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Medicinal plants with anti-plasmodial activity: A comprehensive review

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Abstract

Malaria is one of the life-threatening protozoal diseases in malaria-endemic regions of the world. It caused about 627,000 deaths in 2020. Recently, drug-resistant Plasmodium species was increased against all the available antimalarial drugs. Increased incidence of Plasmodium resistance necessitated continuous introducing of new drugs. Many drugs from natural sources showed potent antimalerial effects. In this review, Web of Science, Reseachgate, PubMed, Academia.edu, Google Scholar and Science Direct were searched for medicinal plants with anti malerial activity to encourage identification of the active ingredients, determination of clinical efficacy, investigation of the mode of action and safety.

Keywords: Medicinal plants; Herbs; Anti-plasmodial; Antimalerial; Pharmacology

1. Introduction

Malaria is one of the lethal parasitic diseases in the world. According to the latest estimates (2022), in 84 malaria endemic countries,, about 247 million cases were registered, with the highest incidence (95%) was recorded in African [1]. It is caused by a *Plasmodium* and transmitted to humans by Anopheles mosquito females [2].

Four *Plasmodium* species transmitted are infected human and transmitted from man to man (*P. falciparum*, *P. vivax*, *P. ovale* and *P. malariae*), with the greatest public health challenge was caused by *P. falciparum* and *P. vivax* [3-5]. The control of malaria needed an integrated program including prevention and treatment with effective antimalarial drugs [3]. The control of malaria, represented a great economic aspect (2.7 billion US $ in 2018) [6]. The development of *Plasmodium* resistance to known antimalerial drug represent further problem and necessitated continuous introducing of new drugs [7-9]. In the current review, Web of Science, Reseachgate, PubMed, Academia.edu, Google Scholar and Science Direct, were searched for anti-malarial plants to encourage further investigation of plants or plant derivatives as potential natural source for novel antimalerial therapies.

2. Medicinal plants with antimalerial effects

2.1. *Ailanthus altissima*

Six alpha-tigloyloxychaparrinone and two quassinoids, ailanthone isolated from *Ailanthus altissima*, revealed antiplasmodial effect against chloroquine-sensitive and chloroquine-resistant strains of *P. falciparum in vitro* [10].

Ailanthus altissima extracts were investigated against *P. berghei* infections in mice and against *P. falciparum in vitro*. The chloroformic extract possessed antiplasmodial effect with (IC_{50} 5 µg/m) *in vitro*, and (ED_{50} 82.94 mg/kg/day) orally in

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mice. The activity was attributed to quassinoid ailanthone contents which showed *in vitro* (IC_{50} 0.015µg/ ml) and *in vivo* (ED_{50} 0.76 mg/kg/day) activities [11-12].

2.2. *Allium sativum*

An ip injection of 50 mg/kg of *Allium sativum* ajoene inhibited the development of malaria induced by *P. berghei* in mice. A single dose of a combination of 50 mg/kg of ajoene and 4.5 mg/kg of chloroquine, in the infection day, completely inhibited the development of infection in mice [13-14].

2.3. *Betula alba*

Betulinic acid isolated from *Betula alba* possessed antiplasmodial activity against chloroquine sensitive and chloroquine resistant *P. falciparum in vitro* with IC_{50} values of 25.9 and 19.6 µg/ml respectively [15-16]. Betulinic acid also inhibited the development of the disease induced by *P. berghei* at 250 mg/kg/day, in a murine malaria model [15-16].

2.4. *Bidens tripartita*

Ethanolic extract of *Bidens tripartite* whole plant at a concentration of 20 µg/ml showed potent anti- *P. falciparum* activity [17-18].

2.5. *Caccinia crassifolia*

The methanol extract of *Caccinia crassifolia* roots possessed significant *in vitro* activity effect against both chloroquine sensitive and chloroquine resistant strains *P. falciparum* [19].

2.6. *Caesalpinia crista*

The nor-caesalpinins and caesalpinins isolated from *Caesalpinia crista* were tested for antiplasmodial effect against *P. falciparum in vitro*. They showed dose dependent antiplasmodial activities. Norcaesalpinin F and caesalpinin K possessed the strongest activity (IC_{50} 120 and 140 nM, respectively) [20-22].

2.7. *Calotropis procera*

The *Calotropis procera* leaves ethanol extract was fractionated by different solvents. Four fractions showed potent *in vitro* antiplasmodial activity. [23-24].

