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*Review Article*

# A Comprehensive Review on Medicinal Plants Potentially as Antimalarial

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ABSTRACT

Antimalarial drugs derived from plants have proven their effectiveness for centuries. The discovery of new antimalarials drugs from natural plant products has been widely studied to overcome drug resistance that threatens the control of malaria. The development of new malaria drugs sourced from plants has been widely performed. The purpose of this review was to create a compilation of plant species that had been investigated as antimalarial drug, its molecular mechanisms of action and ligands, from studies that had been published in Pubmed NCBI, Google scholar, and Researchgate. Several plants that have been investigated as antimalarial drugs include *Aloe* spp, *Allium sativum*, *Alstonia scholaris*, *Morinda citrifolia*, *Andrographis paniculate*, *Carica papaya*, *Momordica charantia*, *Tinospora crispa*, *Moringa oleifera*, *Physalis angulate*, *Nigella sativa*, *Cocos nucifera*, *Piperaceae*. Molecular mechanism of action of *Aloe spp*, *Allium sativum*, *Alstonia scholaris*, *Morinda citrifolia*, *Andrographis paniculata*, *Carica papaya*, *Momordica charantia*, *Moringa oleifera*, *Physalis angulate*, *Nigella sativa*, *Cocos nucifera*, *Piper* spp is by inhibiting the formation of hemozoin, nucleic acids, protein synthesis, oxidative stress, and nitric oxide, affect the transcription and transduction signaling process. Ligands involved in the process were protease, plasmepsin, hemozoin, 3d7 and rkl-9 strains of *Plasmodium falciparum*, glycogen synthase kinase-3*β* (GSK3*β*), *Plasmodium falciparum* Calcium-Dependent Protein Kinase-2 (PfCDPK-2), *Plasmodium falciparum* dihydrofolate reductase-thymidylate synthase (pfDHFR-TS). However, mechanism of action of *Tinospora crispa* is still unclear.

***Keywords***: Antimalarial, Plant, Ethnomedicine, Mechanism of Action, Ligand

## Introduction

Global malaria cases are estimated at 229 million cases and 409,000 deaths with the total percentage of malaria deaths in children below 5 years reaching 67% in 2019. The distribution of most malaria cases occurred in Africa (94%) followed by Southeast Asia (10%).[1] Previously, it was known that only four species of Plasmodium cause malaria: *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale* and *Plasmodium malariae*.[2] The fifth species, *Plasmodium knowlesi*, was first discovered in 1965 as a zoonotic plasmodium found in South-East Asia.[2] Malaria is transmitted through the bite of a female Anopheles mosquito.[2] In the America and Europe, the most common plasmodium species are *P. vivax* and *P. malariae*, while in Africa it is *P. falciparum*.[2]

Malaria treatment relies on pharmacotherapy or drugs.[3] Medicines used for the treatment of malaria include chloroquine, mefloquine, quinine, primaquine, pyremethamine, artemisinin derivatives like artesunate, artemether, arteether and amino alcohols like lumefantrine and halofantrine along with tetracycline, doxycyclines and sulfadoxine.[3]

Treatment of malaria using artemisinin costs only 30 cents and this treatment results in a cure of nearly 90%. However, like treatment with other drugs, treatment outcomes will decrease with the emergence of resistance to these drugs.[4]

Antimalarial drug resistance is a severe global problem.[2] The discovery of resistance to the current malaria drugs has become a threat to malaria elimination.[5] Study to find new antimalarial drug from herbal component that are free from synthetic antimicrobials has been carried out.[6] Research to finding and testing new antimalarials and a potential vaccine are still ongoing.[3]

Throughout human history, isolation and identification of biologically active compounds and molecules from nature has led to the discovery of new therapeutics, prompting the improvement of health and pharmaceutical sectors.[7] Intensive research on the use of plants or natural resources over the past few decades has encouraged discovery of new empirical medicine.[8] That observation process is a subject of ethnopharmacology and ethnobiology whose focus is an approach that assess the effectiveness of traditional preparations.[8]

The discovery of Artemisinin as antimalarial drug derived from a plant that was traditionally used, has proved that ethnomedicine and ethnobiology research is important in the development of new drugs.[9]

The development of molecular technology signed by the discovery of virtual methods that can construct interactions between substrates and receptors called docking study. Molecular docking would help to determine active ingredients and receptors in the development of new drugs.[10] The docking method makes the initial selection of the multi-

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substrate stage in the wet laboratory is easier, however it has the disadvantage that the bioinformatics may not match the wet laboratory result.[10]

The research methods used in the development of antimalarial drug are numerous, these incluse; *in vitro* and *in vivo* studies with the Peters' 4-day suppressive test, curative or Rane test, prophylactic or repository test.[11,12] Ethnomedicine and molecular docking is also very useful and contribute greatly to finding plants with active substrate required in the development of new drugs, including antimalarials.[12] Research on the development of new malaria drugs sourced from plants has been widely carried out. This study aimed to describe medicinal plants that have been used as antimalarial based on ethnomedicine, active compound, molecular mechanism of action and their ligands.

## Materials and Methods

This study was comprehensive review aimed to describe medicinal plants that have been used as antimalarial based on ethnomedicine, their active compound, molecular mechanism and ligands. The articles were taken from the online journal literature. The following searching databases that have been used were PubMed NCBI, Google Scholar and ResearchGate. Data from various studies were analyzed descriptively with aims (1) to present plant that commonly been used in ethnomedicine as antimalarial; (2) to summarize the molecular mechanism of those plant as antimalarial; (3) to describe interaction between substrate or active compound with their ligand based on molecular docking study.

## Result and Discussion

*Medicinal plants as antimalarials based on ethnomedicine*

Knowledge of the use of natural resources such as plants, animals and minerals and their use in health practice is the subject of medical ethnobiology and ethnopharmacology, including ethnomedicine.[8] Ethnobotany and ethnopharmacology are defined as medicinal plants used in traditional medicine and contain elements that are useful for curing diseases in humans or animals. The goal of ethnopharmacology is to develop drugs to treat patients, and ultimately validate the traditional use of medicinal plants.[7]

Ethnomedicine is defined as drugs traditionally used in certain ethnic groups.[14,15] Ethnomedicine can be utilized in the provision of new chemical entities or combinations of certain metabolites which will be investigated further for the development of new drugs. The plants used in ethnomedicine need to be studied because of the increasing trend in the use of herbal medicines in people's lives. By examining the active ingredients, the mechanism of action and the dosage of plants used in ethnomedicine, it will provide safety in the use of these drugs in daily life.[15]

