International Journal of Pharmaceutical research and Applications
Volume 11, Issue 4, Jul.-Aug.2026, pp:1572-1580 www.ijprajournal.com ISSN:2456-4494

Artemisinin Therapy in Infants: A Comprehensive Review.

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Date of Submission: 18-08-2026 Date of Acceptance: 01-09-2026

ABSTRACT:
Malaria is a severe mosquito-borne disease that heavily impacts infants and young children in tropical and subtropical region. Because their immune systems are still developing, infants face a high risk of life – threatening complications, including severe anemia, low blood sugar, and cerebral malaria. Artemisinin and its derivatives – such as artesunate, artemether, and dihydroartemisinin-have transformed malaria care by rapidly killing Plasmodium falciparum parasites. Today, healthcare providers use artemisinin-based combination therapies (ACTs) as the standard treatment for uncomplicated malaria, while relying on injectable artesunate to treat severe cases in infants . Despite their advantages, artemisinin derivatives have limitations such as short half-life, poor bioavailability, and emerging resistance linked to *PfK13* mutations.

KEYWORDS: Artemisinin; infants; malaria; artemisinin-based combination therapy; artesunate; pharmacokinetics; drug resistance

I. INTRODUCTION

Malaria is a life – threatening, acute disease endemic to tropical and subtropical regions. It is transmitted by female Anopheles mosquitoes and caused by parasites of plasmodium genus [1,2]. Historically, the name originates from the Italian term "mal'aria," meaning "bad air"[1]. Despite initial optimistic goals to eradicate malaria by 2030, global infections have recently surged. According to the WHO World Malaria Report, global cases continued to climb in 2023, hitting an estimated 263 million cases across 83 endemic countries. Five nations alone accounted for more than half of these global cases: Nigeria (25.9%), the Democratic Republic of the Congo (12.6 %), Uganda (4.8 %), Ethiopia (3.6%), and Mozambique (3.5%)[3].

The malaria life cycle comprises five stages. In the sporozoite stage, an infected female Anopheles mosquito injects sporozoites into the human bloodstream during a blood meal. In the liver stage, these sporozoites invade liver cells, where they multiply and develop into merozoites. During the blood stage, merozoites are released into the bloodstream and infect red blood cells, progressing through the ring, trophozoite, and schizont stages. In the gametocyte stage, some parasites differentiate into male and female gametocytes within the blood. Finally, in the mosquito stage, gametocytes are ingested by another mosquito, where they develop into sporozoites and migrate to the salivary glands, enabling transmission to a new human host [4-7].

The majority of malaria prevention measures focus primarily on infants and young children. Antigen naivety is a significant factor in this age-related vulnerability: infants do not have a wide range of adaptive immune responses (antibodies, memory B and T cells), which are eventually developed via childhood illnesses [12]. Malaria in infants can be acquired either through the bite of an infected mosquito after birth or through transplacental transmission of parasites from the mother during pregnancy [9]. Infection may be caused by any Plasmodium species, including Plasmodium vivax, Plasmodium falciparum, Plasmodium ovale, Plasmodium malariae, and Plasmodium knowlesi, as well as mixed species infections[8]. Common clinical manifestations of malaria in infants include fever, headache, vomiting, chills, and joint pain. Severe malaria in children is often characterized by anemia, hypoglycemia, and cerebral malaria, which occur more frequently than in adults. Repeated episodes of malaria can also increase a child's vulnerability to responsibility infections, diarrhea, and other illness[10].

International Journal of Pharmaceutical research and Applications
Volume 11, Issue 4, Jul.-Aug.2026, pp:1572-1580 www.ijprajournal.com ISSN:2456-4494

Congenital malaria is defined as the presence of asexual malaria parasites in the peripheral blood pr cord blood of a newborn within the first seven days of life or later, provided that postnatal infection through mosquito bites or blood transfusion has been excluded [11].

Acquired Neonatal Malaria: This term refers to malaria that develops during the first 28 days of life as a result of an infectious mosquito bite or blood product transfusion after delivery [8].

Artemisinin derivatives are the cornerstone of current antimalarial treatment strategies. When used in combination with longer acting antimalarial drugs, they form artemisinin-based combination therapies (ACTs), which are recommended as first-line treatment for Plasmodium falciparum malaria worldwide. These agents are the fast-acting parenteral therapies available for severe malaria and can also be administered rectally in children living in remote areas who are unable to take oral medications reliably. ACTs are also considered an important first-line treatment option for non-falciparum malaria [10].

