

# The Role of Curcumin as An Antimalarial Agent

Andromeda<sup>1</sup>, Savira Ekawardhani<sup>2</sup>, Afiat Berbudi<sup>2,3\*</sup>

<sup>1</sup>Department of Parasitology, Faculty of Medicine, Universitas Pasundan, Bandung, Indonesia

Biomedical Sciences Master Program, Faculty of Medicine, Universitas Padjadjaran, Bandung, Indonesia

<sup>2</sup>Department of Biomedical Sciences, Parasitology Division, Faculty of Medicine, Universitas Padjadjaran, Bandung, Indonesia

<sup>3</sup>Infectious Disease Research Centre, Faculty of Medicine, Universitas Padjadjaran, Bandung, Indonesia

**\*Corresponding author: Dr. Afiat Berbudi, MD**

Department of Biomedical Sciences,  
Faculty of Medicine, Universitas Padjadjaran,  
Jl. Raya Bandung Sumedang Km. 21, 45363  
West Java, Indonesia  
Email: [a.berbudi@unpad.ac.id](mailto:a.berbudi@unpad.ac.id)

## ABSTRACT

Malaria remains a global health burden, with 219 million cases worldwide in 2017, resulting in 435,000 deaths. The main obstacle in malaria treatment is resistance to antimalarial drugs, rendering patients at risk of complications. Consequently, traditional herbs have been widely developed and studied as adjuvant therapies for malaria. Curcumin, an active compound of turmeric has been known to possess antimalarial effects against various *Plasmodium* species. It has a beneficial impact on both parasite removal and endothelial protection and may promote the immune response against *Plasmodium* via increasing the reactive oxygen species production, activating PPAR $\gamma$ /Nrf2 and upregulating CD36 expression in monocytes or macrophages to phagocytose parasite-infected erythrocytes. It can also downregulate the proinflammatory cytokine response and the expression of various adhesion molecules in endothelial cells and may bind to the heterodimer interface of the  $\alpha/\beta$ -tubulin, causing the depolarisation of microtubules in the mitosis phase during cell division. Curcumin also has a role as an antiplasmodial agent via targeting PfATP6, the parasite orthologue of mammalian SERCA (sarcoplasmic-endoplasmic reticulum Ca<sup>2+</sup>-ATPase). Furthermore, it inhibits the formation of  $\beta$ -hematin and glycogen synthase kinase-3 $\beta$  (GSK3 $\beta$ ), a protein kinase that mediates an anti-inflammatory response through NF- $\kappa$ B activation. Moreover, it is a histone acetyltransferase (HAT) inhibitor that is involved in parasite chromatin modifications. In summary, curcumin has a potency to be used as an adjuvant therapy for malaria.

**Keywords:** Curcumin, Malaria, Antimalaria

## Correspondence:

**Afiat Berbudi<sup>2,3\*</sup>**  
Department of Biomedical Sciences,  
Faculty of Medicine, Universitas Padjadjaran,  
Jl. Raya Bandung Sumedang Km. 21, 45363  
West Java, Indonesia  
Email: [a.berbudi@unpad.ac.id](mailto:a.berbudi@unpad.ac.id)

## INTRODUCTION

Malaria remains a global health burden, with 219 million cases of malaria all over the world in 2017 and a mortality rate of 435,000. Most morbidity occurred in the African region with 200 million cases (92%) in 2017, followed by Southeast Asia (5%) and the Middle East (2%). Globally, 3.4% of cases were predicted to be caused by *Plasmodium vivax*, with approximately 56% of cases occurring in Southeast Asia [1].

Malaria is an infection of erythrocyte by the protozoa parasites of the *Plasmodium* genus invaded the human host via the female *Anopheles* mosquito. The types of *Plasmodium* that harmful for human are *P. falciparum*, *P. vivax*, *P. ovale*, and *P. malariae*. Early symptoms of malaria are more less identical to viral infections such as fever, headache, fatigue, abdominal pain, muscle and joint pains, vomiting nausea, but severe symptoms such as coma (cerebral malaria), metabolic acidosis, severe anaemia, hypoglycaemia, acute renal failure or acute pulmonary oedema can develop. The diagnosis of malaria must be confirmed by a parasitological examination with a microscopic test or rapid diagnostic test (RDT) [2,3].

