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Review Article

Antimalaria Activities of Several Active Compounds from Medicinal Plants

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ABSTRACT

The growth and spread of resistance to all first-line antimalarial drugs used in the treatment of malaria today has caused many problems in eradicating malaria in various countries in the world. Researchers have begun to look for candidates for new antimalarial drug compounds derived from natural products that have been scientifically proven to have antimalarial activity. This is done to replace antimalarial drugs that are currently experiencing resistance. Some active compounds that have been successfully isolated from various plants, including curcumin, kaempferol, piperine, andrographolide, α-mangostin, catechin, luteolin and betulinic acid, have been scientifically tested to have antimalarial activity with different mechanisms of action.

Key words: Malaria, Antimalarial, Curcumin, Kaempferol, Piperine, Andrographolide, α-Mangostin, Catechin, Luteolin, Betulinic acid.

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INTRODUCTION

Malaria is still a health problem in the world, with 229 million cases of malaria worldwide and more than 400,000 people suffering from malaria dying each year.[1] The high number of malaria cases is caused by the emergence of various obstacles in eradicating malaria, including the resistance of malaria parasites to available antimalarial drugs, increased Anopheles mosquito immunity to chemicals, and the discovery of side effects from these antimalarial drugs.[2] The growing and widespread resistance to all the first-line antimalarial drugs used in the treatment and prevention of malaria has now caused many problems in the malaria prevention programme.[3] Research to obtain new antimalarial drugs, both synthetic drugs and those derived from natural materials, is continuing, one of which is through the exploration of active compounds from natural materials, especially medicinal plants that have traditionally been used by the community to treat malaria in various endemic areas across the world. The aim is to find new antimalarial compounds that have mild side effects with low toxicity, so that they do not harm the patient.[4] This review article will discuss the active compounds and antimalarial activity of several medicinal plant isolates.

CURCUMIN

Curcumin (1,7-bis (4′hydroxy-3-methoxyphenyl) 1,6-heptadiene, 3,5-dion) is a phytochemical component found mainly in *Curcuma longa* and *Curcuma zanthorrhiza*. Curcumin is often used as a medicine and traditional ingredient to treat various diseases in several countries.[5] Curcumin has several pharmacological activities such as anti-inflammatory,[6-7] antioxidant,[8] anticancer,[9] anticoagulant,[10] hepatoprotective[11] and antibacterial.[12] In addition, curcumin has been shown to have antimalarial activity against *Plasmodium* species.[13-14] The antimalarial activity of curcumin is caused by its ability to inhibit histone acetyltransferase from *P. falciparum*, causing parasitic cell damage.[14] Other studies also report that curcumin can interact with sarco/endoplasmic reticulum Ca^{2+}ATPase (SERCA) in *P. falciparum* which causes the inhibition of a Ca^{2+} ion transporter called PfATP6.[15] Meanwhile, from in vitro antimalarial activity testing, IC_{50} values obtained from curcumin were 5 μM, whereas at concentrations of 50 μM, curcumin was able to reduce the viability of *P. falciparum*, which caused a decrease in parasitic cell proliferation. Other results also reported that at concentrations of 5 μg/ml and 50 μg/ml, curcumin was able to inhibit 79.6% and 100% growth of *P. falciparum*.[16] In addition, in antimalarial testing in vivo with a dose of 100 mg/kg, curcumin was able to inhibit the growth of parasites >80%.[13] Waknine-Grinberg *et al.* reported that the administration of curcumin at a dose of 50 mg/kg, twice daily for 6 days after infection in C57Bl/6 mice infected with *P. berghei* ANKA, can prevent cerebral malaria (CM) and delay death by up to 10 days.[17] In addition, it has been shown in vitro that curcumin reduces the production of proinflammatory cytokines IL6, TNF and IL12p40 in PBMC primed with trophozoites/schizonts stages of *P. falciparum* and downregulated the expression of VCAM1, ICAM1 and E-selectin in TNF-activated human endothelial cells.[18] In addition, other studies report that curcumin can inhibit thrombin-activated platelet adhesion to brain microvascular endothelial cells in vitro[19] which is thought to accumulate in brain microvasculature in murine and pediatric CM patients.[20]

