REVIEW ARTICLE

Phytochemicals in Malaria Treatment: Mechanisms of Action and Clinical Efficacy

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ABSTRACT

Background: Malaria is an illness caused by Plasmodium parasites and transmitted by Anopheles mosquitoes and is still a worldwide threat today, further complicated by emerging resistance to antimalarial drugs. Plant-derived bioactive compounds known as phytochemicals can be used as an alternative or complementary treatment to chemical-based antimalarial drugs. **Aim**: This narrative review aims to discuss the mechanisms of action and clinical efficacy of various phytochemicals in malaria treatment. **Methodology**: Reputable science-based databases such as PubMed, Scopus, Web of Science, and Google Scholar, were used to a great extent to obtain data on this subject within the last decade. The impact of artemisinin, quinine, curcumin, nimbolide, berberine, and other related compounds on the Plasmodium parasites and their effects on growth and the host immune response were examined. The in vitro and in vivo investigations along with comprehensive clinical trials that compare the mechanism, efficiency, toxicity, and applicability of these phytochemicals in today's therapeutic management procedures were discussed. **Results**: The study highlights the importance of phytochemicals in malaria control, particularly in developing treatment protocols and preventing drug resistance. It calls for further research to enhance the effectiveness of phytochemical-based treatments, explore synergistic effects, and address current shortcomings in malaria treatment. **Conclusion**: These results suggest that phytochemicals can be valuable components of a holistic approach to treat malaria and may actively contribute to worldwide initiatives for eliminating malaria.

Keywords: Malaria, Plasmodium, Phytochemicals, Artemisinin, Curcumin, Drug resistance.

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Citing this article
Alum, E.U. Phytochemicals in Malaria Treatment: Mechanisms of Action and Clinical Efficacy. KIU J. Health Sci, 2024: 4(2);

Conflict of Interest: None is declared

INTRODUCTION

Malaria is an infectious disease that affects humans. It is caused by parasitic organisms in the Plasmodium genus and transmitted to humans through a bite from a female Anopheles mosquito [1]. It is common in sub-tropical and tropical climatic regions, with significant incidences reported in sub-Saharan Africa, South Asia, and parts of South America [2]. Despite various worldwide attempts at its control and eradication, malaria still poses a significant threat to global public health because of multiple factors, including the numerous facets of its life cycle, the efficiency of transmission, and issues concerning diagnostics, treatments, and interventions. There are five Plasmodium species that infect humans, these include; Plasmodium falciparum, Plasmodium vivax, Plasmodium ovale, Plasmodium malariae, and Plasmodium knowlesi [3]. Malaria transmission involves several key stages. These include the sporozoite stage, liver stage, blood stage, and gametocyte stage [4]. Symptoms of malaria are numerous and may include: uncomplicated malaria, which comes with fever, chills, headache, and malaise; severe malaria, which has serious complications such as cerebral malaria, severe anaemias, renal failure, hypoglycemia, among others; and serological tests [5]. Malaria diagnosis involves microscopy, rapid diagnostic tests (RDTs), polymerase chain reaction (PCR), and serology. Treatment depends on the species, severity, and time of the clinical sign, as well as the geographical location of the affected patient [6]. Uncomplicated falciparum malaria is treated using artemisinin-combined therapies ACTs, while complicated falciparum malaria is treated with intravenous or intramuscular artesunate or quinine before completing a full course of ACTs once the patient is stabilized [7]. Some control measures include vector-borne control, chemotherapy, and vaccines. Malaria is still a significant challenge to global health, especially in the tropical and subtropical parts of the world[8]. However, there are still many issues that need attention today. These are drug resistance, the few drugs that are available on the market, poor access to treatment, more than one disease at the same time, a lack of accurate diagnostic tools, the difficulty of controlling the vectors, and economic and political instability [9]. The emergence of drug-resistant strains of Plasmodium, especially Plasmodium falciparum, compromises current antimalarial regimens. Another alarming issue is the lack of a pipeline of new antimalarial agents, which can be concerning in the future. Interaction with other diseases and illnesses hinders treatment and care, while diagnostic methods may not be sufficient enough to diagnose the disease correctly or on time [10]. A complex solution is necessary to overcome these issues, which involves the creation of new drugs and diagnostic tools, enhancement of healthcare systems, treatment availability, and continuity of vector control [11] . Flavonoids, alkaloids, terpenoids, and other plant-derived compounds that are referred to collectively as phytochemicals showed potential antimalarial effects in many researches [12]. Contemporary studies on phytochemicals with the ability to combat malaria have emphasised the significance of natural compounds obtained from African medicinal plants. An exhaustive analysis of chemicals examined from 2013 to 2019 found that terpenoids, flavonoids, alkaloids, and quinones were the predominant categories exhibiting anti-malarial effects [13]. Previous computational investigations have successfully identified possible antimalarial phytochemicals derived from Euphorbia hirta. Among these, isorhamnetin and pinocembrin have shown potential as inhibitors of plasmepsin [14]. In view of the growing resistance to anti-malarial current therapies, these results highlight the potential of plant-derived chemicals in the development of novel antimalarial medications.

Another example is artemisinin, which has revolutionised malaria therapy, but the extent of phytochemicals having antimalarial potential has not been fully explored [15]. The actions of phytochemicals against Plasmodium parasites are diverse, such as direct anti-plasmodial effects on growth and replication, disruption of oxidative stress, alteration of host immune response, and interference with haemoglobin metabolism [16]. Appreciation of such mechanisms is important in uncovering new drug targets and finding better treatment modalities. The goal of this study is to establish the ability of phytochemicals to influence malaria treatment and their mechanism of action. It is important to know the interaction between phytochemicals and antimalarial drugs as an adjunct to

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conventional therapy, which may also delay the occurrence of resistance. A thorough synthesis of the literature on phytochemicals' anti-malarial mechanisms of action and effectiveness is thus warranted to define areas for further investigation and guide practice. The use of effective phytochemicals in malaria treatment can highly influence the well-being of people in the world since it creates more treatment options that can be implemented in the scarce resource zone. This review will elucidate the mechanism by which phytochemicals exert their antimalarial effects and assess the efficacy of clinical trials.

METHODOLOGY

Literature Search Strategy

Databases Utilized: An electronic search was conducted to identify any publications pertaining to the role of phytochemicals in the treatment of malaria. The scientific databases PubMed, Scopus, Web of Science, and Google Scholar were used for the analysis.

Search Terms: These following terms were used in the search: phytochemicals, malaria treatment, antimalarial activity, mechanism of action, clinical effectiveness, plant-derived antimalarials, quinine, artemisinin, curcumin, and other phytochemicals.

Inclusion and Exclusion Criteria: The literature search was restricted to human, peer-reviewed articles, clinical trial reports, preclinical studies, and English-language review articles published in the last 10 years. The selection criteria included the type of study, phytochemicals, outcome measures, and language. Studies on malaria treatment or phytochemicals somewhat related to malaria treatment, articles that were not written in English, and articles that were not peer reviewed were some of the articles that were excluded.

