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Antimalarial Activity of Mangrove Plants and Possible Mechanisms of Action: A Scoping Review

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ABSTRACT. Malaria is one of life threatening-infectious diseases with high mortality rate in African regions. Malaria is also one of public health problem in most of Southeast Asia (SEA) regions. This disease is caused by a Apicomplexan parasite; *Plasmodium* sp., which can be transmitted from humans to humans via *Anopheles* sp. To date, the need of a new antimalarial drug is still high, due to the rapid increase of drug resistance. Natural-derived drug candidates are still being used by researchers to develop new antimalarials. One of the natural resources which could potentially be a source of antimalarial agents are mangrove plants. Traditionally, mangrove plants have been employed as antibacterial, antioxidant, anticancer, and antidiabetic. Therefore, we conducted a scoping review to identify, evaluate and summarize findings of newly found antimalarial drug activity from mangrove plants and elaborate the possible mechanism of actions in killing the parasites. From several databases, we found six mangrove species which have been suggested as potential antimalarial sources. Various phytochemical compounds in extracts made from those plants were revealed to exert antimalarial activity. These include alkaloids, flavonoids, tannins, phenols, terpenoids, saponins, coumarins, triterpenes, glycosides, and anthraquinones which were indicated to have antimalarial activity against *Plasmodium*. From eight studies investigating mangrove plant extracts, no toxic effects were shown. Therefore, considering the available evidences, we suggested that mangrove plants can be used as a source for the discovery of antimalarial compounds with promising activities against *Plasmodium* sp. However, deeper understanding on the exact mechanisms of their actions still requires further elucidation.

Keywords: Antimalaria, Anthraquinone, Mangrove, *Plasmodium sp.,* Protozoa

INTRODUCTION

Malaria is a life threatening-infectious disease causing mortality in many part of the world including Africa and the Southeast Asia (SEA) regions, which rank first and second with the highest cases globally (World Health Organization, 2021a; World Health Organization, 2021b). Countries in the Southeast Asia region are geographically tropical in climate. Malaria is caused by *Plasmodium*, the protozoan responsible for malaria's severe form (Milner, 2018). There are 5 species of *Plasmodium* causing malaria: *Plasmodium falciparum*, *P. vivax*, *P. malariae*, *P. ovale*, and *P. knowlesi* (Kifle and Atnafie, 2020). The *Plasmodium* parasite can efficiently be transmitted between humans through its vector, *Anopheles* sp. mosquito which survives in the climate with high temperatures and humidity, such as tropical areas (Autino et al., 2012).

The burden of malaria on the world health needs to be given serious attention and requires prevention and control efforts to overcome. The emergence of antimalarial-resistant parasites has caused serious challenges in malaria control and elimination (Siregar et al., 2015). It was suggested that inadequate subtherapeutic doses or incomplete therapeutic doses in malaria treatment may cause emergence of drug resistant parasites and therefore failure of malaria treatment (Nuralitha et al., 2017). Various mutations in the *Plasmodium* genome have been associated with resistance to antimalarial drugs (Siregar et al., 2015). One of the antimalarial drug resistance is atovaquone resistance in *P. falciparum* and *P. berghei* due to mutations found in cytochrome *b* gene at quinone binding site 1 (Qo_1: M133I, L144S) and 2 (Qo_2: Y268C, Y268N, Y268S, L271V, and K272R) (Siregar, 2008; Fisher, 2012). This is a challenge to control and

prevent malaria disease. Therefore, new antimalarial drugs need to be discovered and developed.

Plants have been an important source of human medicine due to their multiplicity of bioactive compounds. Several kinds of plant including mangrove plants have an important role as source of human medicine through decades. Plants synthesize a large number of different compounds critical for defense mechanisms against predators and microbial infections (Newbold et al., 1997). Several kinds of traditional plants have been shown to have antiparasitic activity, specifically against malaria parasites (Inbaneson et al., 2012). Various methods have been developed and evaluated for extraction of bioactive compounds from plants (Nurcholis et al., 2022). Several natural antimalarial medicines have been discovered and produced from plant sources. Quinine and artemisinin are well known antimalarial compounds derived from plants (Budiarti et al., 2020; Uzor, 2020). Several nations in the Southeast Asian region are located in regions of enormous plant biodiversity as a source of medication. Mangroves, which are tropical vegetation, are one of them. Mangrove plants are often used as medicinal plant source of antioxidant, antibacterial, and antimalarial agents (Assaw et al., 2020; Mardiyanto and Sunarto, 2020). Because they grow in marine environment, mangrove plants may have distinct characteristics from terrestrial plants, and therefore, may synthesize different types of bioactive compounds (Ravikumar et al., 2011a). As it is known to have some pharmacological activities, the mangrove plant may have promising role for the development of new antimalarial drugs (Ravikumar et al., 2011a).