Ethnobotanical study was carried out to survey medicinal plants and their uses for malaria control. Methods that have been used to get information in ethnobotanical study by collecting information from traditional medicine healers via interviewer-administered questionnaires.[16] The benefits of ethnomedicine research are for management, preservation and continuity of the use of medicinal plants for health. Ethnomedicine research is also important to provide a broad and clear picture of plant species that have been used for the treatment of certain diseases.[16]

In an ethnomedicine study in western Ethiopia, *Allium sativum* is used in the treatment of malaria. [16]*Adhatoda vasica, Cassia fistula* and *Swertia chirata* were used in India to treat malaria traditionally. [17]*Tithonia diversifolia*, *Cyperus rotundus*, *Strychnos lingustrina*, *Callicarpa longifolia*, *Plectranthus scutellarioides*, *Amaranthus spinosus*, *Artocarpus champeden*, *Cassia siamea*, *Azadirachta indica*, *Helianthus annuus* and *Blumea balsamifera* are plant used as ethnomedicine in Somalia Ethiopia. *Plectranthus scutellarioides*, *Amaranthus spinosus*, *Artocarpus champeden* were found and used as antimalarial in Kupang, Indonesia.[18]

Various studies on ethnomedicine malaria have been conducted in Indonesia. *Morinda citrifolia* L., *Peronemacanescens Jack* and Vitexpinnata L were traditionally used to treat malaria by tribes in Borneo Indonesia.[19]*Andrographis paniculata*, *Carica papaya*, *Momordica charantia*, *Curcuma xanthorrhiza*, and *Tinospora crispa* were used by Gayo tribes in Aceh Indonesian.[20] *Calotropis gigantea*, *Cleome rutidosperma*, and *Physalis angulate*, *Tamarindus indica* were used by Malacca people, West Timor of Indonesia to treat malaria traditionally. [21]

People in East Java, Indonesia usually use the leaves and seeds of *Eucalyptus alba* to treat malaria. [22]*Azadirachta indica*, *Brucea javanica*, *Cassia siamea*, *Cocos nucifera*, *Eurycoma longifolia*, *Labisia pumila*, *Languas galangal*, *Lansium domesticum*, *Morinda citrifolia*, *Ocimum tenuiflorum*, *Phyllanthus niruri*, *Piper betle*, *Hibiscus crispa rosa-sinensis*, and *Tinospora* were also used orally to treat malaria in Java.[23] The Batak people of North Sumatra Indonesia have traditionally used *C. papaya*, *H. rosasinensis*, *L. domesticum*, *S. laevis*, *P.edulis*, *N. lappaceum*, *E. longifolia* to treat malaria. [24]*Nigella sativa* L or jintan hitam is used traditionally as an antimalarial based on religious knowledge. Most widely plant species known by traditional people as antimalarial medicine are *Eurycoma longifolia* Jack, *Labisia pumila* (Bl.) F.-Vill. and *Tinospora crispa* L. Those drugs are given to malaria patients traditionally in the form of infusion, decoction which is given orally.[23]

*Azadirachta indica* or Intaran and *Tamarindus indica* plants are the most commonly used to treat malaria in Kupang West Timor Indonesia.[25] Plant from Lamiaceae Family or mint family consist of Menthae and Ocimeae tribe, such species are *Mentha piperita*, *Ocimum* spp., *Origanum* spp., were known for their antimalarial Activity.[26] Ethanol extract from *Cassia spectabilis* leaves at a dose of 150mg/ kg BW three times a day has been shown to be effective in inhibiting the growth of *P.berghei* in mice.[27]

Based on a systematic review, plants with antimalarial properties for malaria treatment and/or prophylaxis were *Argemone mexicana*, *Artemisia annua*, *Citrus aurantifolia*, *Nauclea pobeguinii*, *Nycthanthes arbor-tristis* and *Vernonia amygdalina*.[28] The most common medicinal plants used as traditional antimalarial concoction in Papua are *Alstonia scholaris* (L.) R. Br., *Carica papaya* L., *Andrographis paniculata* (Burm. f.) Nees, and *Physalis minima*.[29]*Betula alnoides* used as ethnomedicine in Southeast Asia, South China, Thailand and Northeast India as a tonic, stomachic, carminative, aphrodisiac, increase longevity and the appetite, antimalarial. Its active compound that acts as antimalarial is betulinic acid.[30] *Glycine max* leaves, roots, and seeds had been used traditionally for treatment of wide range ailments including malaria in Sierra Leone. Its biological activities including antimicrobial, antioxidant, antidiabetic, anti- antidepressants. It also has protective effect against cancers of the prostate, breast, and uterus.[31]

*Tithonia diversifolia*, *Momordica charantia*, *Cyperus rotundus*, *Strychnos lingustrina*, *Andrographis paniculata*, *Callicarpa longifolia*, *Tinospora crispa*, *Piper betle*, *Plectranthus scutellarioides*, *Alstonia scholaris*, *Carica papaya*, *Amaranthus spinosus*, *Artocarpus champeden*, *Cassia siamea*, *Azadirachta indica*, *Helianthus annuus* and *Blumea balsamifera* are plant used as ethnomedicine in Somalia, Ethiopia.[18] *Bathysa cuspidata*, *Cosmos sulphureus*, *Cecropia hololeuca*, *Erisma calcaratum*, *Gomphrena arborescens*, *Musa paradisiaca*, *Ocotea odorifera*, and *Pradosia lactescens* are plants that are used as antimalarial in Brazil.[32] *Piper peltatum* has been used as ethnomedicine for malaria in the Amazon region. Root of *P. peltatum* exhibits *in vitro* activity against *P. berghei* in mice. Active metabolite that can be isolated from root of *P. peltatum* is 4-Nerolidylcatechol.[33]

*Olea europaea* Linn (family: Oleaceae) used in east Africa (ethiopia) as ethnomedicine for malaria.[34] Butanol, chloroform, aqueous extract from the leaves of *Olea europaea* were proven to reduce parasitemia by the *Peters' 4-day suppressive test* method with $LD_{50}$ 2000 mg/kg BW.[34] Leaf extracts from *Psidium guajava*, *Ocimum sanctum* and *Murraya koenigii* have been tested for their effectiveness against *P. berghei* infection in mice.[35]*Meriandra dianthera* leaves crude and methanolic extract was effective as antimalarial in mice, it was also proven that this extract can maintain body temperature and body weight during infection and improve survival.[36]

The root and fruit extract of Euphorbiaceae (*Croton macrostachyus*) were used as folk medicine in Ethiopia. Several parameters such as parasitemia, survival, packed cell volume (PCV), weight, thermal have

