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INVESTIGATION OF MEDICINAL PLANTS FOR ANTIMALARIAL ACTIVITY- A REVIEW

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ABSTRACT

Malaria is caused by a group of single-celled organisms known as *Plasmodium*, affecting millions of people. Malaria is one of the major fatal diseases in the world. It is prevalent in over 100 countries and kills the majority under five. Malaria poses a severe threat to humanity as the parasite affects the RBC of the infected individual and houses the same for its replication. Owing to its deadly nature, the cure for the disease becomes indispensable. Several drugs and lead compounds, apart from the one used in allopathy, are being tested for their antimalarial use. The parts and metabolites of several plants are also gaining importance in this regard. The present database of antimalarial plants would help the researcher and phytochemist to formulate the most effective medicine. Malaria was considered one of those incurable diseases, and there were lots of deaths due to the disease. Researchers constantly worked on finding the appropriate treatment for curing the disease. As a result, different antimalarial drugs of synthetic importance to treat the disease came. Before the advent of allopathic medicines, the tribes of different regions used plants and their parts or extracts to cure malaria and its symptoms. Due to the severe side effects of allopathic medicine, interest is turning toward natural sources of antimalarial drugs with minimal

toxicity for human beings. This article briefs about some important antimalarial aspects of various medicinal plants that might serve as potent chemo suppressors for malarial infection.

Keywords: Malaria, *Plasmodium falciparum*, Medicinal plants, Phytoconstituents

INTRODUCTION

The field of pharmacognosy, the study of natural plants and the products obtained from them and investigating their therapeutic value, is gaining more importance in recent years as the adverse effects caused by allopathy in the treatment of various diseases are getting fairly mitigated by treating the same disease with medicinal plants and their therapeutically active metabolites. Using various plants for therapeutic activity is not a recent trend but a traditional practice used by ancient people in different regions of the world. Several plants possess different ranges of pharmacological activity against various pathological conditions. In a screening experiment by Iqbal Ahmed *et al*. **[1]**, the alcoholic extracts of *Emblica Officinalis, Holarrhena antyidysenterica*, *Plumbago zeylancia Terminalia chebula,* and *Terminalia belerica* were found to have a good range of antibacterial activity against the test bacteria. The metabolites of some plants also turned out to be potential compounds of interest for cancer treatment which was discussed by Greenwell M and Rahman PKSM **[2]**.

In this review, the antimalarial effect of various plants has been discussed. Malaria is humans' most pernicious parasitic disease caused by single-cell protozoan parasites called *Plasmodium*. The female *Anopheles* mosquitoes are responsible for the transmission of malaria to humans. Around 300–500 million new malaria cases are reported worldwide annually, according to the World Health Organization (WHO), with children under 5 having a higher mortality rate **[3]**. It is the most common parasitic infection in tropical and subtropical regions **[4]**. Four different types of malarial parasites infect humans. The four types are *Plasmodium falciparum, P. vivax, P. ovale, and P. malariae*. The deadliest is *P. falciparum* **[5]**. Liver damage, clinical jaundice, and liver dysfunction caused by malaria parasites in endemic countries are about 2.5-5.3% **[6]**. Malaria is mainly associated with shaking chills, cold, rigor, fever, and profuse sweating as symptoms **[7]**. The treatment of malaria is becoming a field of interest for researchers as the current drugs of choice are impotent against the *Plasmodium* species as the causative parasites have begun to develop resistance against the drugs used in the treatment of the malarial disease. This review article focuses on several plants and their extracts and metabolites as potent lead compounds for

the creation of alternative antimalarial drug development.

PLANTS USED IN THE TREATMENT OF MALARIA

Nowadays, many plant drugs are used to treat malaria. Raw drugs or isolated secondary metabolites are the major precursors of various conventional medicines. Here, we discuss some traditional medicinal plants assessed scientifically against malaria.

Adansonia digitata

Adansonia digitata is a plant species traditionally used in the healthcare systems of the Msambweni people of Kenya. The plant's stem bark extract in aqueous form exhibited the best chemo-suppression against the *Plasmodium berghei* species. The test was carried *in-vivo* in an infected murine model. The phytochemical screening of the plant found alkaloids and flavonoids in the crude extract and sesquiterpene lactone and saponins in the organic extract **[8]**.

