Advances in Bioresearch
Adv. Biores., Special Issue (3) 2025: 252-259

Print ISSN 0976-4585; Online ISSN 2277-1573
Journal's URL:http://www.soeagra.com/abr.html
CODEN: ABRDC3
DOI: 10.15515/abr.0976-4585. SPL3.25.252259

Advances in Bioresearch

Antimalarial Efficacy of Artemisinin Derivatives from *Artemisia annua* L.: A Review

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ABSTRACT
The extraction of artemisinin from Artemisia annua L., a powerful antimalarial agent, has rendered the plant a focal point of rigorous phytochemical research in recent decades. Artemisinin and its derivatives constitute a vital and effective category of drugs in the battle against malaria. These are acknowledged as the most effective first-line antimalarial agents globally, owing to their quick parasite clearance efficacy and a favourable safety profile with low side effects. Artemisinin and its derivatives demonstrate significant and swift antimalarial efficacy by diminishing malaria parasite numbers and mitigating symptoms. The mechanism of action of artemisinin and its derivatives has garnered significant interest, as elucidating this process is essential for structural modifications aimed at enhancing their antimalarial potency.
Keywords: *Artemisia annua L., Plasmodium falciparum, Malaria, Artemisinins, dihydroartemisinin, ACT.*

Received 03.06.2025 Revised 15.06.2025 Accepted 28.07.2025

How to cite this article:
Koushik S, Suvendu P, Rajkrishna B, Biswajit D & Suchismita C S. Antimalarial Efficacy of Artemisinin Derivatives from *Artemisia annua* L.: A Review. Adv. Biores. Special Issue [3] 2025. 252-259

INTRODUCTION

Artemisia annua L. is a globally grown medicinal herb utilized for the extraction of artemisinin. It is a sesquiterpene lactone with a peroxide constituent which is isolated from the leafy parts of *Artemisia annua* L. that has been used for the treatment of chills and fever for centuries [1]. Presently, the majority of individuals residing in developed as well as developing countries rely entirely on plant based traditional medical methods for their primary healthcare requirements [2-4]. Medicinal importance of *Artemisia annua* L. including its antimalarial activity was confirmed by several researchers. Among the bioactive compounds of the plants Artemisinin is considered as key molecule for antimalarial activities. Artemisinin and its derivatives constitute a crucial and powerful category of drugs in the battle against malaria. Artemisinins are classified as prodrugs for two primary reasons: first, several derivatives are rapidly converted to dihydroartemisinin in vivo, and second, their mechanism of action relies on the activation by cleavage of the endoperoxide bridge [5]. The biocidal sesquiterpene and its semi-synthetic derivatives represent the most potent antimalarial medicines against *Plasmodium* species. Synergistic interactions were exhibited among flavonoids, coumarins, phenolic acids, and arteannuin B with artemisinin in the aqueous extract. The significant parasiticidal efficacy and possible synergistic effects endorse the conventional application of *A. annua* infusions for malaria treatment. The exceptional potency, safety, and accessibility of artemisinin have positioned it as a leading agent in the fight against malaria, significantly affecting millions of lives.

Only five of the over 100 Plasmodium species are capable of infecting humans. The primary etiological agents of malaria are *Plasmodium malariae*, *Plasmodium ovale*, *Plasmodium vivax*, and the highly lethal *Plasmodium falciparum*; however, *Plasmodium knowlesi* poses minimal threat to humans [6]. Transmission of *Plasmodium* commences when an infected mosquito introduces sporozoites into the human circulatory system. The sporozoites go to the liver, infecting hepatocytes and proliferating into

merozoites. Conventional antimalarial medications, including chloroquine, sulfadoxine, amodiaquine, and mefloquine, have been extensively utilized in the treatment of malaria. The resistance of *Plasmodium falciparum* to these medications diminishes their efficacy in eliminating the malaria parasite, significantly complicating malaria prevention and control efforts. Malaria patients administered a tea derived from *A. annua*, in accordance with the dosage guidelines of the Chinese pharmacopoeia, exhibited a fast eradication of malaria parasites from the bloodstream, akin to the effects noted for pure artemisinin [7].