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been investigated to prove the effect of plants as antimalarial.[37] *Russelia equisetiformis* of the family Scrophulariaceae is a medicinal plant used by traditional healers to treat malaria, cancer and inflammatory diseases and it is also claimed to promote hair growth among the Yoruba tribe in Nigeria with toxic dose 5000mg/kgBW.[38] *Commiphora africana* (Family Burseraceae) and *Dichrostachys cinerea* (Family Fabaceae) commonly used as ethnomedicine for malaria in Tanzania. Extracts of *C. africana* (stem bark) and *D. cinerea* (stems bark), exhibited very significant anti-malarial activities in the mouse model.[39] Plant used as ethnomedicine in Ethiopia and neighboring countries such as *Azadirachta indica*, *Tamarindus indica*, *Ajuga integrifolia*, *Aloe* spp., *Acalypha fruticose*, *Melia azedarach*, *Premna schimperi*, *Dendrosicyos socotrana*, *Croton macrostachyus*, *Peponium vogelii*, *Clerodendrum myricoides*, *Fagaropsis angolensis*, *Dodonaea angustifolia*, *Gardenia ternifolia*, *Combretum mole*, *Indigofera spicata*.[40] Summary of medicinal plant that been used as antimalarial were describe in Table 1. Based on descriptions in Table 1, plants that have been used to treat malaria traditionally based on ethnomedicine aspect among others: *Aloe* spp, *Allium sativum*, *Alstonia scholaris*, *Morinda citrifolia*, *Andrographis paniculate*, *Carica papaya*, *Momordica charantia*, *Tinospora crispa*, *Moringa oleifera*, *Physalis angulate*, *Nigella sativa*, *Cocos nucifera*, *Piperaceae*. Part of those plants that traditionally used as antimalarial were leaves, seed, bark, sap, fruit, their preparation such as oral and infused decoction.

**Table 1:** Presentation of Plant used as Malaria Treatment based on Ethnomedicine

| Species plant | Part of plant | Country | References |
|---|---|---|---|
| *Eucalyptus alba* | Leaves and seed | Indonesia | 22 |
| *Alstonia scholaris* | Bark, leaves and sap | Papua nugini, Indonesia, India, Bangladesh, Somalia | 23 |
| *Eurycoma longifolia* | Oral, infuse decoction | Indonesia | 23 |
| *Labisia pumila* | Oral, infuse decoction | Indonesia | 23 |
| *Morinda citrifolia* | Leaves fruit | Indonesia, India, Tahiti, Hawaii, | 20,49 |
| *Andrographis paniculate* | Leaves | Indonesia; Somalia; Southeast Asia, India, Japan, Scandinavia | 29, 41-43 |
| *Carica papaya* | Leaves | Aceh Indonesia, Somalia Ethiopia | 20, 25, 44,45 |
| *Momordica charantia* | Leaves | Indonesia; Somalia, Ethiopia, Asia, Amerika, Middle east | 20, 46-51 |
| *Tinospora crispa* | Oral, infuse decoction, Bark | Aceh Indonesia Somalia Ethiopia | 20 |
| *Curcuma xanthorrhiza* | Root | Aceh Indonesia | 20 |
| *Azadirachta indica* | Leaves | Kupang East Indonesia, Somalia Ethiopia | 40, 52 |
| *Tamarindicus indica* | Fruit | Kupang East Indonesia | 22,25, 40, 52 |
| *Calotropis gigantea* | Leaves | Malaka, west Timor Indonesia | 21, 53 |
| *Cleome rutidosperma* | Leaves Whole plant | Malaka, west Timor Indonesia, India Cameroon | 21,54 |
| *Physalis angulate* | Leaves and whole plant | Malaka, west Timor Indonesia Brazilian, amazon, Iran | 21, 55 |
| *Nigella sativa* | Seed | Indonesia, India, Asia, Arabian, African, Middle east, Far East | 56, 57 |
| *Cocos nucifera* | Fruit Oil, decoction | Indonesia, Malaysia Africa, Nigeria | 58 |
| *Ocimum tenuiflorum, Ocimum spp* | Leaves and root | Indonesia | 26, 35, 59 |
| *Piperaceae (Piper betle, P. umbellatum L, Piper peltatum* | P. umbellatum L, Piper peltatum root used in Brazil Amazone while Piper bettle was used its Fruit, leaves | Indonesia, Somalia, Ethiopia, Amazon, India, Brazil, Costarica, Guetamala | 33, 42, 60 |
| *Zingiber officinale* | Root | India; Indonesia Asia, Africa, India, Jamaica, Mexico, Hawaii, Ethiopia | 42, 61 |
| *Helianthus annuus* | Root and leaves | Somalia, Ethiopia Indonesia, Madagascar | 27, 62 |
| *Allium sativum* | Seed | India, China, Europe, West Ethiopia | 16, 63-66 |
| *Aloe spp* | Leaf latex | Ethiopia, Indonesia, Uganda | 67-70 |
| *Betula alnoides* | Stem bark | Southeast Asia, South China, Thailand and Northeast India | 30 |
| *Glycine max* | leaves, roots, and seeds | Sierra Leone Africa | 31 |
| *Moringa oleifera* | Seed, root, leaves | Indian, Greek, and Egyptian, Indonesia | 71-75 |
| *Blumea balsamifera* | Stem and root | Somalia; Ethiopia, Asia, India, Chinese | 76,77 |
| *Curcuma longa and Curcuma domestica* | Root | Thailand, Nigeria, Indonesia | 78 |

