Anti-malarial plants in Ethiopia and their activities on drug-resistant malaria

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Abstract

In Ethiopia, the impacts of malaria continue to cause a many number of morbidity and mortality that accounts to most-outpatient observations. Ethiopia recently designed to attain nationwide malaria control by 2030 by beginning sub-national elimination in districts with low malaria transmission. However, the rise of drug-resistant parasites, especially Plasmodium falciparum hinder the malaria-containment strategies. Plasmodium falciparum and Plasmodium vivax are dispersed all over Ethiopia, and account for 60% and 40% of malaria cases, respectively. The aim of this report was to overview the phytochemical constituents, diversity, and effect of some compounds on drug-resistant plasmodium species. Many plant species, a total 200 identified by 82 studies, are used in traditional malaria treatments throughout the country. Allium sativum, Carica papaya, and Croton macrostachyus were the more frequently used medicinal plant species. There are so many phytochemical constituents found in medicinal plants used to treat malaria. Alkaloids, flavonoids, phenolics, terpenoids, and glycosides are the most-reported for their effective activity on drug-resistant malaria.

Keywords: anti-malaria, drug resistant, phytochemical constituent, Plasmodium species

Introduction

About 60% of the population of Ethiopia is living in the risky areas, mainly areas that lie below 2000 m above sea level. The western part of Oromia, Amhara, Tigray, and Southern Nation and Nationality and Peoples’ region (SNNP), and most of the entire areas of Benishangul Gumuz and Gambella regions represent the major malarial hotspots in the country. Up to 2030, Ethiopia has planned to eradicate malaria throughout the country. However, the existence of drug-tolerant Plasmodium species has highly influenced the health and economy of Ethiopia. Specially, Plasmodium falciparum has developed resistance to all currently used anti-malarial drugs.

The emergence of malaria species that can resist drugs has led to the findings of many anti-malarial drugs with significant structural difference. Including quinines, triterpenes, sesquiterpenoids, quassinoids, limonoids, alkaloids, lignans, and coumarins are some of the drugs. Medicinal plants are the center of many scientists aimed at discovering optional anti-malarial drugs in many parts of the globe. In Ethiopia, 80% of the population is using different varieties of medicinal plants to treat malaria. The aim of this review is to overview the diversity, phytochemical constituents, and activities of some Ethiopian anti-malarial plant compounds on drug-resistant Plasmodium species.

Malaria in Ethiopia

In Ethiopia, the influence of malaria keeps to cause a substantial number of death that can be considered for most outpatient visits (Esayas et al. 2020). Malaria has been one of the major causes of sickness and deaths in Ethiopia (Esayas et al. 2020). About 60% of the population is living in the malaria risky, which lie below 2000 m above sea level (Esayas et al. 2020). The western lowlands of Oromia, Amhara, Tigray, and SNNP, and almost the entire areas of Benishangul Gumuz and Gambella region are the major malarial hotspots in Ethiopia (Saxena et al. 2003).

According to Solomon et al. (2020), P. falciparum and Plasmodium vivax are the widely abundant malaria parasites in Ethiopia, that are accounted for 60% and 40% of malaria cases, respectively. Plasmodium malariae accounts for less than 1% whereas Plasmodium ovale is rare. The way of transmission for the parasites is a mosquito vector known as Anopheles arabiensis. Ethiopia has recently aimed to attain nationwide malaria eradication by 2030 (FMOH 2017).

Drug-resistant malaria

In Ethiopia, nine studies reported the treatment failures in malaria. The emergence of drug-resistant malaria has raised concerns on the potency and the healing effectiveness of the existing anti-malarial drugs (Abera, Ashebir and Basha 2019). Multidrug-resistant species is present in all malarious areas of Ethiopia (Hailemeskel et al. 2019). Chloroquine-resistant P. vivax malaria has also been reported from Ethiopia. The emergence of drug-resistant parasites, mainly P. falciparum hinder the malaria containment strategies (Koche et al. 2016). Among the species, P. falciparum has developed resistance to nearly all available anti-malarial drugs. The advent of P. vivax resistant to chloroquine and primaquine may, in time, result in a resurgence of vivax malaria as has been seen with P. falciparum (Bloland and World Health Organization 2001).
Table 1. Medicinal plants used to treat malaria in Ethiopia.