WHO has recommended artemisinin-based combination therapy (ACT) for uncomplicated malaria therapy caused by *P. falciparum*. However, artemisinin and ACT resistance has become a major threat to the elimination effort of malaria globally. The drug resistance impacts on therapeutic failures, resulting in the increased patient's

susceptibility to complications, ultimately increasing healthcare costs. Moreover, recently, artemisinin resistance has become an emerging problem, Wang *et al* reported that mutation of F446I in *k13* is linked to delayed parasite clearance. Therefore, the discovery of new antimalarial drugs, combinations of drugs, or new therapeutic strategies is crucial to overcome drug resistance in malaria treatment [1,2,4–9].

Traditional medicines derived from nature have had an important role in therapeutic diseases including malaria. Indeed, about 67% of the medicines currently in the market have been developed from natural ingredients, for example, derivatives of artemisinin and quinine as antimalaria drugs. Artemisinin is derived from the Chinese plant *Artemisia annua* and Quinine is derived from the bark of *Cinchona*. Although artemisinin and its derivatives are effective when applied with other antimalarial combinations, there are limitations regarding short half-life, costs and safety in pregnancy. Traditional medicines are easy to obtain and effective in the treatment of malaria, hence the development of traditional medicine as an adjuvant malaria therapy is important and ongoing research is required. One such component of a medicinal plant developed for additional malaria therapy is curcumin, which is one of the main sources of polyphenols from *Curcuma longa* [5,10–17].

Curcumin or diferuloylmethane (from the roots of *Curcuma longa*) is a major curcuminoid and part of the

*Zingiberaceae* family. It is an important phenol derivative that is known to have anti-inflammatory, anticarcinogenic, antioxidant, antiapoptotic and angiogenesis modulation effects. Curcumin is also known to inhibit NF- $\kappa$ B, TNF- $\alpha$ , IL-6, IL-12, IL-1 $\beta$ , and iNOS. Additionally, curcumin has antimalarial effects against various types of *Plasmodium* species through various mechanisms. Manohar *et al* showed that monocarbonyl analogues of curcumin were useful for combating both chloroquine-sensitive and chloroquine-resistant strains of *P. falciparum* [10,11,18–24]. This article intends to elaborate the role of curcumin as an antiplasmodial in malaria.

## THE ROLE OF CURCUMIN AS AN ANTIMALARIAL AGENT

### Curcumin as a modulator of the innate immune response in malaria infections

The infection level of malaria is often correlated with the parasite burden that elicits a defence mechanism to prevent the parasite from multiplying. Curcumin could play a role as pro-oxidant and antioxidant. The defensive role of ROS (reactive oxygen species) in malaria is related to the clearance of parasites. ROS enhanced the scavenger expression of the CD36 receptor on monocytes or macrophages, which mediates phagocytosis of the non-opsonisation parasite-infected erythrocyte by macrophages [5,25,26]

Curcumin as an immunomodulator in malaria affects different types of immune cells. For example, when administered in mice, curcumin increases phagocytosis of macrophages. Curcumin also increases CD36 expression on human monocytes/macrophages, which is involved in the Nrf2 pathway. CD36 expression is modulated by the stimulation of nuclear receptors of PPAR $\gamma$  or with redox-sensitive transcription factor nuclear related (erythroid-derived 2) factor (Nrf2), transcription factors shown to be triggered on curcumin-treated monocyte/macrophages. Curcumin promotes the immune response through induction of ROS production, resulting in the activation of PPAR $\gamma$ /Nrf2 and upregulating CD36 expression in monocytes or macrophages, thereby increasing the phagocytosis of parasite-infected erythrocytes [5,25,27].

