Mechanism of Action of Curcumin

Subjects: Infectious Diseases

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Curcumin, one of the major ingredients of turmeric (*Curcuma longa*), has been widely reported for its diverse bioactivities, including against malaria and inflammatory-related diseases. Curcumin's low bioavailability limits its potential as an antimalarial and anti-inflammatory agent. Therefore, research on the design and synthesis of novel curcumin derivatives is being actively pursued to improve the pharmacokinetic profile and efficacy of curcumin.

curcumin derivatives antimalaria anti-inflammatory structure–activity relationship

1. Host Proteins as Molecular Targets of Curcumin

Since malaria causes dysregulation in the inflammatory response, the elucidation of the mechanisms of action of malarial infection is important in order to understand the pathways and binding targets for inhibition. One potential mechanism involved in regulating the pathophysiology of malaria was identified to involve the Toll-like receptor (TLR) signaling pathways. TLRs, which are located on the cell surface, recognize the released *Plasmodium* DNA and trigger the initiation of immune responses through the activation of NF-κB [1][2]. The transcription factor NF-κB is a critical signaling protein involved in various inflammatory responses and gene expressions [3][4][5]. NF-κB is found in a dormant state in the cytoplasm and will only be transcribed when it is activated and translocated into the nucleus [2][6]. This transcription factor is the main target protein that directly regulates the pro- and anti-inflammatory cytokines within the body, including COX-2, TNF, IL-1, IL-6, IL-8, IL-10, and chemokines [1][7][8][9]. The dysregulation of these cytokines and chemokines will lead to the expression of malarial symptoms such as fever, and if left untreated, will lead to severe malaria (**Figure 1**). Therefore, NF-κB has become the most targeted factor in the development of antimalarial agents. Another study also established and reported that *P. falciparum* infection leads to the elevation of TNF production, which is the main malarial pathogenic factor, and, hence, could lead to a high risk of severe malaria and even death [10][11][12].

