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Review

Botanical candidates from Saudi Arabian flora as potential therapeutics for *Plasmodium* infection

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ABSTRACT

Malaria is a lethal parasitic disease affecting over two hundred million people worldwide and kills almost half a million people per year. Until now, there is no curative treatment for this disease that has a substantial morbidity. The available chemotherapeutic agents are unable to completely control the infection with the continuous appearance of drug resistance. Consequently, the search for new therapeutic agents with high safety profiles and low side effects is of paramount importance. Several natural products have been investigated and proven to have antimalarial effects either *in vivo* or *in vitro*. A large number of plants have been studied globally for their antimalarial activities. However, studies that have been conducted in this field in Saudi Arabia are not enough. This article presents global and local research on the need for novel natural antimalarial agents with a particular emphasis on studies involving plants from Saudi Arabian flora.

Contents

1. Introduction

Malaria is an infectious disease caused by the bite of an infected female *Anopheles* mosquito bearing intraerythrocytic protozoa of the gene *Plasmodium* (Mehlhorn, 2014). Owing to the presence of antiparasitic drug resistance, experts are looking to find alternate sources of protection such as medicinal plants for malaria treatment.

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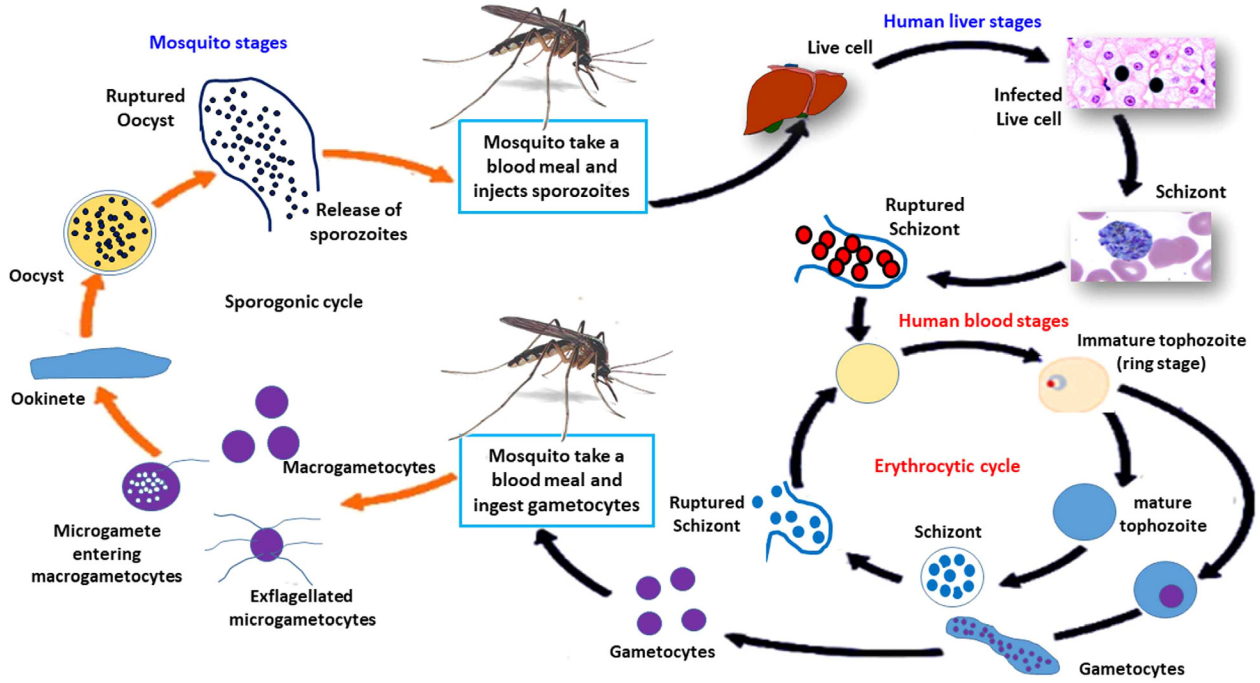

Fig. 1. Sexual and asexual life cycle of *Plasmodium* parasite.

