



THE POTENTIAL OF CURCUMA XANTHORRHIZA AS AN ADJUVANT THERAPY FOR MALARIA: A NARRATIVE REVIEW

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ABSTRACT

Malaria continues to be a major global health issue, associated with high rates of morbidity and mortality. The primary treatment is artemisinin-based combination therapy (ACT), however its effectiveness is being threatened by resistance associated with mutations in the kelch13 (K13) gene. Furthermore, an excessive inflammatory response also plays a role in malaria pathogenesis, making immunomodulation-based therapeutic approaches an important strategy. This study aims to evaluate the potential and mechanism of Curcuma xanthorrhiza (Javanese turmeric or temulawak) as an antiparasitic agent and adjuvant therapy. This narrative review aimed to evaluate the potential of Curcuma xanthorrhiza as an adjuvant therapy for malaria. Literature was collected from PubMed, ScienceDirect, and Google Scholar for studies published between 2010 and 2025 using keywords related to malaria, Curcuma xanthorrhiza, artemisinin resistance, oxidative stress, and immunomodulation. A total of 268 records were identified through the database search. After duplicate removal and eligibility screening, 39 articles met the inclusion criteria and were included in this narrative review. Selected studies included experimental research, reviews, and preclinical investigations relevant to the pharmacological activity of Curcuma xanthorrhiza in malaria management. Evidence indicates that bioactive compounds such as xanthorrhizol, curcuminoids, and terpenoids exhibit moderate antiparasitic activity and significantly regulate inflammatory pathways through inhibition of nuclear factor-kappa B (NF- κ B), cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS), and pro-inflammatory cytokines including TNF- α and IL-6. In addition, antioxidant activity contributes to reducing oxidative tissue damage associated with malaria pathogenesis. Although its direct antiparasitic potency remains inferior to artemisinin-based combination therapy (ACT), Curcuma xanthorrhiza demonstrates promising potential as a host-directed adjunctive therapy capable of enhancing immune homeostasis and mitigating malaria-associated complications. However, current evidence is predominantly limited to in vitro and animal studies.

Keywords: adjuvant; antiparasitic; artemisinin; curcuma xanthorrhiza; immunomodulator; malaria

How to cite (in APA style)

Rosadi, N. K. R., Laksemi, D. A. A. S., & Sudarmaja, I. M. (2026). The Potential of Curcuma Xanthorrhiza as An Adjuvant Therapy for Malaria: A Narrative Review. *Indonesian Journal of Global Health Research*, 8(5), 1125–1134. <https://doi.org/10.37287/ijghr.v8i5.2467>.

INTRODUCTION

Malaria remains a tropical infectious disease with a high global health burden. The disease is caused by the Plasmodium parasite and is transmitted through the bites of infected female Anopheles mosquitoes. Globally, malaria causes significant morbidity and mortality, with over 280,000,000 cases and over 600,000 deaths expected by 2024. Sub-Saharan Africa carries the largest share of the disease burden, accounting for approximately 94% of malaria cases and 95% of malaria deaths globally (Liu et al., 2025; World Malaria Report 2023, 2023). Malaria infections are predominantly caused by five Plasmodium species, with Plasmodium falciparum and Plasmodium vivax being the predominant species. Plasmodium falciparum accounts for over 90% of malaria cases in Africa and is the leading cause of severe malaria and high mortality, while in Asia and Latin America Plasmodium vivax is more common. Children under five years of age are the most vulnerable group to malaria infection and complications, especially in areas with low sociodemographic levels (Huang et al., 2025; Liu et al., 2025). Although various control efforts have reduced malaria incidence in the previous decade, this progress is challenged by antimalarial drug resistance,

particularly to artemisinin, the main component of ACT. Partial resistance has been reported in several endemic areas, potentially reducing the effectiveness of standard therapy. Therefore, monitoring resistance and developing new therapeutic strategies are crucial in future malaria control efforts (Huang et al., 2025; World Malaria Report 2023, 2023).

