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

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. Aponynameae and Lamiales 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 antimalária, das quais 66 diferentes tipos de extratos mostraram ação na eliminação desses parasitas, enquanto 59 desses extratos foram inativos. Deste número total, as...
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 pubescens*, 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 that 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.

For synthetic compounds, IC$_{50}$ values ≤ 10 µM were considered potentially active compounds (Mahmoudi et al., 2006). Regarding compounds derived from plant extracts, the activity values considered active were IC$_{50}$ ≤ 10 µg/mL, and inactive IC$_{50}$ ≥ 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).
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 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 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 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.

![Pie chart showing the proportion of species cited from different families.]

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, Arecales, Asteraceae, Euphorbiaceae, Leguminosae, Meliaceae, and Anacardiaceae (Figure 3).

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

![Pie chart showing the proportion of species cited from different families.]

Source: Authors.

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 | (a) India, (b) Burkina Faso | (a) Whole plant, (b) Aerial part | (a) MeOH, Combination (AP+HC+curcumin), (b) CH₂Cl₂, MeOH, H₂O | (a) Active, (b) Inactive | (a) Mishra et al. (2009); (b) Jansen et al. (2010) |
| *(b) Dyschoriste perrottetii* O. Kuntze | | | | | |
| **ACANTHACEAE** | | | | | |
| *(a) Alstonia congensis* Engl. | (a) - | (a) Root | (a) - | (a) Active | (a) Adams et al. (2011) |
| **ALISMATACEAE** | | | | | |
| *(a) Achyranthes aspera* Duss | (a) Sri Lanka | (a) Stem, leaf, root | (a) EtOH | (a) Inactive | (a) Inbaneson, Ravikumar and Suganthi, (2012) |
| **AMARANTHACEAE** | | | | | |
| *(a), (b), (c), (d) Alchornea latifolia* Klotsch | (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) C₆H₁₄, C₄H₈O₂, 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) |
| *(f) Polyalthia longifolia* (Lam.) Hook.f. & Thomson | | | | | |
| *(g) Pseudomalmea boyacana* (J.F.Machr.) Chatrou | | | | | |
| *(h) Rollinia pittieri* Saff. | | | | | |
| **ANNONACEAE** | | | | | |
| *(a) Ferula oopoda* Boiss. | (a) Iran | (a) Root | (a) MeOH | (a) Active | (a) Esmaeili et al. (2009) |
| **APIACEAE** | | | | | |
| *(a) Alstonia congensis* Engl. | (a) Congo | (a) Root bark | (a) MeOH | (a) Active | (a) Cimanga et al. (2019) |
| **APOCYNACEAE** | | | | | |
| *(a) Schefflera umbellifera* Ball. | (a), (b) | (a), (b), (c) Leaf | (a), (b) MeOH | (a), (b) Inactive | (a), (b) De Villiers et al. (2010) |
| *(b) Seemannaralia gerrardii* R.Vig. | | | | | |
| **ARALIACEAE** | | | | | |
| *(a) Vernonia amygdalina* Delile | (a), (b), (c), (d) Uganda, (e) Burkina Faso, (f) Réunion island, | (a), (b) Leaf, (c) Aerial part, (d) Leaf, (e) Whole plant, (f) Leaf, | (a) Éter, MeOH, (b) C₄H₈, éter, CH₂Cl₂, MeOH, (c) C₆H₁₄, éter, (d), (e) Active, (f), Active | (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); |
| Plant Name | Country | Part Used | Solvent(s) | Activity | Reference(s) |
|------------|---------|-----------|------------|----------|--------------|
| *Stanleya pinnata* Britton | (g) India, (h) Kenya | (g) Aerial part, (h) Whole plant | (d) EtOAc, H₂O, MeOH, (e) CH₂Cl₂, MeOH, H₂O, (f) CH₃Cl₂, MeOH, (g) MeOH, CHCl₃, C₆H₆O₂, BuOH, C₆H₁₄, (h) CH₂Cl₂ | (g), C₆H₁₂/Active | (g) Mohanty et al. (2013); (h) Owuor et al. (2012) |
| *Microglossa pyrifolia* (Lam.) O. Ktze | | | | | |
| *Dicoma tomentosa* Cass. | | | | | |
| *Psidia arguta* Voigt | | | | | |
| *Pluchea lanceolata* (DC.) C.B.Clarke | | | | | |
| *Ageratum conyzoides* L. | | | | | |
| *Balanites aegyptiaca* Delile | (a) Togo | (a) Aerial part | (a) - | (a) Inactive | (a) Karou et al. (2011) |
| *Buddleja salviifolia* (Lam.) Lam. | (a), (b) Reunion island | (a) Stem, leaf, (b) Leaf | (a) CH₂Cl₂, (b) CH₂Cl₂, MeOH | (a), (b) Inactive | (a) Jansen et al. (2010); (b) Jonville et al. (2008) |
| *Nuxia verticillata* Lam. | | | | | |