The mangrove plant has some essential roles in the ecosystem, such as its ecological function to prevent coastal areas from erosion and tsunami damage (Masagca, 2008). The distribution of mangrove plants in coastal areas leads to metabolic differences, adaption to anaerobic and saline soil conditions (Mardiyanto and Sunarto, 2020) which could produce specific phytochemical compounds. Mangrove plants consist of some species from several genera in some countries in the SEA region. There are several genera of mangrove plants: *Avicennia* sp., *Bruguiera* sp., *Ceriops* sp., *Lumnitzera* sp., *Rhizophora* sp., *Sonneratia* sp., *Achrostichum* sp., *Aegiceras* sp., *Excoecaria* sp., *Heritiera* sp., *Osbornia* sp., *Phempis* sp., *Scyphiphora* sp., *Xylocarpus* sp., *Nypa* sp., *Achrostichum* sp., *Achantus* sp., *Cerbera* sp. (Masagca, 2008; Setyawan et al., 1970).

Several mangrove plants which have been investigated exhibit pharmacological activity suitable for antioxidant and antibacterial agents. The mangrove plants used as an antioxidant and antibacterial agents are from the species *Acanthus ilicifolius* (Karim et al., 2021), *Avicennia marina*, *Avicennia officinalis* (Assaw et al., 2020), *Avicennia schaueriana* (Machado et al., 2017), *Bruguiera gymnorrhiza* (Zhang et al., 2007), *Ceriops decandra* (Sasikumar et al., 2011), *Excoecaria agallocha* (Bhuvaneswari et al., 2017), *Lumnitzera racemosa* (Abeysinghe, 2010), *Rhizophora apiculata*, *Rhizophora mangle*, *Sonneratia alba*, and *Sonneratia caseolaris* (Phaechamud et al., 2012; Saad et al., 2012; Suh, et al., 2014). Thus, in the present review we summarized the use of mangrove plants as antimalarials and its possible mechanism of actions.

From several studies, mangroves plants have been suggested as important medicinal resources. The high demand of novel antimalarial drugs has driven growing interest in exploring bioactive compounds from mangroves plants as antimalarial drug candidates. This review highlights the current knowledge and research progress on the potential use of mangrove plants as sources of antimalarial agents.

EXPERIMENTAL SECTION

Our selection criteria include original articles in human, animal, or parasites. We excluded articles in the form of reviews or systematic reviews, opinions, and retracted manuscripts. Our searches were done by utilizing three databases which are PubMed, Scopus and PMC. This search term was for the mangrove plant category—the species of mangrove plants with antimalarial, antioxidant, and antibacterial activity. The search criteria used in this study were described in **Figure 1**. Manual searches were also conducted by observing the list of references from several narrative reviews on mangrove plants.

1. Data category of inclusion, and exclusion criteria:
   A. Inclusion: Original article in human, animal, and parasite.
   B. Exclusion: Review article, systematic review, opinion article in human, animal and parasite, retraction note.
2. Search Strategy

The search strategy of this study using 3 databases (PubMed, Scopus, and PMC NCBI) with certain keywords for advanced search. From the data category of inclusion and exclusion criteria, also search strategy of databases, we describe the flowchart on a diagram in **Figure 1**. This diagram shows a flow to filter the data of research to be summarized in this study. The diagram consists of identification method of search strategy (including the result of databases, screening of articles, and included articles).

RESULTS AND DISCUSSION

Our search from 3 databases has resulted in 8 studies of mangrove plants as having antimalarial compounds (**Figure 1**). The results were summarized in **Table 1**.