| Number | Scientific name of plants | Family name | Local name | Part(s) used | Method of preparation |
|--------|---------------------------|-------------|------------|--------------|----------------------|
| 1      | Allium sativum            | Alliaceae   | Nech shinkurt(A) | Bulb | The bulb taken with ‘injera’ and Capsicum annuum L. for 5 days before eating breakfast. |
| 2      | Carica papaya             | Caricaceae  | Paappaayya  | Leaf/root    | When the leaves become yellow, it will be dried, powdered, and boiled in water and then a cup of boiled leaf powder will be taken for 5 days. |
| 3      | Lepidium sativum          | Brassicaceae| Shinfaa(O),feetoo(A) | Seed | Dried seed, powdered and eaten with injera to get cure from malaria or rubbed on the body for protection from mosquito bite. |
| 4      | Vernonia amygdalina       | Asteraceae  | Eebicha(O)  | Leaf | Leaves crushed and soaked in water and the exudates drunk orally for 5 days. |
| 5      | Justicia schimperiana     | Acanthaceae | Sensel(A)   | Leaf | Crush and squeeze, then drink with with coffee. |
| 6      | Aloe × herbensis          | Aloaceae    | Eret tafa(A) | Latex | Crush and mash, then drink with Tella. |
| 7      | Croton macrostachyus      | Euphorbiaceae| Mekanisa(O) | Fruit, leaf, and bark | Crush and powderize, then drink with water. |
| 8      | Lobelia gibberoa          | Lobeliaceae | Jibara(A)   | Root | Crush and powderize, then drink with water. |
| 9      | Physolacca dodecandra     | Phytolaccaceae| Mehan Endod (A) | Root | Grind, then drink with water. |
| 10     |                           |            |            |              |                      |
| 11     | Cicer arietinum L.        | Fabaceae    | Shimbira(A) | Seed | Germinate, then eat the concoction. |
| 12     | Capsicum annuum           | Solanaceae  | Karis(A)    | Fruit | Chop the concoction, then eat. |
| 13     | Lycopersicon esculentum   | Solanaceae  | Timatim     | Leaf | Squeeze, then drink. |
| 14     | Drogoctia iners           | Urticaceae  | Yewoba medihanit (A) | Leaf | Chopped and mixed with Premna oligotricha and boiled together, one glassful drenched. |
| 15     | Lantana trifolia          | Verbenaceae | Yewoba medihanit | Root | Chopped and soaked with water and mixed with local alcoholic drink (Areke). |
| 16     | Premna oligotricha        | Lamiaceae   | Yewoba medihanit (A) | Leaf | Ground and mixed with water. |
| 17     | Zornia glochidiata        | Fabaceae    | medihanit (A) | Root and bark | Chopped and boiled/concoction with local drinks and boiled coffee leaf. |
| 18     | Euphorbia abyssinica      | Euphorbiaceae| Kulkual     | Root | Crush and drink with milk. |
| 19     | Skebergia capensis sparrn. | Meliaceae  | Lol(A)      | Bark | Infusion of fresh pulverized bark. |
| 20     | Urtica simensis           | Urticaceae  | Sama(A)     | Root | Crushed and dried, then mixed with fresh water, drink one glass of it and drink much amount of milk. |
| 21     | Acacia robusta            | Fabaceae    | Wangey(O)   | Root | Concoction. |
| 22     | Azadirachta indica        | Meliaceae   | Kinina(O) neem(A) | Leaf | Extract Leaf. |

Abera et al. (2019).

Table 2. Some common phytochemicals found in medicinal plants.

| No. | Class of phytochemical | Occurrence as natural product (%) | Role in health care |
|-----|------------------------|-----------------------------------|---------------------|
| 1   | Phenolics              | 45                                | Anti-oxidants, anti-cancerous, cytotoxcients, anti-microbials, and vasodilating. |
| 2   | Terpenoids and Steroids| 27                                | Anti-microbials, detoxifying agents, strengthners, anti-rheumatics, anti-malarial, and hepaticidial. |
| 3   | Alkaloids              | 18                                | Neuropharmaceuticals, anti-cancerous, sedatives, anti-microbials, and insecticidal. |
| 4   | Other chemicals        | 10                                | Anti-inflammatory and immunostimulating. |

Koche et al. (2016).

Ethiopian medicinal plants used to treat malaria

When we see the long history of Ethiopia, up to 80% of the people use traditional medicine, because of the cultural acceptability of healers and local traditional medicines, those medicines do have a relatively low cost and the people cannot easily access modern health facilities (Abera et al. 2019). Ethiopian traditional healers is not only concerned with curing of diseases but also with the protection and advertising of human physical, spiritual, social, mental, and material security.

Most of the communities of Ethiopia use many medicinal plants for the healing of malaria, mainly in rural communities of the country. According to Alebie et al. (2017), in collective, 82 researches screened a total 200 different plants used in traditional malaria treatments in Ethiopia. Table 1 indicates common medicinal plants applied to heal malaria. Allium sativum, Croton macrostachyus, and Carica papaya were the most repeatedly used plant species that are registered by ethnobotanical study in Ethiopia for malaria treatment (Abera et al. 2019).