Andrographis paniculata

Andrographis paniculata, native to Asian regions, showed increased antimalarial activity *in vivo* against the ANKA strain of *Plasmodium berghei*. The chloroform extract of the plant showed complete parasitic growth inhibition at 0.5mg/ml within 24 hours of incubation time, *in vitro*, against the FCR-3 strain of *P. falciparum* **[9]**.

Argemone Mexicana

Argemone mexicana belongs to the family Papaveraceae and is used in the Indian healing systems. The antiparasitic activity of the crude alkaloidal extract and the berberine fraction of the plant was assessed by *in vitro* and *in vivo* methods. The extracts were tested against the *Plasmodium falciparum (*3D7 strain*) in vitro* and showed varying results for each extract. The berberine fraction of *Argemone mexicana* showed high antimalarial activity by recording a low IC_{50} value (34.18 µg /ml) compared with the crude alkaloidal extract (73.84 µg /ml). The *fractions' invivo* activity was assessed using a *Plasmodium berghei*-infected murine model. The crude alkaloidal extract showed more anti-plasmodial activity than the berberine fraction. On co-administering both fractions, the antimalarial efficiency increased many folds *in vivo*. The toxicity of the extracts was almost nil which became evident by using the brine shrimp toxicity bioassay **[10]**.

Artemisia indica

A member of the Compositae family, *Artemisia indica* Willd, was subjected to an activity-guided investigation by Thebtaranonth Y *et al*. **[11]**. It led to the isolation and purification of the crude methanolic extract of the stem of *Artemisia indica*, which yielded exiguaflavanone A, exiguaflavanone B,

maackiain, and 2-(2,4-dihydroxy phenyl)-5,6-methylenedioxy-benzofuran. The antimalarial activity of the compounds was evaluated *in vitro* against the K1 strain of *Plasmodium falciparum*. The EC_{50} value of exiguaflavanone A and exiguaflavanone B was recorded as 4.6 x 10^{-6}g/ml and 7.05 x 10^{-6}g/ml, thus proposing a more substantial antimalarial effect than the latter two compounds.

Azadirachta indica

Azadirachta indica, commonly known as Neem, used in local medicinal systems of the sub-continent as a treatment for different physical setbacks. The leaves of the plant were subjected to phytochemical analysis by Deshpande PK *et al*. **[12]** and were found to have steroids, flavonoids, tannins, phenolic compounds, reducing sugars, triterpenoids, and alkaloids. The extract of the leaves was subjected to antimalarial activity by *in vitro* model against the *P.falciparum* species and by *in vivo* model against *P.vivax*. The positive results were supported by the phytochemical screening of the leaf extract and thus concluding that the pharmacologically active constituents present in the leaf of *Azadirachta indica* bestow the plant with varied healing properties against different pathological conditions, including malaria.

Calotropis gigantea

Sathish PVV *et al*. **[13]** subjected the crude extract of *Calotropis gigantea* to phytochemical screening, which showed the presence of carbohydrates, alkaloids, triterpenes, tannins, flavonoids, phenols, coumarins, saponins, phlobatannins, and steroids. When the methanolic leaf extract of the plant was subjected to antimalarial evaluation opposite the 3D7 strain of *Plasmodium falciparum in vitro*, it showed promising antimalarial potency with an IC_{50} value of 12.17µg /ml. The *in vivo* antimalarial activity against the *Plasmodium berghei* species was also palpable, thus making the methanolic leaf extract of *Calotropis gigantea* a potential candidate for consideration in developing medications against drug-resistant malaria.

Combretum zenkeri

Combretum zenkeri was investigated for antimalarial activity by Oluyemi W *et al*. The plant's chloroform extract showed antimalarial effectiveness against *P. falciparum* (D10 and W2 strains), which are chloroquine-sensitive and resistant species. The IC_{50} value thus reported for the chloroform fraction was less than that of the n-butanol fraction of the same plant against the same strains of *Plasmodium falciparum*. Phytochemical investigation of the plant identified that the antimalarial activity of *Combretum zenkeri* was due to the presence of two homologous

triterpenes, ursolic acid and oleanolic acid **[14]**.