Artemisinin is a sesquiterpene lactone containing an endoperoxide bridge and is available in several derivatives, including dihydroartemisinin (DHA), artesunate, artemether, and arteether[11]. In ACTs, the artemisinin component rapidly reduces the parasite burden during the first three days of treatment, while the partner drug eliminates the remaining parasites, thereby enhancing treatment efficacy and reducing the risk of resistance development[14].Common ACT regimens include Artemether-Lumefantrine, Artesunate-Amodiaquine, Dihydroartemisinin-Piperaquine, Artesunate-Mefloquine, and Artesunate-Sulfadoxine-Pyrimethamine[15]. Despite its potent antimalarial activity, artemisinin has certain limitations, such as poor water solubility, low bioavailability, and a short biological half-life, which can affect its therapeutic performance.

Additionally, it was observed that following prolonged use, several harmful side effects appeared [17]. Adverse effects: This medication is considered to be safer than other antimalarial treatments. Mild side effects such as nausea, vomiting, stomach pain, itching, headaches, and drug-related fever may occur. Contraindication: There are no absolute contraindications for use in pediatric patients [16]. Besides their well-established antimalarial activity, recent clinical studies indicate that artemisinin and its derivatives possess a broad range of therapeutic properties, including antitumor, antiviral, antiparasitic and anti-inflammatory effects, and may also be beneficial in the treatment of various skin disorders [18].

II. HISTORY

The structure of artemisinin is a sesquiterpene lactone endoperoxide isolated from the sweet wormwood herb, Artemisia annua L. (qinghao; shrub with yellow flowers plant used in TCM). According to historical records, qinghao was first used in China for intermittent fevers as early as the 4th century CE[21,28] Qinghao , in particular, is mentioned by the physician Ge Hong who used it and described its use in his medical work Zhouhou .(" Emergency prescriptions kept up one's sleeve) which ultimately provided a lead to following up for new antimalarial agents[19,20].

At last , a modern search for artemisin began under cover of **" Project 523**" in China that started in response to the increased malaria load (during the Vietnam War)from 1967 onward , As part of this national research program, many scientists were assigned the responsibility of finding therapeutic antimicrobials[19,27,28]. Trained in pharmacology and phytochemistry , Tu Youyou joined the program in 1969 to conduct a traditional herbal medicine screening project for possible antimalarial activity .

Tu and her associates concentrated on Artemisia annua after examining over two thousand traditional medicinal prescriptions and assessing hundreds of herbal formulations[19,20]. Before Tu reexamined Ge Hong's ancient literature and realized that high extraction temperatures would destroy the active component, the initial attempts yielded inconsistent results. As a result, the group created an ether-based low- temperature extraction technique that greatly increased antimalarial potency[19,28]. The active ingredients was successfully extracted in 1972 and given the name qinghaosu, which is now known globally as artemisinin, after the extract showed significant effectiveness against malaria parasites in test animals in 1971[19,20,28].

The exceptional efficacy of artemisinin against malaria, especially illnesses brought on by Plasmodium falciparum[20,22,23], was validated by later clinical research. Derivatives including artemether, artesunate, and dihydroartemisinin were created in the ensuing decades to improve treatment efficacy[23,24]. Global efforts to combat malaria were revolutionized in the early 2000s when the World Health Organization endorsed artemisinin – based combination treatments (ACTs) as the first- line treatment for uncomplicated falciparum malaria[25].

When Tu Youyou was awarded the 2015 Nobel Prize in Physiology or medicine for her role in

International Journal of Pharmaceutical research and Applications
Volume 11, Issue 4, Jul.-Aug.2026, pp:1572-1580 www.ijprajournal.com ISSN:2456-4494

the development of a breakthrough treatment for malaria, the significance of this finding was acknowledged on a global scale[26,28]. Millions of lives have been saved by artemisinin and its derivatives, which are still among the best antimalarial medications[23,25].

III. ANTI MALARIAL THERAPY

The use of drugs to prevent and treat malaria, a parasitic illness brought on by Plasmodium species and spread by mosquito bites, is known as antimalarial therapy[32,33]

Goals of anti-malarial therapy:

- Remove the parasites that cause malaria from the blood[32,33]
- Alleviate symptoms like anaemia, chills, and fever[32,33.]
- Avoid death and complications[29,34.]
- Minimize infection transmission and recurrence[29,32.]