Data Collection, Extraction, and Synthesis: Information was gathered from chosen publications, outlining the mode of operation, effectiveness, and toxicity of selected compounds. A general structure of results was followed to include concise overviews of the highlights of the study. The study compared the clinical effectiveness and the pharmacological effects of phytochemicals as malaria treatment approaches plus their possibility of augmenting conventional therapy.

PHYTOCHEMICALS WITH ANTIMALARIAL ACTIVITY

Phytochemicals are a resource of potential antimalarial compounds with multiple actions, which include the generation of oxidative stress, inhibition of relevant metabolic processes, and damage to the cell structures of the parasites. This knowledge has contributed to the understanding of new therapeutic approaches and the synthesis of new antimalarial molecules [17]. It was also evident that many phytochemicals, when administered together with conventional antimalarial drugs, showed synergistic effects. For instance, flavonoids such as quercetin can increase the activity of chloroquine, and curcumin shows promising results showing an augmentation of artemisinin activity [18]. These combinations not only enhance the therapeutic (curative) efficacy but also assist in the prevention of resistance.

Alkaloids: Quinine, one of the oldest and most effective antimalarial agents, is obtained from the bark of the Cinchona tree. Allosteric hindrances affect the ability of the parasite to metabolise heme, which results in continued heme accumulation and ultimately the death of the parasite. Quinine is considered the starting point for the creation of synthetic antimalarials like chloroquine [19]. Artemisinin is derived from Artemisia annua, while artemisinin and its derivatives are currently the main tools used in the fight against malaria. These sesquiterpene lactones thus exhibit their antimalarial property by generating reactive oxygen species (ROS) in the parasite, affecting its proteins and membranes [15]. Artemisinin-based combination therapies (ACTs) are very potent against the P. falciparum parasite [20]. An isoquinoline alkaloid isolated from several plants, namely Berberis species, berberine was found to possess antimalarial activity by interfering with the formation of nucleic acids and proteins in Plasmodium. It also interferes with the stability of the membrane in the parasitic organism [21]. More so, ajmalicine is an alkaloid obtained from Rauwolfia serpentina that inhibits several metabolic enzyme pathways that were found to exhibit antimalarial properties [22].

Terpenoids: Limonene and linalool are terpenoids that interfere with the parasite's cellular functions; however,

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they are less effective than artemisinin. The diterpenoid lactone isolated from Andrographis paniculata, andrographolide, has been reported to have potential antimalarial effects in preclinical studies, which may involve suppression of parasite development and regulation of the host's immune system [23].

Flavonoids: Quercetin is a common flavonoid and has been reported to possess antimalarial properties through controlling the parasite's growth and affecting oxidative stress. It also increases the effectiveness of standard antimalarial drugs whenever they are combined with this one [13]. Another flavonoid with antimalarial activity is apigenin, which interferes with the mitochondrial activity of the parasite, which affects energy metabolism and leads to the death of the parasite [24]. According to Adeoye and colleagues, apigenin and quercetin suppress the synthesis of β-hematin. Their molecular docking research conducted in silico demonstrated that apigenin exhibits the greatest binding affinity and possesses the maximum number of hydrogen bonds. They thus proposed that apigenin and quercetin may function as inhibitors of calcium transport proteins that are linked to malaria [25].

Polyphenols: Curcumin, the active compound of Curcuma longa (turmeric), has proved to possess a wide range of antimalarial properties. It modulates several processes within the Plasmodium parasite, such as the formation of ROS, preventing the polymerisation of heme, and interfering with cellular signaling [18]. Curcumin is also being investigated for its ability to improve the effectiveness of current antimalarial drugs and for overcoming drug resistance [26]. Resveratrol is a polyphenolic compound that is found in grapes and berries and has been observed to possess antimalarial activity in vitro, mainly through the induction of oxidative stress in Plasmodium and inhibition of its growth [27].

MECHANISMS OF ACTION OF PHYTOCHEMICALS AGAINST MALARIA

Inhibition of Plasmodium Growth and Replication

Phytochemicals act against the Plasmodium species at different developmental stages by preventing the growth and multiplication of the parasite. It is worth mentioning that alkaloids like quinine and berberine affect the development and reproduction of malignant parasites [28]. Quinine, which is obtained from the bark of Cinchona trees, cannot be metabolised by the malaria parasite into a form known as hemozoin, and this is toxic to the parasite [29]. Berberine, which is present in Berberis species, prevents the parasite from copying and repairing its DNA, thereby slowing its development and reproduction [30]. Quercetin and kaempferol, two types of flavonoids, exert antimalarial effects by inhibiting the enzymatic actions of the parasite. Quercetin has also been shown to inhibit dihydroorotate dehydrogenase, an enzyme in pyrimidine synthesis that is important for the parasite's DNA replication [31]. Kaempferol stops the action of lactate dehydrogenase, which in turn affects the energy production process of the parasite and thus the death of the parasite [32].

Induction of Oxidative Stress

Oxidative stress may be defined as an imbalance between the generation of reactive oxygen species (ROS) and the antioxidant system, wherein ROS take precedence [33]. Some phytochemicals cause oxidative stress in the parasite, which in turn leads to its death. Artemisinin's activity is triggered by heme or iron within the parasite leading to the production of ROS. These ROS lead to the oxidative damage of the parasite's cellular structures, such as lipids, proteins, and DNA. This results in oxidative stress that affects the cellular membranous structure of the parasite, which in turn causes the parasite's death [34]. Worthy of note is that artemisinin has a different mode of action compared to other antimalarial drugs, which makes it very effective, especially against drug-resistant strains of Plasmodium. Furthermore, curcumin, a polyphenol derived from Curcuma longa (turmeric), causes oxidative stress in Plasmodium parasites by enhancing ROS production and reducing the parasite's antioxidant capacity. This dual action causes a lot of harm to the parasites' cellular machinery and eventually results in death [18]. Furthermore, curcumin has immunomodulatory effects that help the host combat the disease [35].

Modulation of Host Immune Response

Phytochemicals can always alter the immune system of the host to enable it to fight off the Plasmodium parasite [35]. For instance, curcumin has been shown to increase

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the levels of pro-inflammatory cytokines and the phagocytic activity of macrophages, thereby expediting the elimination of the parasite [36]. Polysaccharides from Ganoderma lucidum (reishi mushroom) can exert immunomodulatory effects to improve the clearance of Plasmodium parasites in the host. These compounds enhance the secretion of pro-inflammatory cytokines and enhance the functions of immune cells, including macrophages and natural killer cells [37]. Through enhancement of the immune system of the host, polysaccharides assist in eradicating the parasite from the body. Plants like Panax ginseng, which contains saponins known as ginseng, have been seen to increase the host's immunity against Plasmodium. They stimulate the macrophages and enhance the synthesis of cytokines that lead to the clearance of the infected red blood cells [38]. Saponins have also been shown to have direct antiplasmodial effects by impairing the cell membrane of the parasite. Using an ethanol extract of V. amygdalina leaf, Omoregie and colleagues assessed the in vivo antiplasmodial, antioxidant, and immunomodulatory properties. The results indicate that the ethanol extract of V. amygdalina leaf exhibited activity and a modulatory effect on the immune system against P. berghei infection [39].

