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Medicinal plants with antimalarial activity and antiviral potential: A source of active compounds for the treatment of COVID-19? A review

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Abstract

CoVID-19 is a devastating disease that affects different organs and systems in the human body and is caused by the SARS-CoV-2 virus. This disease had its beginnings in China and has raged around the world, characterizing a pandemic that is difficult to control due to the high transmission capacity of the virus between people. Studies with plants with anti-protozoan activity have been the object of studies for the treatment of CoVID-19, since some of these plants have an antiviral effect. The aim of this study was to conduct a review of the literature on the use of medicinal plants with antimalarial activity as a possible strategy in CoVID-19 therapy. Dozens of plants with antimalarial activity stood out for having antivirals and, considering the diversity of active compounds present in these plants, it is possible to think of these plants as a potential source of new biologically active compounds that could potentially be applicable in therapy against CoVID-19.

Keywords: COVID-19, multi-targeted drugs, medicinal plants, antiviral potential

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1. Introduction

Parasitic diseases, caused by protozoa and other microorganisms, affect a large portion of the world population, causing a great impact on health, limiting the quality of life and development in many countries. Among the main parasitic diseases, malaria stands out, a disease that has occurred in several tropical and subtropical regions of the world since remote times [1-4]. Malaria is an infectious disease caused by species of protozoa of the genus *Plasmodium* and transmission of these protozoa to humans occurs through the bite of a female Anopheles mosquito, which acquired the protozoan by biting another infected person. This means that malaria is not contagious, that is, it is not transmitted from one person to another, except in very rare cases of sharing infected syringes or needles, poorly controlled transfusions, and/or childbirth [5-6].

Plasmodium falciparum is the species that can lead to the development of an acute and rapidly fulminating disease characterized by persistent high fever, orthostatic hypotension and massive erythrocytosis (an abnormal increase in the number of red blood cells accompanied by swollen red legs), capillary obstruction, and death if treated, is not instituted immediately [7]. On the other hand, *Plasmodium vivax*, *Plasmodium malariae* and *Plasmodium ovale* among others cause a milder form of the disease compared to *Plasmodium faciparum* infection [5-6], [8-9].

Insecticide-resistant mosquitoes and antimalarial drug-resistant protozoa represent a major problem for the treatment of infections caused by *Plasmodium falciparum* and individuals affected by the disease present a significant loss in quality of life and undergo pharmacological and hospital treatment [10-12]. Antimalarial drugs used for the treatment and prevention of malaria are classified based on their chemical structure and origin, with most of these drugs being obtained from medicinal plants [13]. The first drug used in the treatment of malaria was quinine, which is a quinoline alkaloid present in trees native to South and Central America and belonging to the genus Cinchona [1-2], [10-13]. However, it was only in the 1920s that research aimed at the synthesis of new compounds to combat this disease had its first success with the synthesis of quinacrine (9-aminoacrinidine) [14]. Although these substances have good activity in the treatment of malaria, their mechanisms of action are not fully elucidated [13]. Furthermore, many effects unrelated to the antiprotozoal effect have been reported with the use of these substances in the clinic. These

observations lead to continuous studies on antimalarial drugs as well as the use of these drugs in the treatment of different patho-physiological conditions [13]. In this way, the concomitant incidence of malaria and viral diseases and the scarcity of new drugs against different viral infections increase studies on the antiviral activity of drugs and natural compounds with antimalarial potential [13]. At the end of the year 2019, there was an epidemic outbreak of Severe Acute Respiratory Syndrome that occurred in China, and its etiological agent was identified as a new coronavirus (SARS-CoV-2). This disease was characterized by the World Health Organization as a pandemic, called CoVID-19 [15]. Despite its rapid identification, its pathophysiological aspects are still not fully understood. The high transmissibility of the virus, the scarcity of antiviral drugs, the potentially large asymptomatic populations that carry and transmit the virus, has made the preventive and clinical management of CoVID-19 extremely challenging. Continued efforts to better understand the pathogenesis of this disease will undoubtedly clarify the best way to deal with the pandemic [16]. Synthetic drugs may have different effects from those that were initially prospected, due to the lack of sufficient selectivity of these drugs to reach only the desired targets, which determines the occurrence of adverse and side effects of these drugs [17-18]. The different extracts of medicinal plant species contain in their compositions several biologically active chemical compounds that can act in isolation or not, that is, in an additive and/or synergistic way against different pathophysiology. Moreover, medicinal plants, as multifunctional chemical entities, have great potential in the treatment of multifactorial disease conditions [19-20].