*Molecular mechanism of antimalarial from medicinal plant*

Molecular docking helps in determining the herbal components that play a role in treating malaria because molecular docking can explain the molecular recognition mechanism between small and large molecules.[79] The docking method makes the initial selection of the multi-substrate stage in the wet laboratory easier. However, it has the disadvantage that the bioinformatic may not match the wet laboratory result.[10] Apart from the molecular docking method, there are several other aspects such as safety, effectiveness, cultural aspects, cost, sustainable availability that also need to be considered in determining herbal components to treat malaria.[3] Research on other malaria drugs has been conducted to replace the standard antimalarial drug that has been resistant, namely chloroquine. The research was conducted using a docking study technology. As is well known, the mechanism of action of the chloroquine group is to inhibit the formation of hemozoin. Chloroquine is known as a malaria drug with a safe therapeutic index. Although the chloroquine class of malaria drugs have been found to be resistant to *P. vivak* and P. falciparum, new malaria drug candidates have been developed which are derived from the structure of chloroquine (chloroquine analogues) including bisquinoline (BAQ) and monoquinoline (MAQ), and it has been proven that MAQ is more selective compared to BAQ.[80]By Docking study method, it has also been proven that aminoquinoline triazine derivatives have better anti-malarial activity than chloroquine *in vitro* and *in vivo*.[81] Research of repurpose drugs as antimalarial using the docking method is relatively cheaper and more practical than the process of finding novel compounds because human toxicity studies and longer procedures are required.[82]Through the docking method, it is known that quercetin and apigenin derived from the *Adansonia digitata* stembark have antimalarial activity. The mechanism of action of quercetin and apigenin are by inhibiting calcium transportation.[83] Through the in-silico docking method it has also been found that curcumin has anti-malarial effects at a dose of 30 mg/ kg BW with a mechanism of action involving glycogen synthase kinase-3β (GSK3β) -inhibitory properties.[84] The major constituent of the roots of *Glycyrrhiza glabra* is glycyrrhetinic acid (GA). The result of *in vitro* studies showed that GA have $IC_{50}$ of 1.69 µg/mL and have adequate docking score. Based on *in silico* pharmacokinetic and drug-likeness studies, it also showed drug-like properties. Doses of 62.5–250 mg/kg have been shown to have an anti-malarial activity of 68–100%.[13] Recent research in the development of antimalarial drugs from plants has utilized nanoparticle technology. The antimalarial effect of *Andrographis paniculata*, *Azadirachta indica* and *Pteridium aquilinum* has been tested in the form of nano particles. The metal sources used including palladium, titanium salt, gold and silver.[41]

*Plasmodium falciparum* adenylosuccinate lyase (PfADSL) is an important enzyme in purine metabolism. Several benzimidazole derivatives have been synthesized and developed into commercially available drugs, however little is known about the design of the template as an inhibitor against *Plasmodium falciparum* adenylosuccinate lyase (PfADSL). Compounds from *Carica papaya* and *Swertia chirata* has affinity to inhibit dihydropteroate synthase of *Plasmodium falciparum*.[85] Medicinal plants have been investigated for their significant antimalarial activity and remain the main focus for scientists and researchers in the development of new antimalarial agents. Phytochemical compounds including alkaloids, phenolic compounds, anthraquinones, and flavonoids are commonly implicated for the antimalarial activity of many plants.[86] Finding new antimalarial drugs from herbal ingredients requires *in vitro* and *in vivo* research efforts, acute and chronic toxicity tests, thus the plants can be a potential antimalarial drug candidates. Summary of molecular mechanism and active compound of Medicinal plants that were mentioned in Table 1 is described further in Table 2.

*Andrographis paniculate*

*Andrographis paniculata, Azadirachta indica, Nyctanthes arbor-tristis, Ocimum sanctum, Piper nigrum, Zingiber officinale* are used in India in decoction form for malaria prevention.[42] *Andrographis paniculate* is an annual herbaceous plant which is a source of natural pharmacophores with many medicinal properties, namely Andrographolide. *Andrographis paniculate* is known in Asia (Japan), Southeast Asia (Malaysia, Thailand, Indonesia), India, China, Scandinavia.[87] It has been proven that it has antiparasitic, anticancer, antiviral, anti-HIV, antidiabetic, antitumor, antiangiogenic, antithrombotic, antibacterial, antiretroviral, anti-inflammatory, hepatoprotective and immunomodulating activities.[87,98] It also showed antipyretic and anti-diarrheal activities. Andrographolides also have been found to inhibit cytochrome P450 alpha-glucosidase and alpha-amylase enzymes that cause type 2 diabetes.[43]

The active phytoconstituent in this plant is andrographolide which is known to have beneficial biological activities.[87] Based on its *in silico* physiochemical properties, andrographolide is a potential drug candidate because it does not violate the five rules of thumb by Lipinski.[98]Andrographolide's mechanism of action that causes its various biological activities, is the ability to act as a bipolar component. It could interact with various inter- and intracellular constituents. Andrographolide can reduce inflammation by blocking the binding of NF-κB oligonucleotides to nuclear proteins thus NF-κB activation is inhibited.[87]*Plasmodium falciparum* infected erythrocytes have shown to induce NF-(kappa) B-regulated inflammatory pathways in human cerebral endothelium. The key to the mechanism of action of Andrographolide as an antimalarial by acting as an anti-inflammatory and transcription factor for the effective control of malaria.[99]

The chloroquine mechanism becomes resistant by inhibiting the activity of the main transporter channel protein, such as *Plasmodium falciparum*- Chloroquine Resistance Transporter (PfCRT) whose role is to regulate the accumulation of chloroquine in digestive vacuoles. It has been shown that mutation changes in the structure of chloroquine lead to the development of chloroquine resistance. Biochemical changes in the surrounding environment will affect the function of chloroquine. Based on research of the reversal effect of chloroquine from verapamil, it has showed the ability of chloroquine to bind certain allosteric sites in PfCRT.[98] Malaria parasite encodes several homologues of aspartic proteases such as plasmepsin I, II and IV which are responsible for degradation of host erythrocyte hemoglobin inside the vacuole of parasite food. Based on the in-silico docking study it was found that andrographolide interact to the ligand binding domain of plasmepsin I, II and IV.[100]

*Alstonia scholaris*

The pulai plant or *Alstonia scholaris* is known as a malaria medicine in communities in India, Bangladesh, Indonesia and Papua New Guinea. Communities in the Riau, East Kalimantan, Manokwari and Papua areas use the bark, leaves and sap of the pulai plant for traditional medicine.[101] The plant parts of *A.scholaris* are rich in various bioactive compounds such as echitamidine, N*α*-formylechitamidine, boonein, loganin, lupeol, ursolic acid, and *β*-amyrin among which the alkaloids and triterpenoids form a major portion.[88,101] In another countries, the parts of plants that have anti-malarial activity are root, bark and whole plant. *Alstonia scholaris* is given as a once-daily infusion to treat malaria traditionally in India.*Alstonia scholaris* also a hepatoprotection that can strengthen and protect liver cells from plasmodium infection.[102]

The concentrated aqueous extract of the leaves or bark of the young tree has been used to treat malaria in Lombok. Antimalarial testing with *Plasmodium falciparum*, revealed that the alkaloids obtained from leaves of *A. scholaris* from Lombok were active.[103] Although traditionally Pulai has benefits as an antimalarial, but the results of the chemical compound test of Pulai have not shown satisfactory results as an antimalarial.[101]*Alstonia scholaris* has antioxidant activity characterized by *in vitro* nitric oxide scavenging activity .[88] However, the direct mechanism of *A.scholaris* as antimalarial has not been widely studied. Based on the description in Table 1 and 2, although *Alstonia scholaris, Nigella sativa, Cocos nucifera* and *Piperaceae* have been widely used in ethnomedicine in several countries and has been widely studied, their mechanism of action as antimalarial still unclear.