Antimalarial Potency and Phytochemical Compounds

Mangrove plants with antimalarial potency contain some phytochemical compounds *Agecerious corniculatum* was shown to have antimalarial activity

against *P. falciparum* in an *in vitro* study (**Table 1**) (Sundaram et al., 2012). Methanolic extract of leaf of *A. corniculatum* prepared using a percolation method exhibited a high percentage of parasitemia suppression in an *in vitro* test, with an IC_{50} value of less than 50 µg/mL. This might be due to the bioactive compounds in this plant. Based on the GC-MS test, *A. corniculatum* contains phytochemical compound of flavonoid-based benzofuran, the chemical constituent was identified as spiro (benzofuran-2(3 H), 1′-(3 cyclohexane)-2′,3-dione, 7-chloro-4′,6) (Ravikumar et al., 2012).

Database	Search Term	Result
PubMed	((human [Title/Abstract]) OR (animal [Title/Abstract])) OR (plasmodium[Title/Abstract])) AND (mangrove[Title/Abstract])) OR (mangroves[Title/Abstract])) AND (plant[Title/Abstract])) OR (Acanthus [Title/Abstract]))) OR (Aegiceras [Title/Abstract])) OR (Avicennia [Title/Abstract])) OR (Bruguiera [Title/Abstract])) OR (Ceriops [Title/Abstract])) (Conocarpus [Title/Abstract])) OR (Derris [Title/Abstract])) OR (Excoecaria [Title/Abstract])) OR (Finlaysonia [Title/Abstract])) OR (Heritiera [Title/Abstract])) OR (Kandelia [Title/Abstract])) OR (Laguncularia [Title/Abstract])) OR (Lumnitzera [Title/Abstract])) OR (Myoporum [Title/Abstract])) OR (Pongamia [Title/Abstract])) OR (Rhizophora [Title/Abstract])) OR (Sonneratia [Title/Abstract])) OR (Scyphiphora[Title/Abstract])) OR (Xylocarpus [Title/Abstract])) AND (antimalaria*[Title/Abstract]))	10 results
Scopus	TITLE-ABS (*human* OR *animal* OR *plasmodium* AND *mangrove* AND *plant* OR *cantus* OR *aegiceras* OR *avicennia* OR *bruguiera* OR *ceriops* OR *conocarpus* OR *derris* OR *excoecaria* OR *lawsonia* OR *heritiera* OR *kandelia* OR *laguncularia* OR *columnifera* OR *myoporum* OR *pongamia* OR *rhizophora* OR *nonnegative* OR *sophophora* OR *xylocarpus* AND *antimalarial*)	7 results
PMC NCBI	((human) OR animal) OR plasmodium) AND mangrove) AND plant) OR acanthus) OR aegiceras) OR avicennia) OR bruguiera) OR ceriops) OR conocarpus) OR derris) OR excoecaria) OR finlaysonia) OR heritiera) OR candela) OR laguncularia) OR lumnitzer) OR myoporum) OR pongamiae) OR rhizophora) OR sonneratia) OR scyphiphora) OR xylocarpus) AND antimalarial	1353 results

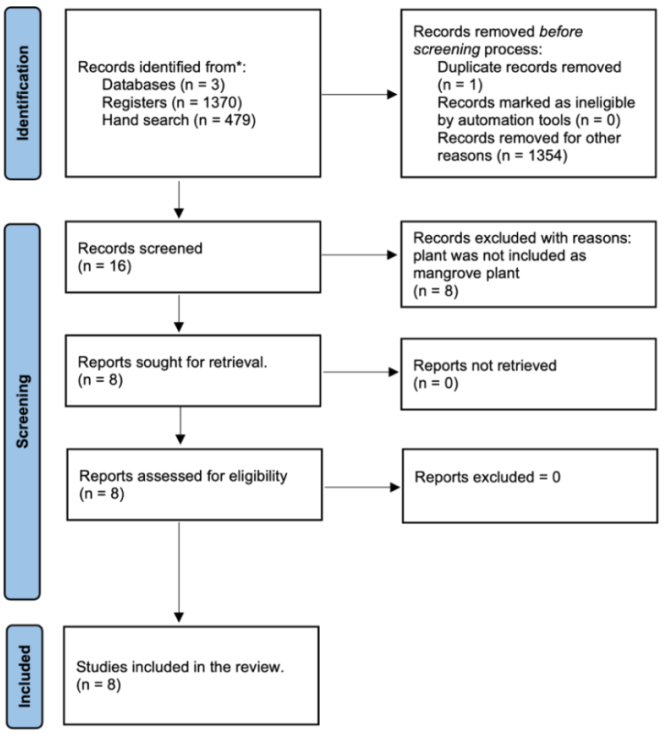

Figure 1. The flow diagram of manuscript selection in the study.

