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Phytochemical-constituents, safety and efficacy of commonly used medicinal plants for the treatment of malaria in Ethiopia-a review

Abstract

Background: Malaria is among the ten top leading causes of morbidity and mortality in children under-5 years. Due to the rise of drug-resistant parasites and limited therapeutic efficacy of the available drugs, there is a need to search novel antimalarial drugs from medicinal plants commonly utilized as traditional medicines. Traditional medicines are often more available, affordable, sometimes are perceived as more effective than conventional antimalarial drugs, cultural acceptable and the relatively lower cost. Hence traditional medicine becomes the novel candidate for the search and development of drugs for the prevention and treatment of malaria.

Objective: The present study aimed to review phytochemical constitute, safety and efficacy commonly used medicinal plants for malaria treatment in Ethiopia.

Methods: A web-based literature search was done by using scientific databases including Pub Med, Science Direct, Web of Science and Google Scholar, with inclusion criteria of full length experimental, ethno-botanical and ethno medicinal survey articles reporting on anti-malarial medicinal plants conducted in Ethiopia.

Results: The most commonly utilized medicinal plants for the treatment of malaria were *Allium sativum, Aloe pulcherrima, Aloe debrana Chrstian, Aloe Sinana, Asparagus africanus, Balanites rotundifolia, Bersama abyssnica, Calpurnia aurea, Clerodendrum myricoides, Croton macrostachyus, Dodonaea angustifolia, Echinops kebericho, Gnidia Stenophylla, Jatropha curcas, Strychnos mitis, Otostegia integrefolia, and Withania somnifera*.

Conclusion and recommendation: Aqueous leaf extract of Strychnos mitis possessed a potent chemo suppression of 95.5 % at a dose of 600mg/kg/day. Further chemical isolation, dosage form development, clinical trial, and toxicological study is recommended.

Keywords: medicinal plants, malaria, phytochemistry, safety, efficacy

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Introduction

According to 2017 WHO malaria report, 394.7 million people was at risk with *Plasmodium falciparum* (98%) and *Plasmodium vivax* (2%). Even though death with malaria decreased from 70,700 in 2010 to 20,800 in 2016,41.5 million malaria confirmed cases was reported in the East African region.[1] *P. falciparum* resistance to artemisinin has been detected in five countries in the Greater Mekong sub-region. In Cambodia, high failure rates after treatment with an ACT have been detected for four different ACTs.[2] Malaria remains a major public health problem in Ethiopia where only 25% of the population live in areas that are free from malaria and still among the ten top leading causes of morbidity and mortality in children under-5.[3] Malaria transmission in Ethiopia is seasonal, depending mostly on altitude and rainfall, with a lag time varying from a few weeks before the beginning of the rainy season to more than a month after the end of the rainy season and transmission peaks bi-annually from September to December and April to May, coinciding with the major harvesting seasons.[4] The prevention of malaria in Ethiopia has relied mainly on early diagnosis and treatment of infection and reduction of human-vector contact by indoor residual spraying (IRS) and long-lasting insecticidal nets (LLINs).[5]

The Action and Investment to defeat Malaria (AIM) 2016–2030 strategy underscored that, malaria is not only a health issue, but also a broader developmental, socio-political, economic, environmental, agricultural, educational, biological, social issue and this strategy laid strong emphasis on the importance of keeping target community at the center of the fight against malaria and highlights the need for inclusive and collaborative efforts to create a malaria-free world by 2030.[6] The rise of drug-resistant parasites especially *P. falciparum* multi-drug resistance hamper malaria containment strategies.[7] In Ethiopia, artemether-lumefantrine replaced sulfadoxine-pyrimethamine (SP) in 2004 due to the increasing resistance of malaria to SP.[8,9] The emergence of artemisinin resistance has raised concerns that threaten the potency of existing anti malaria's and their therapeutic effectiveness of artemisinin which have been the drugs of choice is limited by a number of factors such as short half-life, neurotoxicity, and low solubility which affects their bioavailability. Traditional medicines are often more available, affordable and sometimes are perceived as more effective than conventional antimalarial drugs. Moreover, 80% of the Ethiopian population uses traditional medicine due to the cultural acceptably of healers and the relatively lower cost than modern drugs.[10,11]

The use of plant-derived compounds for mosquito control has been used since time memorials such as quinine and artemisinin. The development of artemisinin derivatives from the traditionally used Chinese plant *Qing hao, Artemisia annua L.,* also reaffirms the potential of ethno botanicals to provide effective drugs for the treatment of malaria. Indigenous knowledge, coupled with a history of safe use and ethno pharmacological efficacy, present a faster approach to discover new antimalarial agents.[12] The increased malaria drug resistance and mosquito vectors to insecticides together with challenges of having effective anti-malaria vaccines, urgent need to search for effective, easily available, affordable and safe alternative anti-malaria drugs is necessary.[13] Historically, In Ethiopia, there are documentations of medicinal plants used traditionally for the treatment of malaria in different parts of the country. However, the preclinical study such as phytochemical constituents, safety and efficacy of the medicinal plants utilized for the treatments of malaria are not documented yet. Therefore, the aims of this study were to review the phytochemical constitute, safety and efficacy commonly utilized medicinal plants for the treatment of malaria and to assess potential source of lead molecule for the development of a new drug for in Ethiopia.

Methods

The study reviewed the published literature on commonly used traditional medicinal plants for the treatment of malaria by using a web-based literature search strategy. Search for published journal articles using scientific databases including Pub Med, Science Direct, Web of Science and Google Scholar with Inclusion criteria of published full length experimental studies, ethno-botanical and ethno medicinal survey articles on anti-malarial medicinal plants conducted in Ethiopia and with exclusion criteria of data from historical documents or non-experimental studies, data from non-open access journal articles or partially accessed (abstract only) articles. The following key terms were used: Ethiopia/Ethiopian plants/Ethiopian medicinal plants/Ethiopian anti-malarial plants, Malaria/Ant malarial/ Anti-malarial plants, Traditional Medicine/Traditional medicinal plants, Medicinal Plants/Medicinal herbs, Ethno botany/Ethno botanical, Ethno pharmacology/ Ethno pharmacological survey and Ethiopian traditional medicinal plants. The study uses Medley reference citation software for the Vancouver referencing style.

