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Review

A review of ethnopharmacology of the commonly used antimalarial herbal agents for traditional medicine practice in Ethiopia

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Malaria is one of the parasitic infections that cause enormous public health, economic, and emotional burden in many tropical and subtropical countries of the world. Resistance of the vector mosquitoes to the current insecticides as well as the emergence of multidrug resistance by malaria parasite to widely used antimalarial drugs has made malaria control and treatment much more difficult. New alternative antimalarial drugs and approaches for mosquito control are urgently required. Ethiopia, as most of the African continent countries, is rich in a wide range of tropical habitats, remarkable biodiversity, and the uses of traditional medicines for treatment of various illnesses. The article thus focuses on review of ethnopharmacological activities (medicinal properties), phytochemistry, and safety (toxicity) of some of the commonly used antimalarial herbal agents in Ethiopia and around which could have significant potential for antimalarial drug discovery and development.

Key words: Medicinal plants, malaria, efficacy and safety, Ethiopia.

INTRODUCTION

In many developing nations of the world, large numbers of people still rely heavily on traditional healers and medicinal plants to meet their daily primary healthcare needs and overcome the problems of resistance and side effects of the currently available antimicrobial agents (Qais et al., 2011). The World Health Organization (WHO) (2011), estimates that 80% of the people living in developing countries almost exclusively use the traditional medicine. Right from its beginning, the documentation of traditional knowledge, especially on the medicinal uses of plants, has provided many important drugs of modern day (Cox and Balick, 1996; Flaster, 1996). Out of the total flowering plants reported from the world, more than 50,000 are used for medicinal purposes (Govaerts, 2001; Schippmann et al., 2002). Among the infectious diseases, traditional use of medicinal plants in malaria as antimalarial drugs for treatment of acute signs and symptoms of malaria, or as mosquito's repellent, is an area of ethnopharmacological interest.

Malaria is one of the parasitic infections that cause enormous public health, economic, and emotional burden in many tropical and subtropical countries of the world. Approximately 3.2 billion people are at risk of malaria each year globally, with 300 to 500 million clinical cases

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and about 2 to 3 million deaths (WHO, 2011). This makes the disease one of the most common infectious diseases worldwide. In Africa, malaria accounts for 10% of the total disease burden (WHO, 2005). In Ethiopia, despite the improvement of malaria control strategy at certain level, the disease remains the leading cause of morbidity and mortality morbidity (Otten et al., 2009; Petros, 2011). The estimates of malaria associated morbidity and mortality across the world are changing, as a recent report by the WHO indicated that promising malaria prevention and control measures, such as insecticide treated mosquito nets and indoor spraying with residual insecticides, have led to a significant drop of the mortality rate by 25% since 2000. On the contrary, resistance of the vector mosquitoes to the currently used insecticides as well as the emergence of multidrug resistance by malaria parasite to widely used antimalarial drugs have made malaria control and treatment much more difficult (WHO, 2011). *Plasmodium falciparum* resistant to chloroquine and sulfadoxine-pyrimethamine is also highly prevalent in Ethiopia (Checchi et al., 2006). Hence, new alternative antimalarial drugs and approaches for mosquito control are therefore urgently required.

It is estimated that over 1,200 plants are reported to possess antimalarial activities. It is however, probable that some of them contain as yet undiscovered powerful active constituents. The ethnomedical approach to the search for new antimalarial drugs from plant sources has proved to be more predictive; some are important modern antimalarial drugs derived from the medicinal plants known to have ethnomedical standing (Olliaro and Witth, 1997; Dharani et al., 2008). The quinolone-based antimalarial quinine isolated from the bark of *Cinchona species* (Rubiaceae) is the first antimalarial drug of plant source and later served as template for the synthesis of the antimalarials chloroquine and mefloquine. The second major group of antimalarial drugs from a natural source is artemisinin (Qinghao) and its derivatives. Artemisinin is isolated from the Chinese plant *Artemisia annua Linn*. (Schwikkard and van Heerden, 2002). Artemisinin-based combination therapies (ACTs) are currently recommended by the World Health Organization (WHO) as the most effective treatment for multidrug resistant *P. falciparum* malaria (WHO, 2011). In traditional medicine, only those medicinal plants considered effective in the treatment of malaria are observed by traditional healers to cure or prevent one or more of the recognized symptoms of malaria. Various parts of plants utilized include fruits, bark, roots, and sometimes leaves in case of antimalarial trees and shrubs. Occasionally, the whole plant is uprooted and used in the preparation of the drug. These plants with antimalarial activities are administered as tea, infusion or decoction. In addition, some plants possess insect repellant or larvicidal activities (Dharani et al., 2008).