Table 1. Summary of mangrove plants used as antimalarials

Type of extracts	Phytochemical compounds	Effects	Suggested mechanism	Ref
Methanolic leaf extract of *Agecerious corniculatum*	Spiro benzofuran	Parasitemia suppression in *in vitro* study, has dose dependent effect. Highest percentage suppression in (91.98 ± 2.40)% with dose 100 µg/mL. Weakest: (2.90 ± 20.09)% with dose 25 µg/mL.	Not reported	Ravikumar et al., 2012
Methanolic leaf extract of *Sonneratia alba*	Alkaloid, flavonoid, quinone, terpenoid, phenolic, tannin, saponin, glycosides	Parasitemia suppression, inhibits parasite growth in *ex vivo* test. Dose 300 µg/mL inhibiting the growth of parasite's life cycle (inhibit the ring stage growth into schizont	Not reported	Muhaimin et al., 2019
Methanolic leaf extract of *Sonneratia caseolaris*	Alkaloid, flavonoid, phenolic, steroid, tannin, quinone, glycosides	Parasitemia suppression in *ex vivo* test	Not reported	Muhaimin et al., 2019
Methanolic leaf extract of *Acanthus ilicifolius*	Alkaloid, flavonoid, terpenoid, phenolic, tannin, saponin, glycosides	Parasitemia suppression in *ex vivo* test	Not reported	Muhaimin et al., 2019
Leaf (or bark) ethanolic extracts of *Avicennia marina*	Coumarins, phenol, xanthoprotein, protein, resin, tannin	Inhibits growth of *Plasmodium* in *in vitro* study. IC_{50} of leaf extract was less than 50 µg/mL indicated active as antiplasmodial, bark extract weakly active.	Not reported	Ravikumar et al., 2011a
Flower (or hypocotyl or collar) ethanolic extract of *Rhizophora apiculata*	Carbolic acid, flavonoid, saponin, xanthoprotein, protein, resin, tannin	Inactive as antimalarial	Not reported	Ravikumar et al., 2011a
Hypocotyl (or flower) ethanolic extract of *Rhizophora mucronata*	Carbolic acid, flavonoid, saponin, xanthoprotein, protein, resin, tannin.	Inactive or weakly active as antimalarial	Not reported	Ravikumar et al., 2011a
Ethanolic leaf extract of *Excoecaria agallocha*	Carbolic acid, flavonoid, saponin, xanthoprotein, resin, tannin	Weakly active as antimalaria	Not reported	Ravikumar et al., 2011a
Ethanolic leaf extract of *Acanthus ilicifolius*	Carbolic acid, phenol, saponin, xanthoprotein, resin, tannin	Inactive as antimalarial	Not reported	Ravikumar et al., 2011a
Ethanolic hypocotyl extract of *Bruguiera cylindrica*	The alkaloid, Carbolic acid, flavonoid, phenol, saponin, xanthoprotein, resin, tannin	Weakly active as antimalarial	Not reported	Ravikumar et al., 2011a

Polyherbal extract of mangrove plant *Aegiceras corniculatum*	coumarins, flavonoids, phenol, saponin, resin, tannin.	*In vitro* test showing a high parasitemia suppression at 65% in a dose of 1.5 mg/mL. *In vivo* test shows the increase of parasitemia suppression with the increased dose of extract.	Not reported	Ravikumar et al., 2011b
Ethanol crude extract of *Avicennia africana*	Alkaloids, saponins, flavonoids, glycoside, tannins, terpenoid	*In vitro*: antimalaria activity to *P.falciparum* (3D7), IC_{50} is under 50 µg/ml, 49.30 ± 4.40 µg /mL. *In vivo* study showed that the parasitemia level decreased with increased extract concentration. The percentage of suppression increased with a higher concentration of extract.	Not reported	Ahmed M., et al., 2021
Chloroform fraction of *Xylocarpus granatum* fruit	Xyloccensin-I and Gedunin.	Active as antimalarial. MIC value of 10 µg/mL. Extract of 50% aqueous ethanol, hexane fraction was marginally active with MIC 50 µg/mL.	Not reported	Lakshmi et al., 2012
Hydroalcoholic root of *Acanthus polystachyus* extract	Tannin, flavonoid, saponin, polyphenol, terpenoid, glycoside, and anthraquinone	Parasitemia suppression. The highest antimalaria activity at a concentration of 400 mg/kg with parasitemia suppression value was 11.53 ± 1.09 and survival time (in days) value was 15.90 ± 1.49.	Fatty acids synthesis in parasite is inhibited by a flavonoid, anthraquinone causing heme detoxification and binding interfered	Derebe and Wubetu, 2019
Methanol extract of *Acanthus polystachyus*	Flavonoid, saponin, tannin, glycoside, phenol, terpenoid, anthraquinone	Parasitemia suppression. Dose 400 mg/kg has the highest antimalarial activity with percent parasitemia of 20.20 ± 1.33% and a percentage suppression value of 49.25% in a 4-days suppression test. Prophylaxis test, the highest antimalaria activity is concentration of 400 mg/kg with percent parasitemia 20.40 ± 1.25% and percent suppression value of 50%.	Bioactive compounds have antiprotozoal potency	Kiffle and Atnafie, 2020

