth. **(b) *Gardenia sokotensis* Hutch.** **(c) *Pavetta corymbosa* (DC.) F.N. Williams Hutch.** **(d) *Nauclea pobeguinii* Merr.** **RUBIACEAE**	(a), (b) Burkina Faso, (c) Togo, (d) Congo	(a), (b) Leaf, (c) -, (d) Stem bark	(a), (b) CH_2Cl_2, MeOH, H_2O, (c) CH_2Cl_2, EtOH, MeOH, (d) EtOH	(a) Inactive (b), (c), (d) Active	(a), (b) Jansen et al. (2010); Koudouvo et al. (2011); (d) Mesia et al. (2012)
(a) *Zanthoxylum chalybeum* Engl. **(b) *Aegle marmelos* (L.) Corrêa** **(c) *Toddalia asiatica* Lam** **(d) *Teclea gerrardii* I.Verd.** **RUTACEAE**	(a) Uganda, (b) India, (c) Kenya, (d) South Africa	(a) Stem bark, (b) Leaf, (c) Root bark, fruit, leaf, (d) Stem bark	(a) EtOAc, H_2O, MeOH, (b) MeOH, (c) MeOH, (d) CH_2Cl_2	(a) EtOAc, H_2O/ Active, (b), (c) Active, (d) Inactive	(a), (b) Adia et al. (2016); Kamaraj et al. (2012); (c) Orwa et al. (2013); (d) Waffo et al. (2007)
(a) *Vitellaria paradoxa* Gaertn. **SAPOTACEAE**	(a) Burkina Faso	(a) Aerial part	(a) CH_2Cl_2, MeOH, H_2O	(a) Active	(a) Jansen et al. (2010)
(a) *Quasia amara* L. **(b) *Quasia amara* L.** **(c) *Eurycoma longifolia* Jack** **SIMAROUBACEAE**	(a), (b) French Guiana, (c) -	(a), (b) Leaf, (c) stem bark	(a) CH_2Cl_2, (b), (c) -	(a) Inactive, (b) Active, (c) Inactive	(a) Houël et al. (2009); (b) Bertani et al. (2012); (c) Bhat and Karim, (2010)

(a) *Solanum nudum* Humb. & Bonpl. ex Dunal (b) *Withania frutescens* Pauq. SOLANACEAE	(a) Colombia, (b) Algeria	(a) Leaf and stalk, (b) Leaf, root	(a) EtOH, (b) (leaf: BuOH, CH_2Cl_2, EtOAc), (root and leaf: MeOH)	(a) Inactive (b) CH_2Cl_2, BuOH/ Active	(a) Vargas-Sinisterra et al. (2018); (b) El Bouzidi et al. (2017)
(a) *Waltheria indica* L. STERCULIACEAE	(a) Burkina Faso	(a) Root	(a) CH_2Cl_2, MeOH, H_2O	(a) Active	(a) Jansen et al. (2010)
(a) *Triumfetta cordifolia* A. Rich. TILIACEAE	(a) Nigeria	(a) Leaf	(a) EtOH	(a) Inactive	(a) Ezenyi et al. (2020)
(a) *Celtis durandii* Engl. (b) *Trema orientalis* (L.) Blume ULMACEAE	(a) Nigeria, (b) -	(a) Root, (b) Stem bark, leaf	(a) EtOH, (b) C_6H_{14}	(a) Inactive, (b) -	(a) Ezenyi et al. (2020); (b) Adinortey, Galyuon e Asamoah, (2013)
(a) *Lantana camara* L. (b) *Lantana camara* L. VERBENACEAE	(a) Reunion island (b) India	(a), (b) Leaf	(a) CH_2Cl_2 (b) $C_4H_8O_2$	(a) Inactive (b) Active	(a) Jonville et al. (2008); (b) Kamaraj et al. (2012)

(AP+HC) combination of *Andrographis paniculata* and *Hedyotis corymbosa*; (-) No information; Dichloromethane=CH_2Cl_2; Hexane=C_6H_{14}, EtOAc=Ethyl Acetate; BuOH=Butanol; Propyl methanoate=$C_4H_8O_2$, Chloroform=$CHCl_3$.

Table 2. Species of medicinal plants used for the treatment of malaria cited in ethnobotanical surveys.