KAEMPFEROL

Kaempferol (3,4' 5, 5,7-tetrahydroxyflavone) is a natural flavonol, a flavonoid derivative, found in various plants and plant-derived foods such as kale, beans, tea, spinach and broccoli.[21-22] Kaempferol has been reported to have high antioxidant properties, which are able to inhibit oxidative stress resulting from the formation of reactive oxygen species (ROS)

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that occur during malaria infections.[23] ROS and oxidative stress are also produced by monocytes and neutrophils which are activated during malarial infection, which cause haemoglobin to degrade,[24-25] thus there is a correlation between antioxidant activity and antimalarial activity of kaempferol.[26] In addition, the antimalarial activity of kaempferol is also caused by its ability to inhibit glycogen synthase kinase-3β (GSK3β) from malaria parasites. GSK3β is reported to play an important role in the host response to malaria parasitic infections.[27-28] By inhibiting GSK3β in mammals, it can also significantly inhibit the activity of recombinant *P. falciparum* (PfGSK3β) protein.[29] Somsak *et al.*, reported that at a dose of 20 mg/kg, kaempferol was able to inhibit *P. berghei* by 52.89%, 40.80%, and 36.63% for each chemosuppressive, chemoprophylactic, and curative trial.[30] Meanwhile, Barliana *et al.*, reported that kaempferol was able to inhibit the growth of *P. falciparum* which is resistant to chloroquine in vitro after 24 hours of therapy with IC_{50} 106 µM.[31] In addition, kaempferol at a dose of 2,000 mg/kg daily for 30 days does not produce signs of toxicity in the form of hepatotoxic, nephrotoxic, haematotoxic, or death in test animals.[30]

PIPERINE

Piperine (1-[5-(1,3-benzodioxol-5-yl)-1-oxo-2,4-pentadienyl] piperidine) is the main amide compound isolated from the *Piper chaba* Hunt fruit,[32] *Piper nigrum* L. (black pepper) and *Piper longum* L. (long pepper).[33] Piperine has been shown to have several pharmacological activities such as antioxidants,[34] anticancer,[35] antidepressive,[36] hepatoprotective,[37] anti-asthmatic,[38] antipyretic,[33] anti-inflammatory,[39] analgesic, and anticonvulsant.[40] In addition, piperine was also reported to have antimalarial activity in vitro against *P.falciparum* 3D7 strains (chloroquine-sensitive) and K1 (chloroquine-resistant) with IC_{50} against 3D7 and K1 *P.falciparum* respectively at 111.5 µM and 59 µM.[32] The antimalarial activity of piperine is due to its ability to inhibit the modulation of expression of all *P. falciparum* resistance genes,[32] including the *P. falciparum* multidrug resistance protein 1 gene (*pfmrp1*), the *pfmrp1* protein coding gene that is a member of the ABC transporter superfamily located on chromosome 1,[41] where this protein has been reported to be involved in the export of folate from malaria parasites into red blood cells,[42] *P. falciparum* multidrug resistance gene 1 (*pfmdr*1) is a homologous P-glycoprotein coding gene located in the parasite digestive vacuole membrane, which is thought to play a role in modulation of antimalarial drug resistance [43] and *P. falciparum* chloroquine resistance transporter (*pfcrt*), a protein-coding gene that is localised to the parasitic digestive vacuole membrane and contains 10 domains that line the membrane in the erythrocytic stage.[44] Piperine might be a promising candidate for the development of new antimalarial drugs, due to its antimalarial potential and low risk of resistance in modulating the *P. falciparum* resistance gene that causes the development of resistance.[32]

ANDROGRAPHOLIDE

Andrographolide (3-[2-[Decahydro-6-hydroxy-5-(hydroxymethyl)-5,8a-dimethyl-2-methylene-1-napthalenyl]ethylidene]dihydro-4-hydroxy-2(3H)-furanone) is a lactone diterpene compound isolated from the *Andrographis paniculata* (Burm. F) Nees plant, commonly known as the "*king of bitters*".[45] Andrographolide has been reported to have several pharmacological activities such as anti-inflammatory, antitumor, antidiabetic, and hepatoprotective.[46] In addition, andrographolide has been shown to have antimalarial activity in vitro and in vivo.[47] The antimalarial activity of andrographolide is due to its ability to inhibit nuclear kappa B (NF-κB) transcription factors induced when erythrocytes are infected with *P. falciparum* [48] by blocking the binding of NF-κB oligonucleotides to nuclear proteins [49] where this pathway is an inflammatory pathway in the human cerebral