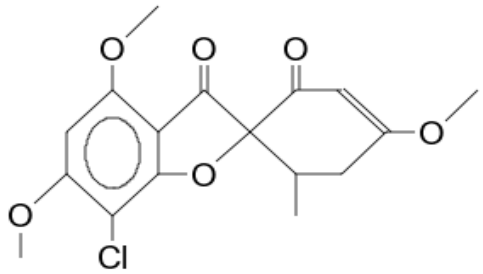

Figure 2. Spiro[benzofuran-2(3H),1'-[3]cyclohexene]-2',3-dione, 7-chloro (SpectraBase, 2023)

Muhaimin et al. (2019) reported that methanolic extract of mangrove plant *Sonneratia alba* decreased the parasitemia level of *P. berghei* ANKA in an *ex vivo* study, with the high level of parasitemia suppression. The *S. alba* leaf extract prevents the growth of the ring to the schizont stage during the *ex vivo* test. This study showed that other species of mangrove plant, *Sonneratia caseolaris* and *Acanthus ilicifolius* exhibit lower antimalarial activities than *S. alba*, with parasitemia suppression values less than 60%. Phytochemical screening of this extract showed that *S. alba* extract contains quinone, alkaloid, flavonoid, phenolic, and other compounds (Muhaimin et al., 2019). Ethanolic leaves extract of *Avicennia marina*, showed an antimalarial activity with IC_{50} value of less than 50 µg/mL against *P. falciparum* chloroquine resistant type in an *in vitro* study. This antimalarial activity was the highest among the other ethanolic extracts of mangrove plant species investigated in this study, such as *Rhizophora apiculata*, *R. mucronata*, *Excoecaria agallocha*, and *A. ilicifolius*, and *Bruguiera cylindrica* with antimalarial activity weakly active and inactive respectively. *A. marina* contains phytochemical compounds such as coumarins, phenol, protein, resin, tannin, and xanthoprotein (Ravikumar et al., 2011a).

Polyherbal extract of mangrove *Aegiceras corniculatum* together with a seaweed showed a high percentage of parasitemia suppression against *P. berghei* at a value of 65% in an *in vitro* study. Besides, this extract combination showed a high inhibition value against *P. falciparum* during *in vitro* test. Meanwhile, an *in vivo* study showed the increase of parasitemia suppression with the increase of extract dose. *A. corniculatum* contains several phytochemical compounds consisting of coumarins, flavonoids, phenols, saponins, resins, and tannins (Ravikumar et al., 2011b).

Ahmed et al. (2022) reported that ethanol crude extract of mangrove plant species *Avicennia africana* showed the IC_{50} value of 49.30 µg/mL (under 50 µg/mL) against *P. falciparum* in an *in vitro* test. Moreover, an *in vivo* study of this extract showed that an increase in the extract concentration could decrease the parasitemia level of *P. berghei*, in line with the suppression percentage. Phytochemical compounds contained in *A. africana* include alkaloids, saponins, flavonoids, glycosides, tannins, and terpenoids (Ahmed et al., 2022). Meanwhile, the chloroform fraction of fruit of mangrove plant *Xylocarpus granatum* showed antimalarial activity with a MIC value of 10 µg/mL against *P. falciparum* NF-54 strain in an *in vitro* study (**Table 1**). In this research, the potential antimalarial compounds were identified as xyloccensin-I and gedunin (**Figure 3** and **Figure 4**) (Lakshmi et al., 2012).