Species and botanical family	Country	Part of the plant used	References
(a) *Justicia betonica* L. (b) *Andrographis paniculata* Nees ACANTHACEAE	(a) Kenya, (b) India	(a) Aerial part, (b) Whole plant	(a) Mukungu et al., (2016); (b) Nagendrappa, Naik and Payyappallimana, (2013)
(a) *Acorus calamus* L. ACORACEAE	(a) Indonesia	(a) Rhizome	(a) Taek et al. (2019)
(a) *Allium cepa* L. ALLIACEAE	(a) Indonesia	(a) Bulb	(a) Taek et al. (2019)
(a) *Elaeis guineensis* Jacq. (b) *Aloe deserti* A.Berger (c) *Aloe macrosiphon* Baker ALOACEAE	(a) Ghana, (b), (c) Kenya	(a) Root, (b), (c) Leaf	(a) Asase, Akwetey and Achel, (2010); (b), (c) Nguta et al. (2010)
(a) *Alternanthera sessilis* (L.) R.Br. (b) *Amaranthus hybridus* L. AMARANTHACEAE	(a) Brazil, (b) Kenya	(a), (b) Leaf	(a) Tomchinsky et al. (2017); (b) Nguta et al. (2010)
(a) *Crimum asiaticum* L. AMARYLLIDACEAE	(a) Indonesia	(a) Leaf, bulb	(a) Taek et al. (2019)

(a) ***Searsia natalensis*** **(Bernh.ex C. Krauss)** **(b)** ***Rhoicissus tridentata*** **(L.f.) Wild and R.B.Drumm.** **(c)** ***Mangifera indica*** **L.** **(d)** ***Mangifera indica*** **L.** **ANACARDIACEAE**	(a), (b) Kenya, (c) Uganda, (d) Cameroon	(a), (b) Root, stem bark, (c) Leaf, (d) -	(a), (b) Mukungu et al. (2016); (c) Tabuti, (2008); (d) Tsabang et al. (2012)
(a) ***Annona reticulata*** **L.** **(b)** ***Annona muricata*** **L.** **ANNONACEAE**	(a), (b) Indonesia	(a) Stem bark, (b) Leaf	(a), (b) Taek et al. (2019)
(a) ***Aspidosperma nitidum Benth.*** **Ex Müll.Arg.** **(b)** ***Aspidosperma schultesii*** **Woodson*** **(c)** ***Himatanthus stenophyllus*** **Plumel** **(d)** ***Himatanthus sucuuba*** **(Spruce ex Müll.Arg.) Woodson** **(e)** ***Alstonia scholaris*** **(L.) R.Br.a** **(f)** ***Alstonia spectabilis*** **R.Br.** **(g)** ***Calotropis gigantea*** **(L.) R. Br.** **(h)** ***Carissa edulis*** **L.** **(i)** ***Laudolphia*** **buchananii (Hall.f) Stapf.)** **(j)** ***Alstonia boonei*** **De Wild.** **(k)** ***Alstonia congensis*** **Engl.** **APOCYNACEAE**	(a), (b), (c), (d) Brazil, (e), (f), (g), Indonesia, (h), (i), Kenya, (j) Cameroon, (k) Nigeria	(a), (b) Bark, (c) Bark, sap, (d) Bark, (e), (f) Stem bark, (g) Leaf, (h) Root, bark, (i), (j), (k) Leaf	(a), (b), (c), (d) Tomchinsky et al. (2017); (e), (f), (g) Taek et al. (2019); (h) Mukungu et al. (2016); Nguta et al. (2010); Tsabang et al. (2012); (i), (j), (k) Dike, Obembe and Adebiyi, (2012)
(a) ***Astrocaryum aculeatum*** **G.Mey** **(b)** ***Euterpe catinga*** **Wallace** **(c)** ***Euterpe oleracea*** **Mart.** **(d)** ***Euterpe precatoria*** **Mart.*** **(e)** ***Socratea exorrhiz*****a (Mart.) H.Wendl** **(f)** ***Elaeis guineensis*** **Jacq.** **ARECACEAE**	(a), (b), (c), (d), (e) Brazil, (f) Ghana	(a) Stalk, (b), (c), (d) Root, (e) Leaf, (f) Root	(a), (b), (c), (d), (e) Tomchinsky et al., (2017); (f) Asase, Akwetey e Achel (2010)
(a) ***Blumea balsamifera*** **(L.) DC.** **(b)** ***Vernonia amygdalina*** **Delile** **(c)** ***Tithonia diversifolia*** **A.Gray** **(d)** ***Launaea cornuta*** **(Hochst. ex Oliv. & Hiern) C.Jeffrey** **(e)** ***Senecio syringifolius*** **O.Hoffm.** **ASTERACEAE**	(a) Indonesia, (b) Uganda, (c) sub-Saharan African, (d), (e) Kenya	(a), (b) Leaf, (c) Stem bark, (d), (e) Root	(a) Taek et al., (2019); (b) Tabuti, (2008); (c) Chinsembu (2015); (d), (e) Nguta et al., (2010)
(a) ***Handroanthus barbatus*** **(E.Mey.) Mattos** **(b)** ***Markhamia lutea*** **(Benth.) K.Schum.** **(c)** ***Spathodea campanulata*** **P.Beauv.** **BIGNONIACEAE**	(a) Brazil, (b), (c) Kenya	(a) Leaf, (b), (c) Stem bark	(a) Tomchinsky et al.(2017); (b), (c) Mukungu et al. (2016)
(a) ***Garuga floribunda*** **Decne.** **BURSERACEAE**	(a) Indonesia	(a) Leaf	(a) Taek et al. (2019)
(a) ***Warbugia ugandensis*** **Sprague.** **CANELLACEAE**	(a) Kenya	(a) Leaf, Stem bark	(a) Mukungu et al. (2016)
(a) ***Cleome rutidosperma*** **DC.** **CAPPARACEAE**	(a) Indonesia	(a) Whole plant	(a) Taek et al. (2019)
(a) ***Carica papaya*** **L.*** **(b)** ***Carica papaya*** **L.a** **CARICACEAE**	(a) Brazil, (b) Indoneseia	(a), (b) Leaf	(a) Tomchinsky et al. (2017); (b) Taek et al. (2019)