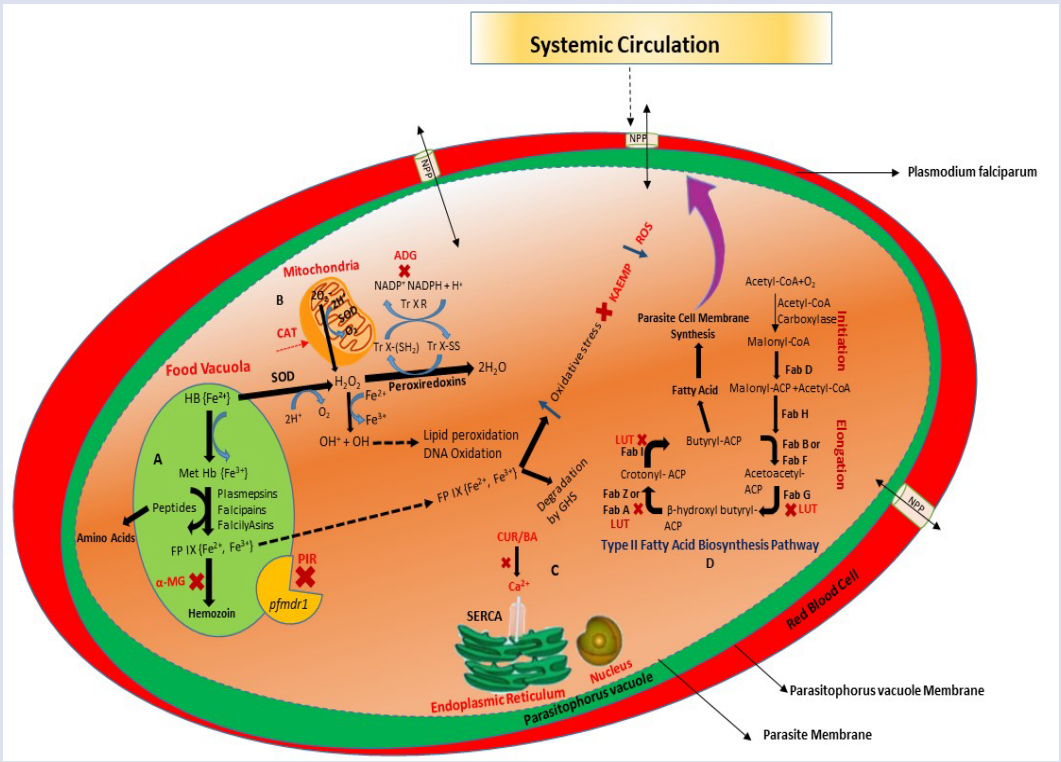
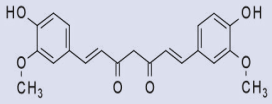
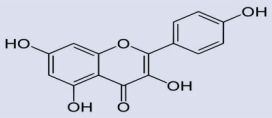
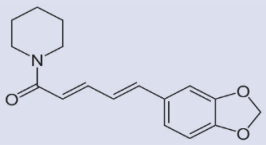
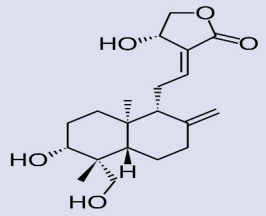
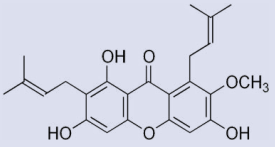
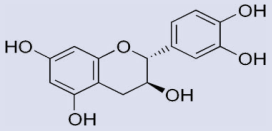
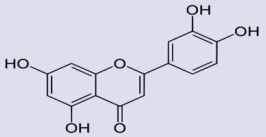
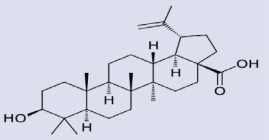


Figure 1. Parasite targets for intervention. **A**) Heme detoxification pathways in the intra-erythrocytic cycle and redox homeostasis in infected red blood cell: α-mangostin inhibit heme degradation in the parasite food vacuole. **B**) The electron transport chain (ETC) of mitochondria involve in the bio-activation of catechin induces the membrane depolarization and disrupt the normal function of mitochondria, through the production of ROS. Furthermore, andrographolide inhibits thioredoxin reductase an enzyme maintains the redox equilibrium in plasmodium species. **C**) Inactivation of SERCA which is responsible for protein synthesis in parasite by curcumin and betulinic acid. **D**) Inhibition of type II fatty acid biosynthesis pathway in *P. falciparum* by luteolin.