Ethiopia, as most of the African continent countries, is rich in a wide range of tropical habitats, remarkable biodiversity, and the uses of traditional medicines for treatment of various ailments (Sofowara, 1993; Giday et al., 2009; Tekalign et al., 2010). Studies conducted on antimalarial activity of several traditionally claimed Ethiopian medicinal plants confirmed their significant antimalarial activities (Debella et al., 2007; Misganaw et al., 2012; Mengistie et al., 2012; Eyasu et al., 2013; Bantie et al., 2014). These plants contain secondary metabolites such as alkaloids, terpenoids, coumarins, flavonoids, chalcones, quinines and xanthones (Dharani et al., 2010). In line with this, the review article was done to review the ethnopharmacological activities (medicinal properties), phytochemistry and safety (toxicity) of some of the commonly used antimalarial herbal agents in Ethiopia.

Commonly used plants for malaria treatment and control in Ethiopian traditional medicine

Medicinal plants with insect repellant/insecticidal and larvicidal activities

Common approaches for malaria vector (mosquito) control include chemical insecticides, biological control, environmental manipulations, and personal protection from mosquito bite. In Ethiopia, chemical insecticides (mainly indoor application of DDT), long lasting insecticide treated mosquito nets (LLITNs), and environmental management are currently the main vector control measures (Ghebreyesus et al., 2006) despite the development of high to moderate levels of resistance of Anopheline mosquito to insecticides (Balkew et al., 2003).

Plant-based products which are believed to be safer than conventional insecticides have so far received little attention despite their widespread traditional use in different parts of Africa (Snow et al., 1987; Seyoum et al., 2002a; Waka et al., 2004). The repellent properties of plants to mosquitoes and other pest insects were well known before the advent of synthetic chemicals. Smoking is still the most widely used means of repelling mosquitoes throughout the rural tropics. The burning of some herbs such as Artemisia (Astraceae) and *Calmus* species in rural areas in China has been used to keep away mosquitoes and protect cattles from blood sucking insects (Hwang et al., 1985). Various plants have been reported to possess repellent activity against mosquitoes including *Azadirachta indica*, *Eucalyptus* spp. (Myrtaceae), *Lantana camara* (Verbanaceae), *Cymbopogon* spp. (Gramineae), *Mentha piperita* (Labiatae) and *Tagetes minuta* (Compositae). Smoke produced by burning of dried leaves of *A. indica* has been used for the protection against mosquitoes since ancient times (Sukumar et al., 1991). Other field investigations based on such traditional knowledge have also supported the potential of different repellent plants against

(a) (b)

Figure 1. (a) The plant *Phytolacca dodecandra* and its berries, and (b) leaves and root of *P. dodecandra* (Source: Asmare et al., in press).

Anopheline and *Culicine* mosquitoes in various parts of Africa by placing fresh plants or smoldering plant parts (Palsson and Jaenson, 1999a, b; Seyoum et al., 2002a, 2003; Waka et al., 2004; Dugassa et al., 2009). Such plants, being readily available and their application methods being simple, are believed to promote their uses as mosquito repellents in cases when mosquitoes bite early evening and/or in situations when other conventional control methods fail or may not be available as required. In Ethiopia, incense fumigation or placement of fresh and aromatic plant parts in houses is widely practiced by rural as well as urban communities to deter nuisance and biting insects. The most commonly used medicinal plants with insect repellent and larvicidal activities in Ethiopia and other African countries are described.

Phytolacca dodecandra L'Herit

P. dodecandra also known as 'soapberry' or 'endod' in Ethiopia, belongs to the family Phytolaceae. It is a perennial climbing plant growing rapidly in Ethiopian highlands (1,600 to 3,000 m above sea level) and produces fruits twice a year from December to February and June to July (Lemma et al., 1979; Karunamoorthy et al., 2008). The powdered fruits/berries (Figure 1) are commonly used in various parts of the country for cloth washing as when it is mixed with water it produces foaming detergent solution. The multi-potential bioactive plant *P. dodecandra* grows naturally in Ethiopian highlands and also cultivated for use in the snail control program (Misganaw et al., 2012).