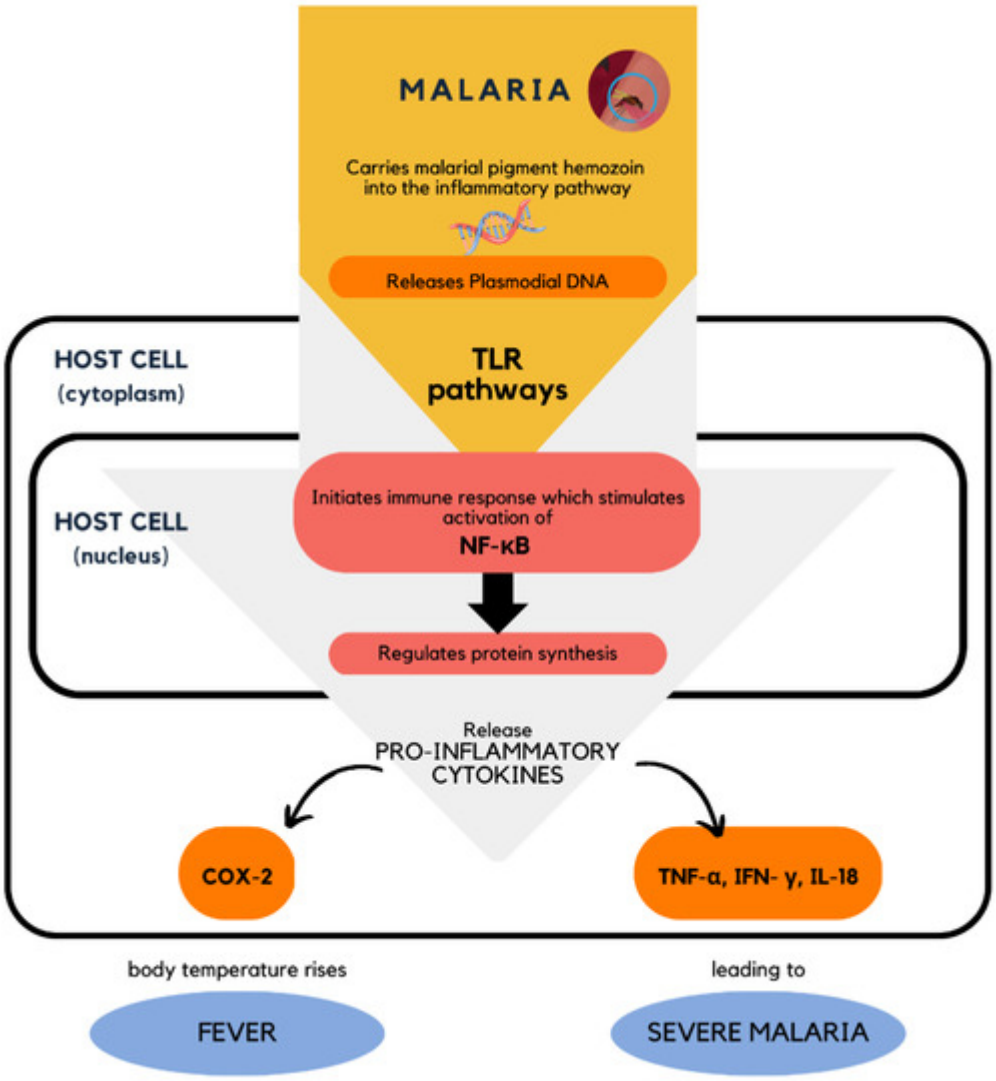

Figure 1. Cellular level mechanism of action of malarial infection in the host cell involving the activation of NF-κB [1].

Curcumin has been proven to suppress the activation and translocation of NF-κB into the nucleus, thus, controlling the level of inflammatory cytokines and the larger inflammatory response. Its ability to interact and inhibit various proteins helps in the elucidation and modulation of the pathophysiology of diseases at the molecular level, including malaria [13][14][15]. The interaction of curcumin with proteins is facilitated by its structural flexibility conferred by the presence of the unsaturated diketo group at the center of curcumin [8][13] (**Figure 2**).

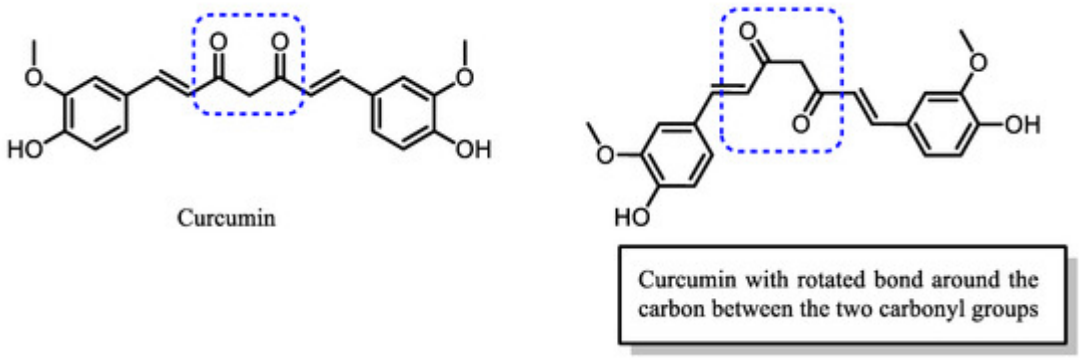

Figure 2. The structural flexibility of curcumin allows for bond rotation around the α-carbon, bridging the two carbonyl groups.

A recent study by Ali et al. on TLR pathways involving the control of the protein kinases Akt and glycogen synthase kinase-3β (GSK3β) also proved NF-κB as a downstream target that regulates anti-inflammatory cytokines [16]. Based on in vivo studies, curcumin was demonstrated to directly inhibit the host GSK3β, leading to the phosphorylation of NF-κB, hence, modulating the regulation of pro- (TNF-α, IFN-γ, and IL-18) and anti-inflammatory (IL-4 and IL-10) cytokine levels [16]. The immunomodulating effect of curcumin in reducing pro-inflammatory cytokine expression can potentially prevent severe and cerebral malaria [17][18]. As evidence to this claim, several in vitro studies have shown that curcumin downregulates pro-inflammatory cytokine production and the expression of cell adhesion molecules in TNF-activated human endothelial cells observed at the trophozoites stage of *P. falciparum* transmission [17]. Furthermore, the inhibition of NF-κB by curcumin also suppresses the generation of reactive oxygen species (ROS), which attenuates the inflammatory response [19][20][21].