Malaria pathogenesis is strongly influenced not only by parasite burden but also by the host immune response. During infection, the immune system activates innate and adaptive immune mechanisms to eliminate *Plasmodium* parasites through the production of pro-inflammatory cytokines such as tumor necrosis factor alpha (TNF- α), interleukin-1 beta (IL-1 β), interleukin-6 (IL-6), and interferon-gamma (IFN- γ). Although these responses are essential for controlling parasitemia, excessive inflammation may contribute to severe malaria manifestations, including cerebral malaria and severe anemia. Conversely, anti-inflammatory cytokines such as interleukin-10 (IL-10) and transforming growth factor-beta (TGF- β) help regulate immune homeostasis and limit tissue damage. Therefore, the balance between pro-inflammatory and anti-inflammatory responses plays an important role in determining malaria severity and has become a potential target for immunomodulation-based therapeutic strategies (Naing et al., 2024; Wilairatana et al., 2022; Hamad et al., 2025).

Artemisinin-based combination therapy (ACT) remains the first-line treatment for uncomplicated malaria due to its rapid parasitocidal activity and high efficacy against *Plasmodium falciparum*. Artemisinin derivatives, including artesunate, artemether, and dihydroartemisinin, act through activation of endoperoxide bridges by heme or iron ions, leading to the generation of reactive free radicals that damage parasite proteins and cellular structures^{4,6}. However, the emergence of partial artemisinin resistance associated with mutations in the K13 gene has become a major challenge in malaria control, highlighting the need for alternative and adjunctive therapeutic strategies. (Azmi et al., 2023; Rosenthal et al., 2024; White and Chotivanich, 2024). Therefore, therapeutic strategies that are not only antiparasitic/antiplasmodial but also capable of modulating the immune system are becoming increasingly important. Host-directed therapy (HDT) approaches are being developed as an alternative strategy by targeting host factors involved in pathogenesis, such as inflammatory pathways and immune defense mechanisms. This strategy may help reduce the risk of drug resistance and can be combined with conventional antimalarial therapy to control inflammation and enhance the immune response to infection (Adderley & Grau, 2023; Wei et al., 2021).

Consistent with this concept, medicinal plants serve as a source of bioactive compounds with anti-inflammatory, antioxidant, and immunomodulatory activities that have the potential to be used as adjuvant malaria therapy. Several studies have shown that combining herbal compounds with artemisinin-based therapy can reduce inflammatory cytokines, reduce oxidative stress, and repair tissue damage in severe malaria compared to single therapy (Ansari et al., 2025; Plirat et al., 2023). However, to date, there are still limitations in integrating evidence regarding the effectiveness of certain medicinal plants as host-directed therapy agents, especially those with combined antiplasmodial and immunomodulatory activity. Furthermore, most studies are still preclinical with a wide variety of extraction methods and doses, thus complicating standardization and clinical translation. In this regard, *Curcuma xanthorrhiza*, as a plant endemic to Southeast Asia with diverse bioactive compounds, has the potential to be a promising candidate for adjuvant therapy. Therefore, this study aims to synthesize scientific evidence regarding the potential of *Curcuma xanthorrhiza* as an antiplasmodial and immunomodulatory agent in the context of host-directed malaria therapy.

METHOD

This article employed a narrative literature review methodology. Data were collected from PubMed, ScienceDirect, and Google Scholar, focusing on: (1) antiplasmodial activity of *Curcuma xanthorrhiza*, (2) immunomodulatory and antioxidant effects, (3) mechanisms of action of artemisinin, (4) artemisinin resistance associated with K13 mutations, and (5) the potential role of

herbal compounds as adjuvant therapy for malaria. The search strategy used the keywords: “*Curcuma xanthorrhiza*” OR “temulawak” OR “Javanese turmeric” AND “malaria” OR “*Plasmodium*” OR “antiplasmodial” OR “antimalarial” AND “immunomodulator” OR “immune response” OR “oxidative stress” AND “artemisinin” OR “artemisinin resistance.” A comprehensive literature search was conducted for publications between 2010 and 2025. A total of 268 records were identified through the database search. After duplicate removal and title and abstract screening, potentially relevant studies underwent full-text assessment based on predefined eligibility criteria. Inclusion criteria included original research articles, review articles, and experimental studies published in English or Indonesian with full-text availability and scientific relevance to the topic. Articles not relevant to the topic or without accessible full text were excluded. The selected studies were then analyzed and synthesized narratively to evaluate the potential of *Curcuma xanthorrhiza* as an adjuvant therapy in malaria management.