IV. CLASSIFICATION OF ANTI-MALARIAL THERAPY

1. Artemisinin-Based Combination Therapies (ACTs)

These are the first-line treatments for uncomplicated malaria caused by Plasmodium falciparum[29,34]

Examples:

- Artemether-Lumefantrine[29]
- Artesunate-Amodiaquine[29]
- Dihydroartemisinin-Piperaquine[29]
- Artesunate-Mefloquine[29]

2. Non-Artemisinin Antimalarials

- Chloroquine[32,33]
- Quinine[32,33,55]
- Mefloquine[32,33]
- Primaquine[32,33]
- Atovaquone-Proguanil[34]

Why Artemisinin Is Used in Babies?

Among the populations most susceptible to malaria-related sickness and death are infants and children under five[29].

When used appropriately, ACTs offer quick fever and parasite clearance, with cure rates frequently above 95%[29,30].

For infants and young children, child-friendly formulations—like dispersible artemether-lumefantrine tablets-improve administration, adherence, and treatment results[30].

Common Artemisinin-Based Combination Therapies for Children:

WHO recommends several ACTs for uncomplicated *P. falciparum* malaria in children and adults, [29] including:

- Artemether-Lumefantrines
- Artesunate-Amodiaquine
- Dihydroartemisinin-Piperaquine
- Artesunate-Mefloquine
- Artesunate-Pyronaridine (for children weighing ≥5 kg) [29]

Severe Malaria in Infants

For severe malaria, WHO recommends **injectable artesunate** as the preferred treatment. Once the child can take oral medication, treatment should be completed with a full course of an ACT [29,31]

Precautions

- Artemisinin derivatives should **not be used alone (monotherapy)** because this promotes drug resistance. [29,32]
- Treatment should follow national malaria guidelines and be based on the child's age, weight, and malaria species [29,34].
- Malaria diagnosis should be confirmed by microscopy or a rapid diagnostic test whenever possible [29,34].

V. MECHANISM OF ACTION OF ARTEMISININ

The antimalarial power of artemisinin relies entirely on its unique endoperoxide bridge, which is essential for antimalarial activity[35].This compound targets nearly all sexual and asexual parasite stages[36,37] .This drug can destroy malaria parasites within a short period, reducing parasite numbers by nearly 10,000-fold per erythrocytic cycle and leading to rapid symptom improvement [38].Direct comparative clinical trials have consistently found artemisinin to be more effective than quinine [39]. The process activates inside infected red blood cells, where the parasite releases iron-rich heme by digesting hemoglobin. During hemoglobin digestion by the malaria parasite, toxic heme is released and normally detoxified by conversion into hemozoin (malarial pigment). Activated artemisinin generates free radicals that react with heme to form heme-artemisinin adducts, which can disrupt heme detoxification and interfere with hemozoin formation. Artemisinin has also been shown to promote breakdown of existing hemozoin. Although these effects suggest that inhibition of heme polymerization contributes to parasite death, some studies indicate that artemisinin does not significantly inhibit hemozoin formation in vivo. Therefore, it is proposed that artemisinin-derived

International Journal of Pharmaceutical research and Applications
Volume 11, Issue 4, Jul.-Aug.2026, pp:1572-1580 www.ijprajournal.com ISSN:2456-4494

radicals primarily kill parasite by alkylating and irreversibly damaging essential parasite proteins and enzymes [35].

VI. PK OF ARTEMISININ

Artemisinin has short elimination half-life (~1hr) [35]. In humans, Artemisinin derivatives convert rapidly into dihydroartemisinin (DHA), their active metabolite form. The liver enzyme CYP2B6 primarily drives this metabolic breakdown. Finally, the body eliminates the drug through a clearance process called glucuronidation[43].The rate of conversion to DHA differs among the derivatives; Artesunate is converted within minutes, whereas artemether and Arteether are metabolized more gradually[44,45].Additionally, artemisinin compounds can induce their own metabolism by stimulating cytochrome P450 enzymes, leading to reduced serum drug concentrations following repeated administrations[35]. The rapid clearance of artemisinin compounds from the human body helps reduce the risk of selecting drug -resistant malaria parasite by minimizing exposure to residual drug concentration. However, their short elimination half-life can also result in lower cure rates and higher recrudescence rates (greater than 25%) when used as shorts course monotherapy for 3-5 days. Furthermore, even a 7-days course of artemisinin alone achieves cure rates of only 80-90% in patient with uncomplicated *plasmodium falciparum* malaria[39,48,49].