| *Boswellia dalzielii* Hutch. | (a) Burkina Faso | (a) Leaf | (a) CH₂Cl₂, MeOH, H₂O | (a) Active | (a) Jansen et al. (2010) |
| *Buxus hyrcana* Pojark. | (a) Iran | (a) Root | (a) MeOH | (a) Active | (a) Esmaeili et al. (2009) |
| *Tamarindus indica* L. | (a) Togo, (b) Burkina Faso | (a) - (b) Leaf | (a) CH₂Cl₂ EtOH, MeOH, (b) - | (a), (b) Active | (a) Koudouvo et al. (2011); (b) Traoré et al. (2008) |
| *Daniellia ogaea* (Harms) Holland | (a) Nigeria | (a) Root | (a) EtOH | (a) Inactive | (a) Ezenyi et al. (2020) |
| *Warburgia stuhlmannii* Engl. | (a), (b) Kenya | (a), (b) Stem bark | (a), (b) MeOH, H₂O | (a), (b) Active | (a), (b) Muthaura et al. (2007) |
| *Psorospermum senegalense* Spach. | (a) Burkina Faso | (a) Leaf | (a) CH₂Cl₂, MeOH, H₂O | (a) Active | (a) Julianti et al. (2013) |
| *Loeseneriella africana* N.Hallé | (a) Burkina Faso, (b), (c) Kenya | (a) Leaf, (b) Stem root, (c) Leaf | (a) CH₂Cl₂, MeOH, H₂O, (b), (c) MeOH, H₂O | (a) Inactive, (b) Active, (c) Active | (a) Jansen et al. (2010); (b), (c) Muthaura et al. (2007) |
| *Maytenus putterlikioides* (Loes.) Exell & Mendonça | | | | | |
| *Maytenus undata* (Thunb.) Blakelock | | | | | |
| *Carica papaya* L. | (a) Indonesia | (a) Leaf | (a) MeOH | (a) Active | (a) Julianti et al. (2013) |
| *Loeseneriella africana* N.Hallé | (a) Burkina Faso, (b), (c) Kenya | (a) Leaf, (b) Stem root, (c) Leaf | (a) CH₂Cl₂, MeOH, H₂O, (b), (c) MeOH, H₂O | (a) Inactive, (b) Active, (c) Active | (a) Jansen et al. (2010); (b), (c) Muthaura et al. (2007) |
| *Psorospermum senegalense* Spach. | (a) Burkina Faso | (a) Leaf | (a) CH₂Cl₂, MeOH, H₂O | (a) Active | (a) Jansen et al. (2010) |
| Plant                        | Country/Region | Part Used       | Extraction Method       | Activity   | Reference                                      |
|-----------------------------|----------------|-----------------|-------------------------|------------|------------------------------------------------|
| *Warburgia stuhlmannii*     | Burkina Faso   | Leaf            | -                       | Active     | Traoré et al. (2008)                           |
| *Terminalia catappa*        | Cameroon       | Leaf            | Methanol                | Active     | Marie et al. (2018); Jonville et al. (2008)   |
| *Terminalia bentzeo*        | Cameroon       | Leaf            | Methanol                | Inactive   | Marie et al. (2018); Jonville et al. (2008)   |
| *Terminalia mantaly*        | Cameroon       | Leaf, bark      | Methanol                | Active     | Marie et al. (2018); Jonville et al. (2008)   |
| *Combretum bentzeo*         | Cameroon       | Leaf            | Methanol                | Inactive   | Marie et al. (2018); Jonville et al. (2008)   |
| *Momordica foetida*         | U.S.A.         | Bark, fruit     | Ethanol                 | Inactive   | Grazioso et al. (2012)                         |
| *Momordica balsamina*       | Kenya          | Leaf            | Methanol                | Inactive   | Obbo et al. (2019); Adia et al. (2016); Benoit-Vical et al. (2006); Kamaraj et al. (2012) |
| *Momordica charantia*       | Colombia       | Leaf, root      | Methanol                | Inactive   | Obbo et al. (2019); Adia et al. (2016); Benoit-Vical et al. (2006); Kamaraj et al. (2012) |
| *Cajanus cajan*             | Cameroon       | Seed, root      | Methanol                | Active     | Jasra et al. (2010)                            |
| *Glycine max*               | U.S.A.         | Leaf, stem      | Methanol                | Active     | Jasra et al. (2010)                            |
| *Glycyrrhiza glabra*        | Iran           | Leaf            | Methanol                | Active     | Ajaiyeoba et al. (2008); Esmaeili et al. (2009) |
| *Bauhinia rufescens*        | Burkina Faso   | Whole plant     | Methanol                | Active     | Esmaeili et al. (2009)                         |
| *Jatropha gossypifolia*      | Burkina Faso   | Whole plant     | Methanol                | Active     | Jansen et al. (2010); Marie et al. (2018); Kamaraj et al. (2012); Traoré et al. (2008); Vical et al. (2006); Ravi Kumar and Suganthi (2012); Jansen et al. (2010) |
| *Cassia siamea*             | Malaysia       | Leaf            | Methanol                | Inactive   | Marie et al. (2018); Kamaraj et al. (2012); Traoré et al. (2008); Vical et al. (2006); Ravi Kumar and Suganthi (2012); Jansen et al. (2010) |