*Curcuma longa*

*Curcuma longa* well known as turmeric is a familiar plant found and used in southern Asia and some parts of Africa.

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**Table 2:** Studies Describing Active Compound and Mechanism of Action of Different Medicinal Plants as Antimalarial

| Species | Mechanism of action | Active compound | References |
|---|---|---|---|
| Piperaceae (*Piper peltatum, Piper betle*). | *in vitro* inhibition of hemozoin formation and isoprenoid biosynthesis | 4-Nerolidylcatechol<br>Flavonoid | 33 |
| *Andrographis paniculate* | inhibit cytochrome P450<br>act as a bipolar component that could interact with various inter- and intracellular constituents | Andrographolide | 43, 87 |
| *Alstonia scholaris* | Not clear | Echitamidine, Nα-formylechitamidine, boonein, loganin, lupeol, ursolic acid, and β-amyrin | 88 |
| *Tinospora crispa* | inhibit protein synthesis in *P. falciparum*, prevent oxidative stress, inhibit NO formation, decrease the expression of the adhesion molecules and act as an inflammatory signaling molecule | N-trans-feruloyltyramine<br>diterpenoids (borapetoside A, B, and C) | 89 |
| *Physalis angulata* | inhibit hemozoin and accumulate in the parasite dietary value | Physalins | 90, 91 |
| *Aloe spp* | stimulate the formation of reactive oxygen | Anthraquinones (Aloin, aloe-emodin, aloe bitter and aloe lectin) | 68 |
| *Allium sativum* | inhibitory effect on cysteine proteases from parasites | Allicin | 65 |
| *Morinda citrofolia* | reduction of NO and PGE2 production, and inhibition of COX-1 and -2 | Anthraquinones and iridoid glucosides | 92 |
| *Momordica charantia* | DMC suppressed the expression of many PPARγ-targeted signaling effectors, including cyclin D1, CDK6, Bcl-2, XIAP, cyclooxygenase-2, NF-κB | 3*β*,7*β*-dihydroxy-25-methoxycucurbita-5,23-diene-19-al (DMC)<br>Cucurbitacins<br>Momordicin | 93,94 |
| *Moringa oleifera* | inhibit hemozoin formation<br>inhibit nucleic acid and protein synthesis, inhibit NF-κB | flavonoid, quercetin, kaempferol | 75, 95 |
| *Cocos nucifera* | inhibit FabZ, FabG and FabI enzymes that is required for *P. falciparum*'s fatty acid biosynthesis | Flavonoid classified as ester of catechin gallic acid. | 96 |
| *Nigella sativa* | Antioxidant<br>inhibit hemozoin formation | thymoquinone, thymohydroquinone, dithymoquinone, thymol, nigellicine, carvacrol, nigellimine, nigellicine, nigellidine, and alpha-hederin | 56 |
| *Carica papaya* | Asparaginase convert L-asparagine to aspartic acid and ammonia also Inhibition hemozoin formation | L-asparaginase<br>flavonoids, tannins, saponins | 75, 97 |
| *Curcuma longa* and *domestica* | Curcumin | as scavenger of reactive oxygen species (ROS), it also acts as anti-inflammatory via inhibition of enzymes cyclooxygenase-2 (COX-2) and 5-lipooxygenase | 78 |

Its ability to cause a yellow color and distinctive aroma makes this plant commonly used as a natural food coloring agent. [104] The advantage of this plant is cheap, easy to find. However, it has low solubility and rapid metabolism, thus it has been developed in the form of nanoparticles and lyposomes. [78]

In addition to treating malaria, *Curcuma longa* is also used to treat jaundice, peptic ulcers, skin problems, diabetes, arthritis, high blood pressure, cold and flu symptoms, convulsions and emotional disorders in Nigeria. [104]*Curcuma longa* and *Curcuma domestica* have bioactive compound curcumin. Research on the health effects of curcumin have been developed. Those studies also prove that curcumin has various biological effect and pleotropic function on human health.[84] Curcuma is used traditionally in Thailand, Nigeria, Indonesia to treat various diseases[104,105] Curcuma involved in modulation of biological processes. It could prevent pathogenesis of diseases due its effective scavenger of reactive oxygen species (ROS) and inhibition of styrene oxidation. Anticancer property of curcumin due its antioxidant effect that could control DNA damage and free radical–mediated lipid

peroxidation.[78] Curcumin also have an important in the health management through its anti-inflammatory effects. It is believed that curcumin shows role as anti-inflammatory via inhibition of enzymes such as cyclooxygenase-2 (COX-2) and 5-lipooxygenase. It was confirmed that its role in the management of diseases via inhibition of pathogenesis of diseases. [78]Curcumin showed role in the reduction of blood parasitemia by 80%–90%. Curcumin also has an effect on *Giardia lamblia* infection *by* inhibiting the parasite growth and adherent capacity, induced morphological alterations and provoked apoptosis-like changes.[78]

*Tinospora crispa*

*Tinospora crispa* is a decidual plant often found in rainforests, it has the ability to treat various diseases including malaria, diabetes, scabies, rheumatism, jaundice, hypertension. This plant contains various components including flavonoids, alkaloids, glycosides, triterpenes, lactones, sterols, lignans, and nucleosides.[89]*Tinospora crispa* has both gram-positive and negative antibacterial activity, also against cholera and syphilitic, this plant also has an antimicrofilarian effect against *B. malayi*, *P. yoelii* and *P berghei* ANKA.[89]

The active component of *T. crispa* is N-trans-feruloyltyramine. It is isolated from aqueous extracts of these plants. Its molecular mechanism is to inhibit NO formation by reducing iNOS expression. The stem of *T. crispa* acts as an anti-inflammatory by decreasing the expression of the adhesion molecules (ICAM-1, VCAM-1) and inflammatory signaling molecule (M-CSF). [89] Stem extract of *T. crispa* containing diterpenoids (borapetoside A, B, and C). It was believed that diterpenoids play a role as antimalarial. Those diterpenoids can inhibit cancer cell growth by preventing oxidative stress caused by reactive oxygen species. In addition, *T. crispa* is said to inhibit protein synthesis in *P. falciparum*.[106]

*Physalis angulate*

*Physalis angulata* is used to treat malaria, asthma, hepatitis, dermatitis, rheumatism. Phytoconstituents of *P. angulata* are glucocorticoids, flavonoids, withanolides and physalins. Physalins is believed as compounds that responsible for the leishmanicidal effects of *P. angulate*. That substance was mostly isolated from the plant's stems and leaves.[90] The mechanism of physalin as an antimalarial is thought to inhibit hemozoin and accumulate in the parasite dietary value, but specific research is needed to prove this. [107]Physalins B, D, F, and G were found to have antimalaria activity based on silico similarity ensemble approach (SEA). [107]