Hydroalcoholic extracts of *Acanthus polystachyus* roots prepared using a maceration method showed antimalarial activity against *P. berghei*-infected mice in a dose-dependent manner. It was demonstrated that all mice received root extracts live longer compared to the the corresponding negative control groups. The highest antimalarial activity was shown by the extract at a concentration of 400 mg/kg with parasitemia suppressive value of 51.49% and survival time value of 15.90 days against *P. berghei*. It was concluded that the root of *A. polystachyus* can be used for development of novel antimalarial drugs. Phytochemical compounds detected in the species *A. polystachyus* include tannins, flavonoids, saponins, polyphenols, terpenoids, glycosides, and anthraquinone (Derebe and Wubetu, 2019). Similarly, Kifle and Atnafie (2020), in another study of *A. polystachyus*, showed that methanol leaf extracts of this plant suppressed parasitemia at all extract concentrations tested. The leaf extract with a concentration of 400 mg/kg showed the highest antimalarial activity with a suppression percentage of 49.25%. For the prophylaxis activity test, the highest antimalarial activity was also exhibited by the extract at concentration of 400 mg/kg with a percent suppression value of 50%. This study was performed *in vivo* against *P. berghei* ANKA. Flavonoid, saponin, tannin, glycoside, phenol, terpenoid, and anthraquinone were among the phytochemical compounds identified in this species. Steroid and alkaloid were not detected. The results of this study supported the traditional application of *A. polystachyus* for treatment of malaria. Of note, the leaves of this plant are traditionally used for treatment of malaria in Ethiopia (Kifle and Atnafie, 2020).

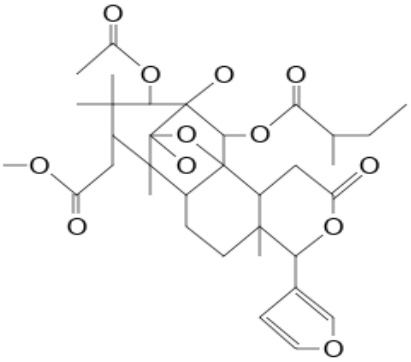

Figure 3. Xyloccensin-I (SpectraBase, 2023).

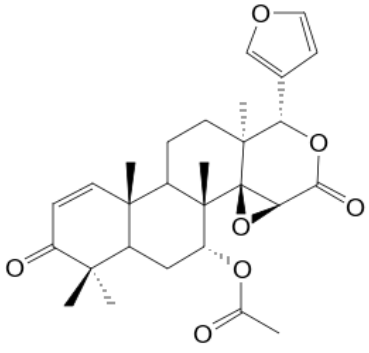

Figure 4. Gedunin (SpectraBase, 2023)

Suggested Mechanism of Antimalarial Activity

Understanding of antimalarial modes of action may accelerate development and discovery of antimalarial drugs (Daskum et al., 2021). According to a recent study, extracts of several species of mangrove plant exhibited antimalarial activity. This antimalarial potency is related to the phytochemical compounds contained in the extracts of the plants. The typical compounds found in mangrove plant species are alkaloids, flavonoids, tannins, phenols, terpenoids, saponins, coumarins, triterpenes, glycosides, and anthraquinones. Studies suggested that several phytochemical compounds exert antimalarial action using different mechanisms.

Out of the eight studies, only two studies reported the possible mechanism of antimalarial action. The survival of parasite dependent on fatty acid synthesis was reduced by flavonoids, meanwhile anthraquinone caused heme detoxification and interfered with protein binding in the *Plasmodium* parasite (Derebe and Wubetu, 2019). The combination of phytochemical compounds in *A. polystachyus* was suggested to inhibit parasite growth (Kifle and Atnafie, 2020).

Other experiments indicated that the anti-plasmodium activity of saponins was due to the ability of these compounds to disrupt the homeostasis of the plasma membrane lipid of the parasites (Derebe and Wubetu, 2019). The proposed mechanisms of antiplasmodial activity of mangrove plants are as illustrated in **Figure 5**. In addition, the mixture of bioactive compounds found in mangrove plants may provide pharmacological benefits to the host, such as stimulating immune response, changing membrane permeability hence limits nutrient entry for the parasites. This study described the suggested mechanism of antimalarial activity in that fatty acids synthesis in parasite is inhibited by a flavonoid, anthraquinone causing heme detoxification and binding of *Plasmodium* parasite interfered (Derebe and Wubetu, 2019).