**Notes:**
- Active: Indicates activity in the respective biological assay.
- Inactive: Indicates no activity in the respective biological assay.
- H: Methanol
- MeOH: Methanol
FABACEAE

(a) *Aphloia theiformis* Benn.  
FLACOURTIACEAE

(a) Reunion island  
(a) Leaf  
(a) CH$_2$Cl$_2$, MeOH  
(a) Active  
(a) Jonville et al. (2008)

(a) *Erodium oxyrrhynchum* 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* C.A.Sm.  
(d) *Clerodendrum rotundifolium* Oliv.  
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), (b), (c) C$_4$H$_8$O$_2$, MeOH  
(b) C$_4$H$_8$O$_2$, MeOH  
(c) C$_4$H$_8$O$_2$, MeOH,  
(d) EtOAc, H$_2$O, MeOH,  
(e) C$_4$H$_8$O$_2$,  
(g) CH$_2$Cl$_2$  
(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$_6$H$_{14}$, éter, CH$_2$Cl$_2$, MeOH, H$_2$O,  
(béter, CH$_2$Cl$_2$, 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), (b), (c), (d), (e) *Ficus benjamina* (Miq.) Corner  
(f) *Ficus exasperata* Vahl  
(g) *Ficus thonningii* Blume  
MORACEAE

(a), (b), (c), (d), (e) 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$_2$Cl$_2$, MeOH, H$_2$O  
(a), (b), (c), (d), (e), (f) Inactive  
(a), (b), (c), (d), (e) Marie et al. (2018);  
(g) Jansen et al. (2010)
| Plant                     | Country  | Part             | Method         | Result         |References |
|--------------------------|----------|------------------|----------------|----------------|-----------|
| Callistemon citrinus     | Cameroon | Leaf             | CH$_2$Cl$_2$, MeOH | Active         | Larayetan et al. (2019); Naghibi et al. (2013) |
| Myrtus communis          | Iran     | Aerial part      | CH$_2$Cl$_2$, MeOH | Active         |           |
| Opilia celtidifolia      | Togo     | -                | CH$_2$Cl$_2$, MeOH | Inactive       | Koudouvo et al. (2011) |
| Fumaria ciliica          | Cameroon | Leaf             | MeOH           | Active         |           |
| Fumaria densiflora       | Iran     | Aerial part      | MeOH           | Active         |           |
| Fumaria Kralikii         | Togo     | Leaf             | MeOH           | Active         |           |
| Fumaria parviflora       | India    | Aerial part      | MeOH           | Active         |           |
| Fumaria rostellata       | Togo     | Leaf             | MeOH           | Active         |           |
| Flueggea virosa          | Kenya    | Leaf             | MeOH           | Active         | Muthaura et al. (2007) |
| Piper tricuspe           | Colombia | Leaf, stalk      | MeOH           | Active         | Vargas-Sinisterra et al. (2018); Kamaraj et al. (2012) |
| Piper nigrum             | India    | Seed             | MeOH           | Active         |           |
| Plantago major           | Colombia | Leaf, stalk      | EtOH           | Inactive       | Vargas-Sinisterra et al. (2018) |
| Crossopteryx febrifuga   | Burkina  | Leaf, (c) -      | EtOH, C$_2$H$_6$O$_2$ | Active         | Jansen et al. (2010); Koudouvo et al. (2011); Mesia et al. (2012) |
| Gardenia sokotensis      | Togo     | Stem bark        | CH$_2$Cl$_2$, MeOH, H$_2$O | Active         |           |
| Pavetta corymbosa        | Congo    | Root bark, fruit, leaf | CH$_2$Cl$_2$, EtOH, MeOH | Active         |           |
| Nauclea pobeguinii       | Togo     | Aerial part      | CH$_2$Cl$_2$, MeOH, H$_2$O | Active         | Jansen et al. (2010); Kamaraj et al. (2012); Orwa et al. (2013); Waffo et al. (2007) |
| Zanthoxylum chalybeum     | Uganda   | Stem bark        | EtOAc, H$_2$O, MeOH | Active         | Adia et al. (2016); Kamaraj et al. (2012); Orwa et al. (2013); Waffo et al. (2007) |
| Aegle marmelos           | India    | Leaf             | EtOAc, MeOH, H$_2$O/ Active | Active         | Bertani et al. (2012); Bhat and Karim, (2010) |
| Toddalia asiatica        | South    | Stem bark        | EtOAc, H$_2$O/ Active | Active         |           |
| Teclea gerrardii         | Africa   | Stem bark        | EtOAc, H$_2$O/ Active | Active         |           |
| Vitellaria paradoxa      | Burkina  | Aerial part      | CH$_2$Cl$_2$, MeOH, H$_2$O | Active         | Jansen et al. (2010) |
| Quasia amara             | French   | Leaf             | CH$_2$Cl$_2$, (b) - | Inactive       | Houël et al. (2009); Bertani et al. (2012); Bhat and Karim, (2010) |
| Quasia amara             | Guiana   | (c) stem bark    |    |    |           |
| Eurycoma longifolia      | Jack     | (a), (b)         | CH$_2$Cl$_2$, (b), (c) - | Inactive       |           |
| Simaroubaceae            |          |                  |                |                |           |
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.    | (a) Kenya, (b) India | (a) Aerial part, (b) Whole plant | (a) Mukungu et al., (2016); (b) Nagendrappa, Naik and Payyappallimana, (2013) |
| (b) Andrographis paniculata Nees |         |                        |            |
| ACANTHACEAE                  |         |                        |            |
| (a) Acorus calamus L.        | (a) Indonesia | (a) Rhizome | (a) Taek et al. (2019) |
| ACORACEAE                   |         |                        |            |
| (a) Allium cepa L.           | (a) Indonesia | (a) Bulb | (a) Taek et al. (2019) |
| ALLIACEAE                   |         |                        |            |
| (a) Elaeis guineensis Jacq.  | (a) Ghana, (b), (c) Kenya | (a) Root, (b), (c) Leaf | (a) Asase, Akwetey and Achel, (2010); (b), (c) Nguta et al. (2010) |
| (b) Aloe deserti A.Berger   |         |                        |            |
| (c) Aloe macrocrophon Baker |         |                        |            |
| ALOACEAE                    |         |                        |            |
| (a) Alternanthera sessilis (L.) R.Br. | (a) Brazil, (b) Kenya | (a), (b) Leaf | (a) Tomchinsky et al. (2017); (b) Nguta et al. (2010) |
| (b) Amaranthus hybridus L.   |         |                        |            |
| AMARANTHACEAE               |         |                        |            |
| (a) Crimum asiaticum L.     | (a) Indonesia | (a) Leaf, bulb | (a) Taek et al. (2019) |
| AMARYLLIDACEAE              |         |                        |            |