PHYTOCHEMISTRY OF ARTEMISININ DERIVATIVES

After the identification of artemisinin, extensive research has been conducted on *A. annua* to assess its phytochemical composition. The plant is rich with a diverse chemical composition, and a wide range of phytochemicals have been identified from the plant [8]. Numerous chemical compounds identified in *A. annua* encompass essential oils containing monoterpenes and sesquiterpenes, coumarins, flavonoids, phenolic acids [9], fatty acids, phytosterols, saponins, tannins, sesquiterpene lactones, and polyalkenes [10]. In the context of antimalarial activity artemisinin have well acknowledged by many researchers. Derivatives of artemisinin from *Artemisia annua* comprise artemisinic acid, deoxyartemisinin, artemisinin, artesunate, and dihydroartemisinin. Structure of artemisinin is a sesquiterpene lactone featuring an internal peroxide bridge, distinguishing it from other current pharmaceuticals [11]. Certain derivatives, including artesunate, artemether, artenimol, artelinic acid, and arteether, are classified as semisynthetic -derivatives [9,11]. The pharmacokinetics of these substances, encompassing the processes of absorption, distribution, metabolism, and excretion, have been investigated in rodent models [12]. The extracts of *A. annua* exhibit differing levels of artemisinin, with dichloromethane extracts demonstrating significant antimalarial efficacy [13]. Several significant phytochemicals in *A. annua* essential oil were examined by many researchers through molecular docking, revealing that specific compounds exhibited a heightened capacity to interact with plasmodial proteins vital to parasite growth and development [14]. The most important bioactive metabolite in the antimalarial efficacy of artemisinin and its derivatives is dihydroartemisinin, with the activity attributed to the presence of the endoperoxide bond [15]. Artemisinin free radicals are thought to establish covalent bonds with heme or parasite proteins, thereby obstructing the synthesis of hemozoin [16]. The protein Plasmodium Falciparum Lactate Dehydrogenase (PfLDH) with the natural ligand 2,6-naphthalenedicarboxylic acid has been considered as potential molecular target for antimalarials due to the parasite's dependence on glycolysis for energy production

Artemisinin derivatives can be delivered via oral, intravenous, intramuscular, and rectal routes [17]. The metabolism of artemisinin is predominantly facilitated by the genes CYP2B6 and CYP3A4 [12]. For individuals with uncomplicated malaria capable of tolerating oral drugs, artemisinin is used in combination treatments (ACTs). Prevalent combinations consist of artemether-lumefantrine, artesunate-amodiaquine, and dihydroartemisinin-piperaquine. These medications are taken orally, usually over a three-day period, ensuring the complete regimen is followed to avert recurrence and resistance. Oral ACTs serve as the primary treatment for mild cases due to their efficacy, safety, and ease of usage in outpatient environments [16-17]. In instances of severe malaria, patients may be incapable of ingesting oral treatment due to emesis, altered awareness, or complications. In these circumstances, artesunate is supplied parenterally, either via intravenous (IV) or intramuscular (IM) routes. The standard dosing regimen includes an initial dose at admission, subsequent doses at 12 and 24 hours, and then daily until the patient transitions to oral therapy. This method facilitates the swift decrease of parasite concentrations in the bloodstream and is endorsed by the World Health Organization for the management of severe malaria [10,15]. In situations where intravenous or oral delivery is impractical especially in children in rural or resource-constrained environments rectal artesunate may be utilised. This approach serves as a pre-referral intervention, diminishing parasite burden and averting disease progression during the patient's transfer to a healthcare center for comprehensive treatment [13]. Rectal delivery facilitates the immediate initiation of lifesaving therapy, especially in regions lacking access to needles or oral medications.