Interference with Hemoglobin Metabolism

The digestion and utilization of host hemoglobin to obtain amino acids is an important function that is vital for the survival of the parasites. Some compounds like quinine interferes with this process hence allowing the toxic heme to build up within the parasite and prove fatal to it [40]. Quinine and quinidine are stereoisomers that interfere with the metabolism of hemoglobin in the Plasmodium parasite. These compounds inhibit the formation of hemozoin thus hindering the detoxification of heme which is a byproduct of hemoglobin digestion. The buildup of toxic heme within the parasite brings about its death [41]. The triterpenoids from Azadirachta indica (neem) act on the hemoglobin metabolism of the Plasmodium parasites. These compounds suppress the enzymes that are required in the breakdown of heme thus provoking the buildup of toxic products. This interference in the heme biosynthesis leads to the production of reactive oxygen species and injury to the parasite culminating in its death [42].

Disruption of Mitochondrial Function

Artemisinin and its related compounds (artesunate and artemether) belong to sesquiterpene lactones, which act on the mitochondria of Plasmodium parasites. These compounds interfere with the electron transport chain, thus causing depolarisation of the mitochondrial membrane and halting ATP synthesis. The energy crisis that occurs within the parasite as a consequence of the virus leads to the death of the parasite [43]. Artemisinin and its derivatives are particularly effective in eradicating multi-drug-resistant strains of Plasmodium. For instance, Punica granatum (pomegranate), which are phenolic compounds, have been known to interfere with the mitochondrial processes in Plasmodium parasites. These compounds affect the function of certain enzymes in the mitochondria and therefore reduce ATP generation and increase ROS formation. It leads to mitochondrial dysfunction and oxidative stress that are toxic to the parasite and lead to its death [44].

IN VITRO, IN VIVO AND CLINICAL EFFICACY OF PHYTOCHEMICALS IN MALARIA TREATMENT

Phytochemicals have been investigated in vitro (cell cultures) and in vivo (animal models) to assess their anti-malarial activity. These studies have given a clue about the effectiveness of plant extracts in treating malaria and the way they work to hinder the growth of Plasmodium parasites. Similarly, there are lots of clinical trials on the anti-malarial efficacy of phytochemicals.

Artemisinin and Derivatives: In vitro experiments involve assessing the impact of phytochemicals using cultured Plasmodium parasites, particularly Plasmodium falciparum, which is the most pathogenic cause of severe malaria. The compound causes oxidative stress and denatures parasite proteins and membranes, thus leading to the quick elimination of the parasites. In vitro, artemisinin has also been found to be active against strains of P. falciparum that are resistant to other antimalarial drugs, hence placing it as a valuable drug in the treatment of malaria [45]. In vivo trials involve evaluating the efficacy of phytochemicals in animal models, usually rodents infected with Plasmodium species, and these have established that artemisinin and its congeners are very potent in eradicating Plasmodium parasites in animal models. These compounds quickly

decrease the level of parasites in the blood and increase the patient's survival, outcomes that have been supported by later human clinical trials [5]. Artemisinin's effectiveness in vivo has also been documented in combination treatments that assist in slowing down resistance. Artemisinin-based combination therapies (ACTs) are the first-line treatment options for malaria, specifically for P. falciparum malaria. The efficacy of ACTs has been established to be high across different trials, with ACTs providing fast parasite clearance and high cure rates [46]. According to WHO, ACTs are the preferred treatment for uncomplicated falciparum malaria. The side effects of artemisinin and its derivatives are few and mild. The side effects include nausea, dizziness, and headaches. Side effects are generally mild but may include an allergic reaction and liver enzyme elevation [47]. Initially employed for the treatment of malaria, artemisinin and its derivatives have demonstrated considerable promise in the treatment of a range of disorders beyond malaria. Recently, Huang et al.[48], reported that artemisinin has the potential to be both safe and efficacious contenders for the treatment of cancer, parasite infections, inflammation, and dermatological conditions in their clinical research. According to Liu and colleagues, the broad range of biological activity of artemisinin is attributed to its distinctive peroxide-containing structure [49]. In comparison to quinine and other artemisinins, artesunate, a hydrophilic artemisinin derivative, has shown greater effectiveness in the treatment of severe malaria [50]. However, Khanal opines that the development of resistance in Plasmodium falciparum is mainly caused by mutations in the Kelch13 protein, and thus presents a significant obstacle to the effectiveness of antimalarial treatments [50]. Current research activities are focused on enhancing the pharmacological characteristics of artemisinin derivatives in order to address clinical constraints such limited solubility, inadequate bioavailability, brief in vivo half-life, as well as the recent development of artemisinin-resistant strains [51]. Additional comprehensive clinical trials are required to thoroughly investigate the antiviral capabilities of these substances [48].

Quinine and Quinidine: Quinine, derived from the bark of Cinchona trees, has been effective in the management of malaria for many years. Nonetheless, quinine is still effective, especially for severe malaria, though it comes with side effects. Quinine was initially tested in culture, where it was shown to suppress the growth of P. falciparum by preventing the parasite from breaking down heme that is toxic to the parasite [52]. Following these findings, it became popular for the treatment of malaria. In animals, quinine has been shown to be efficient in treating malaria by decreasing parasitemia and preventing severe malaria complications. Quinine has been proven safe and effective in vivo, especially for patients with severe or drug-resistant malaria [53]. Quinidine is a stereoisomer of quinine but is also used in clinical situations, although not as often as quinine. Quinine has been exploited for a long time in the treatment of malaria. It is active against Plasmodium falciparum and is used in severe malaria or where ACT is not an option. Clinical trials have established its efficacy in decreasing the parasite load and alleviating the symptoms, though it is less potent than ACTs [54]. Quinine is usually administered with other antimalarials, such as doxycycline or clindamycin, to enhance effectiveness and shorten the course of treatment [55]. Quinine has been reported to cause side effects like tinnitus, dizziness, and gastrointestinal symptoms. Serious side effects include cinchonism, characterised by headaches, nausea, and changes in vision; the risk of hypoglycemia; and cardiotoxicity [54].