Phytochemical constituents, safety and efficacy of commonly used medicinal plants for malaria treatment

Aloe pulcherrima: Family; Aloaceae; vernacular Name; Hargisa dhala (O)

Parts used; Leaf latex, root

Phytochemistry: Two compounds were isolated from the dried latex by preparative TLC and characterized on the basis of their spectroscopic properties and by comparison with literature values Compound **1** was obtained as a pale yellow solid amorphous substance and commonly known as nataloin. Compound **2** was commonly known as 7-hydroxyaloin.[14] Phytochemical investigation of the roots of *A. pulcherrima* has also resulted in the identification of three anthraquinones namely chrysophanol, aloesaponarin I and aloesaponarin II.[9]

Safety and toxicity: Acute toxicity studies indicated that no mortality in both the latex (5g/kg) and isolated compounds (2g/kg) was recorded within 14 days. LD_{50}s of the latex and the isolated compounds was beyond 5000mg/kg and 2000mg/kg body weight, respectively. Weak signs of toxicity such as loss of appetite, hair erection, lacrimation, tremors, convulsions, salivation and diarrhea displayed by the latex could be due to its major constituents, nataloin and 7-hydroxyaloin, as both compounds showed some signs of toxicity.[14]

Efficacy: The latex of the plant significantly decrease ($p<0.05$) in the parasitaemia of test substance-treated groups, particularly those treated with a dose of 200mg/kg and 400mg/kg with the exception of 7-hydroxyaloin, when compared to the untreated group. Maximum percentage chemo suppression was obtained for 7-hydroxyaloin, 56.2% suppression at a dose of 200mg/kg which is comparable with the aqueous solution of the exudate of *Aloe. otallensis* produced (60.7%) parasitaemia suppression at the a dose of 300mg/kg/day body weight.[15] Both the pure compounds and latex produced the highest parasitaemia suppression at the middle dose suggested that 200mg/kg body weight might be the optimal therapeutic dose in mice.[14] The other study by Dele et.al.,[9] showed that the antiplasmodial activities of the two aloesaponarins from the root of *A. pulcherrima* were strong and promising against the chloroquine-sensitive strain and the antibacterial activity of aloesaponarin II was even greater than the reference drug (gentamicin 10µg) against *B. subtilis.*

Aloe debrana Chrstian; Family; Aloaceae; vernacular

Parts used; Leaf latex

Phytochemistry: The leaf latex of *A. debrana* subjected to repeated preparative TLC (silica gel) using chloroform: methanol (4:1) as a solvent system afforded two major compounds with *Rf* values of 0.65 (**1**) and 0.79 (**2**). Compound **1** was unequivocally identified as aloin (10-C-*β*-D-glucopyranosyl-1, 8-dihydroxy-3-(hydroxymethyl)-9(10H)-anthracenone). Compound **2** also obtained as a pale yellow amorphous substance with R*f* value of 0.79 in $CHCl_3$/MeOH (4:1). The structure of compound **2** was established as (*E*)-2-(1-hydroxy-2-methylpropyl) - 8-(6'-*O*-Cinnamoyl)-*β*-D-glucopyranosyl-7-methoxy-5-methyl-chromone.[16]

Safety and toxicity: No signs of toxicity or mortality were observed in mice after oral administration of the latex of *A. debrana*, even at doses as high as 5000mg/kg signifying that the oral LD_{50} was greater than 5000mg/kg. Acute toxicity of the crude methanol extract of *A. debrana* indicated no mortality of mice within 24 hrs up to 3000mg/kg which is comparable with *A. percrassa*, and *A. camperi* species at a dose of 2000mg/kg.[17] Gross physical and behavioral observation of the experimental mice also revealed no visible signs of acute toxicity like lacrimation, hair erection, and reduction in their motor and feeding activities with crude methanol extract of *A. debrana.*

Efficacy: The latex produced a dose-dependent parasitaemia inhibition effect at various doses given orally with the highest suppression of parasitaemia (75.02%) observed at a dose of 60mg/kg/day. Although the exact mechanism of action of the latex has not been elucidated, some plant extracts are known to exert antiplasmodial activity either by causing red blood cell Oxidation or by inhibiting protein synthesis depending on their phytochemical constituents. Aloin showed 48.38% parasitaemia suppression against *P. berghei* at a dose of 25mg/kg/day. Aloin displayed the highest suppression of parasitaemia (78.31%) at a dose of 100mg/kg. HCGMM also showed significant suppression ($p<0.05$) against *P. berghei* at dose levels of 25, 50, and 100mg/kg/day compared to the mice in the negative control group. The methanol extract of *A. debrana* leaves induced 73.95% parasitaemia suppression at the highest dose (600mg/kg) and aqueous extract of the leaves of

A. debrana at 600mg/kg exerted 54.36% parasite suppression (18). In a similar way the other study by Tekalign et al.,[18] also shows *Aloe debrana* species have suppression activity against *P. berghei* malaria parasite.

Aloe. Sinana; Family; Aloaceae

Parts used; Leaf latex

Phytochemistry: Three compounds were isolated from the leaf latex of *A. sinana;* microdontin aloin and aloinoside.[10]

Safety and toxicity: No sign of toxicity or mortality was observed in mice upon oral administration of the latex of *A. sinana,* and the isolated compounds up to the dose of 5000mg/kg. It indicated that that the oral LD_{50} is greater than 5000mg/kg for both the latex and isolated compounds.[10]

Efficacy: The latex had showed dose dependent antimalarial activity, at 100, 200 and 400mg/kg/day dose revealed a 53.4, 62.3 and 68.2% suppression, respectively. All the isolated compounds possess significant antimalarial activity in 4-day suppression test the highest was recorded in aloinoside. The presence of remarkable suppression could be seen also from the life-prolonging (prolongation of the mean survival time) potential of the isolated compounds in malaria-infected mice.[10] The other study indicated that *Aloe sinana Reynolds* is endemic to Ethiopia, where its leaf latex is traditionally used in and around the town of Debre Sina and other central highlands as a wound-healing agent, insecticide and for the treatment of snake bite and malaria by the local people.[19]

Asparagus africanus; Family; Liliaceae; vernacular name; "Seriti (O) and Kestencha (A)

Parts used; root and aerial parts

Phytochemistry: The qualitative study revealed that the plant contained several biologically active major secondary metabolites such as Polyphenols, saponins, phenolic glycosides, phytosteroids and terpens were identified in roots parts of the plant alkaloids, polyphenols, tannins, phenolic glycosides, phytosterols and terpens were revealed in aerial parts(20).