Typical bioactive compounds identified in mangrove plants include alkaloids, flavonoids, tannins, phenols, terpenoids, saponins, coumarins, triterpenes, glycosides, and anthraquinones. Phenolics and certain terpenes are proposed to exert toxic effects on *Plasmodium*. Saponins are proposed to have the ability to disrupt membrane lipid homeostasis. Flavonoids are hypothesized to inhibit *Plasmodium* fatty acid synthesis. Phenol and anthraquinone are suggested to interfere with heme detoxification. These concerted antiplasmodial effects of mangrove plants resulted in suppression of *Plasmodium* infectiveness.

Extraction Method of Mangrove Plant

A number of studies described methods for generating mangrove plant extracts used in antimalarial activity tests. Ravikumar et al. (2012) generated methanolic extract of *Agecerious corniculatum* using percolation method. In another study, leaves of *Sonneratia alba*, *Sonneratia caseolaris,* and *Acanthus ilicifolius,* were extracted by using maceration technique and methanol as extraction solvent (Muhaimin et al., 2019). In the study of Kiffle and Atnafie, 2020, leaf of *Acanthus polystachyus* was ground into powder and macerated with methanol.

In the antimalarial research conducted by Ravikumar et al. (2011a), the leaf and bark of *Avicennia marina*; flower, hypocotyl, and collar of *Rhizopora apiculata*; hypocotyl and flower of *Rhizopora mucronata*; leaf of *Exocecaria agallocha*; leaf of *Acanthus ilicifolius*; and hypocotyl of *Bruguiera cylindrica* were extracted by using percolation method with ethanol solvent and then filter-sterilized (Ravikumar et al., 2011a). The percolation technique was also employed by Ravikumar et al. (2011b) to extract mangrove plant *Agecerias corniculatum* (Ravikumar et al., 2011b). Ahmed et al. (2021) extracted pulverized dried leaves of *Avicennia africana* with cold ethanol using maceration method. The filtrate generated was then concentrated using a rotary evaporator. In order to improve yield, the plant material residues were remacerated three times (Ahmed et al., 2022). The maceration method was also applied by Derebe and Wubetu (2019) to extract fresh root of *A. polystachyus* using 80% methanol. Repeated maceration was also performed to increase yield (Derebe and Wubetu, 2019).

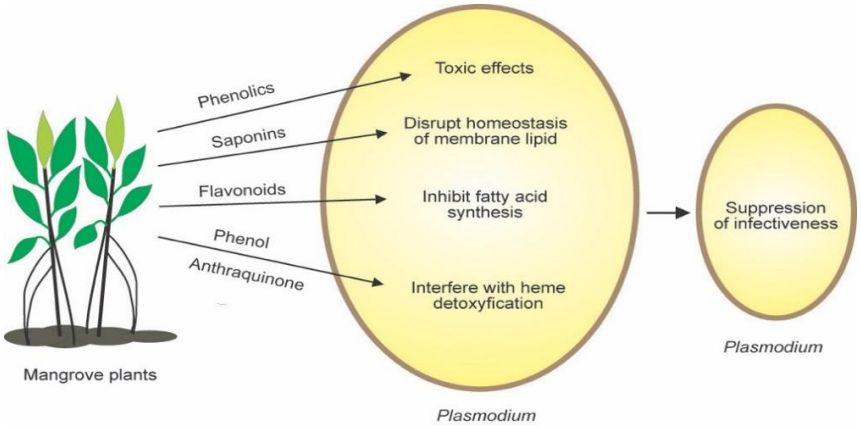

Figure 5. Proposed mechanism of action of mangrove plant bioactive compounds as antiplasmodial agents.

Toxicity Analysis of Mangrove Plant with Antimalarial Activity

Mangrove plant extracts with antimalarial activity were also subjected into toxicity test to determine the safety of each extract. Toxicity tests were conducted *in vitro* and *in vivo* with parameters observation. The erythrocyte observation during *in vitro* test in the methanolic extract of *A. corniculatum*, the ethanolic leaf extract of *Avicennia marina*, and *Aegiceras corniculatum* did not show any chemical and morphological injury (Ravikumar et al., 2011a; Ravikumar et al., 2011b; Ravikumar et al., 2012). An *in vivo* toxicity study showed that the methanol extracts of *A. corniculatum* and *C. antennina* exhibit antiplasmodial activity without any abnormal changes in serum parameters such as AST, ALT, urea, TGL, LDL, VLDL, glutathione peroxidase and TBA. These findings indicated that the extracts of *A. corniculatum* and *C. antennina* cause no toxicity to liver cells (Ravikumar et al., 2011b).