Curcumin: Curcumin has been reported to have an anti-parasitic effect in vitro, where it is able to induce the generation of ROS and interfere with the cellular pathways of P. falciparum. The anti-heme polymerisation effect of curcumin has also been confirmed in various studies [18]. Several in vivo studies have confirmed that curcumin could decrease the parasites in the bloodstream of rodent models of malaria. Recently, Gupta and his colleagues investigated the possibility of curcumin in the treatment of malaria. They reported that curcumin demonstrated a wide range of pharmacological capabilities in combating several disorders, including malaria [56]. According to Kunwittaya et al.[57], curcumin exhibited antimalarial efficacy when tested in vitro, with an IC50 value of around 10 μM. Additionally, it has been shown to protect endothelium cells against apoptosis in models of cerebral malaria [57]. Similarly, the efficacy of

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nanotized curcumin has been demonstrated to be enhanced, as evidenced by a ten-fold increase in growth inhibition of Plasmodium falciparum in vitro (IC50: 0.5 μM) as compared to natural curcumin [58]. Furthermore, comprehensive elimination of parasites and extended survival were shown in P. berghei-infected mice through in vivo experiments with nanotized curcumin [58]. When used in conjunction with other antimalarial treatments, curcumin has been shown to increase the effectiveness of the drugs, indicating that it may have potential as a supportive treatment. However, one has to agree with the fact that there are several drawbacks when it comes to the issue of curcumin bioavailability; hence, further research on better delivery systems is ongoing. Curcumin is an example of an antimalarial compound that has been evaluated in preclinical studies and some clinical trials. It has also demonstrated its efficacy in controlling parasitemia and its clinical manifestation in uncomplicated malaria patients. However, its effectiveness and applicability as a monotherapy remain somewhat more questionable in comparison to ACTs [18]. Nonetheless, curcumin is considered to be safe when taken at the recommended doses. Adverse effects are rare and can be characterised by gastrointestinal symptoms such as nausea and vomiting. To note, high doses of medications may cause severe side effects. Curcumin has many ways of combating malaria that are not easily resistant to drugs, which makes it a potential candidate for malaria control. However, larger randomised controlled trials are required to evaluate its effectiveness in other patients and determine the right dosage schedule [59].

Nimbolide: Nimbolide, a compound isolated from Azadirachta indica (neem), has been tested in clinical trials, revealing antimalarial properties and aiding in parasite clearance. It is thought to exert its effects by suppressing the reproduction of the parasites and regulating the immune system. The use of nimbolide is safe, as shown in clinical trials, with little to no adverse effects on the body. It is believed to be safe when used at the recommended doses, but more studies are required to determine its safety when used for an extended period. Recently, Maafoh and Onyedibe reported that the extract of A. indica to suppressed microgametogenesis and disrupted parasite development and thus provides evidence for its potential as a malaria treatment [60]. Despite the encouraging results obtained in laboratory settings, additional in vivo investigations are required to confirm its effectiveness. Moreover, the exploration of alternative therapeutics is of utmost importance to address the growing resistance to artemisinin-based combination therapies (ACT) [60]. Although the anti-cancer effects of nimbolide have been thoroughly investigated, its potential in the treatment of malaria has not been well explored, thus requiring further research to validate its therapeutic capabilities [61].

Berberine: Berberine, an isoquinoline alkaloid derived from the Berberis genus, has been tested in vitro and was seen to affect P. falciparum by preventing nucleic acid and protein synthesis. It also affects the cell membrane of the parasite in a way that causes the death of the parasite [62]. In a study in 2015, berberine exhibited protective properties against spleen damage caused by Plasmodium chabaudi in mice, by decreasing parasitemia and enhancing splenic structure [63]. Preclinical studies have shown that berberine decreases the parasite load and enhances the overall survival in animal models of malaria. The effects of Berberine on the immune response and host defence systems have also been reported, which is another factor that contributes to its antimalarial actions [64]. A recent extensive review study has shown that berberine possesses antimalarial properties in both animal and human trials. It seems to cause the death of Plasmodium parasites by interfering with their metabolism and preventing them from multiplying [15]. Although not chemically berberine, the closely similar substance bergenin demonstrated strong antimalarial effects against Plasmodium falciparum in laboratory settings and in live mice infected with P. berghei, with minimal toxicity, according to a study by Liang and colleagues [65]. Similarly, Chandel et al. [66] demonstrated that an aqueous extract of Berberis aristata roots, a plant commonly employed for the treatment of malaria, exhibited encouraging antiplasmodial effects against P. berghei in both laboratory and animal settings. The extract showed dose-dependent suppression of chemosuppression and an extended average survival time in infected mice. Berberine is known to have only mild side effects and is not toxic when taken at the correct dosage. There is a possibility of exploring the use of berberine alongside conventional antimalarial

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treatments to enhance efficacy and minimise toxicity. Initial research studies show that such combinations may be useful, although further study is required. Some of the side effects described include gastrointestinal symptoms and allergies, which are generally not very severe [67].

Andrographolide: Andrographolide obtained from Andrographis paniculata has been proven to exhibit potent antimalarial effects in vitro through the suppression of the growth of P. falciparum. It seems that the compound affects the ability of the parasite to carry on its energy metabolism within the mitochondria, thereby inhibiting growth [23]. In animal models, andrographolide has been able to reduce parasite load and enhance the survival rate. Ibraheem and team reported that andrographolide showed the capacity to counteract chloroquine resistance in Plasmodium falciparum either by impeding the process of chloroquine accumulation or impacting the biological activity of the parasite [68]. In response to the limited water solubility and instability of andrographolide, scientists have devised nanoparticle formulations, namely andrographolide-carboxymethyl chitosan nanoparticles, which have enhanced the dissolution of the medication and its antimalarial effects in mice infected with Plasmodium berghei [69]. Notwithstanding these encouraging findings, additional investigation is required to thoroughly assess the potential of andrographolide as an antimalarial drug or supplementary treatment [70]. In a clinical trial in Indonesia, andrographolide has been found to reduce the parasite density and also improve the symptoms of patients with malaria in early phase clinical trials [71]. However, further studies with larger sample sizes and a more randomised controlled trial design must be conducted to assess the efficacy and adverse effects.

SOME HUMAN TRIALS EVALUATING THE EFFECTIVENESS OF PHYTOCHEMICALS

Preclinical studies should provide baseline data on safety, efficacy, and pharmacology, while human trials focus on phytochemicals' ability to treat malaria. Artemisinin from Artemisia annua has been extensively tested in clinical trials to quickly eliminate P. falciparum and decrease malaria-related mortality. Clinical studies have demonstrated that artemisinin and its derivatives, including artesunate, artemether, and dihydroartemisinin, effectively and rapidly eliminate P. falciparum and decrease malaria-associated mortality [72]. Artemisinin-based combination therapies (ACTs) have been ascertained to be the global benchmark when it comes to treating uncomplicated and severe malaria [73].

Quinine has been in use for a long time as it is capable of lowering the number of parasites in the blood of a patient with malaria and also prevents complications in severe cases. However, they have been associated with adverse effects like cinchonism and hypoglycemia and are not as popular as the newer drugs. Quinine is usually used in association with other antimalarials, such as doxycycline or clindamycin, in clinical settings [53]. These combinations have been found to improve the outcome of treatment and reduce the duration of therapy in areas of high drug resistance. In Uganda, Yeka et al. [74] revealed that dihydroartemisinin-piperaquine demonstrated superior performance compared to both quinine and artemether-lumefantrine in treating recurrent malaria, while also reducing the likelihood of recurring infection. Curcumin is a polyphenol obtained from Curcuma longa and has been used in several clinical trials as an adjuvant therapy. In their systematic review, Khairani et al. [75] pointed out that curcumin enhances the efficacy of antimalarial drugs, including artemisinin, by reducing parasitemia and protecting malaria-induced oxidative stress.