Safety and toxicity: The hydroalcoholic extracts showed no lethality to mice at 5,000mg/kg, which is 25 times the median effective dose and no gross behavioural and physical changes were revealed. Intraperitoneal administration also did not produce lethality at doses of up to 1000mg/kg.[20]

Efficacy: The hydroalcoholic extracts of the root and aerial parts of the plant have shown parasite suppressive effects on *P. berghei* infected Swiss albino mice in a dose-related fashion. A high level (46.12 % inhibition with the 600mg/kg), *A. africanus* roots and a 40.73% inhibition of *A. africanus* aerial parts also observed. Therefore, the highest level of inhibition (46.12 %) was observed in 600mg/kg of *A. africanus* roots.[20]

Balanites rotundifolia; Family; Balanitaceae

Parts used; Leaf

Phytochemistry: Phytochemical screening of the 80% methanol leaf extract of *B. rotundifolia* revealed the presence of alkaloids and cardiac glycosides. Terpenoids, flavonoids, and tannins were not detected.[21]

Safety and toxicity: Acute toxicity test at the limit test dose of 2,000mg/kg, neither mortality nor changes related to behavioral, autonomic, neurological, and physical profile were observed during the 14 days' follow-up.[21]

Efficacy: The extract at a dose of 100, 200 and 400mg/kg reveled that a 37%, 42% and 67% parasite suppression, Despite a decrease in parasitaemia level, treatment with the crude leaf extract of *B. rotundifolia* did not prevent loss of body weight in *P. berghei*-infected mice. *B. rotundifolia* extract treatment also prevented a significant decrease in packed cell volume in a dose-dependent manner. The decrease in packed cell volume was highest for 100mg/kg ($P<0.001$) followed by 200mg/kg ($P<0.05$) and 400 mg/kg ($P>0.05$) as compared to chloroquine 25mg/kg. For the curative test, in which the parasitaemia is allowed to establish, 400mg/kg demonstrated comparable effect with chloroquine in preventing the decrease in rectal temperature in reference to normal control, *B. rotundifolia* 100mg/kg, and 200mg/kg ($P<0.001$ for all cases). The extract at 400mg/kg increased the body weight greater than the chloroquine dose, but it was not statistically significant.[21]

Bersama abyssnica fresen; Family; Melianthaceae; vernacular name; Azamir(A)

Parts used; root bark

Phytochemistry: The aqueous and hydroalcoholic extraction of *B. abyssinica* shows the presence of many secondary metabolites tannins, flavonoids, phenolic glycosides, phytosteriods, and saponins.[22]

Safety and toxicity: *B. abyssinica* hydroalcoholic extract showed signs of acute toxicity including diarrhea, gasping, abdominal writhing, muscle weakness (signs of paralysis), rough hair coat and depression. The LD_{50} of *B. abyssinica* was calculated to be 5044mg/kg body weight which is about 12.6 times the maximum effective dose tested (400mg/kg).[22]

Efficacy: The crude extracts were partially reduced parasitaemia and prolonged survival time of mice infected with *P. berghei* but, the hydroalcoholic extract of *B. abyssinica* was the more active and caused 30.01% reduction of parasitaemia at doses of 400mg/Kg on day 4 ($P < 0.05$).[22] An ethnobotanical study of medicinal plants in East Welega Zone Wayu Tuka Distric by Moa et al.,[23] indicated that *B. abyssinica* also used for the treatment of ascaris.

Calpurnia aurea; Family; Fabaceae; vernacular name; chekata(O), digita(A)

Parts used; leaf

Phytochemistry: The result of preliminary phytochemical screening of powdered plant material of *C. aurea* showed the presence of several secondary metabolites including alkaloids, cardiac glycosides, flavonoids, phenols, phytosteriods, saponins, terpenoids and tannins.[24]

Safety and toxicity: The hydromethanolic leaf extract of *C. aurea* acute toxicity revealed the absence of mortality up to the dose level of 300mg/kg body weight of extract administered orally. The oral median lethal dose (LD_{50}) of the extract could be greater than 300mg/kg body weight of the extract.

Efficacy: The result of the 4-day suppressive test indicated that at three dose levels (15, 30 and 60mg/kg body weight) of the extract produced significant ($p<0.001$) parasitaemia reduction compared to negative control. The 15 and 60mg/kg body weight of extract resulted

in higher anti-plasmodial activity (46.14 and 51.15%, respectively), followed by the 30mg/kg body weight (43.34%). In the 4-day suppressive test, the effect of leaf extract of *C. aurea* on packed cell volume (PCV) is indicated that the extract at dose levels of 15 and 30mg/kg body weight had shown some activity on prevention against PCV reduction when compared to negative control but 60mg/kg body weight of extract had not shown a significant ($p>0.05$) prevention activity against PCV reduction compared to negative control.[24]

Clerodendrum myricoides; Family; vernacular name; misrch (A)

Parts used; leaf, root

Safety and toxicity: The acute toxicity study on crude leaf extract of *C. myricoides* by Tekalign et al.,[18] indicated that no mortality of mice within 24hrs up to 3000mg/. Hayelom et al.,[25] also investigated that treatment with the aqueous root extract of *C. myricoides* revealed that there was no behavioral change at 100mg/kg body weight/day treatment as compared to the controls. However, the mice treated with 400mg/kg body weight/day of the aqueous extract showed some behavioral changes. A single-dose administration of 1134mg/kg body weight/day aqueous root-extract showed behavioral changes which include: horripilation, difficult to breathe, grooming, and asthenia which were followed by the death of animals after some hours. Chronic treatments with *C. myricoides* extracts in mice causes reduction in body weight gain, damage to the liver and kidney and changes in some hematological and biochemical parameters in mice.