*Aloe spp*

*Aloe* spp is best known commercially as *Aloe vera*. *Aloe* spp is known for its abilities as fast healing and can treat various ailments. This plant is commonly known as a household plant, containing many nutrients including organic acids, phenol components, proteins, vitamins, enzymes and polysaccharides. [68]The phytoconstituents of *Aloe vera* are anthraquinones, inorganic compounds, amino acids, fatty acids, alkaloids. Based on scientific evidence, the antimalarial activity of this plant is due to anthraquinones and other quinoid compounds. Aloin, aloe-emodin, aloe bitter and aloe lectin are anthraquinones which are valuable in health. [68]

The mechanism of action of anthraquinones is to stimulate the formation of reactive oxygen. Anthrone, homonataloin are contained in leaf latex extract from this plant, thus it can function as an antimalarial. [68] Apart from having antimalarial activity, this plant has anti-inflammatory, antidiabetic, antioxidant, wound healing, anti-cancer, cardioprotective effects, prebiotic and antimicrobial activity. [109]The uniqueness of this plant is that when conditions are less favorable or full of stress, this plant actually produces more flavonoids, anthocyanins and mucilaginous substances. Kumar's research, 2017 showed that the antimalarial activity of anthraquinones lower than the whole extract from *Aloe vera*, it was concluded that the antimalarial activity was due to the interaction of various anthraquinones and other components. [68]

*Aloe weloensis* is traditionally used to treat malaria in Ethiopia. Apart from treating malaria, *A. weloensis* is useful as a treatment for rheumatism, infections, ears, skin lesions, headaches. The leaf latex of *Aloe weloensis* has been tested for its antimalarial activity against *Plasmodium berghei*[67]It has been found that the Aloe plant species obtained in India contain aloin and aloe-emodin. [68]

*Allium sativum*

*Allium sativum* or garlic plants have been used for traditional medicine since ancient times. [63,65]

Combination of garlic and arteether can increase survival and reduce parasite numbers by affecting the NO pathway during infection and influencing the role of T cell subsets. [63] The benefit of garlic for health was first introduced by Louis pasteur in India, China and Europe. [66]Phytoconstituents of garlic such as alliin, allicin, ajoene, vinyldithiins, and flavonoids such as quercetin.[64]

Garlic and its components are known to have activity against parasitic infections such as Leishmania, Schistosoma, Trypanosoma, Giardia, Entamoeba, and Plasmodium. The biological activity of garlic caused by its main component known as thiosulfinate, such as allicin (diallyl thiosulfinate). One study has reported that the mechanism of allicin acting as anti-plasmodial and anti-trypanosomal was due to its inhibitory effect on cysteine proteases of parasites. The components of *Allium sativum* stimulate splenocyte proliferation and synthesis of NO and TNF, thereby stimulating immunity. Allicin can also act as an immune suppressant by inhibiting T cell interactions with endothelial cells thereby reducing inflammation.[65]

*Morinda citrofolia*

*Morinda citrifolia* is better known in the community as noni, is found in India, Tahiti, Indonesia. Various parts of Noni plant such as stem, bark, root, leaf and fruits are used traditionally by Hawaiians and Tahitians as medicines for the treatment of ailments like cough, cold, pain and liver diseases, hypertension, blood pressure, tuberculosis, malaria, intestinal worms, diabetes, loss of appetite, hernias, urinary tract infection, menstrual disorder, cancer, cardiovascular diseases, arthritis. [49]Noni contains 160 phytoconstituents, of which 120 are biologically active components Noni fruit containing ketones, lactones, beta-carotenoids, terpenoids, and proxeronine. It also has antibacterial, anti-fungal, antiviral activity. Noni has pharmacological effects as an antitumor and cancer, anti-psychosis, improves cognitive function, Alzheimer's treatment, antidiabetic, anti-hyperlipidemia, antioxidant and hepatoprotection. [49]

Several phytoconstituents from *M. citrifolia* that have clear biological effects and mechanisms of action including damnacanthal, epigallocatechin gallate (EGCG), alizarin and limonene, polysaccharides, scopoletin, quercetin, xeranine, citrifolinoside, monoterpene, beta carotene, ursolic acid and gallic acid. [49] More recently, three are new compounds, namely, 2-O- (β-D-glucopyranosyl) -1-O- (2E, 4Z, 7Z) -deca-2,4,7-trienoyl-β-D-glucopyranoside, 10 -dimethoxyfermiloside, and 2-caffeoyl-3-ketohexulofuranosonic acid γ-lactone which can be isolated from noni.[92] *Morinda citrofolia's* mechanism of action as antimalaria by inducing phase II enzyme quinone reductase (QR), reducing NO and PGE2 production as well as inhibiting COX-1 and 2.

The active ingredients that cause this effect are anthraquinones and iridoid glucosides which are isolated from its fruit. The filaricidal activity of noni against *W. bancrofti* has been investigated *in vitro*. Noni modulates the immune system through CB2 receptor activation, and IL-4 suppression however, it can increase the production of IFN-gamma cytokines.[92]

*Momordica charantia*

*Momordica charantia* is found in various tropical and subtropical countries such as Asia, America, Middle East and has been used as herbal medicine. The name Momordica comes from Latin for "to bite". The fruits, leaves and roots of *M. charantia* are used in traditional medicine to treat toothaches, skin and gastrointestinal infections and diabetes. It was also believed that intestinal worms, scabies, contraceptive, antimalarial, laxative, rheumatism, gout, and various infections such as leprosy, piles and jaundice can be cured by *M. charantia. Momordica charantia*has also been tested for its effect on HIV infection. The pharmacological effects of *M. charantia* such

as reduce blood sugar levels, immunomodulators, wound healing, anti-tumor, antioxidant and anti-inflammatory. [48]

*Momordica charantia* is used in Nigeria to treat various ailment. [6]*Momordica charantia* is traditionally used as an anti-malarial. [51] Research shows that the water extract of *M. charantia* is effective in treating *P. falciparum* infection with an IC value of 83.64 µg/ ml - 88.14 µg/ ml. [47]*Momordica charantia* has been proven as an antimalarial at a dose of 200mg/ kg BW however, its antimalarial effect lower than *Mirabilis jalapa*. [50]In addition to some toxic symptoms, previous studies have concluded that *M. charantia* may induce symptoms such as hypoglycemic coma in children, abortion or even death in laboratory animals. [48]