Given the pathophysiological complexity of CoVID-19, which can present different symptoms, its treatment requires the selection of more than one pharmacological target. This study aims to discuss the role of plant species with antimalarial activity associated with different pharmacological activities, such as antiviral, anti-inflammatory, and immunomodulatory, which may be relevant to research, development, and production of medicines applicable to CoVID-19 therapy.

2. Materials and methods

The present work is a literature review where the identification of articles of interest was performed using the PubMed databases of the US National Library of Medicine (https://pubmed.ncbi.nlm.nih.gov/), database Medical Literature Analysis and Retrieval System Online (MEDLINE), Scientific Electronic Library Online (SciELO), Latin American and Caribbean Literature on Health Sciences (LILACS), and the search tool attached to the Virtual Health Library (VHL). The Institutional Repository of different Brazilian Universities for researching articles along with theses, dissertations, and monographs was also consulted. The predefined keywords “COVID-19”, “Multi-targeted drugs”, “Medicinal plants”, “Antiviral potential” were used in the searches. The search expression was the Boolean operator "AND", limiting the searches to the words of the title or abstract of articles, in English, Portuguese and Spanish, studies with human beings and/or experimental animals, as well as *in vivo* and *in vitro* studies and/or *ex-vivo*. To ensure the quality of articles, only indexed publications were included in this database and articles that presented title and abstract according to the theme were included and those that did not fit were excluded.

3. Results and discussion

3.1. Main antimalarials

Antimalarial drugs are based on natural products or synthetic compounds produced since the 1940s and are specific to each stage of the *Plasmodium* life cycle [1]. In general, the main antimalarials are classified into two major groups: the first group includes alkaloids derived from cinchona, aminoquinolines and acridines, and these drugs are believed to interfere with glucose metabolism and also with the parasite's ability to digest hemoglobin. The second group includes pyrimidines and biguanides that interfere with the synthesis of tetrahydrofolic acid, an important cofactor in the process of DNA and amino acid synthesis by the parasite [1]. In the first four decades of the 20th century, programs to support research and the synthesis of antimalarial substances received great impetus in several countries. Most drugs developed at the time were composed of quinoline bases, which include 4-aminoquinolines, 8-aminoquinolines and quinoline alcohols [14]. During this period, the most effective of these drugs was chloroquine, however, its use as a prophylactic agent led to the development of resistance by the etiological agents of malaria in many endemic countries [21].

In this way, resistance to chloroquine led to the development of other antimalarial agents, such as mefloquine, which to this day has been used to combat *Plasmodium falciparum* resistant to chloroquine, amodiaquine and hydroxychloroquine. There are two main hypotheses for the mechanism of action of mefloquine, the first is the inhibition of heme crystallization and the second is the inhibition of the endocytosis of host cell hemoglobin [22]. Other drugs, such as some 8-aminoquinolines, are effective against primary and secondary tissue forms of the parasite, as well as its sexual stages. Pamaquine and primaquine are two examples of these drugs. Pamaquine was synthesized in Europe during the 1920s and is one of the oldest antimalarial agents in the 8-aminoquinoline group. Primaquine is the most commonly used drug in this group, usually co-administered with a blood schizonticide agent, such as chloroquine, amodiaquine or pyrimethamine (folate antagonist) [23].

Experimental studies with phenanthrene derivatives, such as halofantrine, have shown the efficacy of this

compound against chloroquine-resistant malaria and the safety of its use in humans has been investigated [1]. In turn, lumefantrine, or benflumetol, is a drug structurally related to mefloquine, quinine and halofantrine, suggesting that they have similar modes of action and antimalarial effects [24].

A class of drugs called folate antagonists can also act as excellent blood schizonticides. Most drugs belonging to these pharmacological classes have a close structural similarity to para-aminobenzoic acid (PABA) and the mechanism of action of these drugs is the inhibition of dihydropteroate synthetase, which is the key enzyme in the production of dihydrofolic acid, which is crucial for the maintenance of the life of the parasite. Two examples of this pharmacological class are the sulfones and sulfonamides, where dapsone has the greatest pharmacological efficacy among the sulfones. Antimalarial sulfonamides include sulfadoxine, sulfadiazine and sulphalene [25]. The second group of folate antagonist drugs consists of drugs that exert their effects by preferentially and selectively binding to the enzyme dihydrofolate reductase-thymidylate synthase and interrupting the life cycle of the parasite. Members of this class of antifolates include pyrimethamine and trimethoprim, and the combination of pyrimethamine and sulfadoxine is able to antagonize serine hydroxymethyltransferase, which is another key enzyme in the parasite's life cycle. All of these drugs have been used for a long time, and descriptions of their proper therapeutic use against malaria have been around since the 1970s [26].