2.8. *Carum carvi*

The anti-malerial effect of of the essential oils of Carum carvi possessed antiplasmodial activity against *P. falciparum in vitro*, with IC_{50} valu <1.0 microg/ml [25-26].

2.9. *Cassia occidentalis*

The antiplasmodial effect of *Cassia occidentalis* extracts was confirmed by several researches [27]. The aqueous and dichloromethane ethanol extracts of the root bark were evaluated *in vivo* against *P. berghei* infection induced in mice. The dichloromethane and ethanol extracts (200 mg/kg) showed marked (> 60%) suppressions of parasitaemia [27-28].

2.10. *Cichorium intybus*

lactucopicrin, lactucin, and guaianolide sesquiterpenes, isolated from Cichorium intybus root aqueous extract possessed anti-plasmodial activity. Lactucopicrin at a concentration of 50 µg/ml and lactucin at a concentration of 10 µg/ml completely inhibited *P. falciparum* [29-30].

2.11. *Cordia myxa*

Cordia myxa alkaloid extract possessed potent antiplasmodial activity as determined by *Plasmodium lactate dehydrogenase production* (IC_{50}= 6.2 µg/ml), moderate antimalerial effect was produced by dichloromethane extract (IC_{50}= 4.2 µg/ml), while the methanol and aqueous extracts showed the least entimalerial effect [31-32].

2.12. *Dodonaea viscose*

A methylene-bridged bisflavonoid, methylenebissantin was isolated from the aerial parts of *Dodonaea viscosa*. The isolated compound was evaluated for the inhibition of *P. falciparum* enoyl-ACP reductase (PfENR). It exhibited a moderate inhibition (IC_{50}: 91.13 µM) against PfENR [33-34].

2.13. *Euphorbia hirta*

The anti-plasmodial activity of *Euphorbia hirta* extract (200-800 mg/kg) was investigated in mice infected with *P. berghei*. The extract possessed significant suppression activity (51-59%) and prophylactic antiplasmodial effect of (25-50%) in comparison with chloroquine (95 %) suppression and prophylactic antiplasmodial effect (81%) [35].

The fractionation of *Euphorbia hirta* aerial parts methanol extract gave quercitrin, afzelin, and myricitrin. All the three compounds inhibited *P. falciparum* proliferation (IC_{50} values of 1.1, 5.4 and 4.1, µg/ml) respectively [36-37].

2.14. *Fumaria species*

Fumaria parviflora exerted caused 18.70% suppression of *P. falciparum* at concentration of 4.85 µg/ml [38-39].

2.15. *Gossypium species*

Gossypol, a disesquiterpene isolated from *Gossypium* species was effective in the immobilization of *P. falciparum* and inhibited potently the lactate dehydrogenase of *P. falciparum* [40-42].

2.16. *Helianthus annus*

Helianthus annus leaves ethanolic extract suppressed the infection by *P. berghei* in mice by 98.1% at a dose of 2 g/kg/day and 98.3% at a dose of 4 g/kg/day for 3 days [43]. The seeds extracts of *Helianthus annus* possessed moderate to good antiplasmodial activity (IC_{50} methanol extract = 0.1µg/ml and IC_{50} petroleum ether extract = 0.6 µg/ml) [44-45].

2.17. *Hibiscus asper*

The anti- *P. falciparum* effect of *Hibiscus asper* extract was tested in rats and *in vitro*. The aqueous leaves extract showed inhibitory effect against *P. falciparum* (IC_{50} values of 19.75 -21.97 µg/ml). The extract significantly inhibited the *P. falciparum* growth in infected rats with a percentage of 95.11% at a dose of 50 mg/kg, 97.68% at a dose of 100 mg/kg and 95.59% at a dose of 200 mg/kg [46-47].

2.18. *Iris pallida*

Iridal, a triterpenoidic compound was tested *in vitro* on *P. falciparum* chloroquine-resistant and -sensitive strains and *in vivo* on *P. vinckei*. The IC_{50} recorded *in vitro* against malaria strain of human was 1.8 to 26.0 microg/ml, while, the ED_{50} in rats by ip route was 85 mg/kg/day [48-49].

2.19. *Lawsonia inermis*

The petroleum ether extract of *Lawsonia inermis* leaves possessed anti-plasmodial effect at concentration of 27 mg/l and ethyl acetate extract at a concentration of 33 mg/l against *P. falciparum in vitro* [50-51].