Efficacy: After four days treatment of mice with crude leaf methanol extract of different doses of *C. myricoides*, the mean parasitaemia of the test groups were found to be 6.52±0.58% in 300mg/kg and 5.92±0.38% in 500mg/kg while the corresponding value of the negative control group were 25.73±1.57%. Statistical analysis using Scheffe's procedure indicated that groups of mice treated with 300mg/kg and 500mg/kg of *C. myricoides* leaf methanol extract showed statistically a significant difference in parasitaemia level as compared to the negative control group ($P<0.05$). The highest suppression of parasitaemia was observed at the dose of 500mg/kg body weight of mice. Ethyl acetate soluble and insoluble extracts (residue) at a dose of 150 mg/kg of *C. myricoides* leaves showed a suppressive effect of 61.30% and 69.31% respectively which have statistically significant difference as compared to negative control ($P<0.05$). While the suppressive effect of hexane extract was 16.21% which is not significantly different from the negative control. Residue and ethyl acetate extracts of *C. myricoides* leaf had better activity.[26] In similar way the other study investigated methanol extract of *C. myricoides* showed 82.5 suppression of parasitaemia at the dose of 600mg/kg body weight of mice.[18]

Croton macrostachyus; Family; Euphorbiaceae; vernacular name; Bissana (A); Bekenisa(O)

Parts used; leaf, root and fruit

Phytochemistry: The hydroalcoholic crude extract of the leaves of *C. macrostachyus* revealed the presence of alkaloids, saponins, phenolic compounds, cardiac glycosides, terpenoids and flavonoids in addition to these compounds hydroalcoholic crude extracts of the fruit and root also revealed the presence of tannins. Anthraquinones and phlabotannins were absent from the crude extract of leaf and fruit, however, present in the root extract.[27,28] Apart from the one compound, triterpene was isolated from the ethanol leaf extract.[27]

Safety and toxicity: The acute toxicity study crude and the solvent fraction of leaf indicated that the extract caused no mortality and no visible signs of overt toxicity at doses of 2 and 5g/kg within the 14 days follow up periods. However, The crude extracts from the fruit and root did not show mortality and sign of toxicity up to a dose of 2g/kg within the 14 days(28–30). Sub-acute toxicity test of methanol and aqueous extracts of *C. macrostachyus* leaf on day 4 showed no statistically significant difference ($P>0.05$) in all the hematological parameters. Significant ($P<0.05$) body weight loss at the highest dose i.e. 1000mg/kg (from 30.20gm to 25.90gm) and body weight gain at 500mg/kg (from 31.34gm to 33.58gm) in aqueous extract and in negative control group (from 26.54gm to 29.36gm) was observed.[30] Similarly the other study confirms that acute toxicity with ethyl acetate, methanol, and aqueous extract of *C. macrostachyus* from stem bark was safe, however, the mice of the isobutanol extract treatment group showed signs of acute toxicity such as gasping, abdominal writhing, muscle weakness ,rough hair coat and depression.[31]

Efficacy: Research by Laychiluh et al.,[29] revealed that percentage of parasitaemia measured in the 4 day test was reduced by the crude leaf extract in *P. berghei* infected mice which is comparable to study done by Tigist et al.,[30] *C. macrostachyus* 600mg exhibited a significant parasite suppression compared to other doses of the extract and the activity was almost comparable to that of chloroquine. Analysis of rectal temperature revealed that 80% methanol extract of *C. macrostachyus* caused significant attenuation of reduction in temperature of *P. berghei* infected mice in a dose-dependent manner. The rank order of parasitaemia inhibition of the solvent fractions was chloroform (75.9%) > methanol (64.2%) > aqueous (38.8%). Maximum inhibition (82.3%) was attained with 600mg/kg dose of the fraction. The other investigation by Laychiluh et al.,[28] Indicated that, the fruit extract 600mg and root extract 600mg of *C. macrostachyus* exhibited a significant parasite suppression 83%and 88% respectively, compared to the other doses, the root extract had better suppressive activity and it increased survival time better than the fruit extract. Analysis of the rectal temperature revealed that 80% methanolic fruit extract of *C. macrostachyus* significantly prevented the reduction of temperature in a dose-dependent manner ($p<0.01$ for fruit 200mg and fruit 400mg; $p<0.001$ for fruit 600mg). The root extract produced a better reduction of rectal temperature and parasitaemia inhibition activity than the fruit extract. The suppression was dose-dependent and 88% for root extract 600mg ,which is more effective than the suppression effects of the ethyl acetate extract of stem bark (82%) of *C. macrostachyus* investigated by Jackie et al.[31] Leaf, fruit, root and stem bark of *C. macrostachuys* have significant antiplasmodial activity against *P. berghei* both in chemotherapeutic and in chemoprotective way. Crushed leaves of *C. macrostachyus* are also boiled in water mixed with *Allium sativum* and taken orally as a remedy for malaria treatment, in addition to this *C. macrostachyus* have potent larvicidal activity against the malaria vector *An Arabiensis*.[28–33]

Dodonaea angustifolia; Family; Sapindaceae; vernacular name; Ketketa(A)

Parts used; leaf, root

Phytochemistry: Three compounds isolated from the active ethyl acetate fractions, pinocembrin, the flavanol santin, and the clerodane diterpene 2-hydroxy-15, 16-epoxyceloda- 3, 13(16), 14-trien-18-oic acid which is similar to the investigation of other species of *D. angustifolia*.[34,35]