Table 1. Active compounds and working mechanisms as antimalaria.

Active Compounds	Chemical Structures	Types of Malaria Parasites	Study Design	Mechanism of Action	References
Curcumin		*1. P. falciparum* strain 3D7 and D10. *2. P. falciparum* strain DD2 and 7G8. *3. P. berghei* strain ANKA.	*In vitro* and *in vivo*	Interacts with sarco/endoplasmic reticulum Ca^{2+}ATPase (SERCA) in *P. falciparum* which causes inhibition of Ca^{2+} ion transporter.	15
Kaempferol		*1. P. falciparum* strain 3D7. *2. P. berghei* strain ANKA.	*In vitro* and *in vivo*	Inhibits oxidative stress resulting from the formation of reactive oxygen species (ROS).	23
Piperine		*1. P. falciparum* strain 3D7. *2. P. falciparum* strain K1.	*In vitro*	Inhibits the modulation of expression of all *P. falciparum* resistance genes.	32
Andrographolide		*1. P. falciparum* strain 3D7. *2. P. berghei* strain ANKA.	*In vitro* and *in vivo*	Reduction in GSH concentration and the activity of the thioredoxin reductase (TrxR) enzyme.	50
α-Mangostin		*1. P. falciparum* strain K1. *2. P. falciparum* strain FCR3. *3. P. falciparum* strain 3D7. *3. P. berghei* strain ANKA.	*In vitro* and *in vivo*	Inhibits haemoglobin degradation process that occurs in the food vacuole of *P. falciparum*.	53, 58, 59
Catechin		*1. P. falciparum* strain DD2. *2. P. falciparum* strain 3D7.	*In vitro*	Induces oxidative stress to *P. falciparum*.	62,63
Luteolin		*1. P. falciparum* strain 3D7. *2. P. falciparum* strain 7G8.	*In vitro*	Inhibits FabG, FabZ and FabI enzymes which involves in parasite fatty acid biosynthesis.	69
Betulinic acid		*1. P. falciparum* strain K1. *2. P. falciparum* strain T9-96. *3. P. falciparum* strain 3D7.	*In vitro*	Ability to bind the *PfATP6* protein and sarco/endoplasmic reticulum Ca^{2+}ATPase (SERCA) in mammals.	75-77

endothelium.[47-48] Meanwhile, Risdawati reported that the antimalarial andrographolide activity was caused by this compound being able to disrupt the parasitic antioxidant defence system as evidenced by the reduction in GSH concentration and the activity of the thioredoxin reductase (TrxR) enzyme.[50] Kusumawardhani, *et al.*, reported that the antimalarial activity of standardised *A. paniculata* leaf extracts (andrographolide levels; 10.82 ± 0.37%) against *P. berghei* in vivo obtained ED_{50} of 12.2223 mg of standardised *A. paniculata* /KgBW leaf extract, equivalent to 1,320 mg of andrographolide compounds.[51] Meanwhile, Sachdeva reported that andrographolide at a dose of 0.1 mg/ml was able to inhibit the growth of malaria parasites in vitro by 53.9%.[52] In addition, Mishra *et al.*, reported that andrographolide showed high malaria parasitic inhibitory activity in rat models in vivo when given with curcumin or artesunate via the intraperitoneal route, and without showing any symptoms of toxicity after administration of the therapy.[47]

