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Review Article

Active Compounds and Antimalaria Properties of some Medicinal Plants in Indonesia – A Review

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ABSTRACT
Indonesia is a tropical country rich with various types of plant that have been empirically used as alternative medicine, especially for malaria disease treatment. The discovery and development of malaria treatment are currently underway, given that there has been a lot of resistance to first-line malaria treatment. The case of resistance has spread around the world that cause many victims, including in Indonesia. With Indonesia has a good environment for the development of malaria disease, therefore it requires serious treatments to prevent the spreading of malaria. Several efforts have been made to reduce the death cases due to malaria in Indonesia, including the discovery of new compounds from nature that has antimalarial compound as a substitute for malaria's drugs that is known has resistance. Research for a new antimalarial compound from nature is based on the experience of Indonesian ancestors who usually used various plants to treat many kinds of disease. Furthermore, research for natural compound especially from Indonesia that has the potency as alternative treatment for malaria is expected to continue to be developed. Some types of plant, such as puspa leaves (*Schima wallichii Korth*), sernai leaves (*Wedelia biflora*), kembang bulan leaves (*Tithonia diversifolia*), bark of cempedak (*Artocarpus champeden*), and sambiloto leaves (*Andrographis paniculata Nees*) have long been used as alternative herbal treatments for malaria in various regions in Indonesia. These plants have been proven empirically efficacious as antimalarial medicine, and several studies haves been conducted on these plants to obtain active compounds that have antimalarial property.

Key words: *Antimalaria, Schima wallichii* korth, *Wedelia biflora*, *Tithonia diversifolia* ((Hemsley) A. Gray), *Artocarpus champeden*, *Andrographis paniculata* Nees.

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INTRODUCTION

Plasmodium is a parasite that causes a dangerous disease known since ancient Greece time: malaria. The symptoms of malaria disease are distinctive and easily recognizable, i.e. Intermittent fever accompanied by chills.[1] Malaria is major health issue in Indonesia, especially in its eastern territories. There were 433,326 cases of malaria in 2005, and increased malaria cases in some areas caused 87 deaths from 18,812 malaria cases across 62 villages in 2005. 90% of mortality associated with *P. falciparum* infection worldwide is caused by severe malaria.[2] The first antimalaria discovered around 1930 was chloroquine. Currently, plasmodium parasites are showing resistance to chloroquine and some antimalarial compounds.[3] Therefore, new antimalarial drugs that could effectively combat the presence of plasmodium are direly needed. Compounds derived from medicinal plants have been used to treat diseases since ancient time and currently it is used as a substance of modern medicine. The advantage of using compounds derived from medicinal plants in the development of new drugs is they have a high affinity to biological receptors present in the human body.[4] With Indonesia is a country rich in medicinal plants, could facilitate research program to solve malaria treatment issues. This review article will discuss active compounds and antimalarial properties of some medicinal plants in Indonesia.

Puspa leaves (*Schima wallichii* Korth.)

Empirically puspa leaves have been used by people for treating fever, therefore it is assumed to have positive effects to treat malaria, since malaria is usually accompanied by acute fever caused by plasmodium infection.[5] Puspa (*Schima wallichii* Korth) appearence is shown in Figure 1. Some medicinal plant's extracts used for antipyretics and analgetics are claimed to be effective against plasmodium or malaria. Therefore, screening for antimalarial active compounds may also be performed through studies of its efficacy as antipyretic or analgesic drugs.[6] Barliana *et al*. have demonstrated the antimalarial effect of puspa leaves. As with the most activities occurs mostly in a fraction of ethyl acetate. Structure identification of the ethyl acetate fraction compound using spectroscopy (IR, UV, NMR, and LC-MS), has identified 5,7,4'-trihidroksi-3-β-ramnosidaflavon. The active compound of kaempferol-3-O-rhamnoside has the capability to inhibit parasitic growth up to 54.3% within 24 hr of incubation period, 83.9% within 48 hr of incubation and up to 96% within 72 hr of incubation compared to controlled study.[7] Previous study conducted by Muhtadi *et al*. also showed antimalarial properties of puspa leaves obtains from ethyl acetate fraction, buthanol fraction and ethanol extract at ED_{50} 72.81, 122.87, and 358.13 mg/kg BW respectively.[5] As a polyphenol, kaempferol-3-O-rhamnoside is able to inhibit lipid peroxidation and cyclooxygenase (COX) enzymes (COX-1 and COX-2). Thus, it can be hypothesized that these antioxidant properties may be responsible for the antiplasmodial acitivity of kaempferol-3-O-rhamnoside.[7]

Sernai leaves (*Wedelia biflora*)