2. Parasite Proteins as Molecular Targets of Curcumin

With regard to parasite proteins, curcumin induces ROS generation in parasite cells, which affects the function of the *Pf*GCN5 histone acetyltransferases (HATs) p300/CREB-binding protein (CBP), thus, inhibiting histone acetylation and the transcription process in the parasite [22]. The generation of ROS is an important antimalarial mechanism as it induces protein and DNA damage within parasite cells, leading to their death [16][23][24]. The specific inhibition of parasite HAT by curcumin prevents the acetylation of K9 and K14 of histone H3. Cui et al. also reported that the antiplasmodial activity of curcumin is attributed, at least in part, to the production of ROS and the downregulation of *Pf*GCN5 HAT activity [25].

Another mechanism of action of curcumin is by disrupting the transmission and development of *Plasmodium* parasites at the erythrocytic stage. As erythrocytes burst to release more merozoites, heme is also released. However, the released heme is highly toxic to the merozoites. Thus, the parasites will be stimulated to convert hematin into its detoxified polymeric form, hemozoin [26][27][28]. Curcumin treatment was reported to inhibit the formation of hemozoins in vitro, as observed through transmission electron microscopy in a study using the *P. falciparum* 3D7 strain [29]. This proved that the antimalarial activity of curcumin is similar to that of quinine and chloroquine [28].

Uncontrolled parasite transmission in the body can develop into fatal severe anemia or cerebral malaria, whose pathophysiology involves the inflammatory response [15][30]. The excessive stimulation of pro-inflammatory cytokines by the parasite subsequently leads to the sequestration of parasites in the brain [31]. Several reports have indicated the ability of curcumin to eliminate parasites at the trophozoite stage, synergistically and effectively better than artemisinin [32][33][34][35]. This observation was also proven using chloroquine-sensitive (CQS) and chloroquine-resistant (CQR) *P. falciparum* strains, with a proposed mechanism of curcumin action against the parasite proteins *Pf*RIO2-kinase and *Pf*GCN5 HAT [33][35][36].

The Knoevenagel condensate curcumin derivatives mentioned earlier were suggested to target the *Pf*ATP6 parasite protein to explain their schizont inhibition activity. This was based on the established target of the reference antimalarial drug, artemisinin, which shares the same binding pocket on *Pf*ATP6 as curcumin [32][37]. The study applied PreADMET predictions, which demonstrated the attachment and interaction of curcumin and its derivatives with the active site of *Pf*ATP6.

The identification of therapeutic targets involved in malarial infection can provide a better understanding of the inhibitory mechanism of antimalarial agents (**Figure 3**) [38][39]. The current knowledge on the action of curcumin derivatives is limited, as their host-targeting mechanisms have not been entirely established (**Table 1**) [14][40][41]. Therefore, future research that can explain an in-depth understanding of the molecular-level mechanism of action of curcumin and its bioactive derivatives will not only help in the development of potent antimalarial and anti-inflammatory agents [42] but also for other diseases [43][44][45].