ANTIMALARIAL MECHANISM OF ARTEMISININ

Artemisinin and its derivatives demonstrate powerful and swift antimalarial efficacy by diminishing malaria parasite concentrations and mitigating symptoms (Fig 1). Compressed leaf tablets of *A. annua* have exhibited considerable antimalarial efficacy in mouse trials, indicating promise for therapeutic application in humans [18]. Expanding upon these preclinical findings, Daddy et al., [19] executed a clinical study to evaluate the effectiveness of desiccated *A. annua* leaves in patients with severe malaria unresponsive to conventional treatments, such as artemisinin combination therapy and intravenous artesunate. The study sought to ascertain if these plant-based formulations could function as an

alternative or supplementary therapy for treatment-resistant malaria. Results from these trials are essential for investigating cost-effective and accessible antimalarial alternatives, especially in areas where drug resistance is an increasing concern. It is a short-acting yet highly effective antimalarial agent. Artemisinin and its derivatives exhibit rapid and robust antimalarial efficacy. The terminal elimination half-life is typically 1-3 hours, leading to undetectable drug levels by 10 hours post-administration [20]. They diminish the quantity of malaria parasites and alleviate malaria symptoms by disrupting the life cycle of the erythrocytic phase of the malaria parasite, particularly influencing the production of merozoites within red blood cells [21]. The mechanism of action of artemisinin and its derivatives has garnered significant interest, as elucidating this process is essential for structural modifications aimed at enhancing their antimalarial potency. The activation of artemisinin depends on the cleavage of its endoperoxide bridge, resulting in the formation of reactive free radical species. The primary mechanism driving antimalarial efficacy of artemisinin is the reductive activation of its endoperoxide bridge by ferrous iron (Fe^{2+}) liberated during haemoglobin degradation in *Plasmodium*-infected erythrocytes. The heme-mediated breakdown of the endoperoxide bridge of artemisinin is believed to generate carbon-centered free radicals [22]. These carbon-centered free radicals alkylate heme and proteins of the parasite, leading to its death. Malarial parasites exhibit significant hemoglobin absorption and degradation throughout the erythrocytic phase of their life cycle [23]. This liberates substantial quantities of free redox-active heme and free ferrous iron (Fe^{2+}), which are believed to be the basis for the parasite selectivity of artemisinin. Artemisinin drugs also interfere with the physiological functioning of *Plasmodium* by targeting proteins, lipids, and nucleic acids, resulting in the demise of the parasites [21]. Unbiased proteomics approaches indicate that artemisinin targeting may be promiscuous rather than selective to a single target [5]. Wang et al. (2015) conducted a study that comprehensively identified over 100 protein binding sites of artemisinin in live parasite strains [24]. Latter it is found that activated artemisinin alkylates and damages many cellular proteins, thereby disrupting multiple key biological functions and resulting in toxicity and lethality in parasites [5]. Artemisinin may disrupt the cytokine-like function of translationally controlled tumor protein (TCTP), indicating that it could eliminate *Plasmodium* parasites through TCTP [25]. In addition to directly generating radicals, artemisinin may interfere with calcium homeostasis, proteostasis, and several cellular processes in *Plasmodium*, enhancing its extensive and powerful effects. Artemisinins usually target the Sarco/Endoplasmic Reticulum Calcium ATPase (SERCA) of *Plasmodium falciparum* [26]. Several studies indicate that artemisinin and its derivatives may induce depolarization of the Plasmodium's mitochondrial and plasma membranes, a phenomenon associated with reactive oxygen species. Resistance to artemisinin in *P. falciparum* is mostly driven by nonsynonymous mutations in the K13 gene, which encodes a protein containing a Kelch propeller domain, situated in the parasite's endoplasmic reticulum and linked to phosphatidylinositol-3-kinase complexes [27,28].

Artemisinin also generates radical or pro-radical molecules containing oxygen include superoxide anion, hydroxyl radical, peroxy radical, hydrogen peroxide, and lipid hydroperoxide. These extremely reactive chemicals impede the life of malaria parasites by destroying essential biomolecules, including lipids, proteins, and nucleic acids, so compromising cellular integrity and function. The reduction of iron from the unstable cytoplasmic iron pool in *Plasmodium*, coupled with iron liberated by heme decomposition, activates artemisinin to produce free radicals, which are essential to its antimalarial efficacy. The presence of iron cleaves the peroxy bridge in artemisinin, resulting in the generation of oxygen-free radicals that subsequently promote the synthesis of carbon-free radicals via electron rearrangement [29]. Saito et al., (2018) reported that Artemisinins are more efficacious and well-tolerated than quinine in pregnancy [30].