(AM+HC) combination of Andrographis paniculata and Hedyotis corymbosa; (-) No information; Dichloromethane=CH₂Cl₂; Hexane=C₆H₁₄, EtOAc=Ethyl Acetate; BuOH=Butanol; Propyl methanoate=C₄H₈O₂, Chloroform=CHCl₃.
| Anacardiaceae | Origin | Part Used | Authors |
|---------------|--------|----------|---------|
| Searsia natalensis (Bernh.ex C. Krauss) | Kenya, Uganda, Cameroon | Root, stem bark, leaf | Mukungu et al. (2016); Tabuti, (2008); Tsabang et al. (2012) |
| Rhoicissus tridentata (L.f.) Wild and R.B.Drumm. | Kenya, Uganda, Cameroon | Leaf, (d) | |
| Mangifera indica L. | Kenya, Uganda, Cameroon | Root, bark, leaf | Mukungu et al. (2016); Tabuti, (2008); Tsabang et al. (2012) |
| Mangifera indica L. | Kenya, Uganda, Cameroon | Leaf, | |

| Annonaceae | Origin | Part Used | Authors |
|------------|--------|----------|---------|
| Annona reticulata L. | Indonesia | Stem bark | Taek et al. (2019) |
| Annona muricata L. | Indonesia | Leaf | Taek et al. (2019) |

| Apocynaceae | Origin | Part Used | Authors |
|-------------|--------|----------|---------|
| Aspidosperma nitidum Ex Müll.Arg. | Brazil, Indonesia, Kenya, Nigeria | Bark, bark, sap, leaf | Tomchinsky et al. (2017); Taek et al. (2019); Mukungu et al. (2016); Nguta et al. (2010); Tsabang et al. (2012); Dike, Obembe and Adebiyi, (2012) |
| Aspidosperma schultesii Woodson* | Brazil, Indonesia, Kenya, Nigeria | Leaf, root, bark | Taek et al. (2019); Mukungu et al. (2016); Nguta et al. (2010); Tsabang et al. (2012); Dike, Obembe and Adebiyi, (2012) |
| Himatanthus stenophyllus Plumel | Brazil, Indonesia, Kenya, Nigeria | Bark, leaf | Taek et al. (2019); Mukungu et al. (2016); Nguta et al. (2010); Tsabang et al. (2012); Dike, Obembe and Adebiyi, (2012) |
| Himatanthus sucuuba (Spruce ex Müll.Arg.) Woodson* | Brazil, Indonesia, Kenya, Nigeria | Leaf | |
| Calotropis gigantea (L.) R. Br. | Brazil, Indonesia, Kenya, Nigeria | Leaf | Taek et al. (2019); Mukungu et al. (2016); Nguta et al. (2010); Tsabang et al. (2012); Dike, Obembe and Adebiyi, (2012) |