One plant which belongs to the same family as *Artemisia annua* is *Wedelia biflora*. This plant has been demonstrated to have an antiplasmodium activity in *in vitro* study.[8] Sernai (*Wedelia biflora*) appearence is shown in Figure 2. Study by Isa has revealed that, methanol extract of sernai leaves is able to inhibit tropozoid stage of *P. falciparum*. Triterpenoid compound in sernai leaves is suspected to be responsible for this effect. In a test conducted using GC-MS, there were 45 peak compounds with the highest concentration of 27.92% identified in the database as kaur-16-en-18-oic acid. The results of bioactivity test as antiplasmodium *in vivo* shows, sernai leaf extract is active with ED_{50} value of 39.952 mg/kg BW.[9] Previous *in vitro* study conducted by Isa, *et al*. and Rinidar, *et al*. also demonstrates that methanol extract of sernai leaf has antiplasmodium properties, proven by IC_{50} value of 5.253 µg/ml during 32 hr

of incubation.[8,10]

Kembang bulan leaves (*Tithonia diversifolia* (Hemley) A. Gray)

Study by Setiyanggono has demonstrated that, the extract of dried kembang bulan leaves inhibits the growth of *P. berghei* with ED_{50} value of 214 mg/kg BW. This study also shows that higher dose of kembang bulan leaves dried extract provides higher level of *P. berghei*.[11] Previous *in vivo* study conducted by Budiarti reveales that, ethanol extract of kembang bulan leaves inhibit *P. berghei* at a dose of 40; 80; 160; and 320 mg/kg BB with ED_{50} value of 114 mg/kg BW and ED_{90} of 475 mg/kg BW.[12] Sesquiterpene lactone *tagitinin C* in the kembang bulan leaf extract has been identified as an active compound that has antiplasmodium property, that has been proven lethal to *P. falciparum* strain FCA (IC_{50}: 0,75 µg/mL).[13,14] In an *in vitro* study, Afiyah has demonstrated that the ether fraction of methanol extract of kembang bulan leaves has antiplasmodium property against *P. falciparum* FCR-3 strain by its inhibition on heme polymerization.[15] Basilico *et al*. reveales that the inhibitory properties of heme polymerization is actually due to one or two mechanisms, namely (1) interaction between terpenoid, phenol and sterol compounds with heme electrolysis system and, (2) compounds with hydroxyl groups which can bind to heme iron ions.[14] Kembang bulan (*Tithonia diversifolia* (Hemley) A. Gray) appearence is shown in Figure 3.

Bark of cempedak (*Artocarpus champeden* Spreng.)

Artocarpus champeden (Moraceae family), also known as cempedak, is one of the plants used as a traditional medicinal herb to treat dysentry, fever and malaria.[16,17,18] Cempedak (*Artocarpus champeden*) appearence is shown in Figure 4. Cempedak contains a complex mixture of various flavonoids: flavanones, flavones, 3-prenylflavones, piranoflavones, oxepinoflavones, dihydrobenzosantone and furanodihid robenzosantone. Furthermore, this plant also contains terpenoid compound of triterpen type, namely cycloartenon, 24-methylensikloartenon, cycloeukalenol, glutinol and steroid compound of β-sitosterol.[19,20,18] The flavonoid compound is a secondary metabolite found in many plants antimalarial properties of this compound have been widely reported.[6] The discovery and development of antimalarial drugs is expected to produce novel, potent and safe drugs for humans. Some studies has reported that bioflavonoid compounds have capability to inhibit the parasites growth via two main targets: 1) inhibit the transport of nutrients needed by parasites, to avoid membrane formation by the malaria parasite during the intraeritrositic stage,[21,22] and 2) inhibit the hemoglobin degradation and heme detoxification to prevent malaria parasite food vacuoles.[23,24,25] Maximus and Wahyuni have reported that methanol extract and dichloromethane extract of cempedak bark has activity as antimalarial against *P. falciparum* 3D7 strain.[26,27] In accordance with this study, another study conducted by Nuri, *et al*. demonstrates that dichloromethane extract of cempedak bark stem also inhibits parasite growth *in vitro* with IC_{50} 0.14432 µg/ml.[28] Furthermore, cempedak bark has also another potential compound with antimalarial properties to be developed as an antimalarial drug.[29] Study by Widyawaruyanti, *et al*. reports that the isolation of dichloromethane extract of cempedak bark shell yields 9 compounds in which two of them are new compounds. Moreover, this study examines the antimalarial property *in vitro* of the nine compounds obtained from fractionation and isolation of dichromomethane extracts of cempedak bark, followed by probit analysis to determine the IC_{50} value of each tested compound (Table 1).[29]

Table 1: IC_{50} value of flavonoid compound from the isolated dichloromethane extract of cempedak bark during *in vitro* antimalarial test.[29]