***Cyperus rotundus* Linn**

Weenen H *et al*. **[15]** tested 49 Tanzanian plants for their antimalarial activity, of which the dichloromethane extract of tubers of *Cyperus rotundus* showed the highest antimalarial activity against the multidrug-resistant strain of *Plasmodium falciparum* (K1 strain). The test was carried out *in vitro*, and the IC_{50} value reported was between 5-10µg/ml for *Cyperus rotundus*.

***Dichroa febrifuga* Lour**

Dichroa febrifuga is a Chinese plant used in their healing systems. The Chinese name of the plant is Chang Shan. The alkaloids febrifugine and iso-febrifugine obtained from the roots of the plants showed antimalarial activity and were used against malarial fevers. While examining the structure of febrifugine, the derivatives of febrifugine were found, named Df-1 and Df-2. The hydrochloric acid salts of the febrifugine derivatives were also investigated for their antimalarial activity. The derivatives showed potent antimalarial activity against the chloroquine-sensitive and chloroquine-resistant strains of *Plasmodium falciparum in vitro*. The *in vivo* activity of the Df-1 derivative was greater than that of Df-2 and was comparable to that of chloroquine **[16]**.

Dodonaea angustifolia

Amelo W *et al*. **[17]** investigated the chloroform, aqueous and n-butanol fractions of the root extracts of *D.angustifolia* for antimalarial potency against the *Plasmodium berghei* species *in vivo*. An infected mouse was subjected to Peter's suppressive test for 4-days to determine the efficiency of the fractions of the root extracts against the *Plasmodium berghei* species. All three fractions showed significant antiplasmodial activity in a dose-dependent manner. The n-butanol extract showed higher chemosuppression against the *Plasmodium* species than the chloroform and aqueous fractions.

Enantia chlorantha

Enantia chlorantha belongs to the Annonaceae family. This plant has been used as an alternative to chloroquine by Nigerians as an antimalarial drug since chloroquine causes itching and other hypersensitivity reactions in the locals. Agbaje EO *et al*. **[18]** experimented by screening the antimalarial activity of the extracts of *Enantia chlorantha*. The aqueous extract administered as a drinking fluid to mice infected by a malarial parasite was found to confer appreciable chemosuppression. The ethanolic extract also rendered a potential antimalarial effect when administered subcutaneously.

Erythrina senegalensis

The methanol and ethyl acetate fraction of the leaves of *Erythrina*

senegalensis showed the highest chemosuppression, at a lower dose (625 µg /ml), against the K1 strain of *P. falciparum* species with the elimination of 71% of the total parasites. The ethanol fraction showed 77-83% of elimination of the parasites at 5000µg /ml. This research supports the traditional use of *Erythrina senegalensis* as an antimalarial agent by the locals of the northern part of Nigeria **[19]**.

***Flueggea virosa* Voigt**

Flueggea virosa is a member of the Euphorbiaceae family in the Comoros region. Ali Mohammed *et al*. **[20]** investigated the antimalarial property of the plants found in East Africa. The hydroethanolic extract of the leaves of the *Flueggea virosa* exhibited potent antimalarial activity against the W2 strain of *Plasmodium falciparum*, which is resistant to chloroquine, pyrimethamine, and proguanil, *in vitro*. The IC_{50} value against the parasite was recorded as 2µg/ml. The study recorded low cytotoxicity on THP1 cells.

Garcinia mangostana

Garcinia mangostana L is a medicinal plant species belonging to the Clusiaceae family. The extracts of the rind of *G. mangostana* exhibit appreciable activity against the 3d7 *Plasmodium falciparum* strain. The antimalarial activity was increased when used along with artemisinin **[21]**.