Medicinal properties, insect repellent and larvicidal activities: *P. dodecandra* is native to sub-Saharan Africa and Madagascar (Lemma et al., 1979; Schemelzer and Gurib-Fakim, 2008) and is used for different medicinal purposes to treat various ailments in humans as well as in animals (Nalule et al., 2011). Various ethnobotanical studies indicate its traditional uses for purgative, antihelmintic, laxative, emetic, diuretic, and antidiarrheal activities (Bizimana, 1994; Schemelzer and Gurib-Fakim, 2008; Nalule et al., 2011). In addition, it is also used to relieve headache and to treat rheumatism, otitis, pneumonia, stomach pain, intestinal roundworms, and skin diseases, for example, wound, itching, skin irritation, ringworms and scabies (Fonnegra and Jimenez, 2007; Schemelzer and Gurib-Fakim, 2008; El-Kamali, 2009). An ethnobotanical study in Wonago woreda SNNPR of Ethiopia by Mesfin et al. (2009) also indicate the traditional use of the leaf juice of this plant for treatment of malaria.

The aerial part of the plant exhibits potential mosquito larvicidal activity. The butanol extract was found to be highly toxic to the second and third instar larvae of *Aedes aegypti*, *Culex pipiens* and *Anopheles quadrimaculatus* (Spielman and Lemma, 1973), and with variable potencies against *Aedes africanus*, *A. aegypti* and *Culex quinquefasciatus* (Debella et al., 2007). A considerable larvicidal and pupicidal activity against immature *C. quinquefasciatus* was demonstrated with this plant extract (berries) using water, petroleum ether, acetone, benzene, and methanol (Misganaw et al., 2012). Its bio potency is dependent on concentration, exposure period, and type of solvent used for extraction. The percent mortality of immature mosquitoes was significantly greater for petroleum ether, acetone and benzene extract at the dose level above 125 ppm and 100% mortality was observed at 1,000 ppm for all the tested solvent extracts.

Phytochemistry: The Ethiopian *Phytolacca* species contains structurally related triterpenoid saponins in which the most potent one has been identified as

Figure 2. The plant *Juniperus procera* Hochst. ex Endl (Source: Hedberg et al., 2005).

Figure 3. The leaves and stem of *Eucalyptus camaldulensis* (Source: Hedberg et al., 2005).

'*Lemmatoxin* (an oleanolic acid glycoside). The potential molluscicide or antischistosomal activity of the extracts of *P. dodecandra* extracts in Ethiopia was isolated using organic solvents for the first time by Lemma et al. (1979).

Juniperus procera Hochst. ex Endl.

The larvicidal activity (larval mortality at 24 h post exposure) of the essential oil extract of *J. procera* (known as 'African juniper' or 'East African cedar') belonging to the family Cupressaceae Figure 2, against the larvae of *An. Arabiensis* has been evaluated under the laboratory and semi-field conditions. Results clearly showed that larval mortality was dose- and time-dependent (Karunamoorthi et al., 2014a). In this study, the mean LC_{50} vs. LC_{90} (concentrations that produce 50 and 90% larvicidal activity, respectively) values of *J. procera* under the laboratory and semi-field conditions were 14.42 vs. 24.65 mg/L, and 24.51 vs. 34.21 mg/L, respectively. The essential oil of *J. procera* exhibited significant repellent activity against female *An. arabiensis in vitro* (Karunamoorthi et al., 2014b). The repellent activity and protection time of the plant at the dose levels of 1, 1.5, 2.5 and 5 mg/cm^2 were 64.10% vs. 92 min, 68.10% vs. 125 min, 72.20% vs. 190 min, and 80.6% vs. 311 min, respectively. The longest protection time (311 min) and highest repellency (80.6%) were observed with 5 mg/cm^2 dose level.

Other plants with mosquito repellent activities

Corymbia citriodora, Eucalyptus camaldulensis Figure 3,

Ocimum suave, and *Ocimum basilicum* including their essential oils are also used traditionally as insect repellants (Watanabe et al., 1993; Seyoum et al., 2002a, b; Dugassa et al., 2009). Thermal expulsion and direct burning on traditional stoves of these plants showed partial but significant protection against the house-entry and biting activity of the two important malaria vectors in Ethiopia - *An. arabiensis* and *An. pharoensis* (Dugassa et al., 2009). With direct burning of the plants in this study, *O. basilicum* showed the highest percentages of repellency (73.11%), while *E. camaldulensis* showed the lowest repellency (65.29%) against *An. arabiensis*. *C. citriodora* produced the highest repellency (72.87%), while *E. camaldulensis* produced the lowest repellency (66.60%) against *An. pharoensis*. With thermal expulsion, *C. citriodora* exhibited the highest repellency (78.69%), whereas *E. camaldulensis* produced the lowest repellency (71.91%) against *An. arabiensis*. *C. citriodora* exhibited the highest repellency (72.9 %), where *E. camaldulensis* produced the lowest repellency (72.2%) against *An. pharoensis*.