Saudi habitat being comprised of a wide region of varied geographical ecosystems and climates. As a result, there is a considerable difference in plant distribution across the Country. Aati et al. (2019) identified 309 genera comprising 471 species of a total of 2253 recognized species belonging to 89 families. Ullah et al. (2020) recorded that 96 genes related to 47 families is being used in Saudi Pharmacopeia. With an average of 29, 7 and 5% respectively, the whole plant leaves, seeds and aerial parts were the most valuable plant parts for herbal preparation in traditional Saudi medicine (Ullah et al., 2020).

At the local level, few studies have investigated antimalarial candidates of natural origin, considering the diversity of flora in Saudi Arabia (Rahman et al., 2004) and the continuous traditional use of ethnomedicinal native plants (Mothana et al., 2014; Al-asmari et al., 2017; Aati et al., 2019).

An ethnopharmacological study of medicinal plants has been performed in the Albaha region of Saudi Arabia (Ali et al., 2017; Awadh et al., 2017; Samaha et al., 2017). Similar studies were conducted in Jazan region (El-Shabasy, 2016; Tounekti et al., 2019) but other regions that may be richer in their fauna were not included. Despite the richness of Saudi Arabian deserts in many plant species belonging to different families, studies on the therapeutic values of these plants are in adequate and require further analysis. This is the first review focusing on the medicinal plants against malaria in Saudi Arabia with basic information about the *Plasmodium* as a dangerous parasite affecting a variety of countries.

2. Malaria parasite life cycle

The life cycle of *Plasmodium* occurs within two hosts, the vector mosquitoes and the vertebrate hosts (Fig. 1). The parasite successfully invades multiple cell types avoiding the host-immune reactions with the aid of many specialized proteins (Florens et al., 2002). The life cycle begins when the female *Anopheles* takes a blood meal from *Plasmodium*-infected individuals. After that, gametocytes (male and female) meet in the mosquito gut to form the zygote. Subsequently, Zygotes grow into oocysts that enter the midgut mosquito wall to grow into oocysts. Development and division of each oocyte creates thousands of sporozoites (sporogony). The oocyst explodes and releases a large amount of sporozoites into the body cavity of the mosquito during the sporogony. Sporozoites begin to enter the salivary glands of mosquitoes. Another phase in the life cycle begins with this sporozoite-bearing mosquito, taking again blood meal from a non-infected person. At this stage, sporozoites are injected from their salivary glands into the human blood, causing the infection of the host. Inside the human host, schizogonic cycle starts. When the infected mosquito bites human, infective sporozoites starts to penetrate the host skin. Subsequently, some sporozoites that have penetrated lymphatic vessels successfully can enter the draining lymph node where they grow partially into exoerythrocytic stages (Vaughan et al., 2008) and may also mount a defensive immune response throughout the T cells (Good and Doolan, 2007). Sporozoites that find a blood vessel can also penetrate the liver in a few hours (Baum et al., 2006; Münter et al., 2009). The sporozoites migrate into liver cells, multiply and grow inside parasitophorous vacuoles. Each sporozoite can gives a huge number of merozoites (Kebaier et al., 2009). Unfortunately, the pre-erythrocytic phase could be described as "silent" phase, with some phatoginic effects but without symptoms and this makes early diagnosis difficult (Vaughan et al., 2008). The merozoites are then carried into the blood stream and begin the blood-stage of infection (Fig. 1). Repeated cycles of parasitic growth create hundreds of new daughter parasites within erythrocytes and invade more erythrocytes. The erythrocytic cycle occurs every 24 h with *P. knowlesi*, 48 h with *P. falciparum*, *P. vivax* and *P. ovale* and 72 h with P. malariae. The cycle ends with the destruction of infected cells and the release of new merozoites that invade more erythrocytes in turn. Consequently, the parasite increase in numbers reaching 10^{13} per host (Florens et al., 2002).