Latest research has emphasised the capacity of alkaloids as antimalarial agents, specifically targeting the increasing worry about drug resistance in Plasmodium parasites [76]. Among the alkaloids, the isoquinoline alkaloid berberine, which is extracted from Berberis, has been investigated in human intervention trials to a lesser extent than artemisinin or quinine. It also appears to be more effective when used in combination with other antimalarial drugs [21]. According to Arena et al. [77] in the scoping review, berberine has the effect of reducing the parasite load and improving symptoms in patients suffering from malaria in the initial phases of the clinical trials on human subjects. However, further studies should be performed to evaluate its use in clinical scenarios. Several studies have investigated the efficacy of andrographolide, a diterpenoid lactone from Andrographis paniculata, in humans as an antimalarial agent. Preliminary findings show that anrographolide

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can decrease the parasite density and ameliorate the clinical signs in patients with uncomplicated malaria [23]. The efficacy of A. paniculata ethanolic extract capsules, at a dosage of 250 mg, taken three times daily for five days, against malaria vivax, malaria falciparum, and mixed malaria patients in an open clinical study conducted in a malaria-endemic area in Indonesia, was estimated to be 94.2%. No adverse reactions were indicated during the course of treatment [71]. However, these trials are still early, and more research is needed within a larger and more diverse sample population to intensify proof of effectiveness. Apart from the phytochemicals, several other plant products and local herbal medicines used by communities across the world have also been tried on human beings. For instance, studies have been conducted on the extracts of plants such as Azadirachta indica (neem) and species in the Cinchona group with regard to their antimalarial effects [78]. Recent research has investigated the potential of Azadirachta indica (neem) in the prevention and treatment of malaria. A comprehensive analysis revealed that neem is efficacious in alleviating symptoms of malaria, however the evidence about its antiparasitic activities is still equivocal [79]. Similarly, another evaluation underscored the potential of neem in suppressing malaria parasites but stressed the necessity for additional investigation [80]. Taken together, some human trials have demonstrated favourable effects, but most of them can hardly be considered conclusive and usually lack the level of controlled conditions necessary for large-scale application.

CHALLENGES AND FUTURE DIRECTIONS

1. Standardization and Quality Control: This is one of the major concerns in the clinical application of phytochemicals because of the issues of variability in the mixture of phytochemicals in the extracts. Differences in plant species, growth conditions, and extraction techniques may influence the amount and potency of phytochemicals, which can impact both effectiveness and side effects [81].

2. Drug Resistance: Phytochemicals are not devoid of the risk of resistance development, though they are relatively less prone than synthetic drugs. This risk can be reduced by frequent follow-up and a combination of therapies [82].

3. Integration into Conventional Therapy: Phytochemicals have to be incorporated into standard antimalarial drug regimens and their safety, efficacy, and dosing have to be determined through clinical trials. Combinations with other antimalarial drugs could improve efficacy and decrease the chances of resistance [15].

4. Challenges and considerations in human trials: There are several challenges associated with phytochemicals in human trials such as, variability in plant extract content, low solubility and poor absorption, safety issues and ethical issues. This is because standardization of extracts is very important in order to achieve accurate results while new and improved drug delivery systems such as nanoparticles and liposomes are being developed to overcome these challenges [83]. Although phytochemicals are believed to be harmless, some may have negative effects and the trials must look out for toxicity and side effects. Ethical issues are also important, especially in areas where conventional treatment is not readily available, to make sure that participants are well informed on the possible consequences and advantages of the treatment [84].

Conclusion

Phytochemicals have emerged as valuable commodities in the fight against malaria as they present various modes of action and improve clinical outcomes. The most famous phytochemical is artemisinin, which has changed the face of malaria treatment worldwide by being the key component of artemisinin-based combination therapies (ACTs). Other phytochemicals, such as quinine, curcumin, berberine, and andrographolide, have also been found to be effective, either alone or in combination with the current conventional antimalarial drugs. These compounds have been shown to effectively prevent the growth of Plasmodium parasites through various modes of action, which include the generation of reactive oxygen species, disruption of parasite metabolism, and modulation of cellular signals. These studies have laid a good stage for clinical research, which showed some of the phytochemicals can help in decreasing parasitemia and enhancing the health of the patients. Nevertheless, the application of many phytochemicals in clinical practices has several drawbacks, such as low bioavailability, lack

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of standardisation, and possible adverse effects. However, present studies and developments in drug delivery systems provide new hope for the establishment of potent and credible phytochemical-based treatments. The effectiveness of phytochemicals in the treatment of malaria therefore emphasises the role of natural products in drug discovery. This is because, as resistance to conventional antimalarials persists as a major challenge, phytochemicals hold the potential to offer new, efficient, and sustainable solutions. Further studies should be directed towards the improvement of the efficacy and safety of these compounds, the investigation of their combination therapy, and overcoming the current barriers to their clinical application. In this way, phytochemicals can significantly contribute to the fight against malaria and its ultimate elimination worldwide.

REFERENCE

1. Egwu CO, Aloke C, Chukwu J, Agwu A, Alum E, Tsamesidis I, et al. A world free of malaria: It is time for Africa to actively champion and take leadership of elimination and eradication strategies. Afr Health Sci. 2022 Dec;22[4]:627–40.
2. Alum EU, Ugwu OPC, Egba SI, Uti DE, Alum BN. Climate Variability and Malaria Transmission: Unraveling the Complex Relationship. INOSR SR. 2024 Jun 28;11[2]:16–22. https://doi.org/10.59298/INOSRSR/2024/1.1.21622
3. Erisa K, Raphael I, P.C. U, Alum E. Exploration of Medicinal Plants Used in the Management of Malaria in Uganda. 2023 Oct 20;
4. Obeagu EI, Alum EU, Ugwu OPC. Hepcidin: The Gatekeeper of Iron in Malaria Resistance. NIJRMS. 2023 Jun 7;4[2]:1–8.
5. Ekpono EU, Aja PM, Ibiam UA, Alum EU, Ekpono UE. Ethanol Root-extract of Sphenocentrum jollyanum Restored Altered Haematological Markers in Plasmodium berghei-infected Mice. Earthline Journal of Chemical Sciences. 2019 Jul 31;2[2]:189–203.
6. Oyegoke OO, Maharaj L, Akoniyon OP, Kwoji I, Roux AT, Adewumi TS, et al. Malaria diagnostic methods with the elimination goal in view. Parasitology Research. 2022 Apr 23;121[7]:1867.
7. Egwu CO, Aloke C, Chukwu J, Nwankwo JC, Irem C, Nwagu KE, et al. Assessment of the Antimalarial Treatment Failure in Ebonyi State, Southeast Nigeria. Journal of Xenobiotics. 2023 Mar;13[1]:16–26.
8. Oladipo HJ, Tajudeen YA, Oladunjoye IO, Yusuff SI, Yusuf RO, Oluwaseyi EM, et al. Increasing challenges of malaria control in sub-Saharan Africa: Priorities for public health research and policymakers. Annals of Medicine & Surgery [Internet]. 2022 Sep [cited 2024 Aug 20];81. Available from: https://journals.lww.com/10.1016/j.amsu.2022.104366
9. Obeagu E, Alum E, Ugwu PC. Hepcidin's Antimalarial Arsenal: Safeguarding the Host. NEWPORT INTERNATIONAL JOURNAL OF PUBLIC HEALTH AND PHARMACY. 2023 Nov 12;4:1–8.
10. Plowe CV. Malaria chemoprevention and drug resistance: a review of the literature and policy implications. Malaria Journal. 2022 Mar 24;21[1]:104.
11. Obeagu EI, Obeagu GU. Emerging public health strategies in malaria control: innovations and implications. Annals of Medicine and Surgery. 2024 Nov;86[11]:6576.
12. Ungogo MA, Ebiloma GU, Ichoron N, Igoli JO, de Koning HP, Balogun EO. A Review of the Antimalarial, Antitrypanosomal, and Antileishmanial Activities of Natural Compounds Isolated From Nigerian Flora. Front Chem [Internet]. 2020 Dec 23 [cited 2024 Aug 27];8. Available from: https://www.frontiersin.org/journals/chemistry/articles/10.3389/fchem.2020.617448/full
13. Bekono BD, Ntie-Kang F, Onguéné PA, Lifongo LL, Sippl W, Fester K, et al. The potential of anti-malarial compounds derived from African medicinal plants: a review of pharmacological evaluations from 2013 to 2019. Malaria Journal. 2020 May 18;19[1]:183.
14. Shah AP, Parmar GR, Sailor GU, Seth AK. Antimalarial Phytochemicals Identification from Euphorbia Hirta against Plasmepsin Protease: an In