The leaves ethyl acetate extract showed anti-plasmodial effect against chloroquine sensitive strain (IC_{50} 9.00 ± 0.68 µg/ml), while its main constituent, fraxetin possessed potent anti-plasmodial activity (IC_{50} 19.21 ± 1.04 µM). The leaves ethyl acetate extract and fraxetin showed potent activity in *P. berghei* infected mice (70.44- 78.77% reduction in parasitaemia). They also caused two-fold elevation in survival time mean, with significant reducing of lipid peroxidation and an significant incrase in antioxidant enzymes [52-53].

2.20. *Mangifera indica*

Mangifera indica stem bark extract was investigated against *P. yoelii nigeriensis.* The extract possessed schizontocidal activity in the early infection [54].

2.21. *Melia azedarach*

The antiplasmodial activities of the extracts of *Melia azedarach* were evaluated *in vitro* against laboratory adapted isolates of *P. falciparum.* The IC_{50} of the extract was 299.7±202.0 ug/ml [55].

2.22. *Musa paradisiaca*

The antimalarial activities of *Musa paradisiacal* leaf extract was tested in mice infected with *P. berghei*. Ethanolic extract of the leaves was a curative treatment at doses of 250, 500 and 1000 mg/kg. Furthermore, the extract effectively corrected the oxidative stress associated with the infextion [56-57].

2.23. *Myrtus communis*

Myrtus communis aerial parts methanol extract was tested for antimalerial effect, by determination of chloroquine sensitive and resistant *P. falciparum* lactate. Furthermore, the parasitemia suppressive effect was carried out to investigate the *in vitro* activity of the *Myrtus communis* extract on *P. berghei*. The extract at a dose of at 10 mg/kg/day, significantly suppressed the parasitaemia (84.8%) in mice after 4 days treatment [58-59].

2.24. *Narcissus tazetta*

Narcissus tazetta ssp. *tazetta* extract, and tazettine, galanthamine and lycorine isolated from the extract possessed antiplasmodial effect against a chloroquine resistant *P. falciparum* strains *in vitro*. The compound, galanthamine exerted the least effect [60-61].

Narcissus tazetta ssp. tazetta extracts and amaryllidaceae alkaloids (crinine-, lycorine-, galanthamine- and tazettine-types) were investigated for antimalerial effects in vitro against *P. falciparum.* Lycorine, haemanthamine and 6-hydroxyhaemanthamine, were the most potent alkaloids and tazettine was the least potent alkaloid against *P. falciparum* [62].

2.25. *Olea europaea*

The antiplasmodial activities of *Olea europaea* (extract and its fractions 200- 600 mg/kg) was studied in *P. berghei* infected mice. The crude extract markedly and dose-dependently decreased parasitemia and increased survival rate. Parasitemia was decreased by n-butanol followed by chloroform and aqueous fractions, the highest reduction was possessed by n-butanol fraction (51%) [63-64].

2.26. *Peganum harmala*

The antiplasmodial potential of *Peganum harmala* seeds extracts was investigated *in vitro*. Ethanolic extract showed the potent effects on *P. falciparum* strains resisted chloroquine (IC_{50}=23 mg/l) [65]. Harmine and harmaline showed a moderate *in vitro* antiplasmodial activity against *P. falciparum* [66].

2.27. *Quercus infectoria*

The *Quercus infectoria* galls acetone extract possessed antimalarial activity *in vitro* (IC_{50} = 5.85 ± 1.90 µg/ml) against the chloroquine-sensitive *P. falciparum* strain. The digestive vacuole PH of the parasites treated by acetone extract was significantly altered in comparison with the untreated parasites [67-68]

2.28. *Rosa damascena*

The *Rosa damascena* petals ethyl acetate extract (rich in phenols) showed *in vitro* antimalerial activity against *P. falciparum* and *in vivo* against *P. berghei*. The extract suppressed the parasitemia, increased survival time of infected mice and restored the haemoglobin level [69].

2.29. *Schinus molle*

The antiplasmodial activity of the extracts of *Schinus molle* was studied in *P. berghei* infected mice. The methanolic crude extract at a dose of 400 mg/kg/day exhibited the maximum antimalerial effect (66.91%), while the chloroform fraction possessed the highest (55.60%) chemosuppressive effect. The extract and fractions increased the survival rate of infected mice, prevent body weight loss and occurrence of anemia [70].