3. Malaria as an epidemic disease

Despite the progress in reducing malaria worldwide, the disease remains endemic in many regions, and the use of appropriate pre-

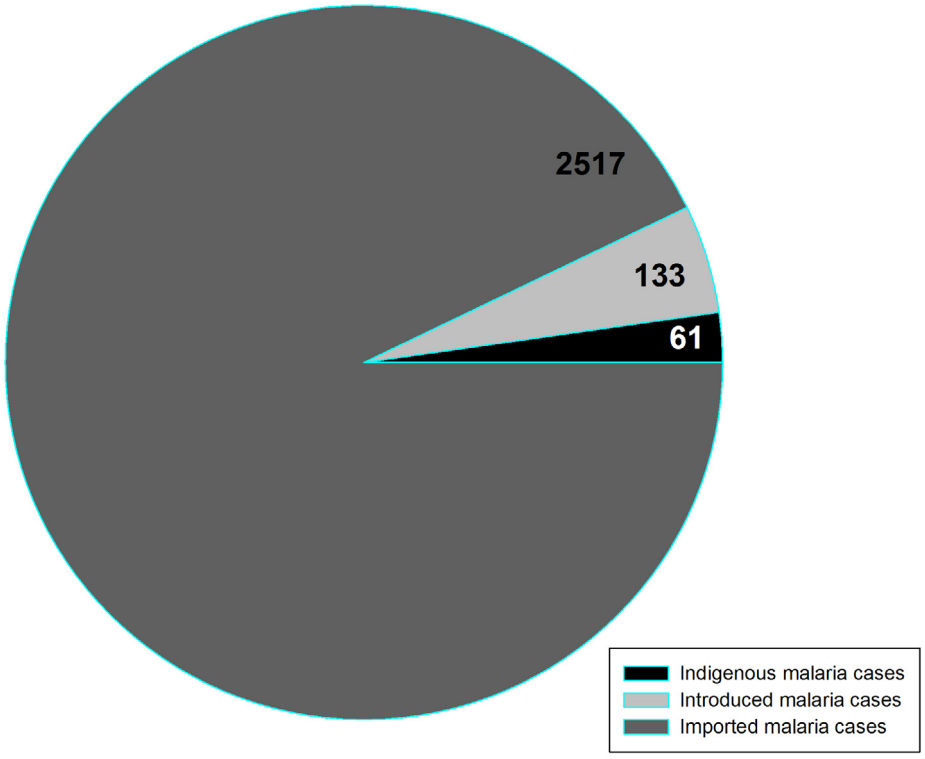

Fig. 2. Malaria cases in Saudi Arabia during 2018.

vention measures by travelers is still inadequate (Mace et al., 2018). The epidemiological profile of the disease is highly variable between age groups, regions and countries (Auburn and Barry, 2017). It is also recognized that malaria is one of the most devastating diseases in history and it affected large parts of India in 1908 and resulted in around one million deaths. In the Soviet Union, the 1922–1923 infection caused more than 10 million cases and at least 60,000 deaths. Similar epidemics have occurred in Sri Lanka (1934–1935), Egypt (1942), Ethiopia (1958), and southeastern Turkey (1977–1978). Malaria has been detected in many countries around the world and its epidemicity is still increasing in some areas (WHO, 2017). In the Arabian Peninsula, malaria is a parasite described by many travelers as a prevailing disease (Sebai, 1987). Baker and Strunk (1991) reported that countries surrounding the Persian Gulf are a good habitat for contagious diseases including malaria. Despite recent advances in research tools with the large number of imported and indigenous malaria cases (Fig. 2), few studies have evaluated malaria epidemiology in Saudi Arabia. The first studies in this area were carried out by the Arabian American Oil Company in 1941 (Sebai, 1987), which indicated that malaria was the most significant health hazard in two major areas of the Eastern province, Al-Hassa and Qatif. Daggy (1958) subsequently described, in detail, the "oases malaria" in this area. Magzoub (1980) conducted malaria surveys in different provinces of Saudi Arabia. Al-Seghayer (1983) and Sebai (1987) reviewed and discussed the malaria situation and its control in Saudi Arabia. Other reports have focused on evaluating of the Saudi Arabia's antimalarial program (Afridi, 1987; Mulla, 1989; Najera-Morrondo, 1996). According to (Al-Seghayer, 1983), the central part of Saudi Arabia (Najd) is free from malaria; the northern and eastern parts have no cases of transmission and the northwestern part has low endemicity. Of the four parasite species, three species of *Plasmodium* are common, *Plasmodium falciparum*, *Plasmodium vivax* and *Plasmodium malaria* with *P. falciparum* as the dominant species representing 87% cases of infection. Few sporadic cases of *Plasmodium ovale* also exist. Indeed, epidemiological studies of malaria in Saudi Arabia should be updated.