An experimental-based study by direct burning of the dried plant materials (leaves and roots) of other four traditional insect/mosquito repellent plants against *An. arabiensis* were investigated by Karunamoorthi et al. (2008). These included *Silene macroserene* ('Wogert' vernacular or local name), *Echinops* spp. ('Kebercho' vernacular name), *Ostostegia integrifolia* ('Tinjut' vernacular name), and *Olea europaea* ('Woira' vernacular name). Results from this study clearly demonstrated that *S. macroserene* (root) was the most potent plant with mosquito repellent efficiency (93.61%). The repellent efficiency of the leaves of *Echinops* spp., *O. integrifolia* and *O. europaea* were 92.47, 90.1, and 79.78%, respectively, in this study.

Medicinal plants with antimalarial activities

Calpurnia aurea

C. aurea, Figure 4 belonging to the family Fabaceae, is known in several local names in Ethiopia, that is, 'chekata' in Afaan Oromo and 'digita' in Amharic.

Medicinal properties and antimalarial activities: The roots of *C. aurea* is claimed to exhibit activity against amoebiasis and giardiasis; the leaf is used against malaria; the leaf together with the seed is used for treatment of diarrhea, rabies and diabetes; and the seed is used for treatment of hypertension. In addition, different parts of the plant (leaves and stems) are also used for wound healing, treatment of leishmaniasis, tapeworm, trachoma, scabies, elephantiasis, swellings, and bacterial infections (Giday et al., 2007). Antibacterial and antioxidant activity of the leaves and stem extract of *C. aurea* has been evaluated using standard *in vitro* method (Adedapo et al., 2008). The antioxidant activity was determined by diphenylpicrylhydrazyl (DPPH) and ferrous reducing antioxidant property (FRAP) methods. The leaf extract showed higher radical scavenging activity as well as activity against both gram-positive and gram-negative bacteria in this study.

The antimalarial activity of the hydromethanolic leaf extract of *C. aurea* at three different dose levels (15, 30, and 60 mg/kg body weight) was demonstrated in a 4-day suppressive test in *P. berghei*-infected mouse model. All dose levels produced significant reduction of parasitemia (46.1, 43.3, and 51.2%, respectively) compared to control (distilled water: 0% suppression) (Eyasu et al., 2013). The highest dose also significantly prolonged survival time of the mice (mean ± SD: 9.6 ± 0.55 days) compared to negative control (mean ± SD: 6.40 ± 0.55 days). In addition, the extract exhibited prophylactic activity when animals were treated with three dose levels (15, 30, and 60 mg/kg body weight) daily for four days before the infection with *P. berghei*. Chemo-suppression rates were 32.8, 25.46 and 36.8%, respectively. The survival time was significantly prolonged (8 ± 0.72 days) only in the group treated with 60 mg/kg body weight of extract as compared to the other two doses (7 ± 0.57 days) and control group (7 ± 0.42 days) in this study.

Phytochemistry: Results of preliminary phytochemical screening of powdered plant material (leaves) from *C. aurea* revealed the presence of several secondary metabolites including alkaloids, cardiac glycosides, flavonoids, phenols, phytosteriods, saponins, terpenoids, and tannins (Eyasu et al., 2013). **Safety and toxicity:** Acute toxicity testing revealed absence of mortality following the oral dose level of up to 300 mg/kg body weight of the second high dose, suggesting that the oral median lethal dose (LD_{50}) of the leaf extracts of *C. aurea* could be greater than 300 mg/kg body weight. This justifies the safety use of the plant extract for malaria treatment (Eyasu et al., 2013).

Withania somnifera Dunal

The shrub *W. somnifera* Dunal Figure 5*,* belonging to the family Solanaceae, is also known by its vernacular or local names as 'ashwagandha', 'Indian ginseng', 'winter Cherry', 'kib kitel' or 'Etse Eyesus' in different languages/areas.