### Curcumin suppresses the proinflammatory cytokine response and adhesion molecule expression in endothelial cells

The sequestration process in malaria that occurs in parasite-infected erythrocytes and non-infected erythrocytes caused by reduced microvascular flow results in blood-brain barrier damage, cerebral oedema, and tissue hypoxia. The release of neurotoxic and inflammatory mediators causes leakage through the blood-brain barrier and disrupts the microvascular endothelium. The sequestration is a consequence of the expression of adhesion molecules, mostly ICAM1, VCAM1, and E-selectin, in brain endothelial cells, that are provoked by excessive production of inflammatory cytokines or by attachment of *P. falciparum* directly. Attachment of *P. falciparum* on brain endothelial cells *in vitro* produces an inflammatory environment through ICAM1 expression [5].

Curcumin demonstrates an anti-inflammatory activity due to the suppression of NF- $\kappa$ B, which has a function in inflammation during malarial parasitic infections. The immunomodulatory effect of curcumin protects against endothelial brain damage induced by the sequestration of parasite-infected erythrocytes. Curcumin is along with

common therapies for cerebral malaria, artemisinin or quinine reduces the number of parasites and inflammation, thereby prevents neurological sequelae. Curcumin also plays a role in the suppression of proinflammatory cytokine (TNF $\alpha$ , IL12p40, and IL-6) production in mononuclear cells of the blood infected with trophozoite/skizon of *P. falciparum*. Moreover, curcumin downregulates the expression of ICAM1, VCAM1, and E-selectin in human endothelial cells induced by TNF $\alpha$ . Proinflammatory cytokines and adhesion molecules regulation observed in mononuclear cells upon curcumin administration are the result of Nrf2 and PPAR $\gamma$  activation. These anti-inflammatory activities inhibit the activation of NF- $\kappa$ B [5,22,28,29]

The incidence of cerebral malaria and the severity of plasmodium infection were associated with high levels of IL-6 [30]. IL-6 was known as a proinflammatory cytokine that plays a role in the migration of neutrophils and macrophages. On the other hand, neutrophil was associated with cerebral malaria manifestation in the experimental study using *Plasmodium berghei* ANKA. Neutrophil depletion inhibited development of the experimental cerebral malaria and reduced the sequestration of monocytes and microhaemorrhage in the mice brain [31,32]. Since several studies revealed the role of curcumin in the inhibition of IL-6, curcumin could have potential effect to prevent cerebral malaria and reduce the severity of plasmodium infection [33,34].

Heme-oxygenase-1 (HO-1) is one of the heme oxygenation subtypes that catalyses heme for iron production, carbon monoxide, and biliverdin, which are switched to bilirubin by biliverdin reductase. The overexpression of the HO-1 will inhibit atherosclerosis, inflammation and oxidative stress, whereas HO-1 induction, a target of cascade Nrf2 activation, suppresses the pathology of cerebral malaria in rats, while the activation of the Nrf2 pathway is a potential therapy in brain inflammatory targets. Curcumin upregulates expression of HO-1 in endothelial cells and inhibits activated thrombin and platelet adhesion in microvascular brain endothelial cells *in vitro* [5,22,28,29,35].

Curcumin as adjunctive therapy of  $\beta$ -arteether (artemisinin derivate) was studied by Memvanga in 2013, who reported that curcumin plays a role in preventing parasite relapse. Curcumin synergises with artemisinin to kill parasites, leading to restored adhesion and sequestration of parasite-infected erythrocytes by inhibiting the activation of NF- $\kappa$ B, thereby downregulating the proinflammatory cytokine response and adhesion molecule expression in endothelial cells. Curcumin disrupts the parasite DNA through the induction of ROS in the infected erythrocytes [27,36]

### Curcumin can disrupt cellular microtubules of *Plasmodium sp*

The target of curcumin in mammalian cells is the tubulin, an essential protein for cell division, causing depolarisation of microtubules in the mitosis phase during cell division due to elevated ROS [18]. The role of curcumin in disrupting microtubules is more prominent in the second cycle. Molecular docking data suggested that curcumin may attach to the heterodimer interface of  $\alpha/\beta$ -tubulin, which causes a change in microtubule morphology. This destabilisation of microtubules may also be a part of global cell damage or due to the targeted effect of curcumin. Impaired microtubules inhibit cellular

functionality including apicoplast morphology, thereby causing decreased *Plasmodium* viability [18,37].