(a) *Elaeis guineensis* Jacq. **COMBRETACEAE**	(a) Kenya	(a) Leaf	(a) Nguta et al. (2010)
(a) *Acmella caulirhiza* Del. **(b) *Microglossa pyrifolia* (Lam.) Kuntze** **(c) *Tithonia diversifolia* (Hemsl.) A. Gray** **(d) *Vernonia amygdalina* Del.** **COMPOSITAE**	(a), (b), (c), (d) Kenya	(a) Aerial part, (b) Root, leaf, (c), (d) Leaf,	(a), (b), (c), (d) Mukungu et al. (2016)
(a) *Bonamia ferruginea* (Choisy) Hallier f. **CONVOVULACEAE**	(a) Brazil	(a) Leaf	(a) Tomchinsky et al. (2017)
(a) *Momordica charantia* L.a **(b) *Gerranthus lobatus* (Cogn.) Jeffrey** **(c) *Momordica foetida* Schumach.** **(d) *Cucumis aculeatus* Cogn** **CUCURBITACEAE**	(a) Indonesia, (b) Kenya, (c) Uganda, (d) Kenya	(a) Leaf, fruit, (b) Leaf (c), (d) Leaf	(a) Taek et al. (2019); (b) Nguta et al. (2010); (c) Tabuti (2008); (d) Mukungu et al. (2016)
(a) *Dichapetalum madagascariense* Poir. **DICHAPETALACEAE**	(a) Benin	(a) Leaf	(a) Yetein et al. (2013)
(a) *Doliocarpus magnificus* Sleumer **DILLENIACEAE**	(a) Brazil	(a) Leaf	(a) Tomchinsky et al. (2017)
(a) *Jatropha curcas* L.* **(b) *Manihot esculenta* Crantz** **(c) *Croton cajucara* Benth.*** **(d) *Jatropha curcas* L.** **(e) *Crotom macrostachuys* Hochst. ex Del.** **EUPHORBIACEAE**	(a), (b), (c) Brazil, (d) Indonesia, (e) Kenya	(a) Seed (b) Root, (c) Leaf, (d), (e) Stem bark	(a), (b), (c) Tomchinsky et al. (2017); (d) Taek et al. (2019); (e) Mukungu et al. (2016)
(a) *Phanera splendens* (Kunth) Vaz* **(b) *Phaseolus vulgaris* L.** **(c) *Senna occidentalis* (L.) Link*** **FABACEAE**	Brazil	(a) Bough, (b) Seed, (c) Seed	(a), (b), (c) Tomchinsky et al. (2017)
(a) *Potalia resinifera* Mart. **GENTINACEAE**	(a) Brazil	(a) Bark	(a) Tomchinsky et al. (2017)
(a) *Harungana madagascariensis* Lam. ex Poir. **HYPERICACEAE**	(a) Kenya	(a) Stem bark	(a) Mukungu et al. (2016)
(a) *Poraqueiba sericea* Tul. **ICACINACEAE**	(a) Brazil	(a) Seed	(a) Tomchinsky et al. (2017)
(a) *Plectranthus amboinicus* (Lour.) Spreng. **(b) *Plectranthus ornatus* Codd** **(c) *Ajuga integrifolia* Buch.-Ham.** **(d) *Clerodendrum johnstonii* Oliv.** **(e) *Rotheca myricoides* (Hochst.) Steane and Mabb.** **(f) *Fuerstia africana* T.C.E.Fr.** **(g) Leucas calostachys Oliv.** **(h) *Ocimun kilimandscharicum* Gürke** **(i) *Plectranthus barbatus* Andrews** **(j) *Ocimum basilicum* L.** **(k) *Ocimum suave* Willd.** **LAMIACEAE**	(a), (b) Brazil, (c), (d), (e), (f), (g), (h), (i), (j), (k) Kenya	(a), (b) Leaf, (c) Aerial part, (d) Leaf, (e) Root bark, leaf, (f), (g), (h) Aerial part, (i), (j), (k) Leaf	(a), (b) Tomchinsky et al. (2017) (c), (d), (e), (f), (g), (h), (i) Mukungu et al. (2016) (j), (k) Nguta et al. (2010)