The presence of an endoperoxide group in the sesquiterpene lactone structure of artemisinin and its derivatives has been linked to its antimalarial properties. It was therefore expected that a drug's therapeutic potency would be increased by adding more of these units. The idea sparked the creation of artemisinin dimers, trimers, and tetramers with different lengths, stereochemistry, and flexibilities. The effectiveness of these potential antimalarials is being studied. Positive outcomes have been observed in a few mouse models [31]. ACT based medicines also exert immunosuppressive effects primarily by inhibiting pathogenic T-cell activation, suppressing B cells, decreasing IgG and IgE immunoglobulin levels, and obstructing the MAPK signaling cascade (phosphorylation of ERK1/2, Jnk, and P38) [32]. Common ACT-based pharmaceuticals employed in the treatment of malaria comprise Artemether-Lumefantrine, Artesunate-Amodiaquine, Artesunate-Mefloquine, Dihydro-artemisinin-Piperaquine, Artesunate-Sulfadoxine/ Pyrimethamine, and Artesunate-Pyronaridine. These combinations are chosen based on the malaria parasite type, local drug-resistance tendencies, patient age, pregnant status, and national treatment protocols.

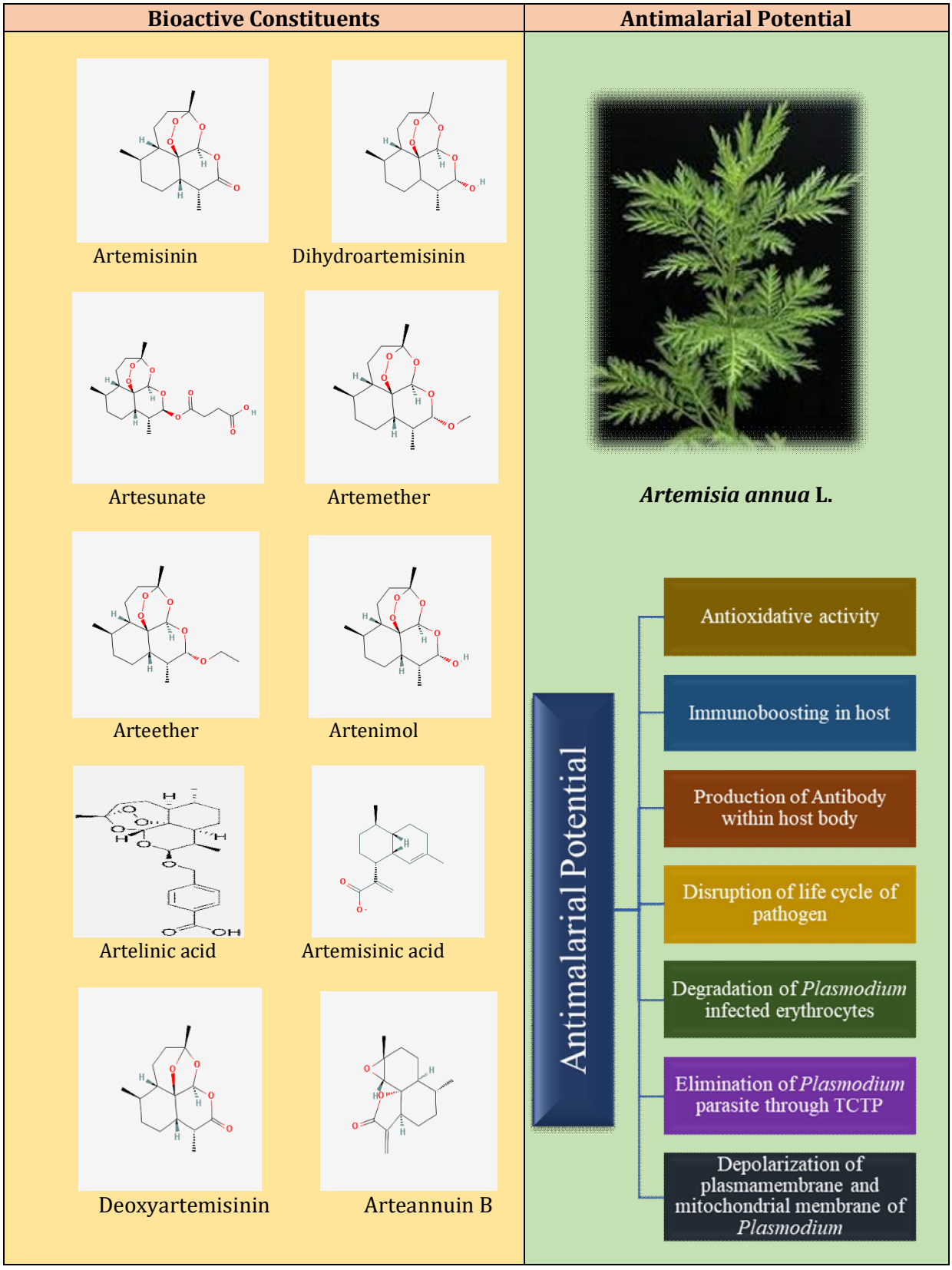

Fig 1: Antimalarial activity Artemisinins derivatives.

LIMITATION

The rise and proliferation of artemisinin resistance present an unparalleled challenge for worldwide malaria management. The malaria parasite has acquired resistance to artemisinin medications,

obstructing the prevention and treatment of malaria. Decreased efficacy jeopardizes the advancements made throughout the period of extensive utilization of this medication class. Several strategies that the parasite may employ to counteract the irreparable harm caused by artemisinins have been suggested. The therapeutic efficacy of artemisinins relies on elevated drug concentrations, brief yet intense exposure, and significant enhancement via metal-catalyzed damage. These criteria delineate pathways by which the parasite may evade the pharmaceutical reaction. Despite extensive investigation of numerous cellular pathways, only a select few genuinely exhibit the traits of resistance. The assessment of their prior literature for evidence of phenotypes indicative of artemisinin resistance consistently yielded data that did not align with the criteria for resistance. Artemisinin is no longer advised for monotherapy, except for parenteral administration in cases of severe malaria [33]