#### Curcumin as an antiapoptotic agent

Kunwittaya *et al* (2014) reported that curcumin has a prospective effect on both parasite removal and endothelial protection, by protecting endothelial cells against apoptosis. The mechanism of apoptosis triggered by the parasite-infected erythrocytes is still unclear, but the citoadherence of the parasite-infected erythrocytes can possibly modulate the expression of the TNF- $\alpha$  superfamily gene in endothelial and gene-related apoptosis (Bad, Bax, caspases and iNOS). Furthermore, the presence of parasite-infected erythrocyte adhesion to brain endothelial cells directly activates the Rho kinase signalling pathway, inducing the generation of ROS by endothelial cells, likely triggering cell death [38].

#### Curcumin inhibits SERCA (sarcoplasmic-endoplasmic reticulum $\text{Ca}^{2+}$ -ATPase) in mammalian cells

Curcumin exhibits an effect on chloroquine-resistant *P. falciparum* strains which have a mutation in PfCRT-K76T. A study conducted by Reddy *et al* (2005) revealed that curcumin inhibits the development of *P. falciparum* at an  $\text{IC}_{50}$  of 5 mM via PfATP6, the orthologue parasite on the SERCA (sarcoplasmic-endoplasmic reticulum  $\text{Ca}^{2+}$ -ATPase) mammalian cells. Curcumin inhibits  $\text{Ca}^{2+}$ -ATPase by stimulating a conformational change, which impedes the ATP from attachment. Artemisinin is also known to have the same function in inhibiting this PfATP6 [21,39]

#### Curcumin inhibits the formation of $\beta$ -hematin

The lifecycle of malaria is complex. Sporozoic *Plasmodium* injected by the infected mosquito will move to the liver and start the hepatic phase. The parasites inhabit the hepatocytes, reproduce and develop into a skizon containing thousands of hepatic merozoites, which are then liberated into the blood and initiate the intraerythrocytic phase by replicating inside the erythrocytes. Parasites that undergo asexual phase will develop into gametocytes and are then transmitted towards a mosquito vector [40].

The active metabolism of haemoglobin occurs on acidic organelles such as lysosomes, food vacuoles with a pH of about 5.0 to 5.4, releasing a large amount of free heme, known as ferriprotoporphyrin. Accumulated ferriprotoporphyrin causes the production of ROS which can induce oxidative stress that triggers the parasite death. Nevertheless, *Plasmodium* parasites require a unique detoxification technique of free heme through alteration to the non-toxic, inert, insoluble, crystal pigment and blackish-brown called hemozoin or  $\beta$ -hematin. Padmanaban *et al* showed that the combination of artemisinin and curcumin inhibits the formation of hemozoin and increases the production of ROS in *P. berghei*-infected rats [40–43]

The formation of  $\beta$ -hematin is considered to be the most essential mechanism for heme detoxification in *Plasmodium*. Some antimalarial drugs such as chloroquine and amodiaquine inhibit the hemozoin formation in food vacuoles, preventing the detoxification of the released heme from its origin, thereby killing the parasites. Research conducted by Abu Lafi *et al* (2019) revealed that curcumin exhibits an inhibitory effect on the formation of  $\beta$ -hematin *in vitro*, with an efficiency of 78.8% compared to amodiaquine (91.8%) and DMSO