Khaya grandifoliola

Khaya grandifoliola belongs to the Meliaceae family. This plant has been in use in the region of West Africa for treating fevers. The antimalarial property of the plant's stem bark was assessed by extracting the powdered stem bark using different solvents. *In vivo* parasitic inhibition was tested using the *P. berghei* infected mice. The *in vitro* antimalarial property was recorded against the multi-drug resistant clone and Nigerian *Plasmodium falciparum* isolates. It was found that the n-hexane extract and purified fractions of the stem bark of *Khaya grandifoliola* responded with a high antimalarial activity both *in vivo* and *in vitro*. The results were comparable to the antimalarial activity of Chloroquine diphosphate, which has been kept as the standard **[22]**.

***Lantana cujabensis* Schauer**

Lantana cujabensis is a shrub of the Verbenaceae family found widespread in the Andean forests and Amazonian of South America. The antimalarial activity of the leaves of the plant extract was exhibited by Ingrid R Marith *et al*. **[23]** in a move to investigate the antimalarial activity of various plants present in the American continent. The ethanolic extract of the dried leaves of *L.cujabensis* was tested for antiplasmodial activity against various plasmodium species. It showed good

antimalarial activity by *in vitro* method against *P. falciparum* species.

***Lippia multiflora* Mold**

Lippia multiflora is used as an ancient medicine in West Africa. The infusion and decoction extracts of the leaves of the plant were evaluated for their antimalarial activity *in vitro* against FcB1-Colombia chloroquine-resistant and F32-Tanzania chloroquine-sensitive strains of *P. falciparum*. The IC_{50} values reported against the two strains were lower than the IC_{50} values of *Azadirachta indica*, which was kept as a standard **[24]**.

Maytenus senegalensis

The ethyl acetate (EtoAc) fraction of the plant's stem bark was tested for antimalarial activity, which showed potent inhibition against the *Plasmodium falciparum* species. The plant traces its use right to the traditional medicinal systems of Tanzania. The EtoAc fraction obtained from the *M. senegalensis* stem bark obtained from the Morogoro region was twenty times more effective than that obtained from the Kagera region **[25]**.

***Momordica balsamina* Linn**

Ramalhete C *et al*. **[26]** investigated certain traditional plants of the Mozambique region for antimalarial activity. For this assessment, various parts, including roots, seeds, barks, and seeds of 15 different plant species belonging to several families found widespread in the Mozambique region, were extracted using different solvents. The 58 extracts thus obtained were tested for antimalarial activity against the 3D7 Chloroquine-sensitive *Plasmodium falciparum* strain. The IC_{50} values were recorded, and the low value was recorded for the ethyl acetate extract of *Momordica balsamina* Linn (Cucurbitaceae). *Momordica balsamina* was concluded with the highest antimalarial activity.

***Myristica fragrans* Houtt**

The extracts of the plant species *Myristica fragrans* were tested for antimalarial activity. It exhibited potent antimalarial activity despite K1 & 3D7 strains of *P. falciparum in vitro* **[27]**.

Myrtus communis

The oil obtained from the leaves and twigs of the plant by hydrodistillation was tested for antimalarial activity. The results were promising and showed potent antimalarial inhibition *in vitro* against the FcB1- Columbia strain and Nigerian strain of *Plasmodium falciparum* **[28]**.

***Nauclea latifolia* Smith**

Nauclea latifolia belongs to the Rubiaceae family, used in treating periodic fevers in the traditional medicinal practices of the Mali region. The aqueous, hydroethanolic, and chloroform extracts of barks and leaves of the plant were evaluated for the antimalarial activity *in vitro* against W2 (Chloroquine-resistant)

strains and 3D7 (Chloroquine - sensitive) of *P.falciparum* which showed appreciable antimalarial activity **[29]**.

Phyllanthus amarus

The antiplasmodial activity of *Phyllanthus amarus*, when tested against a mouse infected with *Plasmodium berghei* species by Blessing AU *et al*. **[30]**, was significant in a dose-dependent manner. The plant extract showed increased inhibition of the parasite growth, whereas the aqueous extract showed increased mouse survival time post-infection. Thus, the extracts and fractions of *Phyllanthus amarus* might be a source for obtaining an alternate antimalarial agent.

