A Review: Active Components In Plants With Antimalarial Activity

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Abstract. A tropical threatening disease, malaria is caused by Plasmodium parasites and resulted in 608,000 fatalities in 2022. The increase in treatment-resistant parasites from Southeast Asia over the past two decades has further prolonged mortality and morbidity. Natural goods have played a significant and distinctive role in improving human health. This is especially evident in the context of malaria, where millions of lives have been saved by the natural products quinine, artemisinin, and its derivatives. The development of novel drugs for the treatment of malaria is an important need, as the fatal malaria parasite, Plasmodium falciparum, has shown a tolerance for quinine and its derivatives and is also showing signs of resistance to artemisinin and its derivatives. Many plants in the world, including in Indonesia, are often used by the community in the treatment of malaria. Active components in plants or herbal medicine that function as antimalarials include alkaloids, endoperoxide, terpenes, polyphenols, etc. The purpose of this review is to discuss the activity of these active components as antimalarial agents.

Keywords. Active component, plants, antimalarial

1 Introduction

Malaria has existed for a long time and is still a problem in the world. *Plasmodium spp*., a member of the apicomplexan parasite family, causes malaria through the bite of the Anopheles mosquito. The annual caseload surpassed two hundred thousand. The vast majority of these infections, approximately 95%, are reported from countries within sub-Saharan Africa. Epidemiological surveillance on a global scale shows that malaria incidence was estimated at 227 million in 2019, climbed to 241 million in 2020 and reached to 249 million in 2022. This escalation was compounded by the COVID-19 pandemic, during which health systems in many regions reallocated significant human and material resources towards pandemic mitigation, potentially disrupting malaria control activities [1], [2]

ICWSDGs 2024, September 09-10, Banjarmasin, Indonesia

DOI 10.4108/eai.9-9-2024.2359028

Malaria control programmes are being hindered by substantial challenges, mainly arising from the growing prevalence and wider geographic spread of resistance to all recommended first-line antimalarial agents for both therapeutic and prophylactic purposes [2] In response to these challenges, research efforts have increasingly focused on bioactive compounds derived from natural resources, particularly medicinal plants with a documented history of traditional use in malaria-endemic regions worldwide, with the aim of developing novel antimalarial agents, whether fully synthetic or phytochemical-based [3], [4]. The therapeutic potential of such plant-derived remedies is influenced not only by their phytochemical composition but also by the quality and integrity of the raw simplicia used [5]

To address the global burden of malaria, the World Health Organisation (WHO) developed the *Global Technical Strategy for Malaria* 2016-2030, which is structured around three core pillars: transforming malaria surveillance into a core intervention; achieving elimination and preventing re-establishment; and ensuring universal access to prevention, diagnosis, and treatment. These pillars are supported by two enabling elements, namely fostering research and innovation, and strengthening the systems and environmental conditions necessary for malaria eradication. Natural products remain an invaluable resource in antimalarial drug discovery, exemplified by the isolation of artemisinin from medicinal plant sources [1]

In the Indonesian context, various medicinal plants have been traditionally employed by indigenous communities for the management of ailments, including malarial fever. A nationwide survey conducted by the Ministry of Health of the Republic of Indonesia in malaria-endemic districts, involving 12,226 respondents, revealed that 20% reported using traditional remedies for the treatment of malarial fever[6]. This review seeks to explore the spectrum of antimalarial and bioactive compounds present in a range of medicinal plants.

2. Active Components From Plants With Antimalaria Activity

Various pharmacological agents have been employed in malaria therapy, among them mefloquine, derivatives of artemisinin, quinine, amodiaquine, and chloroquine [3], [7].The alkaloidal substance, quinine was the initial antimalarial medication extracted from *Cinchona bark*. Chloroquine, a synthetic derivative of quinine, was developed in the 1940s as a 4-aminoquinoline compound. For many years, this medicine was the preferred treatment for malaria because it was effective, inexpensive, and had less side effects [8]However, the used in modern malaria therapy has been limited since the parasites have developed resistance to chloroquine. Mefloquine, a compound structurally similar to quinine, has been developed as a drug for malaria which resistant to chloroquine. However, its usage is restricted due to resistance issues and the occurrence of neuropsychiatric side effects [9], [10].