(10.7%). Curcuminoid isolate is considered to have a similar role to chloroquine, whereby the complex of chloroquine and ferriheme triggers a complex formation that prevents the formation of  $\beta$ -hematin. The interaction between ferriheme and curcumin is likely to allow the interaction of  $\text{Fe}^{3+}$  metal centre with one of the carbonyl groups of curcumin. Furthermore, the side chain carboxyl group of heme will interact with one of the hydroxyl groups of curcumin. Akhtar *et al* revealed that curcumin bound to chitosan nanoparticles could increase the bioavailability of curcumin and metabolic stability; this bond depends on the pH and the maximum bonding occurs at pH 4. These nanoparticles prevent the degradation of curcumin bonds in rat plasma compared to free curcumin. Administration of curcumin bound with chitosan nanoparticles cured rats from *P. yoelii* infection. Curcumin inhibits the synthesis of  $\beta$ -hematin *in vitro* at the value of  $\text{IC}_{50}$  ( $122 \mu\text{M} \pm 2.7$ ) [41,44]

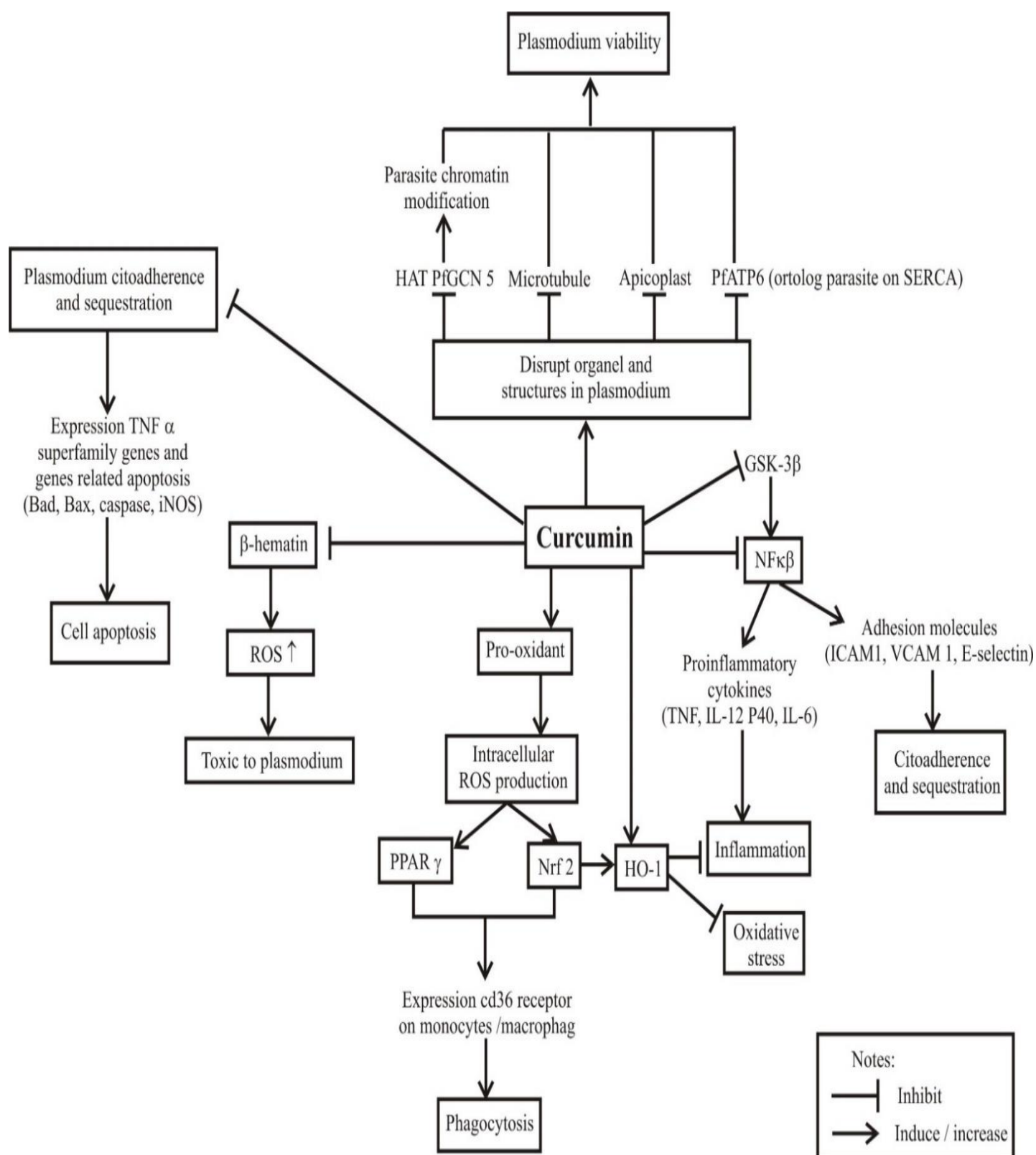
#### Curcumin inhibits GSK-3 $\beta$ (glycogen synthase kinase-3 $\beta$ )