| Arecales | Origin | Part Used | Authors |
|----------|--------|----------|---------|
| Astrocaryum aculeatum G.Mey | Brazil, Indonesia, Kenya | Stalk, root, leaf | Tomchinsky et al., (2017); Taek et al. (2019); Mukungu et al. (2016); Nguta et al., (2010) |
| Euterpe catinga Wallace | Brazil, Indonesia, Kenya | Root, leaf | Taek et al., (2017); Mukungu et al. (2016); Nguta et al., (2010) |
| Euterpe oleracea Mart. | Brazil, Indonesia, Kenya | Root, leaf | Taek et al., (2017); Mukungu et al. (2016); Nguta et al., (2010) |
| Euterpe precatoria Mart.* | Brazil, Indonesia, Kenya | Root, leaf | Taek et al., (2017); Mukungu et al. (2016); Nguta et al., (2010) |
| Socratea exorrhiza (Mart.) H.Wendl | Brazil, Indonesia, Kenya | Root, leaf | Taek et al., (2017); Mukungu et al. (2016); Nguta et al., (2010) |
| Elaeis guineensis Jacq. | Brazil, Indonesia, Kenya | Root | Taek et al., (2017); Mukungu et al. (2016); Nguta et al., (2010) |

| Asteraceae | Origin | Part Used | Authors |
|-----------|--------|----------|---------|
| Blumea balsamifera (L.) DC. | Indonesia, Uganda, Kenya | Leaf, stem bark, root | Taek et al., (2019); Tabuti, (2008); Chinsembu (2015); Nguta et al., (2010) |
| Vernonia amygdalina Delile | Indonesia, Uganda, Kenya | Root | Taek et al., (2019); Tabuti, (2008); Chinsembu (2015); Nguta et al., (2010) |
| Tithonia diversifolia A.Gray | sub-Saharan African, Kenya | Leaf | Taek et al., (2019); Tabuti, (2008); Chinsembu (2015); Nguta et al., (2010) |
| Launaea cornuta (Hochst. ex Oliv. & Hiern) C.Jeffrey | Kenya | Root | Taek et al., (2019); Tabuti, (2008); Chinsembu (2015); Nguta et al., (2010) |
| Senecio syringifolius O.Hoffm. | Kenya | Leaf | Taek et al., (2019); Tabuti, (2008); Chinsembu (2015); Nguta et al., (2010) |

| Bignoniaceae | Origin | Part Used | Authors |
|-------------|--------|----------|---------|
| Handroanthus barbatus (E.Mey.) Mattos | Brazil, Kenya | Leaf, stem bark | Tomchinsky et al. (2017); Mukungu et al. (2016) |
| Markhamia lutea (Benth.) K.Schum. | Kenya | Leaf, stem bark | Mukungu et al. (2016) |
| Spathodea campanulata P.Beauv. | Kenya | Leaf, stem bark | Mukungu et al. (2016) |

| Burseraceae | Origin | Part Used | Authors |
|-------------|--------|----------|---------|
| Garuga floribunda Decne. | Indonesia | Leaf | Taek et al. (2019) |

| Canellaceae | Origin | Part Used | Authors |
|------------|--------|----------|---------|
| Warbugia ugandensis Sprague. | Kenya | Leaf, stem bark | Mukungu et al. (2016) |

| Capparaceae | Origin | Part Used | Authors |
|-------------|--------|----------|---------|
| Cleome rutidosperma DC. | Indonesia | Whole plant | Taek et al. (2019) |