α-MANGOSTIN

α-mangostin (1,3,6-trihidroksi-7-metoksi-2,8-bis (3metil-2-butenil)-9H-xanten-9-on) is the main xanthone compound found in the hull of the *Garcinia mangostana* L fruit.[53] This compound has been reported to have pharmacological activities including anti-inflammatory, anti-tumor, cardioprotective, antidiabetic, antibacterial, antifungal, antiparasitic, antioxidant and anti-obesity agents.[54] In addition, α-mangostin is also reported to have antimalarial activity.[53] Antimalarial activity is suspected of α-mangostin which is a hydroxyxanthones derivative due to its ability to form complexes that are soluble with heme compounds so that it inhibits the formation of parasitic hemozoin, a process in which the malaria parasite protects itself against the effects of heme toxins released after digesting haemoglobin.[55-56] The effect was caused by this compound having an alkyl group located in positions 3 and 6 which interacts with nitrogen atoms contained in

heme propionate compounds thus forming ionic bonds which cause an increase in antiplasmodial activity.[56-57] This is in accordance with the research of Kuncoro, *et al*., which reported that with α-mangostin able to inhibit the development of trophozoite stages into schizon stages in *P. falciparum*, where at the trophozoite stage an increase in haemoglobin uptake, with inhibition of haemoglobin uptake, would result in inhibition haemoglobin degradation process that occurs in the food vacuole of *P. falciparum*.[58] Mahabusarakam *et al*., reported that active α-mangostin inhibits the growth of *P. falciparum* strain K1 (chloroquine and pyrimethamine-resistant) in vitro with IC_{50} of 17 μM.[53] This is in accordance with the results of research by Upegui *et al*., who reported that α-mangostin was more active in inhibiting the growth of *P. falciparum* strain FCR3 (chloroquine-resistant) in vitro with IC_{50} of 0.2±0.01 μM compared to δ-mangostin with IC_{50} is 121.2 ± 1.0 μM, but δ-mangostin is more active in inhibiting the growth of *P. falciparum* strain 3D7 (chloroquine-sensitive) in vitro with IC_{50} of 12.40 ± 1.0 μM compared to α-mangostin with IC_{50} of 36.10 ± 4.9 μM.[59] In addition, Upegui *et al*., also reported that at doses of 100 mg/kg/day twice daily for 7 days, α-mangostin and δ-mangostin were able to reduce the growth of *P. berghei* respectively by 80.7% and 79.9 %.[59] These findings can provide a basis for further research on α-mangostin as a potential compound to be developed into antimalarial drugs.[59]

CATECHIN

Catechin (2R,3S)-2-(3,4-dihydroxyphenyl)-3,4-dihydro-2H-chromene-3,5,7-triol) is the main bioactive compound found in green tea (*Camellia sinensis*).[60] Catechin is reported to have several pharmacological activities including antioxidant, anti-microbial, anti-inflammatory, anti-viral, anti-cancer and anti-allergic properties.[61] In addition, this compound is also reported to have antimalarial activity against *P. falciparum*.[62-63] The antimalarial activity of catechin is due to its ability to induce oxidative stress to *P. falciparum*.[63] Goyal *et al*., reported that Plasmodium is very susceptible to oxidative stress, where an increase in oxidative stress will cause a redox imbalance.[64] Meanwhile, the redox system plays an important role in the survival of Plasmodium in the host cell, by disturbing the redox balance will affect the survival of Plasmodium during the intraerythrocytic stage.[65] Budiman *et al*., reported that active catechin inhibited the growth of *P. falciparum* with IC_{50} of 0.734 μM,[62] this is in accordance with the research of Abdulah *et al*., who reported that catechin could inhibit the growth of *P. falciparum* strain DD2 (chloroquine-resistant) with IC_{50} 198 μM after 24 hours of treatment.[63] Although this is a preliminary study, the results of this study can provide information for further research on catechin as a potential compound as an antimalarial drug.[63]

