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REVIEW: A Review on Herbal Treatments of Malaria

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ABSTRACT

Introduction: Malaria is one of the most common chief health problems all over the world and pharmacotherapy is the common treatment for this disease. Additionally, mankind is blessed with varied range of herbal plants for several ailments which are useful for malaria treatment. The purpose of this investigation is to review the existing studies on the effectiveness of herbal plants in treatment of malaria.

Material and Methods: In this study, related articles were reviewed based on keywords and phrases such as antimalarial drugs, herbal plants, treatment in PubMed, Google Scholar, IranDoc and SID (Scientific Information Database) databases from 2003 to 2022.

Results: The findings revealed that the main problem associated with medical treatment is emergence of drug resistance which leads to treatment failure in significant cases and results in the antimalarials' ineffective drugs. Therefore, the chief available alternative since ancient times is medicinal plants all over the world. The review revealed that more than 2000 medicinal plant species from different families were traditionally used in the treatment of malaria and most of them confirmed antimalarial activities.

Conclusion: It looks critical to take an effective action for developing a perfect malaria vaccine which would work properly by activating the immune system to destroy all the parasites. The current investigation is useful for researchers and pharmaco-therapists.

Introduction

As a parasitic disease, malaria disease is caused by four main species of Plasmodium including P. falciparum, P. malariae, P. ovale and P. vivax. Among these species, P. falciparum is the most harmful one (1). These parasites spread among people through the bites of infected *Anopheles* mosquitoes, called "malaria vectors (2). In the sub-Saharan Africa, Asia, and Latin America, malaria results in significant levels of mortality and morbidity (3). In this regard, the yearly reports estimated almost 3 billion persons, whereas around 1.2 billion people are at high risk of this parasitic infection (4). It is worth pointing that in 2010, malaria led to a significant death rate, chiefly among African children (2). According to WHO, in 2020 around 241 million cases of malaria were reported worldwide. Besides, the estimated number of malaria deaths stood at 627,000 in 2020 (5). Recent data showed that in tropical countries, malaria residues the most predominant infection, causing more than 219 million

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symptomatic cases and 435,000 reported deaths (4). Additionally, the African region had the highest cases as well as death rate, particularly with pregnant women and children younger than 5 were considered as the most susceptible groups (6). Concerning the clinical symptoms of malaria, febrile illness and fever associated with chills, headache, and vomiting to deadly difficulties like severe anemia, respiratory distress in relation to metabolic acidosis, or cerebral malaria are reported which can finally cause death (2).

Treatment Approaches

Treatment approaches of malaria aim to terminate the acute blood infection, to treat the clinical signs, to clear hypnozoites from the liver to avoid future failures and to prevent the spread of contagion (7). Fundamental treatment and healing treatment include chief aspects of treatment. Several pharmacological choices available for this objective such as *Artemisinin, Chloroquine, Mefloquine, Primaquine, Pyremethamine, and Quinine derivatives like arteether, artemether, artesunate,* and *amino alcohols like Halofantrine* and *Lumefantrine along with Doxycyclines, Sulfadoxime, tetracycline* and etc. (5). The challenging issue associated with this treatment is rise of drug resistance which results in treatment failure in significant cases (7).

Herbal Plants Usage in the Treatment of Malaria

Several choices are being used since ancient times for many health ailments, apart from the pharmacological treatment. Approximately 80% of the global population still depend upon the herbal drugs for their health care. Confidence on herbal plants is mainly due to their safety, efficiency, cultural preferences, and their accessibility all the time. The medicinal qualities of plants are recognized by intuition or by trial and errors. Universally, traditional therapists are using numerous medicinal plants for the malaria treatment; though, this practice is not entirely documented by modern medicine. Awareness about traditional medicinal practices and plants is presently communicated from generation to generation mainly by word of mouth. Large number of plant species has been recognized as antimalarial medicinal plants; thus, variety of plants have been identified through ethnobotanical and ethnopharmacological studies as anti-malarial medicinal plants (8).