Medicinal properties and antimalarial activities: This shrub is also cultivated for medicinal purposes in fields and open grounds in Eastern Africa, India, and the Meditranean. *W. somnifera* has been recommended for the treatment of various ailments including polyarthritis, rheumatoid arthritis, painful swellings, asthma, leucoderma, general debility, sexual debility, anxiety neurosis, scabies, ulcers, marasmus, and leucorrhoea (Uddin et al., 2012). The root extract of *W. somnifera* has been shown to exhibit antibacterial activity against *Staphylococcus aureus* (Jaffer et al., 1988). Its traditional

Figure 4. The plant *Calpurnia aurea* (Source: Hedberg et al., 2005).

Figure 5. Pictures showing the leaves and fruit of *Withania somnifera* Dunal (Source: Wickipedia, the free encyclopedia).

use for malaria was reported by the traditional healers in Ethiopia (Asres et al., 2001).

Different parts (mainly root and leaf) of *W. somnifera* have been reported to exhibit antimalarial activities both *in vivo* and *in vivo* (Bogale and Petros, 1996; Dikasso et al., 2006; Dame et al., 2013; Teklemariam, 2005). The *in vitro* antimalarial potency of the chloroform extract of the plant against *P. falciparum* was demonstrated at the IC_{50} of 2.04 µg/ml (Bogale and Petros, 1996). Results of a 4-day malaria suppressive test in *P. berghei*-infected mice also revealed that the column fractions of methanolic extract of the *W. somnifera* leaves significantly suppressed parasitemia at lower doses compared to the crude extract (Dame et al., 2013). Reduction of parasitemia by 44 and 57% was observed at the doses of 200 and 300 mg/kg body weight, respectively, in this study.

Phytochemistry: Qualitative phytochemical screening of chemical constituents related to anti-oxidant activity of the plant root extract revealed the major constituents as alkaloids, flavonoids, phenolics, carbohydrates, tannins, and terpenoids (Mandal et al., 2012). Quantitative phytochemical estimation indicated that *W. somnifera* root extract contains 180.80 ± 0.01 mg/100 mg extract gallic acid equivalent phenolic content, 136.97 ± 0.01 mg/100 mg extract quercetin equivalent flavonoid content, 19.01 ± 0.03 mg/100 mg extract glucose equivalent carbohydrate content, 119.7 ± 0.58 mg/100 mg extract reserpine equivalent alkaloid content, and 0.6 ± 0.01 mg/100 mg extract catechin equivalent tannin content (mean ± SD).

Safety and toxicity: Results of the toxicity testing in mice indicated virtually no toxic effect of *W. somnifera*

Figure 6. *Dodonaea angustifolia* L. (Source: Hedberg et al., 2005).

leaves extract up to the dose levels of 1,000 and 500 mg/kg body weight for the crude extract and column fractions, respectively (Dame et al., 2013).

Dodonaea angustifolia L.

The shrub *D. angustifolia* L., Figure 6 belonging to the family *Sapindaceae*, is widely distributed throughout the tropics and subtropics, although its centre of origin is believed to be in Australia (Little and Skolmen, 1989).

Medicinal properties and antimalarial activities: A wide range of therapeutic applications of *D. angustifolia* has been reported including for treatment of pneumonia, tuberculosis, and other infections; musculo-skeletal and digestive system disorders and injuries (Cook, 1995); and as a botanical pesticide (Ghosh and Ulaganathan, 2004). *D. angustifolia* is also reported to possess analgesic and antipyretic (Amabeoku et al., 2001), antiretroviral (Asres et al., 2001) and antimalarial (Sorsa, 1992; Ali et al., 2004; Simonsen et al., 2001; Clarkson et al., 2004; Tekalign et al., 2010; Mengiste et al., 2012) activities. With regard to its antimalarial activity, methanol extract of the roots of *D. angustifolia* significantly reduced parasitemia in *P. berghei*-infected mice at all dose levels compared to control (distilled water) in a 4-day suppression test (Tekalign et al., 2010). The parasitemia (mean ± SD) of mice treated with 200 and 600 mg/kg body weight of the extract and distilled water were 5.37 ± 0.28, 1.84 ± 0.06, 11.92 ± 0.95%, respectively, showing that the highest parasitemia suppression (84.52%) was observed in the group treated with the highest dose (600 mg/kg body weight). In another 4-day chemosuppressive study in *P. berghei*-infected mice by Mengiste et al. *(*2012), the aqueous extract of *D. angustifolia* seeds significantly reduced parasitemia at the dose levels of 100, 200, and 400 mg/kg body weight. The mean parasitemia (%) vs. chemosuppression (%) on day 4 were 31.6 vs. 17.1%, 27.9 vs. 26.7%, 24.5 vs. 35.8% and 38.1 vs. 0% for the dose levels of 100, 200, and 400 mg/kg body weight of the extract, and distilled water, respectively. The chloroform and butanol fractions of *D. angustifolia* water extract also significantly prevented body weight reduction in a dose-dependent manner. Among all fractions, the butanol fraction particularly prolonged survival time of the treated mice (mean ± SD: 10.2 ± 2.9 days) as compared to that of the mice in the negative control group (8.3 ± 1.0 days) in this study.