Other drugs, such as biguanides, quinones, naphthoquinones, artemisinin, also have antimalarial activity related to their schizonticidal effects and the use of these drugs has helped in the treatment of malaria [1]. From artemisinin, several analogues with varied pharmacokinetic activities have been synthesized, such as sodium artesunate, dihydroartemisinin, arteether and artemether. These sesquiterpene compounds show structural similarity, are blood schizonticides and have gametocidal activity [1]. The literature also reports that important antimalarial drugs are available in different combinations and are marketed worldwide [27-32] and some combinations of these drugs can be seen in Table 1. The prospect of new drugs against malaria has been promising, however, they are still in clinical study [33]. Although the available drugs have been used for the treatment of malaria for some time, it is known that their adverse effects can overlap with the symptoms of the disease itself. Adverse effects include loss of appetite, gastrointestinal disturbances, cardiovascular effects such as orthostatic hypotension, serious neurological and/or psychiatric side effects [34-37] and this condition justifies the search for safer drugs.

3.2. Pathophysiology of CoVID-19: General aspects

The literature reports that human angiotensin-converting enzyme 2 (ACE2) is a functional receptor sequestered by SARS-CoV-2 for cell entry, similar to SARS-CoVACE2 is a protein structure that is found in the cell membrane of several cells, including the cells of the organs of the respiratory system such as the bronchi and lungs, in the cells of the digestive system such as the ileum and stomach, in the cells of the cardiac and renal tissue, among others [38-39]. The high infectivity of the virus is related to mutations in the binding domain of this receptor and the acquisition of a furan cleavage site in the S spike protein. The interaction of the virus with ACE2 can decrease the anti-inflammatory function and increase the effects of angiotensin-II in predisposed patients [16]. The gateway of SARS-CoV-2 to the organism is the upper respiratory tract, with subsequent viral multiplication in the lower respiratory tract and in the mucosa of the gastrointestinal system, which leads to a mild viremia that characterizes the initial infection and that in many individuals this infection can usually be asymptomatic. However, some infected individuals may develop non-respiratory symptoms such as liver and heart damage, diarrhea, and kidney complications. Infections at this early stage are often difficult to control pharmacologically [16].

In very severe cases of SARS-CoV-2 infections, patients experience severe respiratory distress, and most of the time these patients require the assistance of mechanical ventilation to breathe, and the histopathological findings support the diagnosis of very severe cases of this viral infection. and that the genetic and inflammatory susceptibility of patients to cytokines is closely related to the occurrence of Acute Respiratory Distress Syndrome (SARDS). Thus, dozens of candidate genes, including the gene linked to the gene expression of ACE2, interleukin 10 (IL-10), tumor necrosis factor (TNF), vascular endothelial growth factor (VEGF), among others, have been associated with the development from SARDS. Increased plasma levels of interleukin 6 (IL-6) and interleukin 8 (IL-8) are also related to the pathophysiology of this syndrome. All these chemical mediators can be considered biomarkers and the study of these mediators contributes to a molecular explanation of severe SARDS, which implies valuable knowledge for the treatment of individuals infected with SARS-CoV-2 [38-39].

Thus, the literature also reports that substances that have the ability to prevent the virus from binding to receptors on cells in order to negatively interfere with the viral internalization process, the ability to inhibit viral replication by inhibiting the functioning of crucial enzymes for the virus, such as RNA polymerase, proteases, among others, the ability to prevent viremia, as well as the ability to increase the cytotoxic capacity of the immune system, are in some ways potential candidates for effective drugs in the treatment of SARS-CoV-2 [40].