(a) *Persea americana* Mill.* **(b) *Persea americana* Mill.** **LAURACEAE**	(a) Brazil, (b) Nigeria	(a), (b) Leaf	(a) Tomchinsky et al. (2017); (b) Dike, Obembe and Adebiyi (2012)
(a) *Bertholletia excelsa* Bonpl.* **LECYTHIDACEAE**	(a) Brazil	(a) Bark	(a) Tomchinsky et al. (2017)
(a) *Tamarindus indica* L. **(b) *Albizia gummifera* (J.F.Gmel.) C.A.Sm.** **(c) *Erythrina abyssinica* DC.** **(d) *Senna didmobotrya* (Fresen.) H.S.Irwin and Barneby** **(e) *Senna occidentalis* (L.) Link** **LEGUMINOSAE**	(a) Indonesia, (b), (c), (d), (e) Kenya	(a) Leaf, (b), (c) Stem bark, (d) Leaf, (e) Root	(a) Taek et al. (2019); (b), (c), (d), (e) Mukungu et al., 2016)
(a) *Strychnos ligustrina* Blume **LOGANIACEAE**	(a) Indonesia	(a) Stem bark	(a) Taek et al. (2019)
(a) *Guarea pubescens* (Rich.) A.Juss. **(b) *Melia azedarach* L.a** **(c) *Mellia azedarach* L** **(d) *Trichilia emetica* Vahl** **(e) *Azadiractha indica* A.Juss.** **MELIACEAE**	(a) Brazil, (b) Indonesia, (c), (d) Kenya, (e) Nigeria	(a) Bark, root, (b) Stem bark, leaf, (c) Stem bark, leaf, (d) Stem bark, (e) Leaf	(a), Mukungu et al., 2016); (b) Taek et al. (2019); (c), (d) Mukungu et al. (2016); (e) Dike, Obembe and Adebiyi (2012)
(a) *Abuta grandifolia* (Mart.) Sandwith. **(b) *Abuta imene* (Mart.) Eichler** **(c) *Cissampelos mucronata* A.Rich.** **MENISPERMACEAE**	(a), (b) Brazil, (c) Kenya	(a) Leaf (b), (c) Root	(a), (b), (c) Tomchinsky et al. 2017)
(a) *Ficus hispida* L.f. (L.) DC. **(b) *Ficus thonningii* Blume** **MORACEAE**	(a) Indonesia, (b) Kenya	(a) Leaf, (b) Stem bark	(a) Taek et al. (2019); (b) Mukungu et al. (2016)
(a) *Moringa oleifera* Lam. **MORINGACEAE**	(a) Indonesia	(a) Root	(a) Taek et al. (2019)
(a) *Iryanthera hostmannii* (Benth.) Warb. **MYRISTICACEAE**	(a) Brazil	(a) Sap	(a) Tomchinsky et al. 2017)
(a) *Psidium guajava* L. **MYRTACEAE**	(a) Indonesia	(a) Leaf	(a) Taek et al. (2019)
(a) *Nyctanthes arbortristis* L. **OLEACEAE**	(a) India	(a) Leaf	(a) Nagendrappa, Naik and Payyappallimana, (2013)
(a) *Flueggea virosa* (Roxb. ex Willd.) Royle **(b) *Phyllanthus sepialis* Müll. Arg.** **PHYLLANTHACEAE**	(a), (b) Kenya	(a) Aerial part, (b) Leaf	(a), (b) Mukungu et al. (2016)
***Piper nigrum* L.** **PIPERACEAE**	(a) India	(a) Fruit	(b) Nagendrappa, Naik and Payyappallimana, (2013)