As emphasized earlier, the medicinal plants have played significant roles in the treatment of malaria and have been suggested in curbing resistance postured by Plasmodium parasites to conventional antimalarial drugs (9, 10). Conventionally, herbal medicine remains the main support for the treatment of malaria for over thousands of years. The earlier antimalarial drug (quinine) was extracted from the bark of the Cinchona tree, in the family of *Rubiaceae* and in early 1632, a mixture of the Cinchona bark was used for the treatment of human malaria disease (1). The other millennial medicinal plant was *Artemisia annua* that was found in China from which artemisinin was isolated (1). Potentials of herbal medicine have stimulated methodical concerns in the examination of new antimalarial drugs from natural products, which residues an effective approach in malaria control (11). Due to their affordability, accessibility and acceptability, herbal remedy is gaining popularity in both developed and developing countries (9). In this regard, review of studies presented that about 2000 plant-extracted compounds have shown antimalarial effects against P. falciparum (12).

Plasmodium Falciparum's Life cycle

Plasmodium species, known for instigating malaria, belongs to a highly successful phylum called Apicomplexa. All the associates of this phylum are obligate intracellular protozoan parasites (13). Many people have been infected by plasmodia and there is an adjacent relationship of the malaria parasite of humans and the African apes (14). The malaria parasite has a multifaceted life cycle, wherein it requires a host and a vector, to successfully complete its life cycle (15).

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Malaria must enter host's Red Blood Cells to complete its life cycle (16). In this case, infection begins with the release of sporozoites by bite of an infected Anopheles mosquito in blood-meal. Then sporozoites migrate to the liver and invade the hepatocytes. Inside the hepatocytes, the sporozoites undergo schizogony to make schizonts. Finally, the hepatocytes rupture and the merozoites release into the bloodstream. Then, these merozoites invade the uninfected RBCs and undergo schizogonic separation, which can generate 8 to 32 new merozoites. When the infested RBC ruptures, the merozoites re-invade the uninfected RBCs (17). The point is that the clinical manifestations are observed during the blood stage of the contagion. In addition, if an individual get exposed to re-infection, adaptive immunity activates to eliminate the parasite (17).

The following proteins: HRP-1, HRP-2, EMP1 and EMP2 can be observed on the infected RBC surface (18). Four main events such as interaction of any part of the merozoite and the host cell surface, merozoite reorientation affect the entry of merozoite into the RBCs. Thus, its apical prominence makes contact with the host cell, connection becomes irreversible and electron-dense junction is formed between the apical prominence of merozoite and the host cell. Eventually, the parasite gets invaginated into the host cell and parasitophorous vacuole will be formed at this stage (19). This parasite's complex life cycle poses a huge obstacle in the development of a vaccine against it, subsequently at each stage it expresses a plethora of antigens. Accordingly, it is challenging to understand the dynamics of genetic variety before developing an effective vaccine (20).

Methods

In this study, related articles were reviewed based on keywords and phrases such as antimalarial drugs, herbal plants, treatment in PubMed, Google Scholar, IranDoc and SID (Scientific Information Database) databases from 2003 to 2022.

Results

Review of related studies revealed the deteriorating problem of drug resistance, leading to many of the antimalarials' unproductive drugs that enhanced the rate of morbidity and mortality (21). The anti-malarials that are presently in use to treat the patients, have lost their efficacy already. Consequently, it becomes logical to look for a new antimalarial with novel mechanism of action to challenge this life-taking disease (22). The important factor in gaining resistance to antimalarial drugs is "drug pressure" (23). As mentioned in related studies the malaria is getting too difficult to be controlled mostly due to the spread of drug resistance on a large scale (24). A perfect malaria vaccine would work by stimulating the immune system; however, this type of protection would be challenging to attain. Consequently, many of the vaccine inventers have concentrated on generating such a vaccine that would limit the parasite to contaminate other healthy RBCs. Therefore, it would prevent death due to malaria (25). Additionally, several studies have focused on herbal treatment of malaria (26-28).