The role of curcumin as an antimalaria agent is mediated through the suppression of NF- $\kappa\text{B}$ , a transcription factor that is the downstream target of some cell signalling systems involving GSK3 $\beta$ . GSK3 $\beta$  is a serine/threonine kinase that has a function in glycogen metabolism and as one of the protein kinases studied as drug targets for malaria. These kinases are known to be involved in various crucial cellular processes, including modulating cytokine levels during the inflammation. GSK3 $\beta$  can directly phosphorylate and activate NF- $\kappa\text{B}$  p65. Inhibition of GSK3 $\beta$  affects the production of inflammatory cytokines by inhibiting the transcriptional activity of NF- $\kappa\text{B}$ . GSK3 $\beta$  is one of the protein kinases that is a target of malaria therapy [45–47].

#### Curcumin as a histone acetyltransferase (HAT) inhibitor and involved in Plasmodium ROS production

Chromatin plays a crucial role in various cellular processes such as transcription, DNA replication, and DNA repair. The nucleosome, which is part of the chromatin, consists of two pairs of histones H2A, H2B, H3, and H4. Among the post-translational modifications of the histone tail, which plays a role in epigenetic regulation, histone acetyltransferase (HAT) is the most widely investigated. HAT is catalysed by histone acetyltransferases (HATs) and released by histone deacetylases (HDACs). Malarial parasites have a similar chromatin structure with other eukaryotes and encode HAT and HDACs. *P. falciparum* general control nondepressed 5 (PfGCN5) is a HAT that tends to acetylate K9 and K14 from H3 histone. Drugs that impact on HDACs and impede histone acetylation in parasites have powerful anti-parasite actions. Curcumin serves as a HAT p300/CREB-binding protein (GST) inhibitor. Nevertheless, the inhibitory effect of curcumin is selective because curcumin does not suppress the P300/associated factor of GNAT (GEN5-related acetyltransferase), which is the superfamily of HATs. Cui *et al* revealed that curcumin specifically inhibits PfGCN5. Curcumin has capability as a pro-oxidant by triggering the ROS production, resulting in mitochondrial and core DNA damage, as well as triggering pH changes in organelles, thereby causing parasite death. Curcumin-induced hypoacetylation occurs on H3 in K9 and K14, but not on H4 in K5, K8, K12, and K16, suggesting that curcumin causes targeted inhibition of the HAT PfGCN5

involved in parasite chromatin modifications [26,48].