(a) *Pittosporum viridiflorum Sims* PITTOSPORACEAE	(a) Kenya	(a) Leaf, stem bark	(a) Mukungu et al. (2016)
(a) *Paspalum gardnerianum* Nees (b) *Bambusa vulgaris* Schrad. ex J.C. Wendl. (c) *Cymbopogon citratus* Stapf POACEAE	(a) Brazil, (b) Ghana, (c) Nigeria	(a) Whole plant, (b) leaf, (c) -	(a) Tomchinsky et al. (2017); (b) Asase, Akwetey and Achel (2010); (c) Dike, Obembe and Adebiyi (2012)
(a) *Rumex abyssinicus* Jacq. (b) *Rumex steudelii* Hochst.ex A. Rich POLYGONACEAE	(a), (b) Kenya	(a) Leaf, (b) Root	(a), (b) Mukungu et al. (2016)
(a) *Drynaria quercifolia* (L.) J. Smith. POLYPODIACEAE	(a) Indonesia	(a) Tubercle	(a) Taek et al. (2019)
(a) *Maesa lanceolata* Forssk. PRIMULACEAE	(a) Kenyaa	(a) Stem bark, root bark	(a) Mukungu et al. (2016)
(a) *Ampelozizyphus amazonicus* Ducke* RHAMNACEAE	(a) Brazil	(a) Root	(a) Tomchinsky et al. (2017)
(a) *Rubus pinnatus* Wild. ROSACEAE	(a) Kenya	(a) Leaf, fruit	(a) Mukungu et al. (2016)
(a) *Citrus limon* (L.) Osbeck (b) *Melicope latifolia* (DC.) T.G. Hartley (c) *Ruta graveolens* L. (d) *Clausena anisata* (Willd.) Hook.f. ex Benth. (e) *Zanthoxylum gilletii* (De Wild.) P.G.Waterman (f) *Clausena anisata* (Willd.) Hook.f. ex Benth. (g) *Zanthoxylum gilletii* (De Wild.) P.G.Waterman (h) *Teclea simplicifolia* (Engl.) Engl. (i) *Zanthoxylum chalybeum* Engl. RUTACEAE	(a) Brazil, (b), (c) Indonesia, (d), (e), (f), (g), (h) Kenya, (i) Uganda	(a) Fruit peel, (b), (c) Leaf, (d) Leaf, (e) Stem bark, (f) leaf, (g) Stem bark, (h), (i) Root	(a) Tomchinsky et al. (2017); (b), (c) Taek et al. (2019); (d), (e), (f), (g) Mukungu et al. (2016); (h) Nguta et al. (2010); (i) Tabuti (2008)
(a) *Deinbollia pinnata* Schum. &Thonn. SAPINDACEAE	(a) Ghana	(a) Leaf	(a) Asase, Akwetey and Achel (2010)
(a) *Quassia amara* L.* (b) *Simaba cedron* Planch.* (c) *Brucea javanica* (L.) Merr. SIMAROUBACEAE	(a), (b), (c) Brazil	(a) Leaf, (b) Root, (c) Leaf	(a), (b) Tomchinsky et al. (2017); (c) Taek et al. (2019)
(a) *Capsicum frutescens* L. (b) *Physalis angulata* L.* (c) *Solanum stramoniifolium* Jacq. (d) *Physalis angulata* L. (e) *Physalis peruviana* L. (f) *Solanum incanum* L. (g) *Solanum torvum* Sw SOLANACEAE	(a), (b), (c) Brazil, (d) Indonesia, (e), (f) Kenya, (g) Ghana	(a), (b) Whole plant (c) Root, (d) Whole plant, (e) Leaf, (f) Root, (g) Fruit	(a), (b), (c) Tomchinsky et al. (2017); (d) Taek et al. (2019); (e), (f) Mukungu et al. (2016); (g) Asase, Akwetey and Achel (2010)
(a) *Grewia hexaminta* Burret. TILIACEAE	(a) Kenya	(a) Leaf, root	(a) Nguta et al. (2010)