Phytoconstituent of *M. charantia* are Triterpenoids, saponins, polypeptides, flavonoids, alkaloids and sterols. [48] A studied also described that the content of *M. charantia* were trans-nerolidol, apiole, cis-dihydrocarveol and germacrene D. [46] Saponins from *M. charantia* including momordicin, momordin, momordicoside, karavilagenin, karaviloside, and kuguacin which are useful as antiparasitic, antibacterial, antiviral and antifungal. [93]A cucurbitane-type triterpene that called 3*β*,7*β*-dihydroxy-25-methoxycucurbita-5,23-diene-19-al (DMC) were isolated from wild bitter gourd. [94]Phytoconstituents such as glycosides, phytosterols, alkaloids, phenolic, saponins, fats, proteins, fixed oils, flavonoids were also found in *M. charantia*. [110] Cucurbitacins are reported to be the main active constituents of *M. charantia*. It has anti-hyperglycemic, anti-hyperlipidemic, hepatoprotective, anti-obesity, anti-cancer and anti-viral activities.[111] A study had been mentioned that compounds such as charantin, MAP 30, momordin, alpha and beta momorcharins were isolated from *M. charantia*. [51] The effect of DMC is to suppress the expression of many PPAR*γ*-targeted signaling effectors, including cyclin D1, CDK6, Bcl-2, XIAP, cyclooxygenase-2, NF-*κ*B, estrogen receptor *α*, and induced endoplasmic reticulum stress. Research regarding the benefit of *M. charantia* on health is abundant, and it has various phytoconstituents however, it remains unclear which phytoconstituents other than DMC have an antimalarial effect.[94]

*Moringa oleifera*

*Moringa oleifera* plants can be found in Northwest India, and South Africa, Northeast Africa, Madagascar, Tropical Asia, Southwest Asia and Latin America. The Moringa genus plant has important religious, social, cultural, nutritional, and environmental aspects. The Moringa genus plant has been used by the Indian, Greek, and Egyptian people for several purposes such as pain, stress, skin, mental health.[95] *Moringa oleifera* has antioxidant, anti-inflammatory, anticancer, and antihyperglycemic effects.[93] *Moringa oleifera* leaves have pharmacological effects for lowering blood pressure and cholesterol, antifungal, worm treatment, and wound healing, while the roots and stems of *M. oleifera* are useful for reducing spasms, anti-epilepsy, diuretics. The seeds of *M. oleifera* have an antimalarial effect, reduce heat and inflammation. *In vitro* study has also proven that its leaf extract has an antimalarial effect.[72] The roots and leaves of *M. peregrina* that are mixed together with water can be used to treat hypertension, malaria, asthma, stomach disorders, diabetes, and expel a retained placenta.[112] A study had described that extract of *M. oleifera* roots and leaves had antileishmanial activity against *L. donovani* promastigotes. [73]*Moringa oleifera* can also be used to treat thrush, sore throat, bronchitis and improve vision.[71]

The nutrients that contained in *M. oleifera* leaves are very high, including fiber, protein, calcium, iron, vitamin C, and carotenoids, thereby can relief malnutrition.[71] *Moringa oleifera* contains flavonoids, glucosides, and glucosinolates. Moringa leaves are a good source of nutrition because of their vitamin C, vitamin A. Protein in Moringa leaves higher than yogurt and carrots, while its potassium higher than bananas, and its calcium higher than milk. Zeatin in *M. oleifera* is used as a natural plant growth enhancer thereby it can increase crop yields. [73]The dried leaves of *M. oleifera* contain flavonoids and polyphenols. The flavonoids contained in *M. oleifera* are myrecytin, quercetin and kaempferol. Apart from flavonoids, *M oleifera* also contains vitamins E and C.[74]

The antimalarial activity observed in *M. oleifera* extract caused by single or combination those metabolites. The possible mechanisms might be through antioxidant, free radical scavenging, immunomodulatory, intercalation in DNA, inhibition of protein synthesis, interference with the invasion of new erythrocytes by parasites, or by any other unknown mechanisms. [75]*Moringa oleifera l*eaves have an antimalarial effect probably due to its antioxidant capacity that could reduce the body's inflammatory response. [95]Phytoconstituent that would contribute as antimalarial are flavonoid, quercetin, kaempferol. Antioxidant activity of flavonoid, kaempferol, quercetin can inhibit hemozoin formation, thereby it will cause free heme that very toxic for plasmodium. Mechanism of action of quercetin, kaempferol were known by inhibiting nucleic acid and protein synthesis as well as inhibiting nuclear transcription factor-kappa B (NF-κB) that was required in parasite's growth and development.[75]The effect of *M. oleifera* on experimental animals describe that it will increase the numbers of effector CD4 + T cells, IFN-gamma, TNF, Tbet expression, thereby it is concluded that mechanism of action of *M. oleifera* is to restore CD4 + T cell activation, IL-2, and IL-10 [71]

*Carica papaya*

Solvent fractions of *C. papaya* fruit rind and root have been studied for their effectiveness as an antimalarial. [86] The phytoconstituents that are thought to cause those effects including flavonoids, tannins, saponins. *Carica papaya* and *Vernonia amygdalina* will decrease WBC and increase RBC production, which ultimately increased PCV.[52]Previous studies have been found that the administration of *C. papaya* and *V. amygdalina* alone or in combination reduced parasite load, repaired hepatic cell damage and hematological parametersin mice infected by malaria. [52]*Carica papaya* alone or combine with *Delonix regia* bark extract has been shown to improve the immune system in *P. berghei* infection. The dose of *C. papaya* which showed the greatest inhibition against parasitemia was found at 9.75 mg/g.[44]

Asparaginase is useful for converting L-asparagine to aspartic acid and ammonia. Asparaginase will remove Plasmodium's asparagine which required by parasites. Ammonia production resulting from L-asparagine conversion will cause toxicity to parasites that lack of ammonia detoxification machine.[97] Plasmodium's protein has abundant asparagine. Plasmodium get amino acid from hemoglobin degradation of host, thereby its pathway for amino acid is not well developed, however plasmodium still retain a gene encoding asparagine synthetase. Impact of depletion of asparagine will cause development of liver stages, ex-flagellation of male gametocytes and formation of sexual stages are delayed.[97]

*Nigella sativa*

*Nigella sativa* or black seed is a plant that has been often researched and has good medical evidence in health. This plant can be found in Southern Europe, North Africa and Southwest Asia, India, Pakistan, Syria, Turkey, Saudi Arabia, Middle Eastern Mediterranean region, South Europe. [113]Characteristics of *N. sativa* including it is an annual and delicate flowering plant, it has finely divided leaves, its fruits a large with 3-7 united follicles that each of it contain numerous seeds. It has numerous biological effects such as diuretic, antidiabetic, antihypertensive, anticancer, analgesic, antimicrobial, spasmolytic, bronchodilator, hepatoprotective, gastroprotective, renal protective and antioxidant. It is also believed that *N. sativa* have antiparasitic effect and increase immune system.[113] *Nigella sativa* is also a promising drug candidate for treating HIV.[114] *Nigella sativa* has antimalarial presumably due to its antioxidant properties. The phytoconstituent of *N. sativa*, including thymoquinone, thymohydroquinone, dithymoquinone, thymol, nigellicine, carvacrol, nigellimine, nigellicine, nigellidine, and alpha-hederin.[56] Although research regarding benefit of *N. sativa* on health abundant, however its mechanism of action as antimalarial remains unclear.