RESULT

Antiplasmodial Activity of Artemisinin

ACT primarily consists of artemisinin and its derivatives, including artesunate, artemether, and dihydroartemisinin (DHA), used as first-line treatment for malaria caused by *Plasmodium falciparum*. These compounds have very rapid parasitocidal activity in the erythrocytic phase of the parasite and are capable of significantly reducing parasite biomass within a single erythrocytic cycle of approximately 48 hours. This clinical effectiveness is related to the activation of endoperoxide groups by heme or iron ions produced during hemoglobin degradation in infected erythrocytes, which generate reactive free radicals and cause protein damage and disruption of various parasite metabolic pathways (Bridgford et al., 2018; Straimer et al., 2015). Despite their very high antiplasmodial potency, partial artemisinin resistance has been reported in various endemic areas. Clinically, resistance is characterized by slowed parasite clearance after ACT therapy. This phenomenon is correlated with mutations in the *K13* gene, which enhance the parasite's ability to withstand artemisinin-induced oxidative stress. Therefore, monitoring resistance and developing new combination therapy strategies are crucial to maintain the effectiveness of future malaria therapies (Ménard et al., 2016; White & Chotivanich, 2024).

Phytochemical Characteristics and Antiplasmodial Activity of *Curcuma xanthorrhiza*

Curcuma xanthorrhiza is an herbal plant from the *Zingiberaceae* family used in traditional medicine in Indonesia and Southeast Asia. Its rhizomes contain various bioactive secondary metabolites, including terpenoids, curcuminoids, and phenolic compounds. One of the main components of its essential oil is xanthorrhizol, which is a characteristic chemical marker and plays a key role in its pharmacological activity. Furthermore, volatile compounds such as α -curcumene, germacrone, and α -cedrene also contribute to the bioactivity profile of *Curcuma xanthorrhiza* (Rahmat et al., 2021; Simamora et al., 2024). Biologically, secondary metabolites in *Curcuma xanthorrhiza* exhibit anti-inflammatory, antioxidant, and immunomodulatory activities relevant to malaria pathogenesis. Xanthorrhizol and curcuminoids are known to suppress the production of pro-inflammatory cytokines such as IL-1 β , IL-6, and TNF- α and inhibit inflammatory mediators such as cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS). Meanwhile, phenolic compounds are involved in scavenging reactive oxygen species (ROS) and mitigating oxidative stress, which can indirectly support antiparasitic effects (Simamora et al., 2024). The potential antiplasmodial activity of *Curcuma xanthorrhiza* has been evaluated through various experimental approaches. In vitro tests against *Plasmodium falciparum* showed that *Curcuma xanthorrhiza* extract was able to inhibit parasite growth in the erythrocytic phase with varying potency.^{19,21} Consistently, *in vivo* studies using a *Plasmodium berghei* infection model reported a decrease in parasite density and a slowing of infection progression after administration of the extract

The underlying mechanism of this effect is thought to involve inhibition of heme polymerization in the parasite, although most evidence is still limited to experimental studies and requires further

validation through clinical trials (Nurcholis et al., 2024; Rahmat et al., 2021). Antiplasmodial activity is classified based on half maximal inhibitory concentration IC_{50} values, with moderate activity being in the range of 10–50 $\mu\text{g/mL}$. Although specific data against *Plasmodium* are still limited, *Curcuma xanthorrhiza* extract is thought to have activity in this category (Mohd Salleh et al., 2016). Several international studies since 2015 have reported that the ethanol extract of *Curcuma xanthorrhiza* has an IC_{50} value of $279.74 \pm 16.33 \mu\text{g/mL}$, while activity on specific enzyme targets ranges from 9.59–22.76 $\mu\text{g/mL}$. In addition, its main compound, xanthorrhizol, exhibited activity with an IC_{50} of approximately $11.30 \pm 0.27 \mu\text{M}$ (Mohd Salleh et al., 2016).