Test Materials	IC_{50} (µg/mL)	IC_{50} (µM)
Artoidonesianin E	26.2350	75.76
Heteroflavanon C	0.0006	0.001
Artoindonesianin R	0.5246	1.32
Artokarpon A	0.0066	0.12
Heterofillin	0.0156	0.53
Artoindonesianin A-2	0.4999	1.31
Sikloheterofillin	0.083	0.02
Artokarpon B	0.0800	0.18
Artonin A	0.2800	0.55

Based on the table above, it could be noticed that the heteroflavanon C compound has the lowest IC_{50} value of 0.001 µM, whereas artoidonesianin E compound shows the highest IC_{50} value of 75.76 µM.[29] According to Widyawaruyanti, *et al*., a compound is considered effective as an antimalaria drug if it has IC_{50} 0.001-75.3 µM.[30] Based on this provision, the flavonoid compound from isolated dichloromethane extract of cempedak bark has antimalarial activity. The compound heteroflavanone C (IC_{50} = 0.001 µM) has the highest antimalarial activity. It is reported that standard chloroquine antimalarial drugs has IC_{50} of 0.006 µM.[31] It is assumed that the presence of an isoprene chain in the C-8 position of the heteroflavanone C compound results in an increased of its antimalarial property. The presence of an isoprenal chain causes heteroflavanone C to become more non-polar and lipophilic and make heteroflavanon C capable to penetrate the parasitic cell membrane and administer its antimalarial effect. Therefore, the antimalarial property of heteroflavanon C is stronger than chloroquine, which suggests it is more potential to be developed as an antimalarial drug to replace chloroquine which is no longer effective.[29]

Table 2: Active compounds and working mechanisms of some medicinal plants that Exist in Indonesia.

Name of Plant	Active Compound	Mechanism of Action	Reference
Puspa leaves (*Schima wallichii* Korth.)	*Kaempherol-3-O-rhamnosida.*	Inhibits lipid peroxidation and cyclooxygenase (COX) enzymes (COX-1 and COX-2).	[7]
Sernai leaves (*Wedelia biflora*)	*Kaur-16-en-18-oic acid.*	It works at tropozoid stage out of a series of plasmodium growth cycles.	[9]
Kembang bulan leaves (*Tithonia diversifolia* (Hemley) A. Gray)	*Tagitinin C.*	Inhibits heme polymerization.	[14,15]
Bark of cempedak (*Artocarpus champeden* Spreng.)	*Heteroflavanon C.*	Penetrates the parasitic cell membrane, resulting in lysis.	[29]
Sambiloto leaves (*Andrographis paniculata* Nees.)	*Andrographolide.*	Disrupts the parasite's antioxidant defense system as evidenced by the decrease in GSH concentration and the activity of the tioredoxin reductase enzyme (TrxR).	[38,40]

Figure 1: Schima wallichii Korth.[41]

Figure 2: Wedelia biflora.[42]

Figure 3: Tithonia diversifolia (Hemsley) A. Gray).[43]

Figure 4: Artocarpus champeden.[44]

Figure 5: Andrographis paniculata Nees.[45]

Sambiloto leaves (*Andrographis paniculata* Nees.)

Andrographis paniculata Nees., locally known as sambiloto, is a medicinal plant that is empirically used as an antimalaria drug. Sambiloto (*Andrographis paniculata Nees*) appearence is shown in Figure 5. This plant has the main ingredient of lactone andrographolide group compound of ± 2.5% in dried simplicia, while in ethanol extract it is equal to ± 10,69%.[32] Study by Mishra, *et al*., reveals that the sambiloto extract has an antimalarial effect on *P. falciparum in vitro* and its maximum effect is reached at concentration of 125 µg/ml.[33] This is in accordance with the research of Widyowati that reports the isolation of sambiloto leaf can suppress the development of *Plasmodium falciparum* at gametosit stage *in vitro*.[34] An *in vivo* study using mice by Hafid, *et al*. demonstrates the activated lactone (DTL) fraction of sambiloto leaf has an antimalarial activity with ED_{50} 9.17 mg/kgBW in mice. DTL antimalarial properties in single dose (once) per oral 10 and 100 mg/kg BW in mice shows similar effect despite the dose being 10 times higher. Meanwhile, administration of DTL with divided dose (10 mg twice daily) shows stronger activity and was able to inhibit the parasites by 92.22% on average.[35] This research is in line with a previous study conducted by Kusumawardhani, *et al*. that demonstrates antimalarial activity of standardized sambiloto leaf extract (andrographolide level (10.82 ± 0.37)%) administration against the growth of *P. berghei in vivo* in mice as seen from ED_{50} value of 12.2223 mg of standardized sambiloto leaf extract/Kg BW, equivalent to 1.320 mg