The antimalarial activity of hydro-alcoholic crude extract and solvent fractions of *Schinus molle* seeds was evaluated in *P. berghei* infected mice. The crude extract of the seeds and the aqueous fraction showed 69.86% and 73.82% curative rates, respectively. Both the crude extract of the seeds and the aqueous fraction increased survival mean in the infected mice. The aqueous fraction showed 72.39% efficacy in the prophylactic test [71].

2.30. *Tagetes erecta*

Tagetes erecta root methanol, ethyl acetate, chloroform and petroleum ether extracts and bithienyl compound isolated from *Tagetes erecta* root, possessed potent schizonticidal effect on the chloroquine resistant and sensitive *P. falciparum* strains [72].

2.31. *Trigonella foenum-graecum*

Trigonella foenum-graecum was extracted by different solvent systems to assess the anti-plasmodial potential. Ethanol extract (50%) possessed potent anti-plasmodial effects ($IC_{50=}$ 8.75 µg/ml, against chloroquine sensitive and 10.25 µg/ml against chloroquine resistant *P. falciparum*). From the tested fractions of the extracts, ethanol and butanol extracts possessed the highest anti-malerial effect (with IC_{50} <10 µg/ml). The ethyl acetate and chloroform extracts exerted moderate effect (IC_{50} 10 to 20 µg/ml), and water and hexane extracts showed no antimalerial effect (IC_{50} >85 µg/ml) [73].

2.32. *Withania somnifera*

The antiplasmodial activity of *Withania somnifera* was investigated *in vitro*. The root and root bark extracts at a dose of 600 mg/kg inhibited parasitemia by (50.43% and 29.13%) respectively [74]. Steroidal lactone (withanolide) isolated from *Withania somnifera* leaves methanolic extract has a great affinity to kelch 13 protein of *P. falciparum* compared to artesunate and artemether. It showed higher affinity for two distinct binding sites of the *P. falciparum* kelch 13 protein [75].

2.33. *Xanthium strumarium*

The antiplasmodial activity of *Xanthium strumarium* ethanol leaves extract was evaluated in the infection induced by *P. berghei* in mice. The ethanolic leaves extract of *X. strumarium* (150-500 mg/kg) possessed dose dependent suppression in the established and early infections with marked repository activities, with maximum suppression at the dose of 500 mg/kg/ day. 500 mg/kg/day orally, possessed a maximum suppression (88.6% more than chloroquine 88.3%) [76].

2.34. *Zea mays*

The antiplasmodial activities of the *Zea mays* husk ethanol extract and fractions was investigated against chloroquine resistant and chloroquine sensitive. The husk ethanolic extract (187-748 mg/kg, po) exerted significant activity against malaria induced by *P. berghei* when used as prophylactic and curative therapy. Furthermore the ethanol extract and its fractions possessed marked effects against both chloroquine resistant and chloroquine sensitive *P. falciparum* strains. The highest anti-malerial activity was produced by the ethyl acetate fraction, (IC_{50} = 3.69 ± 0.66 µg/ml, resistant strain, and IC_{50} = 9.31 ± 0.46 µg/ml, sensitive strain) [77].

2.35. *Zizyphus spina-christi*

The protective activity of *Zizyphus spina-christi* leaf extracts against hepatic injury induced by *P. chabaudi* was investigated in mice. A significant reducing of parasitemia level and remarkable improvement of anemic picture were recorded in the extract treated mice. The extract also ameliorated the liver enzymes, antioxidant enzymes and histological features of the liver [78].

The neuroprotective activity of *Zizyphus spina-christi* leaf extract against cerebral tissue injuries induced by *P. berghei* was studied in mice. *P. berghei* infections decreased weight, decreased antioxidant enzymes and induced histopathological changes, all these alterations were restored after extract treatment. The extract also reduced the mRNA expression of genes elevated in the brain of mice due to infection (Vdac3, Cacnb4, Glrb, Adam23, and Cabp1) [79].

3. Conclusion

This study reviewed the medicinal plants with antimalarial effects. According to the review, most of plants extracts and compounds aimed the erythrocytic stages of the parasite, which are responsible for the malaria symptoms. Natural therapies are good alternative for the synthetic drugs as a result of high incidence of resistance. However, the active extract still required studying of the effective compounds (few active principles were described), investigation of clinical efficacy, studying of pharmacodynamic and pharmacokinetic effects and determination of safety.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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