Curcuma xanthorrhiza's Immunomodulatory Activity

In addition to its antiplasmodial activity, *Curcuma xanthorrhiza* also exhibits immunomodulatory activity associated with its ability to modulate inflammatory cytokine production and reduce levels of oxidative stress. Bioactive compounds such as xanthorrhizol and curcuminoids are known to influence immune signaling pathways, in relation to its capacity to mitigate oxidative stress, this effect is associated with signaling pathways, including nuclear factor kappa B (NF- κ B) and mitogen-activated protein kinase (MAPK), which are involved in the regulation of pro- and anti-inflammatory cytokine production (Yuandani, Jantan, et al., 2021). TNF- α and IL-6, as representative pro-inflammatory cytokines, are primary mediators of the inflammatory response during infection (Yuandani, Jantan, et al., 2021). Preclinical studies in animal models have demonstrated that administering *Curcuma xanthorrhiza* extract can significantly reduce the levels of these two cytokines. In a study using a mouse model exposed to particulate matter, administration of *Curcuma longa* extract following 30 days of treatment led to a decrease in TNF- α levels to $55,981 \pm 4,689 \text{ pg/mL}$ and IL-6 to $2,292 \pm 0.461 \text{ pg/mL}$, compared to the control group, which showed higher cytokine levels. Furthermore, the study showed that *Curcuma* extract was able to reduce oxidative stress, as indicated by a decrease in malondialdehyde (MDA) systemic levels to $1,542 \pm 0.231 \text{ nmol/mL}$ in the highest dose group (Aminuddin et al., 2023). This anti-inflammatory activity is correlated to the ability of *Curcuma's* bioactive compounds to downregulate the activation of NF- κ B, which contributes to inducing the gene expression of pro-inflammatory cytokines such as TNF- α and IL-6. Inhibition of this pathway leads to a decrease in the production of inflammatory mediators by macrophages and other immune cells, thereby reducing the systemic inflammatory response (Allegra et al., 2022).

In addition to suppressing pro-inflammatory cytokines, *Curcuma xanthorrhiza* can also increase the production of anti-inflammatory cytokines such as IL-10, which functions to suppress excessive inflammatory responses and maintain immune homeostasis (Allegra et al., 2022). Bioactive compounds from the *Curcuma* genus are known to modulate the activity of T cells and macrophages, thereby affecting the regulation of pro- and anti-inflammatory cytokine balance. These cytokine modulation are involved in regulating the differentiation of helper T cell and the adaptive immune response, including the production of IFN- γ , a cytokine important for macrophage activation and the elimination of intracellular pathogens (Yuandani, et al., 2021; Yrahmatuandani, et al., 2021). In addition to modulating cytokines, *Curcuma xanthorrhiza* also exhibits antioxidant activity which is essential for the regulation of the immune system. Key compounds, such as xanthorrhizol, have been shown to possess potent antioxidant activity and can ward off free radicals formed during inflammation. This antioxidant activity can reduce cellular damage induced by oxidative stress and support immune system function. Xanthorrhizol has been reported to exhibit a range of biological activities, including anti-inflammatory and antioxidant properties, thereby contributing to the plant's immunomodulatory effects (Oon et al., 2015).

Consequently, pharmacological studies of *Curcuma xanthorrhiza* indicate that it contains more than 40 active compounds, primarily terpenoids and curcuminoids, which play a role in multiple biological activities, including anti-inflammatory, antioxidant, and immunomodulatory functions. This combination of activities makes *Curcuma xanthorrhiza* a potential natural immunomodulatory

agent that can help control inflammatory responses and oxidative stress in various disease (Rahmat et al., 2021).