LUTEOLIN

Luteolin (3′,4′,5,7-tetrahydroxyflavone) is a common flavonoid that exists in many types of plants, including herbs, vegetables and medicinal plants.[66] Luteolin is reported to have several pharmacological activities including anti-inflammatory, antioxidant, antidiabetic, antimicrobial, and anticancer.[67] In addition, luteolin was also reported to have antimalarial activity against *P. falciparum* strain 3D7 (chloroquine-sensitive) and *P. falciparum* strain 7G8 (chloroquine-resistant) with IC_{50} of 11 ± 1 μM and 12 ± 1 μM, respectively.[68] The antimalarial activity of luteolin is due to its ability to inhibit the development of parasitic growth at the stage of young trophozoites, so the parasite cannot complete the full intraerythrocytic cycle.[68] This compound is also reported to Inhibits FabG, FabZ and FabI enzymes which are involved in parasite fatty acid biosynthesis.[69] In vitro experiments show that luteolin can inhibit the activation of the nuclear factor kappa B (NF-κB) induced by lipopolysaccharide (LPS) and members of the family of mitogen-activated protein kinase (MAPK) ERK, p38, and JNK.[70-71] NF-κB and MAPK are the two main pathways involved in the activation of macrophages in epithelial cells and stromal tissue in response to inflammatory mediators such as TNFα and ILs.[72] It is also an inflammatory pathway in the human cerebral endothelium.[47-48] The results of these studies can make the initial hypothesis that leuteolin can be used as therapy in CM patients, but further research must still be done to see the effectiveness of leuteolin in the treatment of malaria, especially CM.

BETULINIC ACID

Betulinic acid ((3β)-3-Hydroxy-lup-20(29)-en-28-oic acid) is a naturally occurring pentacyclic triterpenoid found in the skin of several plant species, especially white birch (*Betula pubescens*).[73] Betulinic acid has been shown to have several pharmacological activities such as antidiabetic, anti-dyslipidemia, anti-inflammatory, antiviral, anticancer, parasiticidal and anti-infectious.[74] In addition, this compound was also reported to have antimalarial activity against *P. falciparum* strain K1 (chloroquine-resistant) and *P. falciparum* strain T9-96 (chloroquine-sensitive) with IC_{50} of 19.6 mg/ml and 25.9 mg/ml, respectively.[75] This is in accordance with the results of research by Silva *et al*., who reported that active betulinic acid inhibits the growth of *P. falciparum* strain 3D7 (chloroquine-sensitive) with IC_{50} of 18 ± 0.17 μM.[76] Antimalarial activity of betulinic acid is thought to be caused by its ability to bind the PfATP6 protein and sarco/endoplasmic reticulum Ca^{2+}ATPase (SERCA) in mammals so that it interferes with selectivity between parasites and hosts.[77] The development of betulinic acid as an antimalarial for the future is very necessary, given that the antimalarial mechanism of this compound is similar to the drug artemisinin by inhibiting the sarco/endoplasmic reticulum Ca^{2+}ATPase (SERCA) ortholog PfATP6 in *P. falciparum*, where PfATP6 is the only SERCA type Ca^{2+}ATPase sequence in the parasitic genome.[78-79]

CONCLUSION

All of these isolates have been scientifically proven to have antimalarial activity, where each compound has a different mechanism of action in inhibiting the growth of malaria parasites. However, further research must be done to see the effectiveness of these compounds as antimalarials, so that they can be used in the latest malaria treatment, which has now shown resistance to first-line malaria treatment.

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CONFLICTS OF INTEREST

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

ABBREVIATIONS

SERCA: sarco/endoplasmic reticulum Ca^{2+}ATPase; **CM**: cerebral malaria; **IL-6**: interleukin-6; **TNF**: tumor necrosis factor; **IL-12p40:** interleukin-12p40; **PBMC:** peripheral blood mononuclear cell; **VCAM-1:** vascular cell adhesion molecule 1; **ICAM-1:** intercellular adhesion molecule 1; **ROS:** reactive oxygen species; **GSK3β:** glycogen synthase kinase-3β; **PfGSK3β:** *Plasmodium falciparum* glycogen synthase kinase-3β; **Pfmrp1:** *P. falciparum* multidrug resistance protein 1; **Pfmdr1:** *P. falciparum* multidrug resistance gene 1; **Pfcrt:** *P. falciparum* chloroquine resistance transporter; **NF-kB:** nuclear factor-kappaB; **GSH:** glutathione; **TrxR:** thioredoxin reductase enzyme; **LPS:** lipopolysaccharide; **MAPK:** mitogen-activated protein kinase; **ERK:** extracellular signal-regulated kinases; **JNK:** c-Jun N-terminal kinases; **Hb:** haemoglobin; **FP IX:** ferroprotoporphyrin IX (Heme); **GSH:** glutathione; **SOD:** superoxide dismutase; **NPP:** new permeation pathway; **ACP:** acyl carrier protein; **FabD:** malonylCoA-ACP