| Caricaceae | Origin | Part Used | Authors |
|------------|--------|----------|---------|
| Carica papaya L.* | Brazil, Indonesia | Leaf | Tomchinsky et al. (2017); Taek et al. (2019) |
| Carica papaya L. | Brazil, Indonesia | Leaf | Taek et al. (2019) |
| Plant Name                                      | Country       | Part(s)               | Author(s)                          |
|------------------------------------------------|---------------|----------------------|-----------------------------------|
| Elaeis guineensis Jacq.                        | Kenya         | Leaf                 | Nguta et al. (2010)               |
| Acnella caulirhiza Del.                        | (a), (b), (c), (d) Kenya | Aerial part, Root, leaf, Leaf | Mukungu et al. (2016) |
| Microglossa pyrifolia (Lam.) Kuntze            |               |                      |                                   |
| Tithonia diversifolia (Hemsd.) A. Gray         |               |                      |                                   |
| Vernonia amygdalina Del. Compositae            |               |                      |                                   |
| Acmella caulirhiza (Choisy) Hallier f.         | Brazil        | Leaf                 | Tomchinsky et al. (2017)          |
| Microglossa pyrifolia (Lam.) Kuntze            | Indonesia     | Leaf                 | Taek et al. (2019); Nguta et al. (2010); Tabuti (2008); Mukungu et al. (2016) |
| Microglossa pyrifolia (Lam.) Kuntze            | Kenya         | Leaf                 |                                   |
| Tithonia diversifolia (Hemsd.) A. Gray         | Uganda        | Leaf                 |                                   |
| Vernonia amygdalina Del. Compositae            | Kenya         | Leaf                 |                                   |
| Bonamia ferruginea (Choisy) Hallier f.         | Benin         | Leaf                 | Yetein et al. (2013)              |
| Momordica charantia L.a                       | Indonesia, Kenya, Uganda, Kenya | Leaf, fruit, Leaf, Leaf | Tomchinsky et al. (2017) |
| Gerranthus lobatus (Cogn.) Jeffrey             | (c)           |                      |                                   |
| Momordica foetida Schumach.                   | (d)           |                      |                                   |
| Cucumis aculeatus Cogn                        | Kenya         | Leaf                 |                                   |
| Vernonia amygdalina Del. Compositae            |               |                      |                                   |
| Momordica achyriopsis                        | Brazil        | Leaf                 |                                   |
| Acmella caulirhiza                            | (a), (b), (c), (d) Brazil, Kenya, Uganda, Kenya | Seed, Root, Leaf, Leaf, Stem bark | Tomchinsky et al. (2017) |
| Microglossa pyrifolia (Lam.) Kuntze            |               |                      |                                   |
| Tithonia diversifolia (Hemsd.) A. Gray         |               |                      |                                   |
| Vernonia amygdalina Del. Compositae            |               |                      |                                   |
| Jatropha curcas L.*                           | Brazil        | Seed                 | Tomchinsky et al. (2017); Taek et al. (2019); Mukungu et al. (2016) |
| Manihot esculenta Crantz                      | (d)           | Root, Leaf           |                                   |
| Croton cajucara Benth.*                       | (e)           | Leaf                 |                                   |
| Jatropha curcas L.                            | (a), (b), (c), (d) Brazil, Kenya, Uganda, Kenya | Seed | Tomchinsky et al. (2017) |
| Crotom macrostachys Hochst. ex Del.            |               | Stem bark            |                                   |
| Doliocarpus magnificus Sleumer Dilleniiaceae   | Brazil        | Leaf                 | Tomchinsky et al. (2017)          |
| Phanera splendens (Kunth) Vaz*                 | Brazil        | Sead                 | (a), (b), (c) Tomchinsky et al. (2017) |
| Phaseolus vulgaris L.                          |               | Bough                |                                   |
| Senna occidentalis (L.) Link* Fabeaee           |               | Seed                 | (a), (b), (c) Tomchinsky et al. (2017) |
| Potalia resinifera Mart. Gentianaceae          | Brazil        | Bark                 | Tomchinsky et al. (2017)          |
| Harungana madagascariensis Lam. ex Poir. HYPERICACEAE | Kenya       | Stem bark            | Mukungu et al. (2016)             |
| Poraqueiba sericea Tul. Luc. ICACINACEAE       | Brazil        | Seed                 | Tomchinsky et al. (2017)          |
| Plectranthus amboinicus (Lour.) Spreng.         | (a), (b), (c), (d) Brazil, Kenya, Uganda, Kenya | Leaf, Aerial part, Leaf, Leaf, Leaf, Leaf | Tomchinsky et al. (2017); Mukungu et al. (2016) |
| Plectranthus ornatus Codd                      | (e)           | Root, leaf, leaf, Leaf, Leaf |                                   |
| Ajuga integrifolia Buch.-Ham.                  | (f)           |                      |                                   |
| Clerodendrum johnstonii Oliv.                  | (g)           |                      |                                   |
| Rotheca myricoides (Hochst.) Steane and Mahb.  | (h)           |                      |                                   |