4. Chemotherapeutic agents to treat malaria

Chloroquine is the most commonly used antimalarial drug, but its effectiveness has been significantly restricted by the widespread spread of resistance (Dollery, 1999) where for *P. ovale*, *P. malariae*, and most cases of *P. vivax* infections worldwide, it remains effective. Also, several chloroquine-resistant strains of *P. falciparum* remain resistant to its derivatives limiting its utility (Olliaro and Mussano, 2003). In addition to chloroquine, sulfadoxine-pyrimethamine (SP), is another chemotherapeutic agent which has been used to treat uncomplicated *P. falciparum* malaria in many parts of Africa (Dollery, 1999). Quinine has a limited therapeutic spectrum and is less active than chloroquine. Quinine resistance, however, is rare and is still considered to be the first-choice treatment for severe malaria (Dollery, 1999). Artemisinin is also a effective antimalarial agent derived from plant material (Mehlhorn, 2014). The artemisinin group is used to limit elevated malaria and is normally given to treat uncomplicated *P. falciparum* malaria in conjunction with other drugs (White, 2004; Senior, 2005). Mefloquine, another chemotherapeutic agent, acts against the asexual stages of all species of the human malaria parasite, but resistant strains of *P. falciparum* are now prevalent in many parts of Asia. Mefloquine is used as a prophylactic and treatment for uncomplicated multi-resistant *P. falciparum* malaria. Its co-administration with artesunate showed a significant efficacy against uncomplicated *P. falciparum* malaria (Nosten et al., 2000). Atovaquone (hydroxy-1,4-naphthoquinone) is another antimalarial chemotherapeutic agent known globally under the brand name Mepron® Atovaquone is thought to inhibit mitochondrial respiration and induce DNA damage (Canfield et al., 1995; Gao et al., 2018). Halofantrine is a medication often used to treat uncompli-

cated and multi-resistant malaria with some adverse side effects (Nosten et al., 1993; Haeusler et al., 2018). When added to quinine, certain antibiotics, especially clindamycin and tetracycline, provide antimalarial activity (Borrmann et al., 2004). Chemotherapy for malaria must be considered based on the widespread presence of chloroquine- resistant *Plasmodium* species necessitating the use of a combination of antimalarials.