Safety and toxicity: The acute toxicity study indicated that crude leaf extract of *D. angustifolia* shows no mortality of mice within 24 hrs up to 3000mg/kg and solvent fraction of methanolic root extract up to a dose of 2000mg/kg.[18,36]

Efficacy: The antiplasmodial activities of the ethanol extract of the leaves of *D. angustifolia* at a higher dose (300mg/kg) inhibited the parasites by 77.20% but, ethyl acetate fractions, suppression of parasitaemia by 82.00% at the dose of 300mg/kg.[18,26,34] Fractionation showed the ethyl acetate soluble portion of the 80% aqueous methanol extract of the leaves of *D. angustifolia* suppressed parasitaemia in *P. berghei* infected mice significantly (80.28% at 150mg/kg).[34]The n-butanol fraction of methanolic root extract of *D. angustifolia* significantly reduced parasitaemia level as compared to the control group (P<0.001) and the highest suppression (67.51%) was seen with the dose of 600mg/kg body weight which is less potent and effective than ethyl acetate fractions of leaf of *D. angustifolia*.[34,36]

Echinops kebericho; Family; Asteraceae: vernacular name; kebercho(A)

Parts used, root

Phytochemistry: A total of 83 compounds were identified from EO (Essential Oil) of *E. kebericho*. Although sesquiterpenoids were most abundant, many monoterpenoids at low concentration levels were also detected[37,38] which is similar and comparable with the other species of *Echinops*.[39,40] α-Guaiene and β-santalene and the monocyclic sesquiterpenoid hydrocarbon β-elemene, were also observed in the solid phase microextraction in relatively large amounts compared to the hydro distilled *E. kebericho* essential oil.[37]

Safety and toxicity: Acute toxicity studies of graded doses of hydro-alcoholic extract of *E. kebericho* (up to a dose of 5,000mg/kg) did not produce significant changes in behaviours, such as alertness, motor activity, breathing, restlessness, diarrhea, convulsions, coma, and appearance of the animals. No death was observed up to the dose of 5g/kg body weight, indicating that the median lethal dose (LD_{50}) could be greater than 5g/kg body weight in mice.[41]

Efficacy: The chemo suppression effect of *E. kebericho* was 16.93±1.17 %, 29.46±1.93 % and 57.29±1.76 % for 200, 350, 500mg/kg/day doses, respectively. The chemo suppressive effect produced by doses beyond 350mg/kg was very significant (P<0.001) compared with the negative control. All concentrations of extract employed no significant prevention effect on weight loss of mice at all dose levels (p>0.05) compared with the control group but, prevented packed cell volume loss of mice at all dose levels (P<0.001).[41] *E. kebericho* is as a major medicinal plants used by Ethiopian Immigrants in the USA, in Amhara, Northwestern Ethiopia, by Oromo people around Ghimbi District and in West Gojjam Zone of Ethiopia for different types of disease and surprising that *E. kebericho* oil exerted an extremely strong leishmanicidal effect, which was even higher than that of amphotericin B showing significant cytotoxicity.[38,42–45]

Gnidia Stenophylla Gilg; Family; Thymelaeaceae; vernacular name; Kataricha(O); Demer Erit(A)

Parts used, root

Phytochemistry: The genus *Gnidia* contain coumarins, flavonoids, chromones, lignans, neolignans and phenolic compounds.[46,47]

Safety and toxicity: Acute toxicity study of the aqueous root extract at 500, 1000, 2000 and 4000mg/kg did not produce any mortality in both male and female mice during the 72 h observation period. However, the mice treated with extract at 5000 and 6000mg/kg body weight showed some mild symptoms of toxicity within 1–2hrs of the extract administration. Treatment with 800mg/kg extract however, induced significant (P<0.05) rise in the RBC, HGB and in HCT counts when compared to the control levels. Similarly, a significant (P<0.05) increase in basophils count was observed with 800mg/kg body weight extract, the other study also investigated *G. stenophylla Gilg* root extract on did not reveal any detectable gross abnormality stomach, small intestine and large intestine.[48,49] In contrast, lymphocytes count was significantly reduced with 800mg/kg GSG root extract as compared to the control. Serum total protein level appeared to decrease after chronic treatment with 400 and 800mg/kg of extract in a dose-dependent manner and decrease the serum ALP, ALT and urea levels at 400 and 800mg/kg though non significantly. No significant difference was observed in absolute and relative organ weights of extract treated and control mice of either sex. However, there was a slight, but not significant, decrease in absolute and relative weights of spleen at both doses in male mice, but not in females.[48]

Efficacy; Research by Samson et al.,[50] indicated that the aqueous fraction of *G. stenophylla* showed 60.62% suppression at 400mg/kg/day suppression which was the highest. The dichloromethane and butanol fractions showed less activity with about 16.73% at 400mg/kg/day. Comparing the percentage reduction of the control and the extract treated the percentage reduction of the 400mg/kg of the aqueous fraction treated group is significantly different (P<0.05) from the control while for others no significant difference (P>0.05) between that of the negative control.

Jatropha curcas; Family; Euphorbiaceae; vernacular name; Ayderke(A)

Parts used, leaf

Phytochemistry: The preliminary phytochemical screening of the alcoholic extract of various parts of *J. curcas* Linn revealed the presence of alkaloids, phenolic groups, flavonids, saponins, steroids, tannins, cardiac glycosides, and terpenoids, which is similar to the other species of *Jatropha. Gossypiifolia*.[51,52]

Safety and toxicity: Crude methanol leaf extract of *Jatropha curcas* had less toxicity against the test larvae (LC50=92.09ppm; LC90=241.09ppm) as compared to its column chromatographic fractions [*F1*] (LC50=28.65 ppm; LC90=49.20ppm), [*F2*] (LC50=30.40ppm; LC90=49.80ppm) and [*F3*] (LC50=80.70ppm; LC90=123.70ppm). Least toxicity on the test larvae was observed by column chromatographic fraction three [*F3*] (LC50=80.70ppm; LC90=123.70ppm), another study, on the other hand, evaluated the oral acute toxicity of the aqueous and ethanol extracts from leaves of *J. gossypiifolia*, did not show any sign of toxicity in up to 2 g/kg in rats.[52,53]