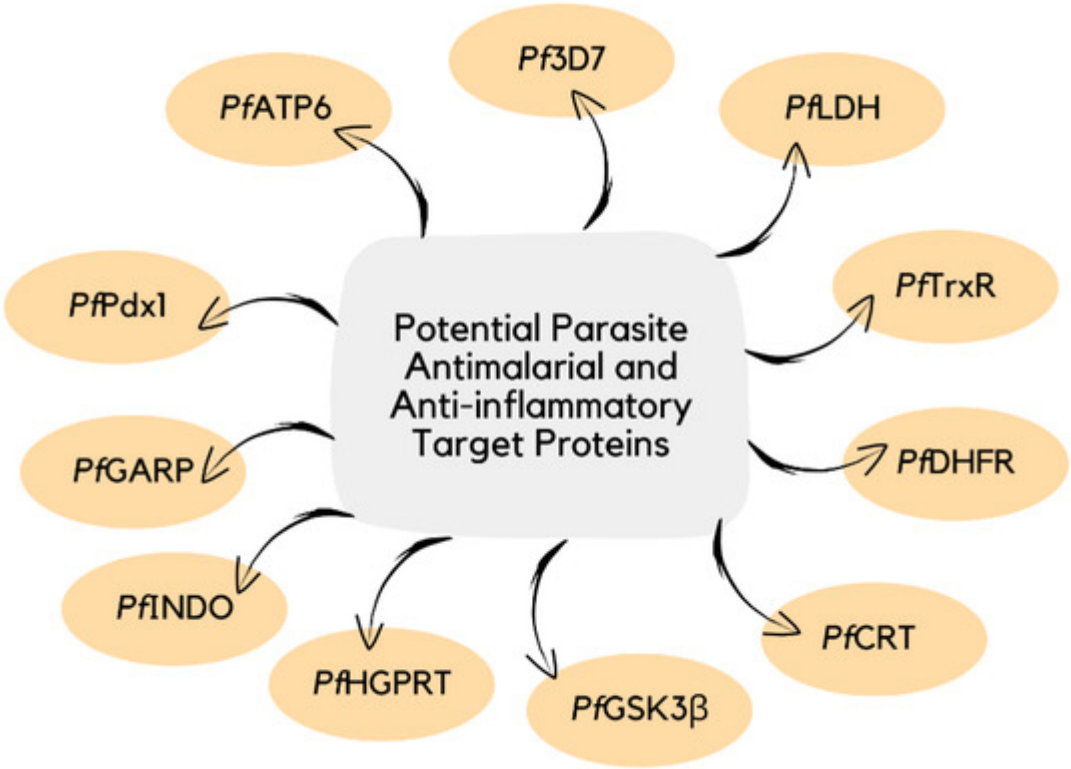

Figure 3. Examples of potential parasite target proteins involved in the pathophysiology of malaria.

Table 1. Antimalarial and anti-inflammatory activities of curcumin and its derivatives.

Activity	In Vitro/In Vivo/In Silico Evidence	References
Antiplasmodium *Pf*ATP6	Curcumin (**1**) reduced *P. falciparum* viability, causing parasitic cell proliferation to decrease. - Reported IC_{50} value: 5 µM.	[37]
	Curcumin (**1**) and its derivatives (**9**, **14**, **15**, **19**, **21**, **23**, **27**, and **28**) showed 100% inhibition of *P. falciparum* growth upon a 50 µ$\square$g/mL dose of treatment.	[32]
	Molecular docking results validated binding of curcumin (**1**) and its derivatives to *Pf*ATP with favorable free binding energy. - Reported free binding energy: Curcumin derivative (**21**): –6.75 kcal/mol (higher than both artemisinin (–6.73 kcal/mol) and curcumin (–5.25 kcal/mol), hence, better interaction with the protein). - Hydrogen bonding with Lys1213 and Leu1044	[32]
	In vitro study using CQR *P. falciparum* showed potent antimalarial activity of curcumin (**1**), with reported IC_{50} value of ~5 µ$\square$M. In vivo treatment of *P. berghei*-infected mice with 100 mg/kg curcumin showed: - More than 80% inhibition of parasitic growth. - A 29% increase in survival rate.	[46][47]
	Curcumin treatment on *P. berghei*-infected C57Bl/6 mice delayed mice death by 10 days and prevented cerebral malaria. Dose: 50 mg/kg, twice daily for 6 days.	[48]
	Curcumin exhibited antimalarial activity in *P. berghei*-infected mice. Dose: 300 mg/kg daily for 4 days (60.22% parasitemia inhibition). Dose: 80 mg/kg daily for 4 days (60.21% chemosuppressive effect).	[49][50]
Antiplasmodium *Pf*3D7	Curcumin (**1**) showed potential inhibition of parasite transmission at the trophozoite stage. Curcumin derivative (monocarbonyl curcumin) - Reported IC_{50} values against CQS: 1.97 µM, CQR: 1.69 µM. Curcumin derivative (**13**) - Reported IC_{50} value: 1.97 µM.	[51]