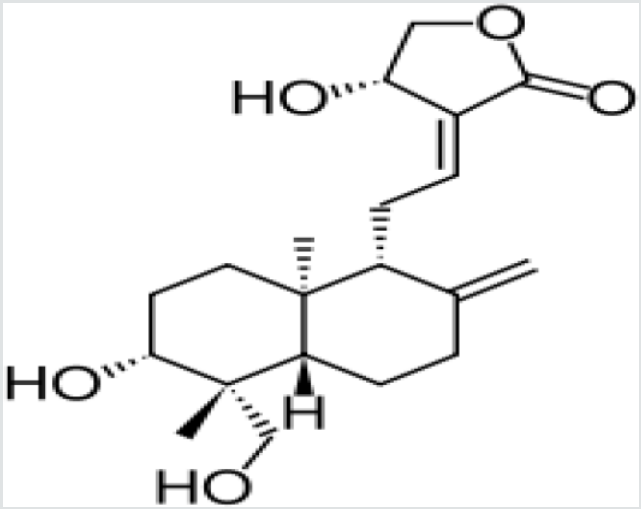

Figure 6: Structure of andrographolide molecules.[46]

of andrographolide compound.[36] Meanwhile, a study by Mishra states that andrographolide synergized well with curcumin and artesunate. *In vivo*, andrographolidecurcumine has 81% higher antimalarial property than the control study and is able to prolong its life by 2-3 times.[37] Gudhate, *et al*. reports that there is lactone compound found in sambiloto leaf of andrographolide (Figure 6).[38] Andrographolide is a compound belonging to the trihidroksilactone group with its molecular formula $C_{20}H_{30}O_5$.[39] Risdawati states that the mechanism of andrographolide produces antimalarial property by disrupting the parasite antioxidant defense system as evidenced by the decrease in GSH concentration and the activity of thioredoxin reductase enzyme (TrxR).[40]

CONCLUSION

Indonesia is a country that has various types of medicinal plants that have the potential properties to be developed as an alternative medicine for malaria treatment (Table 2). All these plants have been empirically proven and scientifically tested. This is inseparable from the active compounds contained in the plant that has antimalarial properties with different antimalarial work mechanism. This study on medicinal plants can hopefully be used to improve the latest malaria treatment that is now exhibiting resistance to the first-line malaria treatment.

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CONFLICT OF INTEREST

No conflict of interest to declare.

ABBREVIATIONS USEDD

IR: infra red; **UV:** ultra violet; **LC-MS:** liquid chromatography–mass spectrometry; **GC-MS:** gas chromatography–mass spectrometry; **ED50:** median effective dose; **ED90:** 90% effective dose; **IC_{50}:** median inhibitory concentration; **DTL:** diterpen lactone; **GSH:** glutathione; **TrxR:** thioredoxin reductase enzyme; **COX:** cyclooxygenase.

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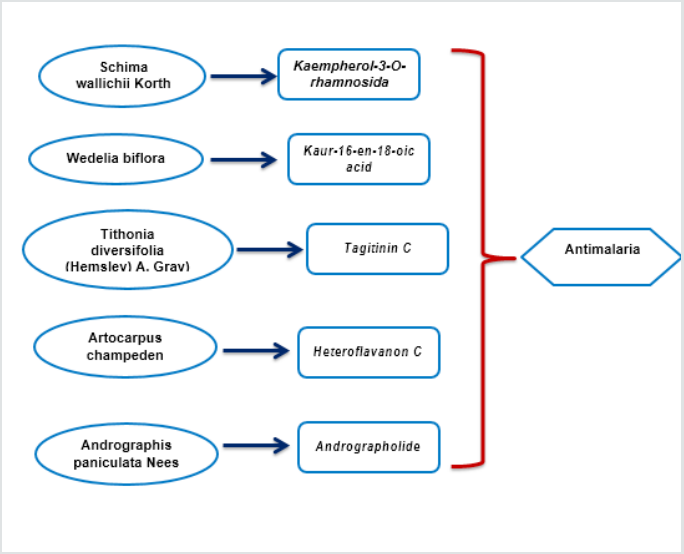
GRAPHICAL ABSTRACT



SUMMARY

- Indonesia has various types of plants that have activity as an antimalarial agent.
- *Schima wallichii, Wedelia biflora, Tithonia diversifolia, Artocarpus champeden, Andrographis paniculata* Nees are widely used as traditional medicine in Indonesia to treat malaria.
- These plants have been proven empirically and scientifically to combat malaria.
- The active compound in each plant has been identified against malaria via different mechanisms.

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