The compound artemisinin, characterised by an endoperoxide bridge, is derived from the medicinal plant *Artemisia annua*, also referred to as sweet wormwood. Its semisynthetic analogues (artemether, arteether, and artesunate) are recognised as among the most efficacious antimalarial agents, particularly in settings where resistance to conventional treatments has emerged. To slow the

spread of drug resistance, the World Health Organization (WHO) recommends that these agents be administered in combination with other antimalarials, a regimen termed artemisinin-based combination therapy (ACT). However, research has documented indications of *Plasmodium spp* resistance developing against ACT. [1], [11]

3 Alkaloids

Researchers have identified alkaloids as the most important compound for antimalarial activity. To determine the presence of alkaloid components in a plant extract, a qualitative phytochemical examination is used using Wagner's or Draggendroff's reagents [5]. Members of this alkaloid class are distinguished by a nitrogen-containing heterocyclic moiety, typically arranged in a terpenoid framework. Structural diversity within this group arises from variations in the terpenoidal backbone, which can significantly influence biological activity. Notably, cassane-type diterpenes and indoloterpenes isolated from *Caesalpinia minax* [12], [13], *Polyalthia oliveri*, and *Strychnos nux-vomica* have been reported to exhibit superior antiplasmodial potency [9]. Within *C. minax*, caesalminines A and B, bearing a γ-lactam ring, demonstrate remarkable inhibitory effects with IC_{50} values of 0.42 μM and 0.79 μM, respectively, underscoring the contribution of the lactam moiety to their activity profile [9]. Conversely, N-acetyl-polyveoline and N-acetyl-8-polyveolinone, derived from *P. oliveri*, display only moderate suppression of *Plasmodium falciparum* growth, suggesting a less optimal structural configuration for high-level antiplasmodial efficacy. The *Greenwayodendron suaveolens* tree yields the polyalthenol and N-acetyl-polyveoline. These alkaloids have been found to be effective against *P. falciparum* [8], [9], [10].

Indoloquinolines, an alkaloid with antimalarial properties, have a dual mechanism of action: obstructing the creation of hematin (similar to chloroquine) and interacting with DNA. Quinoline, like chloroquine, acts as an antimalarial by inhibiting the formation of hematin in the parasite's acidic digestive vacuole. This will stop hemoglobin digestion and convert hemozoin into a harmless form. The presence of basic nitrogen in indoloquinolines enhances the compounds' ability to act as bases. This allows the substance to accumulate in the Plasmodium's food vacuole, effectively exerting its antimalarial effects [14].

Classified as an alkaloid, the compound piperine is identified as the main amide present in the fruits of *Piper chaba* Hunt, *Piper nigrum* L. (black pepper), and *Piper longum* L. (long pepper), with its chemical structure defined as 1-[5-(1,3-benzodioxol-5-yl)-1-oxo-2,4-pentadienyl] piperidine [15], [16] Beyond its traditional uses, piperine is recognised for a wide range of pharmacological actions, including antioxidant, anticancer, antidepressant, hepatoprotective, anti-asthmatic, antipyretic, anti-inflammatory, analgesic, and anticonvulsant effect. Laboratory studies have revealed that piperine demonstrate antimalarial efficacy against both chloroquine-sensitive (*P. falciparum* 3D7 strains) and chloroquine-resistant (K1). Its mode of action involves interference with several drug-resistance-associated genes, including *pfmrp1*, an ABC transporter gene from chromosome 1, responsible for folate export to host erythrocytes. Another gene, *pfmdr1*, encoding a P-glycoprotein homologue within the parasite digestive vacuole membrane that modulates drug sensitivity. Lastly, *pfcrt*, which codes for a multi-domain transmembrane protein linked to *P.*

falciparum chloroquine resistance during the erythrocytic stage. Given these molecular interactions and its relatively low risk of inducing resistance, piperine stands out as a potential lead molecule for next-generation antimalarial drug design [3], [4], [7], [16].