transacylase; **FabH:** β-ketoacyl-ACP synthase III; **FabG:** β-ketoacyl-ACP reductase; **FabA or FabZ:** β-hydroxyacyl-ACP dehydratase; **FabI:** enoyl- ACP reductase; **FabB and/or FabF:** β-ketoacyl-ACP synthase I and II; **CUR:** curcumin; **KAEMP:** kaempferol; **PIR:** piperine; **ADG:** andrographolide; **α-MG:** α-mangostin; **CAT:** catechin; **LUT:** luteolin; **BA:** betulinic acid.

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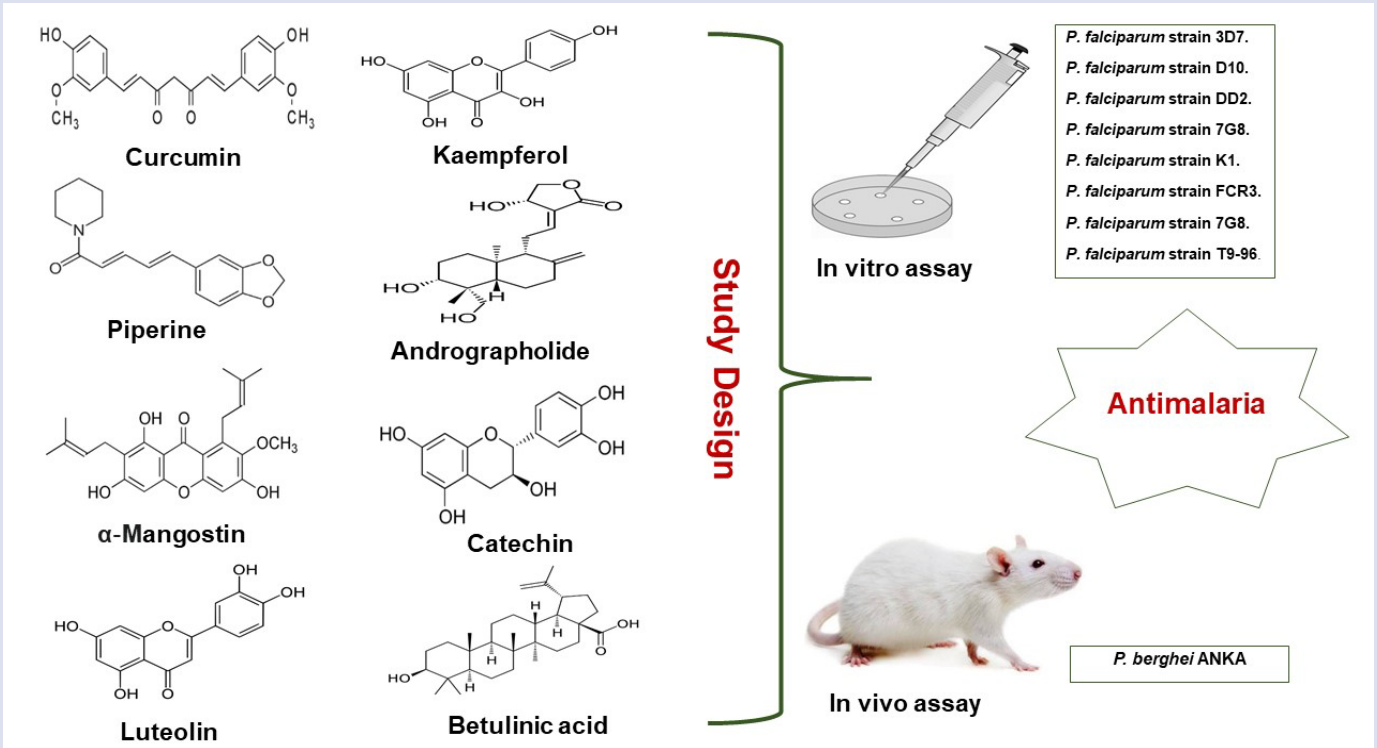
GRAPHICAL ABSTRACT



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