*Cocos nucifera*

Coconut tree in ethnomedicine is used as a treatment for diarrhea, arthritis, fever, asthma, malaria, and diuretic.[96] *Cocos nucifera* has also been studied for its effects on *Trypanosoma cruzi*, *Leishmania donovani*, malaria and breast cancer cells. Its phytoconstituents are polyphenol, flavone, sterol, fatty acid and chlorophyll.[96] Dose of 200

and 400mg/kg *C. nuciferae* has been proven to have anti-malarial effects.[115] *Cocos nuciferae* contains flavonoids such as acacetin, apigenin, baicalein, chrysin, genistein, kaempferol, luteolin, that have been shown to have antimalarial activity. Catechin compounds are known to have antimalarial activities. The development of the malaria parasite requires fatty acid synthesis which is necessary for biogenesis of parasitic membranes and lipid, retain parasitic membrane proteins through glycosylphosphatidylinositol groups. *Plasmodium falciparum* fatty acid biosynthesis requires 3 enzymes namely FabZ, FabG and FabI. The most active compounds of *C. nuciferae* that effective against parasites are flavonoids, which are classified as ester of catechin gallic acid. It has been described that flavonoids inhibit FabZ competitively, while FabG is inhibited noncompetitively, and FabZ and FabG are competitive inhibitors for FabI.[96]

*Piper spp*

*Piper* species is known as spices in the kitchen, whose secondary metabolites have various health benefits, including to treat urological, liver, skin and gastric disorders, it also can treat urological problems, skin, liver and stomach ailments, wound healing, antipyretic and anti-inflammatory. In addition, *Piper* species could be used as natural antioxidants and antimicrobial agents in food preservation.[60] The genus *Piper*, belonging to the Piperaceae family, consists of five subgenera and about 1400 species spread over the tropics and subtropics areas. Of these, only 83 species have been used in traditional medicine.[60] Leaves of *P. betle* in ethnomedicine were used to treat parasite, fungal, bacteria, antiseptic, aphrodisiac, astringent, carminative, expectorant, laxative, epistaxis. There were 26 species of *Piper*s that had activity in dealing with parasitic infections, but the most common were *P. aduncum, P. betle* and *P. longum*. The parasite species that have been overcomed by *Piper* spp are *Plasmodium falciparum*, *Trypanosoma cruzi* and *Leishmania* spp.[60]

Root of *P. peltatum* in Amazon and Brazil area were used to treat malaria traditionally.[18,33] Infusions of leaves and roots of *P. peltatum* in Brazil's traditional medicine were used to treat erysipelas, malaria, leishmaniasis and hepatitis. [60] It was found that active compound of *P. peltatum* was 4-Nerolidylcatechol.[18,33] Based on *in vivo* study, it was found that the leaf extract of *P. betle* demonstrated significant schizonticidal activity[116.] Essential oil (Eos) from *P. betle* leaves contain phenylpropanoids and aromatic compounds while EOs from whole plant contain chavibetol, allylcatechol, methyl eugenol, and estragol, α terpinene, p-cymene, 1,8-cineole, β-caryophyllene, α-humulene.[60] It has been concluded in previous study that the mechanism of action of *Piper* spp as an antimalarial by inhibiting hemozoin formation and isoprenoid biosynthesis.[33] Table 3 describes previous studies that investigated the receptor (active compound) and ligands of medicinal plants that have anti-malarial effects. The study that investigated receptors (active compounds) and ligands from plants such as *Alstonia scholaris, Morinda citrifolia, Cocos nucifera*, Piperaceae has not been found yet.

**Table 3**: Studies Investigate Receptor and Ligand of Plants as Antimalarial based on Docking

| No | Plant | Receptor (active compound) | Ligand | Reference |
|---|---|---|---|---|
| 1 | *Andrographis paniculata* | Andrographolide | | 100 |
| 2 | *Aloe spp* | Aloin microdontin | | 117 |
| 3 | *Allium sativum* | Alliin | | 118 |
| 4 | *Alstonia scholaris* | - | - | - |
| 5 | *Morinda citrifolia* | - | - | - |
| 6 | *Carica papaya* | Benzyl Glucosinolate | Dihydropteroate Synthase 2 | |
| 7 | *Momordica charantia* | β-carboline derivative (1r,3s)-methyl 1-(benzo[d][1,3]dioxol-5-yl)-2,3,4,9-tetrahydro-1h-pyrido[3,4-b]indole-3-carboxylate, | 3d7 and rkl-9 strains of p. falciparum | 119 |
| 8 | *Moringa oleifera* | Phytol | pfDHFR-TS | 121 |
| 9 | *Tinospora crispa* | Benzeneethanamine and camphenol | Protease | 106, 122 |
| 10 | *Physalis angulate* | Physalin B and D | Hemozoin | 108 |
| 11 | *Nigella sativa* | Thymoquinone | Protease | 123 |
| 12 | *Cocos nucifera* | - | - | - |
| 13 | *Piperaceae* | - | - | - |
| 14 | *Curcuma longa, curcuma domestica* | Curcumin | glycogen synthase kinase-3β (GSK3β) | 84 |

## Conclusion

*Aloe spp, Allium sativum, Alstonia scholaris, Morinda citrifolia, Andrographis paniculate, Carica papaya, Momordica charantia, Tinospora crispa, Moringa oleifera, Physalis angulate, Nigella sativa, Cocos nucifera and Piperaceae* are species of plant that have been used as anti-malarial based on ethnomedicine approach. Molecular mechanism of medicinal plant that has been used as antimalarial varies; including inhibition of several mechanism enzymes, metabolism and synthesis.

Molecular mechanism of *Alstonia scholaris, Morinda citrifolia, Cocos nucifera* and *Piperaceae* as anti-malarial are still unclear, thus *e*xtensive research on those plants is required.

## Conflict of Interest

Authors declare no conflict of interest

## Authors' Declaration

The authors hereby declare that the work presented in this article are original and that any liability for claims relating to the content of this article will be borne by them.

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