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(a) *Cecropia ficifolia* Warb. ex Snethl. **URTICACEAE**	(a) Brazil	(a) Leaf	(a) Tomchinsky et al. (2017)
(a) *Stachytarpheta cayennensis* (Rich.) Vahl* **(b) *Lantana trifolia* L.** **VERBENACEAE**	(a) Brazil, (b) Kenya	(a), (b) Leaf	(a) Tomchinsky et al. (2017); (b) Mukungu et al. (2016)
(a) *Rhoicissus tridentata* (L.f.) Wild and R.B.Drumm. **VITACEAE**	(a) Kenya	(a) Root	(a) Mukungu et al. (2016)
(a) *Aloe* sp. **XANTHORRHOEACEAE**	(a) Kenya	(a) Leaf	(a) Mukungu et al. (2016)
(a) *Alpinia zerumbet* (Pers.) B.L.Burtt & R.M.Sm. **(b) *Zingiber officinale* Roscoe** **ZINGIBERACEAE**	(a) Brazil, (b) India	(a) Leaf, (b) Rhizome	(a) (Tomchinsky et al., 2017); (b) Nagendrappa, Naik and Payyappallimana (2013)

Source: Authors.

In the present study, the most frequently cited species were selected during the review of the literature, which describes in detail which part of the plant was used, which method was used for the extraction of chemical compounds and the result of inhibition of *P. falciparum* for each species studied (only for the studies that report these details). In addition, scientific knowledge is also linked to common sense, in order to clarify the real effects of these plants with medicinal potential.

In this regard, the botanical species *Plectranthus barbatus Andrews*, mentioned in the ethnobotanical survey by Mukungu et al. (2016), was tested for its ability to inhibit *P. falciparum in vitro*. After extraction of the possible active component by Owuor et al. (2012), it was observed that the leaf extract of this plant was inactive when evaluated against strain D6 (sensitive to chloroquine) and strain W2 (resistant to chloroquine).

For the species *Mormodica charantia* L., studies such as those by Abdillah *et al.* (2019) demonstrate a high plasmodial inhibition of 0.17 ± 0.12 µg/mL against *P. falciparum* strain 3D7 (chloroquine-sensitive), in addition, this ethnospecies has been studied regarding its anti-inflammatory potential (Fang et al., 2007) and antimicrobial activity (Ponzi et al., 2010).

The species *Momordica foetida* Schumach., belonging to the Cucurbitaceae family, showed low inhibitory concentration against strains D10 (sensitive to chloroquine) and K1 (resistant to chloroquine) (Waako et al., 2005). However, the study by Adia et al. (2016) using *P. falciparum* strains NF54 (sensitive to chloroquine) and FCR3 (resistant to chloroquine), showed high inhibition (≤ 10 µg/mL) with the ethyl acetate and water extraction method. The extraction method, plant species and part of the plant used were the same for both studies, so it is not clear why the results diverged. One of the factors that possibly influenced this divergence of results may have been the differences in the extraction solvent, therefore, in the extraction yield and in the extracted metabolite. For example, with dichloromethane, mainly non-polar metabolites are extracted. In contrast, with methanol, polar to nonpolar metabolites are extracted (Tajbakhsh et al., 2021).

Similar to the species *M. foetida*, another result of inactivity was also observed for the plant *Carica papaya* L. when the ethanolic extracts of the leaves were tested against two strains *P. falciparum*, one chloroquine-sensitive and the other chloroquine-resistant (Kovendan et al., 2012). However, the study by Julianti *et al.* (2013), revealed a high inhibition of 4.8 µg/mL against the *P. falciparum* K1 strain using a methanolic extract of the leaves. Upon analysis of the two studies, it is evident that the extraction method directly influenced the antiplasmodial action of this ethnospecies.