The mechanism of action of artemisinins pertains to their efficacy against the malaria parasite. Current antimalarial strategies mostly rely on artemisinin combination treatments. Although artemisinin exhibits rapid beginning of action and significant efficacy against malaria parasites, its limited solubility in both aqueous and lipid mediums complicate its administration via intravenous injection [34]. Consequently, it is alarming that parasites exhibiting reduced susceptibility to this treatment class have evolved in Southeast Asia, prolonging the clearance of parasites from patients [35]. The development of artemisinin resistance in *Plasmodium falciparum* poses a major threat to malaria control and elimination. Clinically, artemisinin resistance is characterized by diminished parasiticidal efficacy and prolonged parasite clearance, resulting in an elevated likelihood of treatment failure after artemisinin-based combination therapy [36]. Antimalarial resistance can be identified through diminished in vivo or in vitro responses, or by employing molecular markers known to facilitate drug resistance. Investigations have also examined the application of dried whole-plant Artemisia annua, which mitigates the development of malaria medication resistance and can surmount resistance to artemisinin. The extracts of *A. annua* exhibit differing levels of artemisinin, with dichloromethane extracts demonstrating significant antimalarial efficacy [13]. A further drawback of artemisinin is its brief half-life post-administration, as it is predominantly converted by CYP2B6 into inactive metabolites [37]. Artemisinin-based combination medicines are the foundation of modern malaria treatment; nonetheless, the emergence of resistance in *Plasmodium falciparum* jeopardizes worldwide malaria control successes. Artemisinin's biochemical diversity, which targets many parasite pathways concurrently, initially indicated a low likelihood of resistance development; however, clinical and molecular evidence now reveals that *Plasmodium falciparum* can evolve complex adaptive mechanisms. These limitations not only facilitate the establishment of drug-resistant Plasmodium strains but also undermine long-term treatment efficacy.