3.3. Antimalarials in different pharmacological targets against CoVID-19

Pharmacodynamics is a branch of pharmacology that studies the response of the biological system to a drug and drug specificity is a measure of the ability of a receptor

to respond to a single ligand [41-42]. The low specificity of a drug often results in possible side effects in the body. In fact, it is not uncommon for a drug to be developed with a theoretical action, while a side effect may emerge as the new target role [41-42]. Thus, different pharmacological activities are also associated with antimalarials. Chloroquine is used in the clinical protocol of autoimmune diseases such as rheumatoid arthritis [43] and lupus erythematosus [44] and in use in antitumor therapy as an inhibitor of cellular autophagy [45]. Primaquine also has its use in the prophylactic therapy of pneumonia in patients with Acquired Immunodeficiency Syndrome [46-47]. Regarding mefloquine, studies indicate its efficacy in the treatment of leishmaniasis [48]. Substances isolated from plants with antimalarial activity have also shown effects different from those initially recommended, such as quinine in the prevention of colic during hemodialysis [49] and artemisinin with multiple pharmacological actions, demonstrated *in vitro* and *in vivo*, as anticancer, antiparasitic and anti-inflammatory, among others [50-51].

Since the early 1970s, researchers have been interested in another property of antimalarial drugs, such as their antiviral activity. Thus, an evaluation of the effect of these substances on viruses of various structures and replication modes was performed [52]. In an updated literature review [13] the authors describe the results of *in vitro* and *in vivo* studies of antimalarial agents for use against viral infections where most of these agents are of natural origin and extracted from medicinal plants. Although several antimalarial drugs have shown some form of antiviral activity [13], [52], the focus of study and application against SARS-CoV-2 was initially chloroquine and hydroxychloroquine [53]. Chloroquine (CQ), an older antimalarial, and its derivative hydroxychloroquine (HCQ) have become increasingly popular in an attempt to find an effective treatment for CoVID-19. In vitro studies have also demonstrated potent antiviral properties of CQ and HCQ. The use of these drugs, however, can be associated with serious side effects. In recent months, several prospective studies have revealed conflicting results regarding the use of CQ and HCQ. Their recommendation as preventive drugs for healthy, asymptomatic infected people awaits a proper double-blind clinical trial [53-54]. The view of the Pan American Health Organization and the WHO on the use of chloroquine and hydroxy-chloroquine for treatment and prophylaxis against CoVID-19 is that each country is sovereign to decide on its clinical protocols for the use of medicines. Although hydroxy-chloroquine and chloroquine are licensed products for the treatment of malaria and other diseases, there is no scientific evidence to date that these drugs are effective and safe in the treatment of CoVID-19 [55].

Recently, artemisinin and its derivatives have gained prominence in the treatment of CoVID-19 [46]. The antimalarial action of artemisinin derivatives is different from chloroquine and hydroxychloroquine, but their immunomodulatory effects against inflammatory diseases and viral replication are similar. Thus, artemisinin appears to have the ability to decrease the secretion of macrophage-derived pro-inflammatory cytokines, particularly tumor necrosis factor [51]. In general, it appears that artemisinins may assume an immunosuppressive therapeutic potential in persistent inflammatory immune reactions in macrophages due to their ability to inhibit the release of pro-inflammatory cytokines [51]. *In vitro* studies demonstrated antiviral properties in which artemisinin inhibited human cytomegalovirus (hCMV) replication through a reduction in the DNA binding activity of NF-κB and Sp1. Many of these pathophysiological processes are also present in respiratory diseases. Thus, artemisinin and its derivatives can potentially be used for the treatment of respiratory diseases [51]. *Artemisia annua* extract has excellent antioxidant activity, and this biological effect is attributed to the large amounts of phenolic compounds present in the extract and derivatives of *Artemisia annua*, such as artesunate, are a promising new drug in the treatment of pulmonary fibrosis through the inhibition of pro-fibrotic molecules [56]. Artemisinin-based combination therapy (ACT) at expected blood concentrations after administration of the same doses used in the treatment of malaria determines in vitro inhibition of SARS-CoV-2 replication. The combination mefloquine-artesunate at a dose of 550 mg/250 mg determines 72.1% of virus inhibition. Although *in vitro* activity is not necessarily linked to clinical efficacy, assessing the in vitro activity of ACT against SARS-CoV-2 may provide some answers as to whether the use of antimalarials might be indicated in combating the spread of the CoVID-19 pandemic [57].