Silico Approach. Folia Medica. 2019 Dec 31;61[4]:584–93.
15. Angupale JR, Tusiimire J, Ngwuluka NC. A review of efficacy and safety of Ugandan anti-malarial plants with application of RITAM score. Malaria Journal. 2023 Mar 17;22[1]:97.
16. Tajuddeen N, Van Heerden FR. Antiplasmodial natural products: an update. Malaria Journal. 2019 Dec 5;18[1]:404.
17. Gomes ARQ, Cunha N, Varela ELP, Brígido HPC, Vale VV, Dolabela MF, et al. Oxidative Stress in Malaria: Potential Benefits of Antioxidant Therapy. Int J Mol Sci. 2022 May 25;23[11]:5949.
18. Jamil SNH, Ali AH, Feroz SR, Lam SD, Agustar HK, Mohd Abd Razak MR, et al. Curcumin and Its Derivatives as Potential Antimalarial and Anti-Inflammatory Agents: A Review on Structure–Activity Relationship and Mechanism of Action. Pharmaceuticals (Basel). 2023 Apr 18;16[4]:609.
19. Tse EG, Korsik M, Todd MH. The past, present and future of anti-malarial medicines. Malaria Journal. 2019 Mar 22;18[1]:93.
20. Assefa A, Fola AA, Tasew G. Emergence of Plasmodium falciparum strains with artemisinin partial resistance in East Africa and the Horn of Africa: is there a need to panic? Malaria Journal. 2024 Jan 25;23[1]:34.
21. Uzor PF. Alkaloids from Plants with Antimalarial Activity: A Review of Recent Studies. Evid Based Complement Alternat Med. 2020 Feb 12;2020:8749083.
22. Kashyap P, Kalaiselvan V, Kumar R, Kumar S. Ajmalicine and Reserpine: Indole Alkaloids as Multi-Target Directed Ligands Towards Factors Implicated in Alzheimer's Disease. Molecules. 2020 Apr 1;25[7]:1609.
23. Dwivedi MK, Mishra S, Sonter S, Singh PK. Diterpenoids as potential anti-malarial compounds from Andrographis paniculata. Beni-Suef University Journal of Basic and Applied Sciences. 2021 Jan 23;10[1]:7.
24. Ullah A, Munir S, Badshah SL, Khan N, Ghani L, Poulson BG, et al. Important Flavonoids and Their Role as a Therapeutic Agent. Molecules. 2020 Nov 11;25[22]:5243.
25. Adeoye AO, Olanlokun JO, Tijani H, Lawal SO, Babarinde CO, Akinwole MT, et al. Molecular docking analysis of apigenin and quercetin from ethylacetate fraction of Adansonia digitata with malaria-associated calcium transport protein: An in silico approach. Heliyon. 2019 Sep 1;5[9]:e02248.
26. Amin R, Melody Devi C, Sarkar D, Sharifi-Rad J, Sönmez Gürer E, Oana Docea A, et al. Curcumin-loaded nanomedicines as therapeutic strategy in malaria management. eFood. 2023;4[5]:e113.
27. Farhan M, Rizvi A. The Pharmacological Properties of Red Grape Polyphenol Resveratrol: Clinical Trials and Obstacles in Drug Development. Nutrients. 2023 Oct 23;15[20]:4486.
28. Kumatia EK, Zoiku FK, Asase A, Tung NH. Anti-malarial activity of the alkaloid, heptaphylline, and the furanocoumarin, imperatorin, from Clausena anisata against human Plasmodium falciparum malaria parasites: ex vivo trophozoitocidal, schizonticidal and gametocytocidal approach. Malaria Journal. 2023 Sep 9;22[1]:264.
29. Sullivan DJ. Quinolines block every step of malaria heme crystal growth. Proceedings of the National Academy of Sciences. 2017 Jul 18;114[29]:7483–5.
30. Neag MA, Mocan A, Echeverría J, Pop RM, Bocsan CI, Crișan G, et al. Berberine: Botanical Occurrence, Traditional Uses, Extraction Methods, and Relevance in Cardiovascular, Metabolic, Hepatic, and Renal Disorders. Front Pharmacol. 2018 Aug 21;9:557.
31. Owoloye A, Enejoh OA, Akanbi OM, Bankole OM. Molecular docking analysis of Plasmodium falciparum dihydroorotate dehydrogenase towards the design of effective inhibitors. Bioinformation. 2020 Sep 30;16[9]:672–8.
32. Han JH, Lee EJ, Park W, Ha KT, Chung HS. Natural compounds as lactate dehydrogenase inhibitors: potential therapeutics for lactate dehydrogenase inhibitors-related diseases. Front Pharmacol [Internet]. 2023 Oct 17 [cited 2024 Aug 27];14. Available from: https://www.frontiersin.org/journals/pharmacology/articles/10.3389/fphar.2023.1275000/full
33. Alum EU. ANTIOXIDANT EFFECT OF Buchholzia coriacea ETHANOL LEAF-EXTRACT AND FRACTIONS ON FREUND'S ADJUVANT-INDUCED ARTHRITIS IN ALBINO RATS: A COMPARATIVE STUDY. Slovenian Veterinary Research [Internet]. 2022 Apr 22 [cited 2024 Apr