5. Natural products as alternatives to chemotherapeutic agents

Natural products have been historically utilized as therapeutics since ancient times before the discovery of chemotherapeutics. Natural products have been found and used for the treatment of different diseases from several sources, such as plants, animals, microbials, and marine sources. However, the percentage of secondary metabolites screened for bioactivity is poor because of the substantial biodiversity in natural sources (Mushtaq et al., 2018). Nature is a valuable reservoir of novel bioactive compounds. Recently, it was estimated that approximately 50% of medications validated from 1981 to 2010 were of natural origins. For example, in the field of cancer therapeutics, natural products have been discovered and confirmed to have significant anti-cancer activity (Herranz-López et al., 2018). From 1940 to 2010, 175 anti-cancer drugs have been developed. Of these, 48.6% drugs are of either natural origins or were derived from natural products (Gurnani et al., 2014). Many new drugs of natural origin are now being evaluated and applied in various phases of clinical trials. With the emergence of multidrug-resistant microbes, the search for new therapeutic lead compounds becomes necessary. Because of their high chemical diversity, natural compounds are still a source of many therapeutic agents in the fields of oncology, metabolic disorders, and immunosuppression (Butler, 2005; Monciardini et al., 2014). According to the World Health Organization (WHO), 80% of the world's population is dependent on the folk medicine obtained from plants for primary health care (Dias et al., 2012). Since ancient times, the use of medicinal plants to treat parasitic diseases has been well recognized and documented. e.g. by the use of *Cinchona succiruba* (Rubiaceae) as an antimalarial. Specific natural products (e.g. licochalcone A, benzyl- and naphthylisoquinoline alkaloids, and artemisinin) have showed antiprotozoal activity when tested experimentally (Kayser et al., 2001). Indeed, there is a very large number of therapeutics of natural origin have been applied to treat many disease conditions. However, still many natural compounds require further investigation to determine their therapeutic potentials.

6. Antimalarial activities of natural products

Unfortunately, *Plasmodium* strains have established resistance to all medication currently available. As a result, efficient and non-drug-resistant antimalarial drugs are urgently required. Since the discovery of the first antimalarial drug in the 1800s, natural products have been a valuable source for developing new antimalarial therapeutic agents (Newman and Cragg, 2016). Since that, various discovered antimalarial therapeutics were of natural origin. In 1820, Pelletier and Caventou introduced quinine as the first antimalarial drug to be isolated from Cinchona succirubra bark. After near 200 years, quinine was approved for administration by the Food and Drug Administration in 2004. In addition to malaria, Quinine can be used to treat numerous disease conditions like dyspepsia, fever, mouth and throat diseases, and cancer (Dias et al., 2012). Artemisinin, the current antimalarial drug of choice produced from the leaves of *Artemisia annua* is useful for treating multidrug-resistant malaria. Traditionally, artemisinin is used as an antiseptic, antidiabetic, antispasmodic, anti-helminthic, and depurative agent (Tariq et al., 2014; Ali et al., 2016, 2017). Artemisinin and its semi-synthetic forms have shown greater effectiveness than quinine in both children and adults **(**Zhang et al., 2012**).** In addition, the most effective treatment for malaria caused by *P. falciparum* infection is possibly the use of artemisininin in conjunction with other drugs known as artemisinin-based combination therapy (ACT) (WHO, 2017). Zhang et al. (2016) examined the effects of more than 2000 plant extracts on two different strains of *P. falciparum*. Most of these plants displayed significant antimalarial activity. When further investigated to recognize their antimalarial components, the phytochemical isolation of these plants followed by bioassays revealed ten new and thirteen existing active compounds (Libman et al., 2008; Ma et al., 2008). For instance, polysyphorin and rhaphidecurperoxin, extracted from *Rhaphidophora decursiva* (Araceae), showed antimalarial activity against *P. falciparum* W2 clones. (Zhang et al., 2001). It was reported that, two trichothecenes, the roridine E of R. Decursiva (Araceae) and verrucarin L acetate from *Ficus fistulosa* (Moraceae) have reported to inhibit parasite growth (Zhang et al., 2002; Pan et al., 2018). The anti-plasmodial effects of plant extracts from *Picrolemma huberi* and *Picramnia latifolia* have also been documented (Berthi et al., 2018). In another study, four natural compounds have exhibited potent anti-malarial effects (IC50 < 50 nM), and low cytotoxicity (cell viability > 90%) when tested against the *P. falciparum* 3D7 strain (Nonaka et al., 2018). The *in vitro* antioxidant and antimalarial activities of the leaves, pods and bark extracts of *Acacia nilotica* (L.) Del have been confirmed (Sadiq et al., 2017). The *in vivo* antimalarial activity of the leaves extracts of *Strychnos mitis* in *Plasmodium berghei*-infected mice was also previously demonstrated (Fentahun et al., 2017). When the antimalarial efficacy of the whole Cymbopogon citrate plant against both *P. chabaudi* AS and *P. berghei* ANKA was assessed, the whole *C. citrate* plant demonstrated higher antimalarial activity than herbal infusion or chloroquine when used as a prophylactic therapy (Chukwuocha et al., 2016). *In vitro* antiplasmodial action has been tested in ethnopharmacologically selected South African plant species and several plant species have been shown to possess antimalarial activity. *Tabernaemontana elegans, Vangueria infausta, Albizia versicolor, Capparis tomentosa, Dichrostachys cinerea, Rauvolfia caffra, Xylopia parviflora, Bridelia mollis, and Cussonia spicata* all showed varying levels of antimalarial activity (Bapela et al., 2019). A previous study by Abbas et al (2007) was conducted to examine the aerial part of *Commiphora opobalsamum L.* (Burseraceae) growing in Saudi Arabia. The ethyl acetate extract was moderately active against *Plasmodium falciparum;* this effect was attributed to syringic acid. The antiplasmodial activities of the methanol extracts of 42 plants collected from the western region of Saudi Arabia were subsequently evaluated. The anti-plasmodial activity was tested *in vitro* against a chloroquine-resistant strain (K1) and sensitive strain (FCR3). The methanolic extracts of 34 plants showed good activity, whereas the extracts of seven plants were inactive (Abdel-Sattar et al., 2009, 2010). Anti-plasmodial effect was investigated in four extracts of different genera which are *Chrozophora oblongifolia*, *Ficus ingens*, *Lavandula dentata* and *Plectranthus barbatus* (Al-Musayeib et al., 2012). Another collection of plants was screened *in vitro* against the erythrocytic schizonts of *P. falciparum*, whereas extracts of *Caralluma penicillata* and *Acalypha ciliata* showed acceptable activity against *P. falciparum* (Mothana et al., 2014). Another research reported that *Azadirachta indica* ethanol extract has beneficial role on neuronal networks in the inflamed central nervous system of *P. berghei* ANKA-infected mice (Bedri et al., 2013). The dichloromethane extract of *Garcinia mangostana* was found to be active against erythrocytic schizonts of *P. falciparum in vitro* (Al-Massarani et al., 2013; Chaijaroenkul et al., 2014). Our group has investigated more than one of the traditionally used