Clinical studies have already started to evaluate the efficacy of artesunate against CoVID-19. Based on the National Institutes of Health (NIH) Clinical Trials website, there are four clinical trials in the early stages of progress using artesunate in the treatment of CoVID-19 [58-61]. The World Health Organization (WHO) welcomes the innovations made around the world, including with regard to the adaptation of medicines, the use of traditional medicine, and the development of new therapies in the search for potential treatments against the disease caused by SARS-CoV-2. WHO recognizes that traditional, complementary, and alternative medicine offers several benefits. There is a long history that shows the important role of traditional medicine in health care for the population. In this context, medicinal plants such as *Artemisia annua* are indicated as possible therapeutic agents for the treatment of CoVID-19 and, therefore, deserve a broader clinical evaluation to determine their efficacy and adverse effects [62].

3.4. Medicinal plants and association of pharmacological activities with therapeutic potential in CoVID-19

The literature reports that single-target drugs do not always determine the expected pharmacological effect on the body, even if they successfully inhibit or activate a specific target. One reason for this is that the human organism can

affect efficacy in a compensatory way and the pathophysiology of diseases involves several complex aspects. Thus, the concept of multi-targeted drug design has been proposed [63]. Considering the complexity of the pathophysiology of CoVID-19, the main pharmacological targets for the treatment of this disease are those that involve inflammatory and immunological processes, in addition to the action against the virus itself. In this context, Table 2 presents some important species with antimalarial activity described in the literature that also has antiviral and/or anti-inflammatory and/or immuno-modulating action.

Among the 27 plant species with antimalarial activity, indicated in Table 2, twenty-one of these species showed results with some antiviral and also anti-inflammatory, and/or immuno-modulating activity and these plants may indicate a promising possibility for therapy with CoVID-19, individually or together with other plants or medicines, however, it is obvious and imperative that the plant species indicated above in Table 2 should undergo clinical studies to assess their efficacy against the disease. Although the cost and time related to the development of new drugs and the proof of their clinical efficacy are significant, it is understood that the paradigm that only synthetic drugs per se are effective and safe in the treatment of diseases must be questioned. Therefore, the ethnobotanical and scientific knowledge of medicinal plants and their multiple uses must be consolidated and disseminated in a systematic and consistent manner. As the clinical studies presented in this work point out, the use of synthetic drugs in association with medicinal plants can provide an effective therapeutic form against SARS-CoV-2 or symptoms caused by the virus, as is the case of the anti-inflammatory and immunomodulatory activities that these plants can present.

3.5. Final considerations

With the emergence of CoVID-19, substances of plant and synthetic origin with antimalarial activity have been used in the treatment of this disease, albeit empirically, as many of these substances have multi-target activity. Although chloroquine and hydroxy-chloroquine are examples of synthetic derivatives modeled on quinine, with in vitro and in vivo activity and tested against SARS-CoV-2, these drugs have not demonstrated therapeutic efficacy in clinical studies performed. Three species of medicinal plants with antimalarial activity addressed in this work (*Artemisia annua*, *Cinchona officinalis*, and *Vernonia amygdalina*) are targets of clinical studies for the treatment of CoVID-19 and their pharmacological effects may be promising for this purpose. The effects of artesunate (artemisinin-derived semi-synthetic compound) both *in vitro* and *in vivo* and in clinical trials are also being the focus of attention for possible action of this medicinal plant-derived compound against SARS-CoV-2. As the COVID-19 pandemic spreads, researchers around the world are exploring drug options to combat this ongoing challenge. In this sense, medicinal plants may represent an excellent source of obtaining new biologically active and safe compounds in the treatment of this disease.

Table 1: Main drugs used in the treatment of malaria

Associations of different drugs	Drugs Names
Combination of artemisinin derivatives and antimalarials from other classes	1. Artemether/Lumefantrine 2. Artesunate/Sulfadoxine/Pyrimethamine 3. Artesunate/Amodiaquine 4. Artesunate/Pyronaridine 5. Dihydroartemisinin/Piperaquine 6. Doxycyclin /Artesunate
Other drug combinations	1. Doxycycline/Quinine 2. Doxycycline/Mefloquine 3. Clindamycin/Quinine 4. Clindamycin/Artesunate 5. Clindamycin/Mefloquine 6. Sulfadoxine/Pyrimethamine 7. Chloroquine/Primaquin 8. Chloroquine/Bulaquine 9. Dapsone/Chlorproguanil 10. Atovaquone/Proguanil

Table 2: Plant species with antimalarial activity and other potential pharmacological actions in proposing treatment with CoVID-19