Phytochemistry: Phytochemical screening of powdered plant materials (seeds) of *D. angustifolia* showed the presence of many secondary metabolites such as tannins, alkaloids, phytosteriods, saponnins, and polyphenols (Mengiste et al., 2012).

Safety and toxicity: Acute toxicity test suggested that none of the methanol extract doses of the *D. angustifolia* root extracts caused death in mice within 24 h following the oral administration at the dose level up to 3,000 mg/kg body weight (Tekalign et al., 2010). Similarly, gross physical and behavioral observation of the experimental mice revealed no visible signs of lacrimation, hair erection, or reduction in their motor and feeding activities. The aqueous extract of *D. angustifolia* seeds was shown to be well tolerated when administered orally to mice up to a dose of 4,500 mg/kg body weight (Mengiste et al., 2012). This dose level is about 11 times of the maximum effective dose tested in the study (400 mg/kg body weight), suggesting the LD_{50} of the extract of greater than 4,500 mg/kg body weight.

Croton macrostachyus Hochst

Croton macrostachyus Hochst Figure 7, belonging to the

family Euphorbiaceae, is commonly found on forest edges along rivers, around lakes, woodlands, wooded grasslands, and along roadsides. It is native to Ethiopia, Eritrea, Kenya, Nigeria, Tanzania, and Uganda. In Ethiopia, it is used for the treatment of malaria in several endemic areas (Kapingu et al., 2000; Gidey et al., 2007; Gidey et al., 2009; Orwa et al., 2009).

Medicinal properties and antimalarial activities: Ethnobotanical and pharmacological studies revealed that various parts (stem barks, leaves, and fruits) of *C. macrostachyus* possess a wide range of activities (Tilahun and Mirutse, 2006; Gidey et al., 2007; Gidey et al., 2009; Mesfin et al., 2009; Asmare et al., in press). These include antidiabetic (Kapingu et al., 2000), purgative and anti-inflammatory (Mazzanti et al., 1987), antibacterial and antifungal (Desta, 1993; Taniguchi and Kubo, 1993; Mesfin et al., 2009) and antimalarial (Sorsa, 1992; Mesfin et al., 2009) activities. The fruit extract showed promising antimalarial activity *(*Mohammed et al., 2014; Bantie et al., 2014). Moreover, the methanol leaf extract also exhibited larvicidal activity against late third instar larvae of *An. arabiensis*, a predominant malaria vector in Ethiopia (Karunamoorthi and Ilango, 2010).

In an *in vivo* study, the methanol extract of *C. macrostachyus* showed dose-dependent chemosuppressive effect at various dose levels, that is 200 (21.1%), 400 (27.7%), and 600 (34.3%) mg/kg body weight in *P. berghei*-infected mice (Mohammed et al., 2014). The mice treated with chloroquine were completely free from parasitemia on day 4 in all groups (100% suppression). The crude methanol extract of *C. macrostachyus* significantly suppressed parasitemia at all dose levels compared to the negative control groups (distilled water), but did not significantly prolong the survival time of infected mice. Similarly, the aqueous extract at the doses of 200, 400, and 600 mg/kg body weight significantly reduced% parasitemia (26.14, 30.50 and 50.53%, respectively) compared to the negative control group in this study.

In another *in vivo* study, the crude leaf extract and solvent fractions (chloroform, methanol, and aqueous fractions) of *C. macrostachyus* showed suppressive effect on parasitemia of 44 to 91 and 12 to 76%, respectively, in *P. berghei*-infected mice in a 4-day suppression test. The inhibitory activity was dose-dependent (200, 400, and 600 mg/kg body weight for all extract), with potency being lower than chloroquine (100% suppression) (Bantie et al., 2014). Similarly, the curative effect of the crude extract and chloroform fraction were in the range of 39 to 83 and 66 to 82%, respectively, for all the three dosage regimens in this study. The crude extract also significantly prevented loss of body weight and reduction in temperature, but did not affect packed cell volume of the experimental mice as compared to the control group. Moreover, all doses of the chloroform fraction significantly prevented the reduction in rectal temperature and packed cell volume (PCV) reduction.