The anti-malarial plant species identified in different regions of Ethiopia classified in to 71 different plant families including Fabaceae, Lamiaceae, Euphorbiaceae, Asteraceae, Cucurbitaceae, Solanaceae, Rubiaceae, Aloaceae, Acanthaceae, Moraceae, Bras-
Table 3. Phytochemical constituents of medicinal plants used to treat malaria in Ethiopia.

| Number | Plant scientific name | Plant vernacular name | Compound name |
|--------|------------------------|-----------------------|---------------|
| 1      | Carica papaya          | Paappaayya (Afan Oromo) | Alkaloid, flavonoid, tannin, saponin, and phenol |
| 2      | Vernonia amygdalina    | Ebicha (Afan Oromo)    | Alkaloid, flavonoid, tannin, saponin, and phenol |
| 3      | Allium sativum         | Nech shinkurt (Afan Oromo) | Alkaloid, flavonoid, tannin, saponin, and phenol |
| 4      | Justicia schimperianna | Sensel (Amharic)      | Terpenoid, anthraquinones, glycosides, and steroids |
| 5      | Croton macrostachyus   | Mekanisa (Afan Oromo) | Polyphenol, tannins, steroids, anthraquinones, phlobatanins, carotenoids, and xanthoproteins |
| 6      | Phytolacca dodecandra  | Mehlan (Amharic)       | Alkaloid, flavonoid, and phenol |
| 7      | Lepidium sativum       | Shinfaa (Afan Oromo) and fetoo (Amharic) | Terpenoid |
| 8      | Capsicum annuum        | Karia (Amharic)       | Phenol, flavonoid, and protoanthocyanidins |
| 9      | Aloe pulcherrima       | Hargisa (Amharic)    | Nataloid, 7-hydroxyaloin, three anthraquinones (chrysophanol, aloesaponarin I, and aloesaponarin II) Aloin |
| 10     | Aloe debrana Christian | Eret (Amharic)       | Microdorlin, aloin, and aloinoside |
| 11     | Aloe Sinana            | Seriti (Afan Oromo) and Kestencha (Amharic) | Polyphenols, saponins, phenolic glycosides, phytosterols, terpenes, and alkaloids |
| 12     | Asparagus africanus    | Endod (Amharic)       | Alkaloids and cardiac glycosides |
| 13     | Balanites rotundifolia | Azamir (Amharic)     | Tannins, flavonoids, phenolic glycosides, phytosterols, and saponins |
| 14     | Bersama abyssnica fresen | Chekata (Afan Oromo) and digita (Amharic) | Alkaloids, cardiac glycosides, flavonoids, phenols, phytosterols, saponins, terpenoids, and tannins. |
| 15     | Calpurnia aurea        | Bissana (Amharic) and bekennisa (Afan Oromo) | Alkaloids, saponins, phenolic compounds, cardiac glycosides, terpenoids, and flavonoids |
| 16     | Croton macrostachyus   | Keteri (Amharic) and dermer Erit (Amharic) |分配到菲托林酸，多羟基拆解酸，neolignans，phenolic compounds |
| 17     | Dodonaea angustifolia  | Ketketa (Amharic)     | Pinocembrin, the flavanol santin, and the clerodane diterpenes |
| 18     | Echinops kebericho     | Kebercho (Amharic)    | Sesquiterpenoids, monoterpenoids, α-Guaiene and β-santalene and monocyclic sesquiterpenoid hydrocarbon β-elemene |
| 19     | Gnidia Stenophylla Gilg | Kataricha (Afan Oromo) and demer Erit (Amharic) | Flavonoids, chromones, lignans, neolignans, and phenolic compounds |
| 20     | Jatropha curcas        | Ayderke (Amharic)     | Alkaloids, phenolic groups, flavonoids, saponins, steroids, tannins, cardiac glycosides, and terpenoids |
| 21     | Strychnos mitis       | Yedingamast (Afan Oromo) | Alkaloids, tannins saponins, flavonoids, terpenoids, steroid, phenols, and glycosides |
| 22     | Otostegia integrifolia | Tinjut (Amharic)      | Flavonoids, phenols, terpenoids, saponins, steroids, and glycosides |
| 23     | Withania somnifera     | hanzo (Afan Oromo) and gizawa (Amharic) | Tannins, alkaloids, polyphenols, flavonoids, phytosterols, phenolic glycosides, polyphenol, sphytosteroids, and saponins |

Abera et al. (2019); Muhammed and Idris (2019); Nduche et al. (2019); Irene et al. (2012); and Rizwan et al. (2015).
sicaceae, Capparidaceae, Asclepiadaceae, Anacardiaceae, Apocynaceae, Apiales, Malvaceae, Meliaceae, Rutaceae, Ranunculaceae, Rosaceae, Menispermaceae, and Verbaceae (Table 1).