Scientific name	Family	Part of the plant and/or your products	Pharmacological activities	Inhibited virus type	References
Ageratum conyzoides	Asteraceae	Leaves, whole plant and aerial parts	Antimalarial/anti-inflammatory/antiviral	Entero viruses	[64-67]
Ampelozizyphus amazonicus	-	Bark, root and leaves	Antimalarial/anti-inflammatory/immunomodulatory/antiviral	Herpes simplex virus	[68-70]
Argemone mexicana	Papaveraceae	Isolated compounds, extracts and fractions of the species	Antimalarial/anti-inflammatory/antiviral	Human immunodeficiency virus	[71-72]
Artemisia annua, Artemisia opiacea	Asteraceae	All parts of the plant	Antimalarial/antiviral, immunomodulatory and anti-inflammatory	Cytomegalovirus, hepatitis B virus, hepatitis C virus, human papilloma virus, human immunodeficiency virus	[13], [27], [51], [73-74]
Bidens pilosa	Asteraceae	Acetone extract, aqueous extracts	Antimalarial/antiviral/anti-toxoplasm	Herpes simplex virus	[75-78]
Calophyllum spp.	Calophyllaceae	Isolated substance from organic extracts of stem bark	Antimalarial/anti-inflammatory/antiviral	Human immunodeficiency virus	[79]
Canna indica	Cannaceae	Leaves	Antimalarial/anti-inflammatory/immunomodulatory/antiviral	Human immunodeficiency virus I	[64], [80-83]
Cedrela odorata	Meliaceae	Stem bark	Antimalarial/anti-inflammatory	Not rated	[64], [84-85]
Cinchona pubescens *Cinchona calisaya* *Cinchona officinalis* *Cinchona succirubra*	Rubiaceae	Tree bark	Antimalarial/antiviral/anti-inflammatory	Herpes virus type I, dengue virus, chikungunya virus, human immunodeficiency virus	[13], [52], [73-74]
Citrus aurantifolia	Rutaceae	Decoction and infusion of leaves and flowers, fruit	Antimalarial/immunomodulatory/anti-inflammatory	Not rated	[87-88]

		juice and essential oil			
Cryptolepis sanguinolenta	Apocynaceae	Roots	Antimalarial/anti-inflammatory/antiviral	Herpes simplex virus 1	[27-28]
Morinda lucida	Rubiaceae	Leaves, stem and root	Antimalarial/anti-inflammatory	Not rated	[89-90]
Nauclea pobeguinii	Rubiaceae	Stem bark extract	Antimalarial/anti-inflammatory	Herpes simplex virus 2	[91-93]
Nyctanthes arbortristis	Oleaceae	Leaves and seeds	Antimalarial/immunomodulatory	Encephalomyocarditis virus	[94-96]
Physalis angulata	Solanaceae	Isolated substances (physalins) from extracts of the whole plant, aerial parts	Antimalarial/immunomodulatory/anti-inflammatory/antiviral	Poliovirus-I, herpes simplex virus-I, measles virus and human immunodeficiency virus-I	[97-99]
Piper spp.	Piperaceae	Leaves	Antimalarial/anti-inflammatory/antiviral	Bovine herpesvirus 1 poliovirus (*Piper regnelli*)	[100-102]
Psidium guajava	Myrtacaceae	Leaves	Antimalarial/anti-inflammatory/antiviral	Influenza virus type A	[103-104]
Quassia amara	Simaroubaceae	Leaves, bark and roots	Antimalarial/antiviral/anti-inflammatory	Herpes simplex, coxsackie virus and vesicular stomatitis virus	[105-107]
Struchium sparganophora	Asteraceae	Leaves	Antimalarial/anti-inflammatory	Not rated	[66-67], [108]
Tithonia diversifolia	Asteraceae	Leaves and trunks	Antimalarial/anti-inflammatory/antiviral	Herpes simplex virus type 1 and type 2	[66], [109-110]
Vernonia amygdalina	Asteraceae	Leaves	Antimalarial/immunomodulatory/anti-inflammatory	Not rated	[105], [111-112]
Ximenia americana	Olacaceae	Stem, bark, leaves	Antimalarial/anti-inflammatory/antiviral	Human immunodeficiency virus I and II	[113-115]
Xylopia vielana	Annonaceae	Leaves, stem bark and fruits	Antimalarial/anti-inflammatory	Not rated	[116]

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