In this regard, the World Health Organization (WHO) in 2018 highlighted that no substantial development was reported in reducing worldwide malaria (5). As referring to the earlier investigations, it highlights Charles Louis Alphonse Laveran, French army surgeon. The first one who noticed malaria parasites exist in an infected patient's blood on 6th of November in 1880s. He was awarded Nobel Prize in 1907 (29). Then, in 1947 it was revealed that around 75 million out of 330 million people were estimated to be infected from malaria, which led to mortality rate of 0.8 million per year (30). At that time, resistance to the mostly frequently used drug, artemisinin, the first-choice drug class as antimalarial to threat mankind was observed in the realm of remedies (31). Because of challenges of drug resistance towards Plasmodium species, it seems to be a

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crucial need for screening and developing new compound(s) to treat this disease (32). The noteworthy point is that ethno-pharmacology serves as one of the best sources to find a plant derivative which can be used as a pattern or a component of preparing antimalarial drugs. The following ***Tables*** summarize the main findings of related studies in this regard.

Table 1. Evolution of studies all over the world

Authors	Year	Main Findings
Bahekar & Kale (8)	2013	Pharmacotherapy is considered as the main treatment for Malaria. However, the main challenge is emergence of resistance for many of drugs. Therefore, to solve this problem, the main available alternative is medicinal plants.
Ishola et al. (33)	2014	The leaves, roots, stem barks or whole parts of 41 plants from 27 families including *Alstonia boonei*, *Azadirachta indica*, *Carica papaya*, *Cymbopogon citrates*, *Enantia chlorantha*, *Mangifera indica*, and *Morinda lucida* were recognized in antimalarial traditional recipes.
Ranasinghe et al. (34)	2015	Native medical awareness about herbal medicines and mixtures of local herbs were reported as an integral part of malaria case management in Sierra Leone.
Suleman et al. (26)	2017	Based on ethnomedicinal investigation, a total of 28 species of plants were used in the traditional treatment of malaria. In addition, the literature search revealed that 124 medicinal plant species were reported to be conventionally used for the treatment of malaria specially in Ethiopia.
Noronha et al. (28)	2019	Review of related studies revealed that no vaccine has yet been developed for malaria because the parasite changes the interaction of the metabolic pathways during its life cycle. However, nature still suggests a plethora of secondary metabolites which needs further investigation. Thus, plant-based medicines traditionally play dominant role in treatment of malaria.
Tetteh et al. (27)	2020	Clinical safety and effectiveness of a Ghanaian commercial product named "Time Herbal Mixture" (THM) was confirmed in this study. This product was extracted from the leaves of *Solanum torvum* and *Vernonia amygdalina* and the stem bark of *Spathodea campanulata* and *Bombax buonopozense*. The findings highlighted this product's effectiveness in treating malaria.
Erhirhie et al. (35)	2021	Findings highlighted that majority of herbal antimalarial drugs showed synergistic effects with CAMDs. In this case, *Vernonia amygdalina* was the most surveyed plant compared to others.
Appiah et al. (36)	2022	Some of commonly used therapeutic plants in malaria treatment are *Moringa oleifera*, *Sarcocophalus lalifolius, Poaceae, Sapindaceae*, *Arecaceae, Annonaceae, and Solanaceae*.
Ray et al. (37)	2022	In herbal medicine, *Callicarpa tomentosa* is used to treat fever, liver injury, skin infections, and mouth ulcers. Its juice in combination with salt is used as an anthelmintic recipe, while the seeds are used to treat swellings, malaria, hydrocele, and blood loss, and an aqueous leaf derivative is administered as an antiseptic to treat asthma, boils, cough, ulcers, and wounds.
Wen et al. (38)	2022	Phytochemical researches have recognized more than 252 compounds from *Agrimonia pilosa Ledeb*., including flavonoids, isocoumarins, lignans, m-benzotrienols, organic acids, pentacyclic triterpenoids, phenols, tannins, volatile oils, and other chemical compounds. The constituents and derivatives extracted from *Agrimonia pilosa Ledeb*. express numerous pharmacological effects, such as anticancer, anti-inflammatory, antioxidant, antitumor, analgesic activities, and etc.