| Fuerstia africana T.C.Fr.                      | (i)           |                      |                                   |
| Leucas calostachys Oliv.                       | (j)           |                      |                                   |
| Ocimum kilimandscharicum Gürke                 | (k)           |                      |                                   |
| Plectranthus barbatus Andrews                  | (l)           |                      |                                   |
| Ocimum basilicum L.                            | (m)           |                      |                                   |
| Ocimum suave Willd. Lamiaceae                  | (n)           |                      |                                   |
| Name                                                                 | Country/Region  | Part                  | Authors          |
|----------------------------------------------------------------------|-----------------|-----------------------|------------------|
| **Lauraceae**                                                        |                 |                       |                  |
| *Persea americana* Mill.*                                            | (a) Brazil, (b) Nigeria | (a), (b) Leaf          | (a) Tomchinsky et al. (2017); (b) Dike, Obembe and Adebiyi (2012) |
| *Bertholletia excelsa* Bonpl.*                                        | (a) Brazil      | (a) Bark               | (a) Tomchinsky et al. (2017) |
| **Tamarindaceae**                                                    |                 |                       |                  |
| *Tamarindus indica* L.                                               | (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) |
| *Albizia gummifera* (J.F.Gmel.) C.A.Sm.                              |                 |                       |                  |
| *Erythrina abyssinica* DC.                                            |                 |                       |                  |
| *Senna didmobotrya* (Fresen.) H.S.Irwin and Barneby                   |                 |                       |                  |
| **Leguminosae**                                                      |                 |                       |                  |
| *Bertholletia excelsa* Bonpl.*                                        |                 |                       |                  |
| *Tamarindus indica* L.                                               | (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) |
| *Albizia gummifera* (J.F.Gmel.) C.A.Sm.                              |                 |                       |                  |
| *Erythrina abyssinica* DC.                                            |                 |                       |                  |
| *Senna didmobotrya* (Fresen.) H.S.Irwin and Barneby                   |                 |                       |                  |
| **Oleaceae**                                                         |                 |                       |                  |
| *Strychnos ligustrina* Blume                                         | (a) Indonesia   | (a) Stem bark          | (a) Taek et al. (2019) |
| **Meliaceae**                                                        |                 |                       |                  |
| *Guarea pubescens* (Rich.) A.Juss.                                   | (a) Brazil, (b) Indonesia, (c), (d), (e) Kenya | (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) |
| *Melia azedarach* L.                                                 |                 |                       |                  |
| *Mellia azedarach* L.                                                |                 |                       |                  |
| *Trichilia emetica* Vahl                                             |                 |                       |                  |
| *Azadirachta indica* A.Juss.                                         |                 |                       |                  |
| **Menispermaceae**                                                   |                 |                       |                  |
| *Abuta grandifolia* (Mart.) Sandwith.                                | (a), (b) Brazil, (c) Kenya | (a) Leaf (b), (c) Root | (a), (b), (c) Tomchinsky et al. 2017 |
| *Abuta imene* (Mart.) Eichler                                        |                 |                       |                  |
| *Cissampelos mucronata* A.Rich.                                      |                 |                       |                  |
| **Moraceae**                                                         |                 |                       |                  |
| *Ficus hispida* L.f. (L.) DC.                                        | (a) Indonesia, (b) Kenya | (a) Leaf, (b) Stem bark | (a) Taek et al. (2019); (b) Mukungu et al. (2016) |
| *Ficus thonningii* Blume (L.) DC.                                     |                 |                       |                  |
| **Menispermaceae**                                                   |                 |                       |                  |
| *Moringa oleifera* Lam.                                              | (a) Indonesia   | (a) Root               | (a) Taek et al. (2019) |
| **Myristicaceae**                                                    |                 |                       |                  |
| *Iryanthera hostmannii* (Benth.) Warb.                                | (a) Brazil      | (a) Sap                | (a) Tomchinsky et al. 2017 |