**Figure 1:** Schematic diagram showing the effects of curcumin

**Table 1:** Possible antimalarial mechanisms of curcumin

No.	Impacts on <i>Plasmodium</i>	Dosage Treatment & Subjects	Possible Mechanisms	References
1	Increases intracellular ROS production and phagocytosis	Curcumin 10 $\mu$ M in human THP-1 monocytes	Curcumin induces intracellular ROS production resulting in the activation of PPAR $\gamma$ /NRF2 and upregulates CD36 expression in monocytes or macrophages, thereby increasing phagocytosis of the parasite-infected erythrocytes	Mimche <i>et al</i> <sup>25</sup>
2	Suppression of citoadherence and subsequent parasite sequestration	Curcumin and lipid-based drug delivery systems (LBDDSs) combined with $\beta$ -arteether (30 mg/g) in <i>Plasmodium berghei</i> ANKA. In vivo in <i>Caco-2</i> cells	Curcumin reduces citoadherence and subsequent parasite sequestration of parasite-infected erythrocyte by inhibiting the activation of NF- $\kappa$ B, which suppresses the proinflammatory cytokine response and adhesion molecule expression in endothelial cells	Memvanga <i>et al</i> <sup>27</sup>
3	Increases intracellular ROS production and disrupts <i>Plasmodium</i> microtubules	Curcumin 5 $\mu$ M in 3D7, chloroquine-sensitive strain of <i>P. falciparum</i>	<ul style="list-style-type: none"> <li>- Curcumin can produce ROS which induces cytotoxicity and disrupts <i>Plasmodium</i> microtubule stabilisation</li> <li>- Curcumin binds to heterodimer <math>\alpha/\beta</math>-tubulin triggering the alteration of microtubule morphology</li> <li>- Curcumin disrupts schizogony and apicoplast segregation and function</li> </ul>	Chakrabarti <i>et al</i> <sup>18</sup>
4	Inhibition of apoptosis	Curcumin 10 $\mu$ M in murine brain microvascular endothelial cells (bEnd.3)	<ul style="list-style-type: none"> <li>- Curcumin protects against apoptosis in endothelial cells</li> <li>- Curcumin upregulates mitochondrial biogenesis which may inhibit apoptosis</li> </ul>	Kunwittaya <i>et al</i> <sup>38</sup>
5	Inhibition of PfATP6	Curcumin 5 $\mu$ M ( <i>in vitro</i> ) and curcumin 100 mg/kgW	Curcumin inhibits parasitemia via targeting PfATP6, the parasite orthologue of SERCA ( <i>Sarcoplasmic-endoplasmic reticulum Ca<sup>2+</sup>-ATPase</i> ) mammalian cells	Reddy <i>et al</i> <sup>21</sup>



6	Inhibition of formation of $\beta$ -hematin	Curcumin 0.4 mM	Curcumin inhibits the formation of $\beta$ -hematin in <i>Plasmodium</i>	Abu Lafi <i>et al</i> <sup>41</sup>
7	Inhibition of GSK-3 $\beta$ ( <i>glycogen synthase kinase-3<math>\beta</math></i> )	Curcumin 30 mg/kgW in rats with infected with <i>P. berghei</i> NK65	Curcumin inhibits <i>glycogen synthase kinase-3<math>\beta</math></i> that affects the proinflammatory cytokines production by inhibiting the transcriptional activity of NF- $\kappa$ B	Ali <i>et al</i> <sup>45</sup>
8	Inhibition of HAT from <i>P. falciparum</i>	Two CQS (3D7 and D10) and two CQR strains (Dd2 and 7G8) of <i>P. falciparum</i> treated with curcumin 25-100 $\mu$ M	Curcumin inhibits HAT from <i>P. falciparum</i> <i>general control nondepressed 5</i> (PfGCN5) recombinant and downregulates nuclear HAT involved in parasite chromatin modifications	Cui <i>et al</i> <sup>26</sup>

## CONCLUSION

Indonesia is a country with various types of medicinal plants that have the potential to be developed as alternative medicines for malaria treatment. Turmeric has been used empirically to relieve some diseases including infection. Several studies have shown the beneficial impact of curcumin, an active compound of turmeric, as an antimalarial agent. Curcumin can increase intracellular ROS production through inhibition of the formation of  $\beta$ -hematin and phagocytosis of parasite-infected erythrocytes. Moreover, curcumin plays a role in disrupting *Plasmodium* organelles such as microtubules, apicoplast, and PfATP6, as well as affecting parasite chromatin modification through inhibition of HAT. The future development of curcumin/derivatives is urgently needed to maximise the activity of this drug, especially addressing the low bioavailability of curcumin. Nevertheless, due to these antiplasmodial mechanisms, curcumin/derivatives have the potential to become an adjuvant therapy for malaria in the future. This review on the antimalarial effects of curcumin can be used as the basis for the development of new drugs for malaria treatment, which is of increasing importance due to the emergence of resistance to the first-line malaria treatments.

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## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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