Efficacy: Zewdneh et al.,[53] revealed that the highest mortality larvicidal for the crude methanol extract was recorded at 500ppm, 99.56%, while it was at 125ppm for the fractions *F1* and *F2*, 100%. At the 125ppm, larval mortalities among *F1*, *F2* and *F3* were not significantly different (P>0.05) while at 62.5ppm, larval mortalities among *F1*, *F2* and *F3* were significantly different (P<0.01). Crude methanol leaf extract of *J .curcas* had similar larvicidal activity to 0.5ppm Temephos at test concentrations ranging from 125-1000ppm while Column chromatographic fractions *(F1* and *F2*) of crude methanol leaf extract of *J. curcas* showed similar larvicidal activities

to 0.5ppm Temephos at 62.5 and 125ppm test concentrations. This investigation is similar to study by Samuel et al.,[54] which indicated that *J. glandulifera* showed excellent antiplasmodial activity.

Strychnos mitis; Family; Loganiaceae; vernacular name; Yedingamst (A), mulqaa, Satto(O)

Parts used, leaf

Phytochemistry: Phytochemical screening of hydromethanolic leaves of *S. mitis* showed the presence of different secondary metabolites like alkaloids, tannins saponins, flavonoids Terpenoids, Steroid, phenols and glycosides which is comparable with other species of the plant.[55,56]

Safety and toxicity: Selamawit et al.,[55] investigated the acute toxicity study of *S. mitis* indicated that both hydromethanolic and aqueous extract of *S. mitis* leaves caused no mortality up to 2000mg/kg oral doses within the first 24 hours as well as for the following 14 days and the experimental mice who ingested the crude aqueous, chloroform and methanol leaf extracts of *S. mitis* also did not show any indication of gross physical or behavioral changes.

Efficacy: Hydromethanolic and aquoeus extract of *S. mitis* leaves have prominent antiplasmodial activity against chloroquine sensitive *P. berghei* infected Swiss albino mice. The highest percentage suppression of hydromethanolic extract was 93.97% at 600mg/kg/day of the extract, and percentage Suppression of aqueous extract was 95.5% at 600mg/kg/day of the extract after four day suppressive test, which is comparable to chloroquine (25mg/kg) (100%). The N-hexane fraction and the higher two doses (200mg/kg and 400mg/kg) of chloroform and aqueous fraction of *S. mitis* leaves protected the mice from body weight loss as compared to negative control after four day suppressive test, this investigation is comparable with antiplasmodial activity of other species of Strychnos, *S. usambarensis, S. icaja, S. variabilis, S.angolensis* and *S. memecyloides*.[55,57]

Otostegia integrefolia; Family; Lamiaceae; vernacular name; tinjut (A)

Parts used, leaf

Phytochemistry: Yiketel et al.,[58] and Zewdneh et al.,[59] investigated that Methanol extract of *O. integrefolia* has a wide range of bioactive compounds including flavonoids, phenols, terpenoids, saponins, steroids and glycosides because of its high polarity which is comparable with *O. persica* species.[60] The ethyl acetate extract was also positive for flavonoids, phenols, terpenoids, saponins, steroids and glycosides, however, the petroleum ether was able to extract very limited compounds.[58] Abyot et al.,[61] isolated a Compound, which was exhibited a molecular ion peak at m/z 320 consistent with a molecular formula of $C_{20}H_{32}O_3$ from dried hydroalcoholic leaf extract of *O. integrifolia*. It was identified as the labdane diterpenoid otostegindiol based on its 1H and 13C NMR spectral features.

Safety and toxicity: The safety of *O. integrifolia* indicated that no signs of toxicity or mortality were observed in mice after oral administration of the total leaf extract, even at doses as high as 5000mg/kg signifying that the oral LD50 was greater than 5000mg/kg. Sub-acute toxicity study shows no statistically significant differences (P>0.05) were observed when weight and packed cell volume were compared in each group between pre-treatment and post-treatment. Sign of toxicity such as change in animal behavior, lacrimation, weight loss, hair erection and mortality were not recorded both in acute and sub-acute toxicity testing which is parallel with other species of the plant.[59–62] Slight reduction in packed cell volume observed in the extract-treated groups in sub-acute toxicity test might be due to the presence of saponins in the crude extract which are known to cause hemolysis by increasing the permeability of the plasma membrane.[61]

Efficacy: Hydroalcoholic leaf extract of *O. integrifolia* possesses potent activity against *P. berghei* malaria parasite in vivo with a maximum percent parasitaemia inhibition of 80.5 at a dose of 600mg/kg/day and revealed that the extract has dose-dependent activity with significant (P<0.001) parasitaemia inhibition when compared to the negative control. The crude leaf extract was able to prevent loss of body weight and reduction in packed cell volume of *P. berghei* infected mice and other findings showed that *O. persica* potentiated the effect of chloroquine on the chloroquine-sensitive *P. berghei*.[61-63] The *labdane diterpenoids otostegindiol* isolated from the active EtOAc fraction produced a dose-dependent parasetemia inhibition effect with the highest percent suppression values of 73.16 at a dose of 100mg/kg/day which is statistically significant (P<0.001) compared to the negative control.[61] Ethnobotanical study by Mirutse et al.,[45] and Getaneh et al.,[64] also indicated that *O. integrifolia* was used for the treatment of malaria in different parts of Ethiopia.