4 Endoperoxide

Endoperoxide is a compound that exhibits antimalarial properties and contains a dioxin bridge. The antimalarial mechanism of endoperoxide is divided into two stages. The first stage is the activation phase which includes activities mediated by iron. Endoperoxide breakdown releases an unstable material known organic free radicals or electrophilic species. The second stage is the alkylation phase, which results in covalent bonds between the active compound and malaria proteins [3], [9].

Malaria parasites contain heme iron, released during the digestion of host haemoglobin. The heme iron plays a critical role, with Fe21-heme believed to be the primary trigger for artemisinin activation. Clinically, endoperoxides are employed both for the rapid clearance of malaria infections and for the management of drug resistant *Plasmodium spp* strains. They are categorised into two generations based on their origin. The first generation includes artemisinin, extracted from *Artemisia annua* Linn, and its semisynthetic derivatives, arteether, artemether, and artesunate, which are produced via structural modification of the parent molecule [4], [7]. These agents exert their activity against *Plasmodium spp* within erythrocytes by means of the endoperoxide bridge (C-O-O-C), a distinctive chemical motif capable of inducing parasite death. The second generation is represented by dihydroartemisinin, a lactol-based derivative of artemisinin. Another example is plakortide fatty acid, a cyclic peroxide metabolite synthesised by marine sponges of the genus *Plakortis* (family Plakinidae) [4]. Endoperoxides have various advantages due to the lack of cross-resistance. This active compund has a more rapid initiation of action in comparison to other antimalarial drugs. Two problems of utilizing this endoperoxide are its limited duration of action and transient efficacy, which can result in accelerated re-infection [9].

5 Terpenes

Terpenoids constitute the largest group of secondary metabolites in plants, with more than 35,000 varieties identified. These molecules are formed from repeating isoprene units (2-methylbuta-1,3-diene), each containing five carbon atoms, which make up the hydrocarbon backbone. Their classification depends on the number of isoprene units incorporated: compounds with a single unit are called hemiterpenoids, those with two units are monoterpenoids, three-unit forms are sesquiterpenoids, and those with four units are classified as diterpenoids. [4]. Terpenoids play a pivotal role in ecological processes, including the attraction of animals that disperse pollen or seeds, the inhibition of germination and development of neighboring plants, and the interaction between plant-insects and plant pathogens. In addition to these properties, terpenoids have several

pharmacological effects, including antimalarial, antiviral, anti-inflammatory, anti-cancer, and suppression of cholesterol formation [3], [7].

Wedelia biflora, belonging to the same botanical family as *Artemisia annua,* is locally referred to in Indonesia as 'sernai' leaf. Methanolic extract from these leaves have been shown to inhibit the development of the *P. falciparum* trophozoite stage, an effect attributed to the presence of triterpenoid compounds [17]. Similarly, dried leaves of *Tithonia diversifolia* (commonly known as "Kembang Bulan") produce an extract capable of suppressing *P. berghei* growth in murine models, with an ED_{50} value of 214 mg/kg body weight. Tagitinin C, a sesquiterpene lactone recognised as one of the principal bioactive compounds in *Tithonia diversifolia*, has shown potent antiplasmodial effects, exhibiting an IC_{50} value of 0.75 µg/mL against the *Plasmodium falciparum* FCA strain [17], [18]. Additional bioactive components with antimalarial potential are also present in Kembang Bulan leaves. Ngum et al. reported that a flavonoid-rich extract from *T. diversifolia*, through combined antiplasmodial and immunomodulatory actions, holds promise as an antimalarial treatment. Administration of the extract to *P. berghei*-infected rats resulted in immunomodulatory effects, including upregulation of TNF-α and IFN-γ, enlargement of the spleen, stimulation of peritoneal cell metabolic and phagocytic activity, and an increase in nitric oxide and reactive oxygen species production. These effects were also observed in methylprednisolone-induced immunocompromised rats when compared with controls [19].