In the antimalarial study of Derebe and Wubetu (2019), the root extract of *A. polystachyus Delile* was also subjected to acute oral toxicity test using young female mice. A single dose of 2000 mg/kg was administered to each experimental mouse orally. Results showed that there was no physical and behavioral abnormalities observed suggesting that the LD_{50} value of the extract was higher than 2000 mg/kg which indicated that the extract was non-toxic (Derebe and Wubetu, 2019). Similarly, Kifle and Atnafie (2020) also conducted acute oral toxicity test for methanol leaf extract of *A. polystachyus* and found that the extract did not cause mortality or any toxic effects. The LD_{50} value of the extract was revealed to be higher than 2000 mg/kg bodyweight further supported the non-toxic evidence of the *A. polystachyus* extract (Kifle and Atnafie, 2020).

In general, the toxicity studies showed that the mangrove plant extracts have no toxic effects based on both in *in vitro* and *in vivo* methods. However, in order to develop the new candidates of antimalarial, there are some further analyses need to be carried out. Detailed chemical analysis of bioactive compounds found in the plant candidates using advanced methods such as LC-MS/MS (Laureano et al., 2015), may facilitate drug development. In addition, preclinical characterization of mangrove bioactive compounds need to be carried out to determine their spectrum of activities against multiple life cycle stages of the human malaria parasites especially artemisinin-resistant *Plasmodium* (Le Bihan et al., 2016).

Future Studies to Develop Mangrove Plants as Antimalarial Candidate

The increasing prevalence of *P. falciparum* resistance to artemisinin and its derivatives has posed substantial and immediate challenges to global malaria control and elimination efforts and discovery of novel compounds effective for combating drug resistant parasites is of urgency (Azmi et al., 2023). Mangrove plants may contain unique structural diversity for discovery of novel lead compounds of antimalarial activity. This study has identified several mangrove plants, *Acanthus polystachyus*, *Agiceras corniculatum*, *Acanthus polystachyus* and *Agiceras corniculatum* having the potential to be used as a source of antimalarial drugs. Future studies should be directed towards selection of more mangrove plant candidates, screening of antimalarial activity, identification, characterization and structural elucidation of bioactive compounds, druggability assessment, followed by preclinical and clinical evaluation. Traditional wisdom in selecting right mangrove plant candidates can be adopted to discover better leads for antimalarial drug research and development. Antimalarial activity-guided fractionation of mangrove plant extracts may be helpful to identify active compounds. Metabolomics-based platform may assist elucidation of antimalarial mode of action of the discovered lead compounds. Should mangrove plant extracts to be used for malaria treatment, standardization is critical to minimize variability between lots and manufacturers of the same extract. Furthermore, *in vivo* studies are critical to investigate the antimalarial activity of mangrove plant for development of antimalarial drug candidates. *In vivo* experiments are also important to find the optimal dose treatment, bioavailability, pharmacokinetics mechanism and potential toxicity of antimalarial candidates (Rocha e Silva, et al., 2015).

CONCLUSIONS

Several species of mangrove plant such as *A. corniculatum*, *S. alba*, *A. marina*, *A. africana*, *X. granatum*, and *A. polysta*chyus have antimalarial activity based on *in vitro*, *ex vivo* and *in vivo* studies. Suggested mechanism of antimalarial action of species tested is related to phytochemical compounds contained in their extracts. According to toxicity tests both *in vitro* and *in vivo*, mangrove plant extracts were indicative of non-toxic. Future studies should be directed toward identification and structural elucidation of active compounds discovered in potential mangrove plants followed by detailed studies on antimalarial efficacy and mechanism of action, also antimalarial bioactivity of each potential compound against drug resistant-*Plasmodium*.

Ethics Approval And Consent To Participate

Not applicable.

Consent For Publication

Not applicable.

Availability Of Data And Material

Not applicable

Competing Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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Author's Contribution

AFMR: conceptualizing, writing the original draft, drawing figures and reviewing
WAA: conceptualizing, writing, and reviewing
ML: conceptualizing, writing, reviewing and editing
MM: writing, reviewing and editing
IMA: conceptualizing, writing, drawing figures; editing
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