Phytochemistry: Recently, fourteen secondary metabolites have been isolated from *C. macrostachyus*. These include phenolics and triterpenes of the lupane and hopane groups (Tala et al., 2013). The ethanol and water extracts from the leaves of *C. macrostachyus* were found to contain phytochemical constituents such as saponnins, flavonoids, carbohydrates, free amino acids, and vitamin C (Asmare et al., in press). Phytochemical screening of the hydroalcoholic crude extract of the leaves of *C. macrostachyus* also revealed alkaloids, saponins, phenolic compounds, cardiac glycosides, tannins, terpenoids, and flavonoids (Bantie et al., 2014).

Safety and toxicity: Acute toxicity testing of the methanol and water extracts (oral dosage ranges from 500 to 1,000 mg/kg body weight) of *C. macrostachyus* leaves in mice showed no gross physical and behavioral changes including, rigidity, sleep, diarrhea, depression, abnormal secretion and hair erection for 24 h and no mortality occurred within the observation period of two weeks (Mohammed et al., 2014). In the sub acute toxicity test, both methanol and aqueous extracts of *C. macrostachyus* showed no significant difference in all the hematological parameters (body weight, PCV %, white blood cell (WBC) count, and hemoglobin) on day 4 after dosing as compared to that of day 0. Similarly, there was no significant difference in the body weight changes observed in this study.

In another acute toxicity study in mice, the methanol extract of the *C. macrostachyus* leaves at a single oral doses of 2 and 5 g/kg body weight caused no mortality within the first 24 h and up to 14 days observation period (Bantie et al., 2014). Results from the study suggested safety profile of this herbal extract in the study mice. Physical and behavioral observations of the experimental mice did not show any visible signs of overt toxicity such as lacrimation, loss of appetite, tremors, hair erection, salivation, and diarrhea.

Plants in the genus Stephania

The genus *Stephania* Figure 8, belonging to the family Menispermaceae, is a large family of about 65 genera and 350 species which are distributed in warmer parts of the world. The members of this family are mostly herbs or shrubs but rarely trees. The plants of the genus *Stephania* are slender climbers with peltate and membranous leaves. The flowers are umbelliform cymes while inflorescences are axillary and arising from old leafless stem (Gaur, 1999).

Medicinal properties and antimalarial activities: The plants of the genus *Stephania* are widely distributed, and

Figure 7. A picture showing the leaves of the plant *Croton macrostachyus* (Source: Asmare et al., in press).

Figure 8. Pictures of some Stephania plants: (a) *Stephania abyssinica* Walp. and (b) *Stephania cephalantha* Hayata (Source: *Wikipidia*, the free encyclopedia).

have long been used in folk medicine for the treatment of various ailments including asthma, tuberculosis, dysentery, hyperglycemia, fever, intestinal complaints, sleep disturbances and inflammation, cancer, and malaria (Kirtikar and Basu, 2004). The ethanol extract of *Stephania glabra* (Roxb.) Miers was also investigated for its antimicrobial activity against five bacterial species (*Staphylococcus aureus, S. mutans, S. epidermidis, Escherichia coli* and *Klebsiella pneumonia*), and six fungal species (*Aspergillus niger, A. fumigatus, Penicillum citranum, Microsporum gypseum, Microsporum canis* and *Trichophyton rubrum*) and was found to be active against most of these tested microorganisms with minimum inhibitory concentration (MIC) range of 50 to 100 µg/ml (Semwal et al., 2010). The aqueous extract of *S. abyssinica* Walp leaves showed significant antimalarial activity *in vitro* against chloroquine sensitive and resistant laboratory adapted strains of *P. falciparum* with IC_{50} of greater than 30 µg/ml (Muregi et al., 2004).

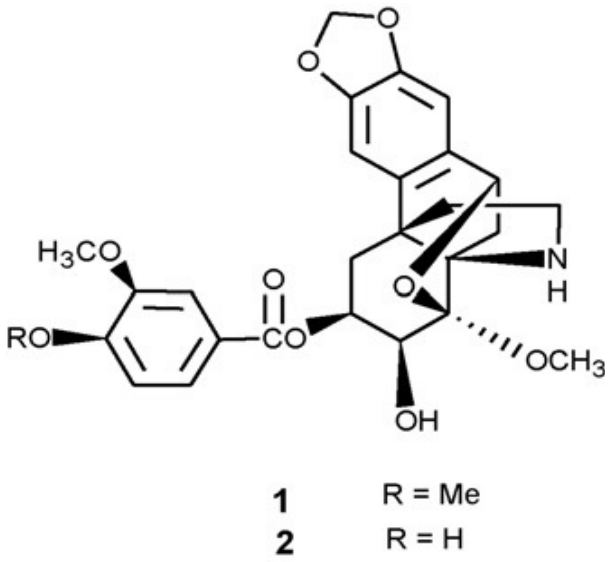

Figure 9. The bioactive constituents identified from the plant *Stephania abbysinica* Walp. (Dagne et al., 1993).