13];59[1]. Available from: https://www.slovetres.si/index.php/SVR/article/view/1150
34. Barman M, Dandasena D, Suresh A, Bhandari V, Kamble S, Singh S, et al. Artemisinin derivatives induce oxidative stress leading to DNA damage and caspase-mediated apoptosis in Theileria annulata-transformed cells. Cell Communication and Signaling. 2023 Apr 17;21[1]:78.
35. Yuandani, Jantan I, Rohani AS, Sumantri IB. Immunomodulatory Effects and Mechanisms of Curcuma Species and Their Bioactive Compounds: A Review. Front Pharmacol [Internet]. 2021 Apr 30 [cited 2024 Aug 27];12. Available from: https://www.frontiersin.org/journals/pharmacology/articles/10.3389/fphar.2021.643119/full
36. Cordeiro MCC, Tomé FD, Arruda FS, da Fonseca SG, Nagib PRA, Celes MRN. Curcumin as a Stabilizer of Macrophage Polarization during Plasmodium Infection. Pharmaceutics. 2023 Oct 21;15[10]:2505.
37. Seweryn E, Ziała A, Gamian A. Health-Promoting of Polysaccharides Extracted from Ganoderma lucidum. Nutrients. 2021 Aug 7;13[8]:2725.
38. Kim JH, Kim DH, Jo S, Cho MJ, Cho YR, Lee YJ, et al. Immunomodulatory functional foods and their molecular mechanisms. Exp Mol Med. 2022 Jan 25;54[1]:1–11.
39. Omoregie ES, Pal A. Antiplasmodial, antioxidant and immunomodulatory activities of ethanol extract of Vernonia amygdalina del. Leaf in Swiss mice. Avicenna J Phytomed. 2016;6[2]:236–47.
40. Coban C. The host targeting effect of chloroquine in malaria. Curr Opin Immunol. 2020 Oct;66:98–107.
41. Herraiz T, Guillén H, González-Peña D, Arán VJ. Antimalarial Quinoline Drugs Inhibit β-Hematin and Increase Free Hemin Catalyzing Peroxidative Reactions and Inhibition of Cysteine Proteases. Scientific Reports [Internet]. 2019 [cited 2024 Aug 27];9. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6817881/
42. Alzohairy MA. Therapeutics Role of Azadirachta indica (Neem) and Their Active Constituents in Diseases Prevention and Treatment. Evid Based Complement Alternat Med. 2016;2016:7382506.
43. Gunjan S, Sharma T, Yadav K, Chauhan BS, Singh SK, Siddiqi MI, et al. Artemisinin Derivatives and Synthetic Trioxane Trigger Apoptotic Cell Death in Asexual Stages of Plasmodium. Front Cell Infect Microbiol [Internet]. 2018 Jul 26 [cited 2024 Aug 27];8. Available from: https://www.frontiersin.org/journals/cellular-and-infection-microbiology/articles/10.3389/fcimb.2018.00256/full
44. Benchagra L, Berrougui H, Islam MO, Ramchoun M, Boulbaroud S, Hajjaji A, et al. Antioxidant Effect of Moroccan Pomegranate (Punica granatum L. Sefri Variety) Extracts Rich in Punicalagin against the Oxidative Stress Process. Foods. 2021 Sep 18;10[9]:2219.
45. Sawant SS, Gabhe SY, Singh KK. In Vitro Effect on Plasmodium falciparum and In Vivo Effect on Plasmodium berghei of Annomaal, an Oily Fraction Obtained from the Seeds of Annona squamosa. Molecules. 2023 Jul 17;28[14]:5472.
46. Dhorda M, Amaratunga C, Dondorp AM. Artemisinin and multidrug-resistant Plasmodium falciparum – a threat for malaria control and elimination. Curr Opin Infect Dis. 2021 Oct;34[5]:432–9.
47. WHO | Regional Office for Africa [Internet]. 2024 [cited 2024 May 22]. User Guide for the Malaria Strategic and Operational Plan Costing Tool. Available from: https://www.afro.who.int/publications/user-guide-malaria-strategic-and-operational-plan-costing-tool
48. Huang Y, Yang Y, Liu G, Xu M. New clinical application prospects of artemisinin and its derivatives: a scoping review. Infectious Diseases of Poverty. 2023 Dec 11;12[1]:115.
49. Liu X, Cao J, Huang G, Zhao Q, Shen J. Biological Activities of Artemisinin Derivatives Beyond Malaria. http://www.eurekaselect.com [Internet]. [cited 2024 Aug 28]; Available from: https://www.eurekaselect.com/article/96007
50. Khanal P. Antimalarial and anticancer properties of artesunate and other artemisinins: current development. Monatsh Chem. 2021 Apr