Unlike the species *M. foetida* e *C. papaya*, the results of two studies for the ethnospecies *Albizia gummifera* (J.F.Gmel.) C.A.Sm. corroborated the inhibition of *P. falciparum in vitro* at concentrations below 5.0 µg/mL (Orulla *et al.*, 1996; Ofulla *et al.*, 1995). These data reveal high antiplasmodial inhibition, a promising result for this plant.

Similar to that observed for *A. gummifera*, two studies on the botanical species *Flueggea virosa* (Roxb. ex Willd.) Royle's inhibition of *P. falciparum in vitro* showed promising results. Inhibitory activity against chloroquine-sensitive (D6 and 3D7) and chloroquine-resistant (W2 and K1) strains was obtained with concentrations below 25 µg/mL (Muthaura et al., 2007; Singh et al., 2017).

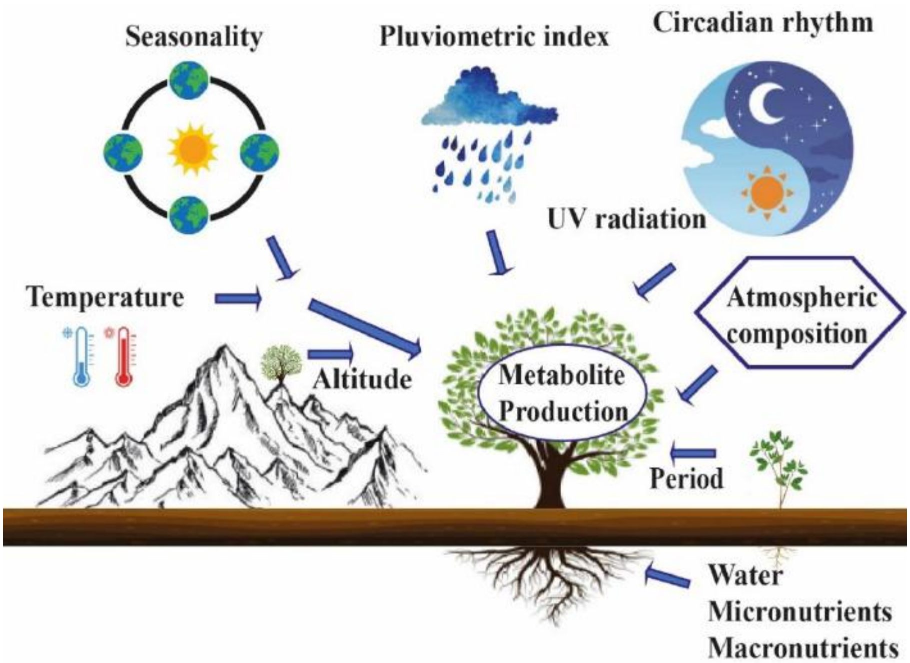
Although other plants with results of proven activity were not mentioned in ethnobotanical surveys in this study, they also showed promising results of in vitro inhibition against *P. falciparum* (Table 1), however, other studies must be carried out in order to confirm this inhibition in models (*in vivo*) and characterization of secondary metabolites since few studies describe this part of the photochemistry.

The results observed for these ethnospecies validate how important it is to have scientific proof of their true therapeutic effects for medicinal use, not only for the treatment of malaria, but of all the pathologies for which the population makes use of these plant extracts (Martinez et al., 2020).

In this study, in addition to correlating scientific knowledge with popular knowledge, we also sought to carry out a survey of the main environmental conditions that can affect the production of secondary metabolites in a plant, and, consequently, make its possible principle active component ineffective.

Due to challenges along the way, some factors have affected the quality and quantity of active compounds in plants; thus, throughout evolution, plant species have adapted and developed mechanisms that allowed for their survival in different ecosystems of the world. That is, the same plant species is found in different countries with different climates. However, it should be noted that the metabolites depend on conditions such as: temperature, hydric stress, age (period), altitude, seasonality, circadian rhythm, UV radiation, atmospheric composition and the region or biome in which the plant species is adapted or inserted (Figura 4) (Gobbo-Neto et al., 2007).

Figure 4. Main factors that can influence the accumulation of metabolites secondaries in plant.



Source: Authors.