Table 1.
Summary of Selected Studies on Antiplasmodial and Immunomodulatory Effects of *Curcuma xanthorrhiza*

Author (Year)	Study Type	Model	Compound	Outcome Measure	Key Findings	Limitation
Nurcholis et al. (2024)	Experimental	<i>In vitro</i> (Plasmodium)	Essential oil of <i>C. xanthorrhiza</i>	Parasitemia inhibition	Dose-dependent antiplasmodial activity	Lack of extract standardization
Aminuddin et al. (2023)	Experimental	<i>In vivo</i> (rat)	<i>C. xanthorrhiza</i> extract	TNF- α , IL-6, MDA	Reduced pro-inflammatory cytokines and oxidative stress	Not malaria-specific model
Yuandani et al. (2021)	Experimental	<i>In vivo</i>	<i>Curcuma</i> spp. extract	IL-10, IFN- γ	Modulated immune response via cytokine balance	Not specific to <i>C. xanthorrhiza</i>
Plirat et al. (2023)	Experimental	<i>In vivo</i> (Plasmodium)	Herbal + artesunate	Parasitemia, survival	Improved parasite clearance and survival	Different herbal species used
Deharo & Ginsburg (2011)	Experimental	<i>In vitro</i>	Plant-derived compounds	Drug interaction	Demonstrated potential synergism	Not specific to <i>C. xanthorrhiza</i>
Allegra et al. (2022)	Review	-	Curcumin	NF- κ B, TNF- α , IL-6	Downregulated inflammatory pathways	Not malaria-specific
Simamora et al. (2024)	Review	-	Xanthorrhizol	COX-2, iNOS, NF- κ B	Anti-inflammatory pathway inhibition	Limited experimental validation
Wilairatana et al. (2022)	Meta-analysis	Clinical	-	IL-6	Elevated IL-6 linked to severe Malaria	Observational data
Naing et al. (2024)	Review	Clinical	-	TNF- α , IL-6	Pro-inflammatory cytokines associated with severity	No intervention analysis

DISCUSSION

The studies summarized in the table demonstrate that artemisinin and *Curcuma xanthorrhiza* possess distinct yet potentially complementary roles in malaria therapy. Artemisinin remains the first-line treatment due to its high efficacy in rapidly reducing *Plasmodium falciparum* biomass through a direct parasitocidal mechanism. In contrast, *Curcuma xanthorrhiza* demonstrates more prominent immunomodulatory, anti-inflammatory, and antioxidant properties, which contribute to regulating the host response during infection. This distinction suggests that malaria therapy requires not only parasite elimination but also modulation of the immune response and oxidative stress, both of which contribute to disease pathogenesis. Conceptually, the differences in effectiveness between these two agents reflect the distinct biological targets underlying their pharmacological activities. Artemisinin acts directly on the parasite and produces a rapid parasitocidal effect, thereby playing a major role in reducing parasitemia. Conversely, *Curcuma*

xanthorrhiza does not exhibit comparable antiparasmodial potency; however, it exerts significant biological effects in maintaining immune homeostasis and reducing tissue damage induced by inflammation and oxidative stress (Buthelezi et al., 2025; Rahmat et al., 2021; Aminuddin et al., 2023). Therefore, *Curcuma xanthorrhiza* is more appropriately positioned as an adjuvant therapy rather than as an alternative to primary antimalarial treatment.

Comparison of the Mechanisms of Action of Artemisinin and *Curcuma xanthorrhiza*

The fundamental differences in the mechanisms of action of these two agents underlie their potential therapeutic synergism. Artemisinin works through the activation of endoperoxide groups by heme or Fe²⁺ ions in infected erythrocytes, which generate reactive free radicals and damage essential proteins in the parasite, disrupting various biological processes and leading to the death of *Plasmodium falciparum* (Wang et al., 2015). This mechanism is also associated with the emergence of resistance mediated by mutations in the *K13* gene, which increases the parasite's ability to withstand oxidative stress and slows parasite clearance (Bridgford et al., 2018; Straimer et al., 2015). In contrast, *Curcuma xanthorrhiza* works primarily through modulating the host immune response and controlling oxidative stress. Bioactive compounds such as xanthorrhizol and curcuminoids are known to inhibit key inflammatory pathways such as NF- κ B and MAPK, thereby suppressing the production of pro-inflammatory cytokines such as TNF- α and IL-6 and helping maintain a balanced immune response (Yuandani, Nugraha, et al., 2021). Furthermore, antioxidant activity, demonstrated by the reduction of biomarkers such as MDA, reflects a protective role against tissue damage induced by oxidative stress (Aminuddin et al., 2023; Oon et al., 2015). These differences in mechanisms suggest that artemisinin and *Curcuma xanthorrhiza* act on two distinct yet complementary axes: direct parasite elimination and modulation of the host response. Interactions between antiparasmodial compounds can be additive, synergistic, or antagonistic, depending on their respective mechanisms of action. Combination approaches based on natural ingredients and conventional drugs have the potential to produce synergistic effects that enhance therapeutic efficacy without significantly increasing toxicity (Deharo & Ginsburg, 2011).