Piper retrofractum

A dimer of carbamide isolated from *Piper retrofractum* stems demonstrated vigorous antimalarial activity with an IC50 value of 2.7g/ml. Against the 3rd and 4th instar larvae of *Culex quinquefasciatus* and *Aedes aegypti*, the plant's ripe and unripe fruit extracts demonstrated substantial larvicidal activity *in vivo* **[31]**.

***Plumbago indica* Linn**

The active constituent, plumbagin, present in the roots of *Plumbago indica* Linn exhibited *in vitro* antimalarial activity against the 3D7 and K1 strains of *Plasmodium falciparum*. The *in vivo* efficiency of the constituents was assessed in *Plasmodium berghei* infected mice by a 4-day suppressive test, which showed satisfying results **[32]**.

Rauwolfia serpentina

Antimalarial activity of the dried powdered leaf of *Rauwolfia serpentina* was assessed by a 5-days curative test. The dried leaf's hot water and ethanolic extract were subjected to prophylactic and curative antimalarial tests using *P. berghei* NK65 infected mice. The experiment report elucidated the plant's antimalarial nature and supported the use of the plant as an antimalarial agent by the Mandi ethnic community of Bangladesh **[33]**.

Rhaphidophora decursiva

Rhaphidophora decursiva belongs to the Araceae family and yields a secondary metabolite trichothecene roridin E which was screened for antispasmodic nature. The study was an initiative by Wen-Hui Pan *et al* **[34]** to determine the antiplasmodial activity of the metabolites of the members of different families. The trichothecene roridin E was screened for the antimalarial nature *in vitro* against the *P. falciparum* 3D7 strain. It exhibited a promising antimalarial nature by reporting very low IC_{50} values against the 3D7 strain of *Plasmodium falciparum*.

Tamarindus indica

Tamarindus indica is an essential leguminous plant of the Fabaceae family. The fruit pulp of the plant was assessed for antimalarial activity. Several extracts of the

fruit pulp treated with 96% ethanol were screened for antiplasmodial activity against the *P.falciparum* species using the Jar method of Trager and Jensen. The hexane, methanol, chloroform successive, and water extract of the fruit pulp were assessed. The successive chloroform extract exhibited moderate anti-plasmodial activity against the parasite with an IC_{50} value of 34.8µg /ml, the highest among the other solvent extracts of fruit pulp **[35]**.

Vernonia amygdalina

In vivo antimalarial activity of extracts of different parts of *Vernonia amygdalina* was assessed by Anthonia OA and Benjamin HR **[36]** against the drug-sensitive *Plasmodium berghei* species infected in mice. Leaf extract of the plant showed 67% inhibition of *Plasmodium berghei*. The root-bark extract of *Vernonia amygdalina* showed 53.5% chemo suppression against the same species of *Plasmodium berghei*.

Vernonia colorata

Vernonia colorata was assessed for antimalarial potency. The aerial portion of the plant was subjected to antiparasitic activity against the chloroquine-sensitive strain PoW and chloroquine-resistant clone Dd2 of *Plasmodium falciparum*. The lipophilic extracts of the aerial portion exhibit promising antimalarial activity against the test plasmodium species. Phytochemical screening of the lipophilic extracts yielded four sesquiterpenes 11β, 13-dihydrovernodalin, vernodalol, 11 β, 13 - dihydrovernolide, and 11 β, 13, 17, 18-tetrahydro vernolide. The former two compounds exhibited the strongest antimalarial activity with an IC_{50} value of 1.1 µg /ml and 4.8 µg /ml **[37]**.

CONCLUSION

The research towards developing an alternate drug for treating malaria is gaining more importance as malaria-causing *Plasmodium* species are developing resistance against the current drugs of choice. The plant sources might serve as a potential and cheap source of antimalarial drugs if adequately exploited and formulated. Side effects due to allopathic drugs can also be reduced by the use of drugs obtained from natural sources. Plants susceptible for antimalarial activity should be properly utilized. Evaluating and screening different plants and their extracts justify using them in traditional healing systems for treating malarial infection. The results of investigating the antiplasmodial nature of different plants could serve as a base for developing the phytoconstituents and lead compounds of interest into antimalarial formulation by researchers.

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