In addition, it is important to consider some issues regarding the period in which a plant was collected, since the quality and nature of the active constituents are not constant throughout the year (Gobbo-Neto et al., 2007). In this sense, variations in their chemical compounds may occur at different times of the year. Studies report that there are seasonal variations in the secondary metabolites of essential oils (Pitarević et al., 1984; Schwob et al., 2013), phenolic acids (Grace, Logan e Adams, 1998; Zidorn e Stuppner, 2001), flavonoids (Brooks et al., 2004; Jalal et al., 1982), saponins (Kim et al., 1981; Ndamba et al., 1993), alkaloids (Elgorashi et al., 2002; Roca-Pérez et al., 2004), and tannins (Feeny et al., 1968; Salminen et al., 2001).

In the spring, *Digitalis obscura* leaves present very low concentrations of cardenolides and lanatosides. However, it is possible to observe a rapid accumulation of these substances in the summer, and during the autumn they decrease again (Roca-Pérez et al., 2004). This same variation also occurs with *Hypericum perforatum*, popularly known as São João's herb. These substances increase from 100 ppm (parts per million) in the winter to 3000 ppm in the summer (Southwell et al., 2001).

The age and development of the plant, as well as the different types of plant organs, can also contribute to the total amount of metabolites produced (Bowers et al., 1993). The sesquiterpene lactones produced by *Arnica montana* are used as anti-inflammatory agents. This plant species in the young phase accumulates helenalin derivative. This substance is reduced to almost zero around six weeks after leaf formation. However, unlike helenalin, the levels of dihydrohelenalin increase greatly and remain constant for a long period of time (Schmidt et al., 1998). *Gentiana lutea* leaves have a high concentration of C-glycosides in the flowering stage; O-glycosides and isoorientin are found in large amounts before their floral development (Menković et al., 2000).

In addition to age and seasons of the year, the adaptation of each plant species to different biomes has allowed plants to develop in a considerable temperature range, from tropical climates to arid environments and temperatures below 0. However, variations in temperature, as well as hydric variation, directly affect the production of secondary metabolites (Evans, 1996). Studies by Zobayed, Afreen e Kozai (2005) evaluated the alteration of secondary metabolites under temperature stress in *Hypericum perforatum*. In this study, it was possible to observe that temperatures above 35ºC and below 15ºC reduced the photosynthetic efficiency of the leaves, resulting in a low assimilation of CO_2, compromising the production of secondary metabolites.

Along with high temperatures, low temperatures also significantly influence the quantity of secondary metabolites. *Artemisia annua*, for example, after suffering metabolic stress showed a 60% increase in its levels of artemisinin, an active substance against *P. falciparum*. On the other hand, it was possible to observe a rapid decrease in dihydroartemisinic acid, which had been converted to artemisinin (Wallaart et al., 2000).

Issues related to seasonality and amount of rainfall can influence the production of secondary metabolites. In *Hypericum perforatum*, it is possible to observe an increase in the production of flavonoids, hypericins and chlorogenic acid in flowers under hydric stress, while the concentration levels of hyperforins drop drastically (Waterman e Mole, 1989).

Few studies report the relationship between changes in active compounds in high altitude regions. Of the few studies documented, a decrease was observed in deterpene alkaloids in *Aconitum napellus* and piperidines in *Lobelia inflatas* at high altitudes (Evans, 1996).

4. Conclusions

In view of the results obtained in this study, it is possible to observe the growth in *in vitro* studies with plants with medicinal potential for treating malaria, in addition, it is worth mentioning that many important findings have already been reported and implemented by the pharmaceutical industries. However, it is still necessary to invest in studies and technologies to detect new chemical targets with antimalarial potential.

In this study, in addition to conducting a systematic literature review, we also sought to confirm whether the plants mentioned in ethnobotanical surveys and *in vitro* studies had effects on malaria parasites. Of the 8 plants cited in botanical surveys, 5 ethnospecies were also being studied for their therapeutic potential for malaria *in vitro*. This correlation demonstrated the importance of combining empirical and scientific knowledge in the search for strategies for new prototypes of natural origin for various diseases, as well as the geo-environmental conditions of the site of this plant, since these factors can alter its chemical components.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

The team from the Research Centro de Pesquisa em Medicina Tropical (CEPEM/SESAU) and Instituto Federal de Educação, Ciência e Tecnologia de Rondônia (IFRO), Porto Velho-CALAMA, and the study collaborators.

Funding

The authors express their gratitude to the staff of the Centro de Pesquisa em Medicina Tropical (CEPEM/SESAU) and Instituto Federal de Educação, Ciência e Tecnologia de Rondônia (IFRO), Porto Velho-CALAMA, for their financial support.

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