The diterpene lactone andrographolide, isolated from *Andrographis paniculata* (Burm. f.) Nees—widely known as "sambiloto" is recognised for a broad spectrum of pharmacological effects, including anti-inflammatory, anticancer, antidiabetic, hepatoprotective, and antimalarial properties, supported by evidence from both *in vitro* and *in vivo* studies [20], [21], [22] Mechanistic studies have revealed that andrographolide, the major bioactive constituent of *Andrographis paniculata*, exerts its antimalarial action partly by suppressing nuclear factor kappa B (NF-κB) activity in *Plasmodium falciparum*-infected erythrocytes and by compromising the parasite's antioxidant defence system. This includes reducing intracellular glutathione (GSH) levels and inhibiting thioredoxin reductase (TrxR) enzyme activity [20], [23] In vivo assays of standardised *A. paniculata* leaf extracts containing 10.82 ± 0.37% andrographolide showed antimalarial activity against *P. berghei* with an ED_{50} of 12.2223 mg/kg body weight, corresponding to 1.320 mg of andrographolide. Additionally, Sachdeva reported that andrographolide at 0.1 mg/mL inhibited malaria parasite growth in vitro by 53.9% [16], [24]

6 Polyphenol

Polyphenols are naturally occurring antioxidants available in forms suitable for routine human consumption. Major dietary sources include tea, coffee, red wine, dark chocolate, and other cocoa-rich products, as well as a wide range of fruits, legumes, cereals, and vegetables. From a medical perspective, polyphenols have been associated with beneficial effects in the prevention and management of various conditions, including diabetes, gastrointestinal disorders, cardiovascular disease, and neurodegenerative disorders [9]

In Indonesia, the leaves of *Schima wallichii* Korth, commonly referred to as puspa, have been reported to possess significant antimalarial activity. The majority of this bioactivity is localised

within a minor fraction of the ethyl acetate extract, identified as containing 5,7,4′-trihydroxy-3-β-rhamnosidaflavone. The primary active compound, kaempferol-3-O-rhamnoside, has demonstrated the ability to suppress parasite growth by 54.3% at 24 hours, 83.9% at 48 hours, and up to 96% at 72 hours of incubation, relative to untreated controls. [16], [17].

Cempedak, scientifically named *Artocarpus champeden*, is categorised under the Moraceae family and used as a traditional medicinal herb for the treatment of dysentery, fever, and malaria. Cempedak includes a diverse combination of flavonoids, including flavanones, flavones, 3-prenylflavones, piranoflavones, oxepinoflavones, dihydrobenzosantone, and furanodihydrobenzosantone In addition, this plant also contains triterpenoid compounds, specifically cycloartenon, 24-methylensikloartenon, cycloeukalenol, glutinol, and β-sitosterol, which is a steroid molecule [16]. Flavonoids are secondary metabolites that are widely present in various plants. The chemical has been extensively documented for its antimalarial effects [3], [4], [10]. Several studies have indicated that bioflavonoid compounds can effectively inhibit the growth of parasites through two primary mechanisms. Firstly, they inhibit the transportation of essential nutrients required by parasites, thereby preventing the formation of membranes by the malaria parasite during the intraerythrocytic stage. Secondly, they inhibit the degradation of haemoglobin and the detoxification of heme, which ultimately prevents the formation of food vacuoles in the malaria parasite [9], [25]

Curcumin is a naturally occurring phytochemical predominantly found in *Curcuma longa* and *Curcuma zanthorrhiza*. Chemically, it is identified as 1,7-bis(4′-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione [26] Curcumin is commonly utilized as a medicinal substance and traditional component for the treatment of diverse ailments in several nations [17] Curcumin exhibits several pharmacological properties including anti-inflammatory, antioxidant, anticancer, anticoagulant, hepatoprotective, and antibacterial effects. Furthermore, curcumin has demonstrated antimalarial effect against many Plasmodium species. The antimalarial activity is achieved by inhibiting the acetyltransferase enzyme from *P. falciparum*, resulting in damage to parasite cells. Curcumin is also capable of binding to the sarco/endoplasmic reticulum Ca^{2+}-ATPase (SERCA) enzyme in *P. falciparum*.This interaction leads to the suppression of a specific Ca2+ ion transporter known as PfATP6 [3], [15], [16]