Activity	In Vitro/In Vivo/In Silico Evidence	References
Antiplasmodium *Pf*DXR	In silico and in vitro studies validated synergistic binding of curcumin (1) to *Pf*DXR protein with fosmidomycin. - Presence of methoxy substituent on the phenyl groups facilitated parasite elimination: (**43**)—55%. (**46**)—57%.	[52]
Antiplasmodium *P*GCN5 HAT	In vitro study suggested curcumin (**1**) as a potent inhibitor of p300/CBP (CREB-binding protein) as tested on four *P. falciparum* strains. - Reported IC_{50} values—3D7: 24.69 µM, D10: 22.93 µM, 7G8: 29.61 µM, Dd2: 27.45 µM.	[16]
Antiplasmodium *Pf*TrxR	In vitro study using CQS (D6 clone) and CQR (W2 clone) *P. falciparum* strains showed that curcumin (**1**) inhibited *Pf*TrxR protein with an IC_{50} value of 2 µM.	[53]
Antiplasmodium *Pf*HGPRT *Pf*SAHH	In silico simulation using Molegro Virtual Docker (MVD) and admetSAR showed high binding energy of curcumin (**1**) to the protein. - Reported binding energy: - *Pf*HGPRT: −175.97 kcal/mol. - *Pf*SAHH: −138.30 kcal/mol.	[41][54]
Antimalaria ROS	In vitro study showed that curcumin (**1**) induced intracellular ROS production related to PPARɣ/Nrf2 activation. - Reported IC_{50} value: 10 µM.	[19][55]
Antimalaria	In vitro study using NF54 intraerythrocytic-form *P. falciparum* strain reported highly potent antiparasitic activity of curcumin (**1**). - Reported IC_{50} value: 0.59 µM.	[56]
	In vitro study using 3D7 clone strain of *P. falciparum* reported synergistic antimalarial effect of curcumin (**1**) with dihydroartemisinin and reduction in hemozoin formation upon several consecutive treatments of curcumin. - Reported IC_{50} value: 2.2 µg/mL.	[24]
	In vitro study showed the effectiveness of curcumin–artemisinin combination therapy with additive interaction in killing *P. falciparum*. In vivo study using *P. berghei*-infected mice showed 100% survival upon	[56]

Activity	In Vitro/In Vivo/In Silico Evidence	References
	treatment. Dose: 750 µg.	
	In vivo study on *P. berghei* ANKA-infected mice revealed treatment of curcumin (**1**) reduced parasitemia level and increased survival rate. Dose: 50 mg/kg daily.	[57]
	In vitro study shows reported IC_{50}: - Curcumin Encapsulated to PLGA: 292.6 µg/mL. - Curcumin (1): 1000 µg/mL. In vivo study on *P. berghei*-infected mice and murine RAW 264.7 macrophages using curcumin encapsulated in PLGA showed 56.8% parasite suppression (higher than free curcumin with 40.5% suppression). Dose: 5 and 10 mg/kg.	[58]
Anti-inflammatory COX-2	In vitro study using DPPH radical-scavenging assay showed anti-inflammatory activity of curcumin and its derivatives. Reported IC_{50} value and % inhibition: - Curcumin (**1**)—IC_{50} value: 11.06 µM, 35.0% inhibition. - Derivative (**2**)—IC_{50} value: 10.71 µM, 58.1% inhibition. - Derivative (**3**)—IC_{50} value: 9.70 µM, 61.0% inhibition.	[59]
	Molecular docking using FlexX program validated COX-2 as a target protein and showed binding of curcumin (**1**) and curcumin derivatives (**2**, **3**). Favorable interactions: - Hydrogen bonding interaction with Arg120. - van der Waals interactions with Val523, Val116, Ala516, and Try355.	[59]
Anti-inflammatory NF-κB	In vivo study on *P. berghei* ANKA-infected mice upon treatment of curcumin (**1**) showed inhibition of NF-κB activation, which reduced expression of adhesion molecules and suppressed pro-inflammatory cytokines level. Dose: 100 mg/kg daily for 4 days.	[60]
Anti-inflammatory GSK3β	In vivo study on *P. berghei* NK65-infected rats upon treatment of curcumin (**1**) showed inhibition of host GSK3β, leading to the phosphorylation of NF-κB and regulation of pro- (decrease in serum TNF-α and IFN-γ levels) and anti-inflammatory (IL-10 and IL-4) cytokines. Dose: 3, 10, and 30 mg/kg.	[11]
Anti-inflammatory	In vivo study on *P. berghei* NK65- and ANKA-infected mice upon treatment of curcumin (**1**).	[61]

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Activity	In Vitro/In Vivo/In Silico Evidence	References
	Reported activity: - Significant decrease in inflammatory cytokine levels including serum p53, TNF-α, CRP, and IL-6. - Inhibition of mPT pore opening, F_0F_1 ATPase activity and mLPO. Dose: 50 mg/kg.	

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