herbs in Saudi Arabia. *Indigofera oblongifolia* displayed important antimalarial and antioxidant effects and preserved the host spleen tissue from *P. chabaudi*-induced injuries (Dkhil et al., 2015a; Lubbad et al., 2015). *I oblongifolia* also modulated the hepatic gene expression profile changes induced by blood stage malaria (Al-Shaebi et al., 2018). Also, Berberine chloride has exhibited protective role for *Plasmodium chabaudi*-induced murine hepatic damage (Dkhil et al., 2015b) and it also exerted ameliorating effects in *Eimeria papillata* (Dkhil et al., 2015c) and *schistosoma mansoni* (Dkhil, 2014) infections. Furthermore, the beneficial impact of *Punica granatum* peel extract on murine spleen-induced malaria has been reported (Mubaraki et al., 2016) and liver (Hafiz et al., 2016) injuries. Moreover, we reported that *Ziziphus spina-christi* (L.) leaf extract alleviated myocardial and renal dysfunction and inhibited liver and spleen injury associated with sepsis in mice (Dkhil et al., 2018) A recent study confirmed that fern-synthesized silver nanoparticles (AgNP) have potential as new therapeutic agents against chloroquine-resistant *P. falciparum* (Panneerselvam et al., 2016).

7. Conclusion

Since malaria is considered a disease that affects most people worldwide and does not have an effective vaccine, researchers have used natural medicinal plants to combat malaria due to the absence or reduction of side effects. To produce novel anti-malarial agents, researchers have attempted to extract crude and bioactive compounds from these plants. Research should be conducted to further analysis and discover new compounds for treating malaria.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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