Annisa, et al conducted study on the antimalarial activity of red bajakah roots. They found that the administration of ethanol extract resulted in a decrease in parasitemia. The red bajakah root, scientifically known as *Spatholobus littoralis Hassk*, is well known for its antioxidant capabilities due to the presence of phenolic xanthones. These compounds have the ability to effectively capture free radicals that are produced during malaria infection. Additionally, it has the ability to inhibit the process of heme polymerization in a controlled environment, therefore limiting the breakdown of harmful free heme into harmless hemozoin crystals [27], [28].

Mashuri et al. revealed that *Mangifera odorata*, sometimes known as Kweni mango, has anti-malarial activities. This fruit contains certain metabolite secondary chemicals, such as flavonoids and phenolics. However, this effect requires further investigation[29]

The stem bark of *Mangifera rufocostata* is valued in traditional medicine for its therapeutic potential. A study by Mustikasari et al. demonstrated that this species exhibits notable antioxidant properties, suggesting a role in mitigating oxidative stress-related diseases, including malaria. Ethanol extracts of *M. rufocostata* stem bark demonstrated potent antioxidant capacity, with an IC_{50} of 8.254 ppm. Phytochemical analysis confirmed the presence of tannins, phenolics, flavonoids, and

saponins [30] The principal constituents identified in the extract were gallic acid, quinic acid, mangiferin, and vanillyl glycol, indicating that the methanol extract of *M. rufocostata* stem bark has potential as a future biological medicine resource [31]

In addition, various plant species from the Mandiangin forest in South Kalimantan have been shown to contain high concentrations of bioactive secondary metabolites, including flavonoids, tannins, and alkaloids. Research by Nugroho et al. reported that *Leea indica* possessed the highest flavonoid content (70.892 ± 0.34 mg/mL QE), while *Aglaia* sp. extracts recorded the greatest tannin (2.101 ± 0.02 mg/mL GAE) and alkaloid (25.30 ± 0.71%) levels [32]. *Passiflora foetida* exhibited the highest saponin concentration (31.78 ± 2.97%) [33] These findings indicate that Mandiangin rainforest plants contain phytochemicals with significant medicinal value, as reflected in their potent antioxidant and anti-inflammatory activities. Notably, *P. foetida* and *L. indica* displayed the greatest antioxidant activity, whereas *P. foetida*, *Aglaia* sp., and *Caesalpinia* spp. exhibited the most significant anti-inflammatory effects [32]

Numerous plants referenced previously exhibit antioxidant and anti-inflammatory effects that could be useful in the management of malaria. The pathogenesis of malaria involves significant contributions from both the inflammatory and oxidative processes in the manifestation of clinical signs. The utilisation of herbs containing antioxidant and anti-inflammatory compounds could represent a complementary or alternative strategy for malaria therapy.

7. Conclusion

Scientific evidence demonstrates that all of these isolates exhibit antimalarial properties, with each compound inhibiting malaria parasite proliferation through distinct mechanisms of action. Further research is warranted to assess the potential of these compounds as antimalarial agents against emerging *Plasmodium* strains resistant to standard first-line therapies. In addition, certain plants possess antioxidant and anti-inflammatory properties; thus, their antimalarial effects may not involve direct parasite clearance but rather the reduction of oxidant levels and inflammatory mediators, thereby preventing or alleviating clinical symptoms.

8 Acknowledgment

This article was funded by Universitas Lambung Mangkurat through the 2024 competency research grant.

9 Conflict of Interest

The authors state that no conflicts of interest are associated with the preparation or publication of this article.

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