Withania somnifera; Family; Solanaceae; vernacular name; hanzo (O), gizawa(A)

Parts used, leaf, root and root bark

Phytochemistry: Study by Dawit et al.,[20] showed that tannins, alkaloids, polyphenols, flavonoids, phytosterols and phenolic glycosides, were identified in *W. somnifera* leaves and alkaloids, polyphenols, phenolic glycosides, phytosteroids and saponins were identified in the root barks, which is comparable to with the chemistry of other *Withania* species.[65]

Safety and toxicity: The hydro alcoholic extracts of *W. somnifera* leaves and root barks, showed no lethality at doses up to 5,000mg/kg, when given through intra gastric route (which is 25 MED, 200mg/kg). Similarly, intra peritoneal administration of the same extracts doses of up to 1000mg/kg did not produce lethality.[20]

Efficacy: The percent of inhibition of the hydro alcoholic extract of *W. somnifera* leaves was (54.49 %), *W. somnifera* roots (50.73 %) and *W. somnifera* root barks (50.80 %). *W. somnifera* root barks also significantly prevented the drop in PCV at dose levels of 600mg/kg in comparison with the negative control group of mice (p=0.004) and *W. somnifera* root and leaf extracts possess antidiabetic and antihyperlipidemic activities in alloxan-induced diabetic rats by another research.[20,66]

Other medicinal plants like, *Osyris quadripartita, Vernonia amygdalina, Ajuga integrifolia, Melia azedarach, Peponium vogelii* and *Premna schimperi* had also in vivo antimalarial activity and lack of toxicity.[11,13,67–70] The methanol extract of *A. integrifolia* contained alkaloids, terpenoids, flavonoids, steroids, saponins, tannins, anthraquinone, phenols, fats and oils. Aqueous leaf extract of *Vernonia amygdalina* showed the presence of alkaloids, tannins, saponins, glycosides, and cardiac glycosides, with arthraquines and steroids in trace amount which was comparable with other study plus clinical trial of *V. amygdalina* in Uganda showed. *V. amygdalina* appears to be a moderately clinically effective and nontoxic treatment for malaria in adult semi-immune patients.[67,70–72]

In the overall our ethnobotanical review data in (Table 1 & Figure 1) reveals that, most Ethiopian community utilized several medicinal plants for the treatments of malaria especially in rural communities of the country. Some of the medicinal plant species studied by

ethnobotanical survey and experimental study, in this study were also medicinally used for malaria treatment in other African countries.[87–91] *Allium sativum, Croton macrostachyus* and *Carica papaya* were the more frequently cited species of medicinal plants by ethnobotanical study in Ethiopia for malaria treatment which was comparable to another study and *Withania somnifera* and *Croton macrostachyus* were commonly used by most of the traditional practitioners in other part of Ethiopia.[92–94]

Table 1 Ethno botanical studies of medicinal plants those used for the treatment of malaria

Scientific name of plants	Family name	Local name	Part(s) used	Method of preparation	Frequency	References
Allium sativum	*Alliaceae*	Nech shinkurt(A)	bulb	The bulb taken with 'injera' and Capsicum annuum L. for 5 days before eating breakfast	10	(23),(43),(44),(73),(74),(75),(76),(77),(78)
Carica papaya	*Caricaceae*	Paappaayyaa	Leaf/root	When the leaves become yellow, that means getting to dry, powdered and boiled in water and a cup of tea will be taken For 5 days.	7	(23),(79),(80),(64),(75),(81),(78)
Lepidium sativum	*Brassicaceae*	Shinfaa(O),feetoo(A)	seed	Dried seed powdered and eaten with injera to get cure from malaria or rubbed the body for protection from mosquito bite	4	(23),(73),(75),(77)
Vernonia amygdalina	*Asteraceae*	Eebicha(O)	leaf	Leaves crushed and soak in water and the exudates drunk orally for five days	3	(23),(75),(78)
Justicia schimperiana	*Acanthaceae*	Sensel(A)	leaf	Crush and squeeze then drink with coffee	3	(82),(76),(45)
Aloe weloensis	*Aloaceae*	Eret tafa(A)	latex	Crush and mash then drink with Tella	5	(82),(83),(74), (64),(78)
Croton macrostachyus	*Euphorbiaceae*	Mekanisa(O)	Fruit, leaf, bark	Crush and powderize then drink with water	10	(82),(43),(44),(73),(74),(64),(45),(77),(81),(78)
Lobelia gibberoa	*Lobeliaceae*	Jibara(A)	root	Crush and powderize then drink with water	1	(82)
Phytolacca dodecandra	*Phytolaccaceae*	Mehan Endod (A)	root	Grind then drink with water	4	(82),(73),(74),(84)
Cicer arietinum L.	*Fabaceae*	Shinbira(A)	seed	Germinate then eat the concoction.	1	(82)
Capsicum annuum	*Solanaceae*	Karia(A)	fruit	Chop the concoction then eat	2	(82),(64)
Lycopersicon esculentum		Timatim	leaf	Squeeze then drink	1	(82)
Droguetia iners	*Urticaceae*	Yewoba medihanit (A)	leaf	chopped and mixed with *Premna oligotricha* and boiled together one glassful drenched	1	(85)
Lantana Trifolia	*Verbenaceae*	Yewoba medihanit	root	chopped and soaked with water and mixed with local alcoholic drink (Areke)	1	(85)
Premna oligotricha	*Lamiaceae*	Yewoba medihanit (A)	leaf	ground and mixed with water	1	(85)
Zornia glochidiata	*Fabaceae*	medihanit (A)	Root bark	chopped and boiled/concoction with local drinks and boiled coffee leaf	1	(43)
Euphorbia abyssinica	*Euphorbiaceae*	Kulkual	root	Crushing and drink with milk	2	(43),(78)
Skebergia capensis Sparrm.	*Meliaceae*	Lol(A)	bark	Infusion of fresh pulverized bark	1	(43)
Urtica simensis	*Urticaceae*	Sama(A)	root	crushed and dried the n mixed with fresh water, drink one glass of it and drink much amount of milk	1	(43)
Acacia robusta	*Fabaceae*	Wangey(O)	root	Concoction	1	(83)
Azadirachta indica	*Meliaceae*	Kinina(O) neem(A)	leaf	extract Leaf	3	(83),(64),(78)