The integration of these two mechanisms theoretically has the potential to produce a more comprehensive therapeutic effect, combining rapid reduction in parasitemia and control of systemic inflammation (Deharo & Ginsburg, 2011). This approach aligns with the concept of host-directed therapy, which is increasingly emerging as a strategy to improve the effectiveness of infection treatment and overcome the limitations of parasite-targeted therapies. The clinical implications of these findings are particularly relevant in the context of increasing artemisinin resistance (Adderley & Grau, 2023; Wei et al., 2021). Mutations in the *K13* gene, which contribute to resistance, suggest that therapeutic approaches focused solely on parasite targets have long-term limitations (Straimer et al., 2015). In this regard, the use of *Curcuma xanthorrhiza* as an adjuvant therapy could potentially provide additional benefits through mechanisms independent of the parasite target, and therefore theoretically unaffected by these mutations. The anti-inflammatory and antioxidant effects of *Curcuma xanthorrhiza* also have the potential to reduce disease severity and prevent complications caused by systemic inflammation and oxidative stress (Adderley & Grau, 2023; Wei et al., 2021). Furthermore, *Curcuma xanthorrhiza* has the potential to have organ-protective effects and prevent tissue damage in severe malaria cases (Rahmat et al., 2021).

These findings indicate that the bioactive components of *Curcuma xanthorrhiza* possess relevant pharmacological potential, although most evidence is still limited to preclinical studies. This is important considering that malaria pathogenesis is determined not only by parasite burden but also by a dysregulated immune response that can lead to organ damage. Therefore, a therapeutic approach that combines parasite elimination and tissue protection has the potential to provide broader clinical benefits. However, most of the available evidence still comes from experimental *in vitro* and *in vivo* animal studies. Consequently, generalization to humans is still limited. Variations in extraction methods, dosages, and active compound composition also pose challenges in

standardizing the use of *Curcuma xanthorrhiza*. Moreover, direct evidence regarding the synergistic effects between artemisinin and *Curcuma xanthorrhiza* is still limited. Therefore, further research is needed, including combination studies in animal models and controlled clinical trials in humans, to evaluate the efficacy, safety, and potential pharmacodynamic interactions of these two agents. Overall, these studies indicate that *Curcuma xanthorrhiza* has the potential to serve as a promising adjuvant therapy in the treatment of malaria. Combination-based approaches that integrate parasite elimination and modulation of the host response may be a more effective strategy in addressing the challenges of resistance and the complexity of malaria pathogenesis in the future.

CONCLUSION

Malaria persists as a major global health challenge with high morbidity and mortality rates, especially in Sub-Saharan Africa. Artemisinin remains a primary therapy due to its potent antiparasitic activity and its ability to rapidly reduce parasite biomass through oxidative stress induction. However, the emergence of partial resistance linked to mutations in the K13 gene presents new challenges and encourages the need for additional therapeutic approaches that also consider the role of the host immune response. *Curcuma xanthorrhiza* possesses pharmacological potential due to its bioactive compounds such as xanthorrhizol, curcuminoids, and terpenoids, which have anti-inflammatory, antioxidant, and immunomodulatory properties. These activities have the potential to help control excessive inflammation and oxidative stress in malaria infections. Although its direct antiparasitic activity is lower than that of artemisinin, these biological properties demonstrate the potential of *Curcuma xanthorrhiza* as an adjuvant therapy that can enhance the effectiveness of conventional antimalarial therapy. Overall, *Curcuma xanthorrhiza* cannot yet replace artemisinin, however it has the potential as a supporting agent in combination therapy through its immunomodulatory and tissue protection mechanisms. Further development requires experimental and clinical research, including evaluation of combinations with ACT, toxicity testing, and human clinical trials.

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