Table 1. Evolution of studies in Iran

Authors	Year	Main Findings
Motevali Haghi et al (39)	2003	Findings showed that although the ethanolic extract of *peganum harmala* was not as effective as chloroquine in decreasing parasitemia; however, it significantly decreased the parasitic load when compared to control and placebo groups.
Karbalaee Pazki et al (40)	2014	This study highlighted the effect of the alcoholic extract of *Turkish herb* as an effective Malaria treatment.

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Saburi et al (41)	2016	Concerning malaria disease, except for proven cases of iron deficiency anemia and vascular adhesion caused by Sticky shaped cell (Knob), reducing the level of hemoglobin and hematocrit, today as part of pancytopenia and severe Thrombocytopenia, plasmodium infection is called irrefutable. All of this, along with the occurrence of inflammation caused by the secretion of inflammatory cytokines and complement activation can be too complex clinical picture of malaria in patients with hematologic if it appears.
Abedi Madiseh et al (42)	2016	The outcomes of the study indicated the potential effect of the alcoholic extract of *saffron* on P. berghei.
Elmi et al (43)	2019	Findings revealed that the treatment of P. berghei infected mice by *Ginger plant* was 62% effective. Further researches on the use of this plant in the treatment of malaria infection with increasing the therapeutic dosage of the drug or preparation of various chloroformic and water extracts of the plant was suggested by the researchers.
Najm et al (44)	2019	The findings highlighted that alcoholic extract of *Artemisia fragrance* in 75 mg/kg mice weight concentration had a significant effect on P. berghei parasite.

Conclusion

Malaria is one of the most common main health problems all over the world and prevalence of resistance by malaria parasites to conventional antimalarial drugs has revitalized the examination of herbal medicine as an alternative. Likewise, the increasing rate of herbal antimalarial remedies in mixture with conventional antimalarial drugs, both synthetic and semi-synthetic, has stimulated researchers to validate their herb-drug interaction effects (35). In this realm, decoction, concoction and eating/chewing were found to be the most regularly employed herbal remedy preparation methods. Particularly, anti-malarial herbal remedies were directed by oral route.

As highlighted earlier due to the increasing challenges of drug resistance, it is getting very difficult to treat patients suffering from this disease. Concerning this issue, no vaccine has been developed for malaria because the parasite keeps changing the interaction of the metabolic pathways during its life cycle. However, the nature still suggests a plethora of secondary metabolites which have yet to be discovered. Due to this issue, plant-based medicines have been used conventionally to treat malaria. Consequently, one can hope that plant derived drugs can demonstrate to be the source of novel lead compound to control malaria (28).

Accordingly, the improvement and development of new antimalarials from the highly active natural products, which have already been discovered, is vital to overcome the resistance of Plasmodium to available antimalarial drugs. Hence, there is a need to work on plants which have already been revealed to have antimalarial activity through further *in vitro* and *in vivo* testing in animal models of malaria followed by sub-acute and chronic toxicity tests. This is probable to show appropriate candidate molecules which may serve as leads and it can be optimized as a new antimalarial treatment path. This task requires enhancing capacity in the various facets of such an approach. Regrettably, this capacity is inadequate at the moment. However, this new perspective and this novel strategy if pursued from drug discovery research on to preclinical followed by clinical studies will surely yield the much desired highly efficacious and safe antimalarials drug. Though, further studies comprising controlled clinical trials are essential before specific traditional therapies can be suggested on a large scale.

Conflicts of interest

Authors declare no conflict of interests.

Authors' contributions

All authors have intellectually committed to the study design and process. The final manuscript was revised and accepted by all authors.

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