Table continued

Scientific name of plants	Family name	Local name	Part(s) used	Method of preparation	Frequency	References
Balanites aegyptiaca	*Balanitaceae*	Bedeno (O)	leaf	Concoction Crushed and tie	1	(83)
Canthium pseudosetiflom	*Rubiaceae*	Medhel(H)	leaf	Ground, macerated with water, filtered and drunk	1	(86)
Vepris glomerata	*Rutaceae*	Kena(H)	Bark/leaf	Fresh leaves or mixed with bark cut stood in water, filtered and (drunk)	1	(86)
Cadaba farinosa	*Capparidaceae*	Dhela(H)	root	Chopped, boiled with meat soup and drunk	1	(86)
Cyperus distans	*Cyperaceae*	Gebezdhesha(H)	Bark/Root	Roots or mixed with inner bark, chopped, macerated in water, mixed with milk and drunk	1	(86)
Aloe otallensis	*Aloaceae*	WelqanteH	Exude	Mixed with honey and milk, and drunk	1	(86)
Ozoroa insignis	*Anacardiaceae*	Salbana(H)	Bark	Inner part peeled off, chopped, macerated in water, filtered and drunk	1	(86)
Carissa spinarum	*Apocynaceae*	Akemba(A)	root	Crushed, infusion prepared in water, filtered, and drunk	1	(86)
Moringa stenopetala	*Moringaceae*	Kelanqi(H),shiferawu(A)	Leaf/Root	Fresh leaves or roots or both boiled, allowed to cool, filtered, mixed with honey and drunk	2	(86),(78)
Withania somnifera	*Solanaceae*	Kumo(O)	leaf	The leaf is powdered, juiced and drunk for 4 days.	1	(44)
Artemisia afra	*Asteraceae*	Chugughee	leaf	Powdered fresh/dry leaves nixed with butter is taken with coffee orally before breakfast for three days	2	(73),(81)
Dodonia angustifolia	*Sapindaceae*	Tahses(T),kitkita(A)	seed	Grind and eat it with honey	3	(74),(64),(45)
Olea europaea	*Oleaceae*	Awlie	bark	Boil it in water and drink the fluid	1	(74)
Silene macrosolen	*Caryophyllaceae*	Saerosaero(T)	root	Crush and place it on fire for fumigation	1	(74)
Calpurnia aurea	*Fabaceae*	Digita(A)	leaf		1	(64),
Gardenia lutea	*Rubiaceae*	Gambelo	root		1	(64)
Lobelia	*Campanulaceae*	Jibira(A)	root		1	(64)
Otostegia integrifolia	*lamiaceae*	Tinjut(A)	leaf	Taken orally in syrup form	2	(64),(45)
Plumbago zeylanica	*Plumbaginaceae*	amira	leaf		1	(64)
Prunus persica	*rosaceae*	kok	seed		1	(64)
Schinus molle	*anacardiaceae*	Kundo berbere	seed		1	(64)
Zehrenia scarba	*cucurbitaceae*	Yekura hareg	Root/leaf		1	(64)
Datura stramonium	*Solanaceae*	Manjii(O)	fruit	Powdered fruit of *Datura stramonium* is mixed with honey and 3-4 spoons are eaten with pounded *Allium sativum*	2	(75),(78)

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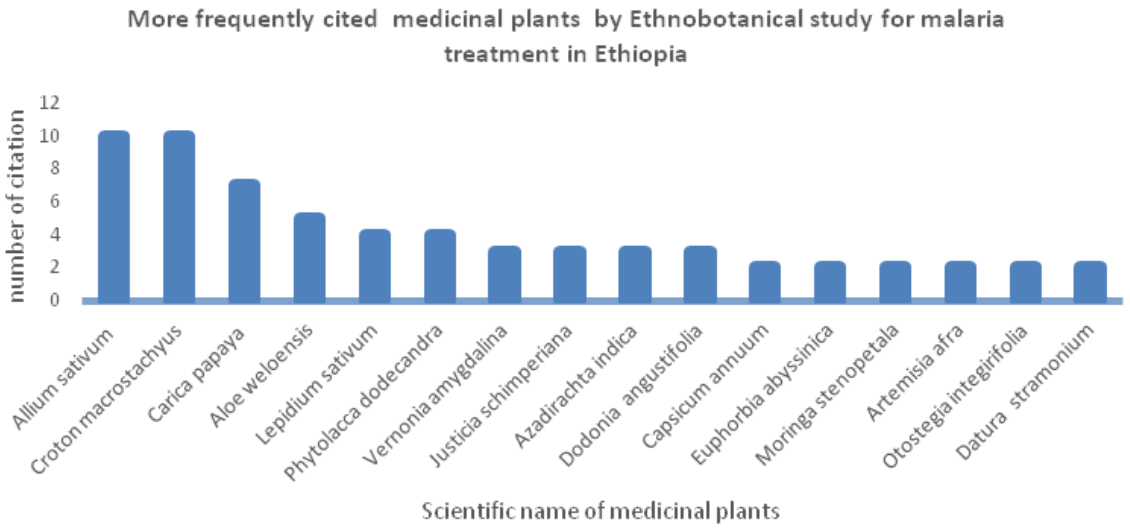

Figure 1 More frequently cited medicinal plants for the treatment of malaria in Ethiopia.

Conclusion and recommendation

This review showed that aqueous leaf extract of *Strychnos mitis* possesses potent activity against *P. berghei* malaria parasite in vivo with a maximum percent chemo suppression of 95.5 % at a dose of 600mg/kg/day, however, further phytochemical analysis is necessary to isolate the compound which is active against *P. berghei* malaria parasite. The root of *Croton macrostachys* and ethyl acetate fractions of leaf extract of *Dodonaea angustifolia* also exhibited a significant parasite suppression. The hydroalcoholic root bark extract of *Bersama abyssnica fresen* showed sign of acute toxicity and chronic treatment of mice with aqueous root extract of *Clerodendrum myricoides* damage liver and kidney. The study highlighted phytochemistry, safety and efficacy of experimentally studied medicinal plants for malaria treatment in Ethiopia, except few studies further chemical isolation are necessary. Dosage form development, clinical trial and toxicological study is also recommended.

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Conflicts of interest

The authors have declared that there is no conflict of interest with regarding to the authorship and publication of this review article.

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