As shown in Table 3, many remedies are prepared from the leaf and parts of the medicinal plants. The reason why many traditional practitioners use the leaf parts, compared to others for remedial preparation is due to their accessibility and to prevent them from extinction (Okello and Kang 2019). Because, collecting the root parts of those plants for preparation of traditional medicines has negative impacts on the future life of the plants.

According to Wadood et al. (2013), anti-malarial herbal medicines were mainly given through oral route (82.7%), while rarely given via nasal (5.5%), and whole body (2.8%). And also fresh solid remedies were also eaten and chewed directly upon collection. For the meantime, powdery materials were smoked and applied via nasal (Wadood et al. 2013).

Common phytochemicals found in traditional medicinal plants

Typically, the plant chemicals have been categorized as primary or secondary metabolites, based on their function to the plant. The primary metabolites include the common sugars, amino acids, proteins, purines and pyrimidines of nucleic acids, chlorophylls, and so on, whereas the secondary metabolites are the leftover plant chemicals including alkaloids, terpenes, flavonoids, lignans, plant steroids, curcumin, saponins, phenolics, and glucosides (Alebie et al. 2017).

Plant chemicals are chemical substances that are manufactured by plants, to help them resist pathogens and pests. When the plants are consumed without knowing of their cellular actions or mechanisms, plant chemicals can be poisoned the peoples (Ntie-Kang et al. 2014).

According to Wadood et al. (2013), the primary compounds include Chlorophyll, proteins, and common sugars and the secondary compounds include terpenoids, alkaloids, and phenolic compounds. The class of terpenoids are useful in attracting beneficial mites. Alkaloids are applied as anaesthetic agents. Alkaloids are applied as anaesthetic agents that are present in medicinal plants. Terpenoids are useful to prevent inflammation, cancer, malaria, over cholesterol synthesis, and virus and bacterial activities. Terpenoids are also crucial in attracting useful mites and consuming the herbivorous insects.

Phytochemical constituents of Ethiopian anti-malarial traditional medicinal plants

According to Abera et al. (2019), each plant may have different chemicals. Those different chemicals of medicinal plants used to treat malaria. The table finalizes most of the plant chemicals that are obtained from the Ethiopian anti-malarial medicinal plants.

The plants bioactive compounds, particularly the bitter principles (alkaloids and terpenoids), indicate their application in the making of traditional medicines against malaria, fever, and inflammation (Koche et al. 2016). Plants are known to be a rich reservoir of bioactive secondary metabolites, and are both obtained from plant origin (Muiva-Mutisya et al. 2014).

Activities of phytochemicals on some drug-resistant malaria

The occurrence of drug-resistant Plasmodium species has affected the health and economic status of the population. This has imitated the scientists to discover many anti-malarial remedies with significant structural varieties, including quinines, triterpenes, sesquiterpenoids, quassinoids, limonoids, alkaloids, lignans, and coumarins. Plants have been identified as a healthy source for drug discovery and interestingly, the secondary compounds that are obtained from plants and are still clinically used now a days in the treatment of severe malaria (Pinheiro et al. 2019).

Anti-malarial activities of the most common compounds on some drug-resistant parasites are briefly described below.

- **Alkaloids**: several are positive against CQ-sensitive and CQ-resistant strains of *P. falciparum* in vitro (Moges and Moges 2019). Alkaloids are involved in resistance reversal (Rasonazo et al. 2011).
- **Flavonoids**: are previously seen as a promising class of NPs exhibiting anti-malarial and anti-plasmodial activities (Moges and Moges 2019).
- **Phenolics**: found to be active against chloroquine-sensitive (D6) and chloroquine-resistant (W2) strains of *P. falciparum* (Ramanandraibe et al. 2008).
- **Terpenoids**: are inhibitor of the drug-resistant *P. falciparum* (Goulart et al. 2004).
- **Glycosides**: the glycosides only showed weak to moderate anti-plasmodial activities against the D6- and W2-resistant strains of *P. falciparum* (Moges and Moges 2019).

Conclusion

Around 80% the population of Ethiopia uses traditional medicines because the people accept traditional healers and local pharmacopoeias, the low cost of traditional medicine as we compared it the modern one, and also there is a limitation to get modern health services. Traditional healers in different parts of the country used many species of plants for the treatment of malaria. In this report, 24 anti-malarial medicinal plant species are listed. This report showed that, there is a potential for isolation of compounds effective against drug-resistant malaria from medicinal plant extracts. These plants consist of different types of phytochemicals that can be used to produce effective anti-malarial drugs. These chemicals naturally exist in the medicinal parts that have a defensive role against various diseases. A large number of compounds, which have anti-malarial property found in 15 plants are reported in this report. Alkaloids, flavonoids, phenolics, terpenoids, and glycosides have potential effect on some drug-resistant Plasmodium strains.

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Supplementary data

Supplementary data are available at FEMSMC online.

Conflict of interest. None declared.
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