| **Myrtaceae**                                                        |                 |                       |                  |
| *Psidium guajava* L.                                                 | (a) Indonesia   | (a) Leaf               | (a) Taek et al. (2019) |
| **Oleaceae**                                                         |                 |                       |                  |
| *Nyctanthes arboristis L.*                                           | (a) India       | (a) Leaf               | (a) Nagendrappa, Naik and Payyappallimana, (2013) |
| **Phyllanthaceae**                                                   |                 |                       |                  |
| *Flueggea virosa* (Roxb. ex Willd.) Royle                           | (a), (b) Kenya  | (a) Aerial part, (b) Leaf | (a), (b) Mukungu et al. (2016) |
| *Phyllanthus sepialis* Mill. Arg.                                    |                 |                       |                  |
| **Piperaceae**                                                       |                 |                       |                  |
| *Piper nigrum* L.                                                    | (a) India       | (a) Fruit              | (b) Nagendrappa, Naik and Payyappallimana, (2013) |
| Plant Name | Country | Part(s) of Plant | Reference(s) |
|------------|---------|-----------------|--------------|
| *Pittosporum viridiflorum* | Kenya | Leaf, stem bark | Mukungu et al. (2016) |
| *Paspalum gardnerianum* | Brazil | Whole plant | Tomchinsky et al. (2017); Asase, Akwetey and Achel (2010); Dike, Obembe and Adebiyi (2012) |
| *Paspalum gardnerianum* | Ghana | Leaf | Mukungu et al. (2016) |
| *Paspalum gardnerianum* | Nigeria | Stem bark | Mukungu et al. (2016) |
| *Bambusa vulgaris* | Kenya | Leaf | Mukungu et al. (2016) |
| *Cymbopogon citratus* | Brazil | Whole plant | Tomchinsky et al. (2017); Asase, Akwetey and Achel (2010); Dike, Obembe and Adebiyi (2012) |
| *Cymbopogon citratus* | Ghana | Leaf | Mukungu et al. (2016) |
| *Cymbopogon citratus* | Nigeria | Stem bark | Mukungu et al. (2016) |
| *Rumex abyssinicus* | Kenya | Leaf | Mukungu et al. (2016) |
| *Rumex steudelii* | Kenya | Root | Mukungu et al. (2016) |
| *Drynaria quercifolia* | Indonesia | Tubercle | Taek et al. (2019) |
| *Maesa lanceolata* | Kenya | Stem bark, root bark | Mukungu et al. (2016) |
| *Ampelozizyphus amazonicus* | Brazil | Root | Tomchinsky et al. (2017) |
| *Rubus pinnatus* | Kenya | Leaf, fruit | Mukungu et al. (2016) |
| *Citrus limon* | Brazil | Fruit peel | Tomchinsky et al. (2017); Taek et al. (2019); Mukungu et al. (2016); Nguta et al. (2010); Tabuti (2008) |
| *Melicope latifolia* | Indonesia | Leaf | Mukungu et al. (2016) |
| *Clausena anisata* | Kenya | Leaf | Mukungu et al. (2016) |
| *Zanthoxylum gilletii* | Kenya | Stem bark | Mukungu et al. (2016) |
| *Zanthoxylum gilletii* | Uganda | Leaf | Taek et al. (2019) |
| *Deinbollia pinnata* | Ghana | Leaf | Asase, Akwetey and Achel (2010) |
| *Quassia amara* | (a), (b), (c) Brazil | Leaf, Root, Leaf | (a), (b) Tomchinsky et al. (2017); (c) Taek et al. (2019) |
| *Simaba cedron* | (a), (b) Brazil, (c) Nigeria | Leaf | Taek et al. (2019) |
| *Brucea javanica* | (a), (b), (c) Brazil, (d) Indonesia, (e), (f), (g), (h) Kenya, (i) Uganda | Leaf, Stem bark, Leaf, Leaf, Stem bark, Leaf, Root | Mukungu et al. (2016); Nguta et al. (2010); Tabuti (2008) |
| *Capsicum frutescens* | Brazil | Whole plant | Tomchinsky et al. (2017); Taek et al. (2019); Mukungu et al. (2016); Asase, Akwetey and Achel (2010) |
| *Physalis angulata* | Brazil | Root | Tomchinsky et al. (2017); Taek et al. (2019); Mukungu et al. (2016); Asase, Akwetey and Achel (2010) |
| *Physalis peruviana* | Kenya | Leaf | Mukungu et al. (2016) |
| *Solanum torvum* | Ghana | Fruit | Tabuti (2008) |
| *Solanum incanum* | Kenya | Root | Mukungu et al. (2016) |
| *Solanum torvum* | Kenya | Fruit | Mukungu et al. (2016) |
| *Zanthoxylum gilletii* | Kenya | Fruit | Mukungu et al. (2016) |
| *Teclea simplicifolia* | Kenya | Root | Mukungu et al. (2016) |
| *Zanthoxylum chalybeum* | Kenya | Root | Mukungu et al. (2016) |
| *Deinbollia pinnata* | Ghana | Leaf | Asase, Akwetey and Achel (2010) |
| *Grewia hexaminta* | Ghana | Leaf, root | Nguta et al. (2010) |
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 \( \textit{Plectranthus barbatus} \) Andrews, mentioned in the ethnobotanical survey by Mukungu et al. (2016), was tested for its ability to inhibit \( P. falciparum \) \textit{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 \( \textit{Mormodica charantia} \) L., studies such as those by Abdillah et al. (2019) demonstrate a high plasmodial inhibition of \( 0.17 \pm 0.12 \mu \text{g/mL} \) 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 \( \textit{Momordica foetida} \) 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 (\( \leq 10 \mu \text{g/mL} \)) 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 \( \textit{M. foetida} \), another result of inactivity was also observed for the plant \( \textit{Carica papaya} \) 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 \( \mu \text{g/mL} \) 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.
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 CO₂, 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 (Wallarta 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 inflata 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.

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