1;152[4]:387–400.
51. Martino E, Tarantino M, Bergamini M, Castelluccio V, Coricello A, Falcicchio M, et al. Artemisinin and Its Derivatives; Ancient Tradition Inspiring the Latest Therapeutic Approaches Against Malaria. Future Medicinal Chemistry. 2019 Jun 1;11[12]:1443–59.
52. Gachelin G, Garner P, Ferroni E, Tröhler U, Chalmers I. Evaluating Cinchona bark and quinine for treating and preventing malaria. J R Soc Med. 2017 Jan;110[1]:31–40.
53. Na-Bangchang K, Karbwang J. Pharmacology of Antimalarial Drugs, Current Anti-malarials. In: Kremsner PG, Krishna S, editors. Encyclopedia of Malaria [Internet]. New York, NY: Springer; 2019 [cited 2024 Aug 28]. p. 1–82. Available from: https://doi.org/10.1007/978-1-4614-8757-9_149-1
54. Blasco B, Leroy D, Fidock DA. Antimalarial drug resistance: linking Plasmodium falciparum parasite biology to the clinic. Nat Med. 2017 Aug 4;23[8]:917–28.
55. Gaillard T, Madamet M, Pradines B. Tetracyclines in malaria. Malaria Journal. 2015 Nov 10;14[1]:445.
56. Gupta B, Sharma PK, Malviya R, Mishra PS. Curcumin and Curcumin Derivatives for Therapeutic Applications: In vitro and In vivo Studies. http://www.eurekaselect.com [Internet]. [cited 2024 Aug 28]; Available from: https://www.eurekaselect.com/article/137990
57. Kunwittaya S, Treeratanapiboon L, Srisarin A, Isarankura-Na-Ayudhya C, Prachayasittikul V. In vitro study of parasite elimination and endothelial protection by curcumin. adjunctive therapy for cerebral malaria [Internet]. 2014 Mar 20 [cited 2024 Aug 28]; Available from: https://eldorado.tu-dortmund.de/handle/2003/33411
58. Ghosh A, Banerjee T, Bhandary S, Surolia A. Formulation of nanotized curcumin and demonstration of its antimalarial efficacy. IJN. 2014 Nov 20;9[1]:5373–87.
59. Urošević M, Nikolić L, Gajić I, Nikolić V, Dinić A, Miljković V. Curcumin: Biological Activities and Modern Pharmaceutical Forms. Antibiotics (Basel). 2022 Jan 20;11[2]:135.
60. Maafoh C, Onyedibe K. Alternative First-line Malaria Treatment. Ann Afr Med. 2024;23[1]:5–12.
61. Elumalai P, Ezhilarasan D, Raghunandhakumar S. Molecular Targets of Nimbolide for Anti-Cancer Therapy: An Updated Review. JEP(T) [Internet]. 2022 [cited 2024 Aug 28];41[2]. Available from: https://www.dl.begellhouse.com/journals/0ff459a57a4c08d0,5ba9bad964993800,2ccec8f74e26bda1.html
62. Tuzimski T, Petruczynik A. New trends in the practical use of isoquinoline alkaloids as potential drugs applicated in infectious and non-infectious diseases. Biomedicine & Pharmacotherapy. 2023 Dec 1;168:115704.
63. Dkhil MA, Alazzouni AS, Al-Quraishy S, Al-Shamrany A, Lubbad MY, Al-Shaebi EM, et al. Berberine Protects Against murine malaria-Induced Spleen Tissue Damage. Biomed Res. 2015;26[2].
64. Dkhil MA, Al-Quraishy S, Al-Shamrany A, Alazzouni AS, Lubbad MY, Al-Shaebi EM, et al. Protective effect of berberine chloride on Plasmodium chabaudi-induced hepatic tissue injury in mice. Saudi Journal of Biological Sciences. 2015 Sep 1;22[5]:551–5.
65. Liang J, Li Y, Liu X, Huang Y, Shen Y, Wang J, et al. In vivo and in vitro antimalarial activity of bergenin. Biomedical Reports. 2014 Mar 1;2[2]:260–4.
66. Chandel S, Bagai U, Semwal RB, Semwal DK. Antiplasmodial activity of aqueous extract of Berberis aristata roots against Plasmodium berghei-infected BALB/c mice. Pharmaceutical Biology. 2015 Dec 2;53[12]:1735–40.
67. Habibi P, Shi Y, Fatima Grossi-de-Sa M, Khan I. Plants as Sources of Natural and Recombinant Antimalaria Agents. Mol Biotechnol. 2022 Nov 1;64[11]:1177–97.
68. Ibraheem ZO, Majid RA, Sidek HM, Noor SM, Yam MF, Abd Rachman Isnadi MF, et al. In Vitro Antiplasmodium and Chloroquine Resistance Reversal Effects of Andrographolide. Evidence-Based Complementary and Alternative Medicine. 2019;2019[1]:7967980.
69. Retno SARI AW. Development of Andrographolide-Carboxymethyl Chitosan Nanoparticles: Characterization, in vitro Release and in vivo Antimalarial Activity Study [Internet]. Turkish Journal of Pharmaceutical Sciences; 2018 [cited 2024 Aug 28]. Available from:

https://turkjps.org/articles/doi/tjps.53825
70. Ren X, Xu W, Sun J, Dong B, Awala H, Wang L. Current Trends on Repurposing and Pharmacological Enhancement of Andrographolide. Current Medicinal Chemistry. 28[12]:2346–68.
71. Makmur T, Siregar FA, Siregar S, Lubis IA, Bestari R, Zein U. Open Clinical Trial of Sambiloto (Andrographis paniculata) Ethanolic Extract Capsules in Treatment of Malaria Patients in Batubara District, Indonesia. Med Arch. 2022 Dec;76[6]:419–25.
72. Adebayo JO, Tijjani H, Adegunloye AP, Ishola AA, Balogun EA, Malomo SO. Enhancing the antimalarial activity of artesunate. Parasitol Res. 2020 Sep 1;119[9]:2749–64.
73. Takyi A, Carrara VI, Dahal P, Przybylska M, Harriss E, Insaidoo G, et al. Characterisation of populations at risk of sub-optimal dosing of artemisinin-based combination therapy in Africa. PLOS Global Public Health. 2023 Dec 1;3[12]:e0002059.
74. Yeka A, Tibenderana J, Achan J, D'Alessandro U, Talisuna AO. Efficacy of Quinine, Artemether-Lumefantrine and Dihydroartemisinin-Piperaquine as Rescue Treatment for Uncomplicated Malaria in Ugandan Children. PLOS ONE. 2013 Jan 22;8[1]:e53772.
75. Khairani S, Fauziah N, Wiraswati HL, Panigoro R, Setyowati EY, Berbudi A. The Potential use of a Curcumin-Piperine Combination as an Antimalarial Agent: A Systematic Review. J Trop Med. 2021 Oct 11;2021:9135617.
76. Saufi NAUM, Hatta UUM, Rashid FNAA, Mohammat MF. Alkaloids as Antimalarial Compounds: A Review of Recent Studies. Mini-Reviews in Organic Chemistry. 20[8]:786–99.
77. Arena L, Zanamwe M, Halleux CM, Carrara V, Angus BJ, Ariana P, et al. Malaria patient spectrum representation in therapeutic clinical trials of uncomplicated malaria: a scoping review of the literature. Malaria Journal. 2023 Feb 10;22[1]:50.
78. Tabuti JRS, Obakiro SB, Nabatanzi A, Anywar G, Nambejja C, Mutyaba MR, et al. Medicinal plants used for treatment of malaria by indigenous communities of Tororo District, Eastern Uganda. Tropical Medicine and Health. 2023 Jun 12;51[1]:34.
79. Mbugi EV, Sife AS, Ruzegea M, Msoffe GEP, Daniel B, Kabyemela E, et al. Effectiveness of Azadirachta indica (neem tree) on prevention and treatment of clinical human malaria: A systematic review. East Africa Science. 2021 Mar 15;3[1]:34–43.
80. Therapeutic Potentials of Neem Against Malaria Parasite: A Review | Dutse Journal of Pure and Applied Sciences. [cited 2024 Aug 28]; Available from: https://www.ajol.info/index.php/dujopas/article/view/250909
81. Ajayi OE, Yoon SY, Moon S, Kim KH, Kim JH, Chung JW, et al. Variability in Phytochemical Contents and Biological Activities among Adenophora triphylla Genotypes. Applied Sciences. 2023 Jan;13[20]:11184.
82. Ansari MA, Shoaib S, Alomary MN, Ather H, Ansari SMA, Hani U, et al. Deciphering the emerging role of phytocompounds: Implications in the management of drug-resistant tuberculosis and ATDs-induced hepatic damage. Journal of Infection and Public Health. 2023 Sep 1;16[9]:1443–59.
83. Domínguez R, Pateiro M, Munekata PES, McClements DJ, Lorenzo JM. Encapsulation of Bioactive Phytochemicals in Plant-Based Matrices and Application as Additives in Meat and Meat Products. Molecules. 2021 Jun 29;26[13]:3984.
84. Rodríguez-Negrete EV, Morales-González Á, Madrigal-Santillán EO, Sánchez-Reyes K, Álvarez-González I, Madrigal-Bujaidar E, et al. Phytochemicals and Their Usefulness in the Maintenance of Health. Plants. 2024 Jan;13[4]:523.