COMBINATION THERAPIES WITH ARTEMISININ DERIVATIVES

Artemisinin derivatives are the primary antimalarial agents for the treatment of severe *Plasmodium falciparum* malaria. Numerous researchers have investigated diverse methods to enhance the utilization of artemisinin to optimize its advantages. Altering current antimalarial protocols has been regarded as the most expedient method to enhance treatment efficacy. Artemisinin-based combination treatments (ACTs) integrate artemisinin derivatives with additional antimalarial agents to reduce the emergence of parasite resistance. Possible alterations encompass an extended ACT course, the alternating use of several ACT regimens, and the implementation of triple ACTs. Artemisinin is presently utilized in combination therapy for the treatment of uncomplicated *Plasmodium falciparum* malaria, rather than as a monotherapy, to mitigate the emergence of artemisinin-resistant parasites [14]. ACTs consist of a rapidly acting artemisinin derivative combined with a slower-acting partner drug that operates via a distinct mechanism; the disparate pharmacokinetic profiles of the co-administered medications guarantee comprehensive treatment of all blood parasites and mitigate the risk of developing drug resistance. Artemisinin derivatives are typically used with established companion medications such as lumefantrine, mefloquine, amodiaquine, sulfadoxine-pyrimethamine, or piperaquine. Combining it with mefloquine enhanced the long-term removal of parasites and worked well in regions that were resistant to many drugs [38]. In ACTs, artemisinin primarily eradicates the majority of the parasite biomass in the initial days of treatment, whereas residual concentrations of the partner medicine eliminate the remaining parasites to avert recrudescence [33]. The concurrent use of various pharmaceuticals with distinct mechanisms of action might enhance therapeutic efficacy by addressing numerous biological targets and diminish the dosage of each medicine, hence yielding a more tolerable side effect profile. It has been demonstrated that the combination of ART, its derivatives, and nanocarriers is highly beneficial in the various applications of these medications [39]. The utilization of artemisinin (ART) and its derivatives, along with ACTs, has significantly diminished the global malaria load. ART is the sole first-line antimalarial medication currently devoid of extensive drug resistance [40]. The establishment of

resistance to ART and ACT in certain places has raised concerns regarding the sustained efficacy of ART in malaria control. The distinctive antimalarial effect of ART is the result of the hyperactivation of its peroxide bridge by heme, an unavoidable consequence of the hemoglobin metabolism of parasites in erythrocytes. Consequently, substantial quantities of free radicals are generated, capable of alkylating several plasmodium proteins and macromolecules, resulting in swift parasite mortality [41]. The ART-derived pharmaceuticals are effective against many strains of the malaria parasite due to their distinctive molecular structure and demonstrate expedited clearance of malaria parasites from the bloodstream compared to other current anti-malarial medications [42]. Peroxide-based drugs also demonstrate significant action against several phases of the parasite's life cycle, characterised by good selectivity and minimal toxicity [43]. Motivated by the antimalarial efficacy of ART and its derivatives, numerous synthetic peroxide-based molecules are currently undergoing various phases of preclinical and clinical development for malaria treatment.

CONCLUSION

Artemisinin exhibits greater antimalarial activity relative to numerous other plant-derived secondary metabolites, underscoring its distinctive pharmacological features. Notwithstanding its extensive utilisation, the exact antimalarial mechanism of artemisinin and its derivatives remain ambiguous, posing difficulties for drug development, clinical applications, and malaria control initiatives. Additional research is essential to comprehensively comprehend the mechanisms by which artemisinin influences malaria. Comprehensive understanding and further exploration into the biological properties of *Artemisia annua*, especially its principal components like artemisinin and other vital metabolites, will yield enhanced insights into its therapeutic uses and possible medicinal advantages. This enhancement may improve the antimalarial efficacy of artemisinin and its derivatives, creating new opportunities for therapeutic uses and treatment techniques in diverse medical domains.

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