Figure 10. *Asparagus africanus* Lam. (Source: Hedberg et al., 2005).

Phytochemistry: Over the last five decades, extensive research on phytochemistry has been performed on several plants in the genus *Stephania* due to their significant traditional uses. These plants are major sources of more than 200 bioactive alkaloids (forexample, morphines, hasubanalactams, hasubanans, aporphines, and berberines), flavonoids, lignans, steroids, terpenoids, and coumarins (Semwah et al., 2010). The reported phytochemicals from *Stephania abyssinica* Walp. include *4-O-methylstephavanine* (1) and *stephavanine* (2) (Figure 9) (Dagne et al., 1993).

Safety and toxicity: Apart from various medicinal uses, some plants of the genus *Stephania* have been reported for their acute toxicity. The oral administration of aqueous extract of wet and dry root tuber of *Stephania cepharantha* Hayata produced acute toxicity with LD_{50} (the dose that produces 50% mortality) values of 41.4 and 22.9 g/kg body weight, respectively (Chen et al., 1999). In another study, *S. sinica* (anshuling) was shown to produce hepatotoxicity (Haller et al., 2002).

Other medicinal plants with antimalarial activities

Asparagus africanus Lam. (Family Asparagaceae) Figure 10 is traditionally used in treating various human ailments in Ethiopia including malaria. The *in vivo* antimalarial activity of chloroform, butanol and aqueous fractionates (100, 200, and 300 mg/kg body weight) of *A. africanus* roots against a chloroquine sensitive strain of *P. berghei* was assessed using the 4-day suppressive test. All of the three fractions showed significant parasitemia suppression at all dose levels in a dose-related manner (Yared et al., 2012). The butanol fraction showed the highest (85.9%) parasitemia suppression at the dose of 300 mg/kg body weight per day, while the aqueous residue induced parasitemia suppression of 66.8% at the same dose. The chloroform fraction also showed significant parasitemia suppression at all orally administered dose levels. The butanol fraction significantly prolonged the survival time at the highest dose (mean of 11 days) compared to control (mean of 7.8 days) in this study.

Ethnopharmacological studies on other plant species including *Aloe species* (more than 400 species in the family of Xanthorrhoeaceae) Figure 11, *Azadirachta indica,* and *Tamarindus indica* also suggested promising antimalarial activities of these plants which are commonly used in Ethiopia especially around Shinile District of Somali Region (Mesfin et al., 2012). For the antimalarial activities of *Aloe* species in this study, the ethanol and aqueous leaf extract at the dose of 650 mg/kg body weight caused 73.9 and 58.1% parasitemia suppression, respectively, in a 4-day chemosuppression test in *P. berghei*-infected mice model. Similarly the ethanol and water extracts of *A. indica* leaves induced 54.7 and 21.4% parasitemia suppression at the dose of 650 mg/kg body weight. The water extract of the *T. indica* fruits showed the highest parasitemia suppression (81.0%) at the dose of 650 mg/kg body weight.

CONCLUSION

Medicinal plants have provided valuable and clinically useful sources of antimalarial drugs. In the light of increasing level of multidrug resistant malaria, traditional medicine could be an important affordable and sustainable alternative source of treatment. The traditional uses of most plants for treatment of malaria in Ethiopia have been supported by *in vitro* and *in vivo* studies. Preliminary phytochemical components and toxicity of such plants have also been investigated to

Figure 11. *Aloe succotrina* (leaves and flowers) (source: Wikipedia, the free encyclopedia).

some extent to assure their safety profiles. In addition, there is a vast majority of unexplored flora and folklore of which if they are systematically explored will provide additional new leads and drugs for malaria treatment andcontrol. Further studies for antimalarial drug discovery and development should focus on the identification of the active constituents as well as pharmacokinetic profiles of the promising candidates studied so far in the area.

Conflict of Interest

The authors have not declared any conflict of interest.

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