VII. DOSE CALCULATION

For children, dosage calculation is based on pharmacokinetics and physiological approaches**.** Children between 2 months and 5 years of age are particularly vulnerable to severe and cerebral malaria. Malnourished children require special attention because intestinal villous atrophy can delay and reduce gastrointestinal absorption of antimalarial drugs. As a result, the absorption of drugs such as lumefantrine may be markedly reduced, with reported bioavailability as low as 5 % in some malnourished children.

Limited pharmacokinetic data are available for malnourished paediatric patients, although nutritional status is known to significantly influence drug absorption and disposition. Consequently, the same dosing regimens used for well-nourished children are generally applied in clinical practice. While body weight-based calculations such as WHO, young's rule, Clark's rule, Area Rule and Allometric Scaling suggest lower doses of artemether **(0.34mg/kg)** and lumefantrine **(6mg/kg)** may be sufficient, higher doses recommended by the WHO are often maintained in malnourished children to compensate for their reduced drug absorption and ensure adequate therapeutic exposure[13].

Table 1**:** Dose calculation for artemisinin therapy

Age	Weight/kg	Height/cm	World Health Organization	Young's Rule	Clark's Rule	Area Rule	Allometric Scaling
2months	05.30	57.30	20	1.1	6.2	13	17
6months	07.60	66.60	20	3.2	8.9	17	23
1yr	09.30	75.00	20	6.2	10.9	20	26
2yr	11.80	87.30	20	11.4	13.9	25	32
3yr	14.10	95.50	20	16.0	16.6	28	36
5yr	18.30	109.80	40	23.5	21.5	35	44

VIII. RESISTANCE OF ARTEMISININ IN BABIES:

Artemisinin resistance, first identified in Cambodia[50], and has since spread throughout the Greater Mekong Subregion. This drug resistance is heavily linked to genetic mutations in the Plasmodium falciparum Kelch 13 (PfK13) [51]. Proposed resistance mechanisms include reduced ring-stage susceptibility, enhanced stress-response pathways, increased phosphatidylinositol-3-phosphate (PI3P) levels, and parasite dormancy[52]. Host immunity influences the emergence and spread of resistance, which is more common in low-transmission areas[53]. Widespread resistance has contributed to multidrug-resistant malaria and reduced ACT efficacy, highlighting the need for continuous monitoring and development of new antimalarial drugs[54].

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Volume 11, Issue 4, Jul.-Aug.2026, pp:1572-1580 www.ijprajournal.com ISSN:2456-4494

Table 2 : COMPARISION BETWEEN NATURAL AND SYNTHETIC ANDRUGS

FEATURES	NATURAL DRUG	SYNTHETIC DRUG
SOURCE	Drugs Derived from natural sources such as medicinal plants. Examples: Quinine (*Cinchona* bark), Artemisinin (*Artemisia annua*) [56].	Drugs Produced by chemical synthesis in laboratories. Examples: Chloroquine, Primaquine, Mefloquine, Pyrimethamine [57].
EXAMPLE	Quinine, Artemisinin [58]	Chloroquine, primaquine, Mefloquine, Pyrimethamine[59]
PRODUCTION PROCESS	Process involved are cultivation, harvesting, extraction and purification of medicinal plants [60]	These drugs are produced using by controlled industrial chemical synthesis [60].
AVAILABILITY	The Supply depends on crop yield, climate and cultivation, duration. Artemisinin production requires more than a year from planting to extraction. The supply depends on crop yield, climate, and cultivation duration [60].	These can be Can be produced continuously on an industrial scale without relying on agriculture [60].
CHEMICAL STRUCTURE	These are naturally occurring molecules characterized by complex structures and stereochemistry[60].	Generally designed to allow easier synthesis and structural modification [60].
COST STABILITY	Prices may vary due to dependence on agricultural dependence and variable production[60,61].	Manufacturing costs are generally more predictable [59].
RESISTANCE ISSUES	Reports indicate Reduced susceptibility to quinine, and concerns have arisen regarding resistance to artemisinin resistance have emerged[50].	Widespread resistance has developed against chloroquine and pyrimethamine [66].

IX. NATURAL COMPOUNDS USED IN INFANT ANTIMICROBIAL THERAPY

1.Lactoferrin

Lactoferrin, an iron-binding naturally occurring glycoprotein found in human breast milk, has been demonstrated to have antibacterial, antiviral, antifungal, and anti-inflammatory properties. Its antibacterial activity is a result of both the removal of iron from microbes, which prevents their utilisation for metabolic processes by various bacteria and of the direct damage caused to the membrane structure of the microbes themselves by lactoferrin. Clinical studies support the use of lactoferrin as a supplement to decrease the incidence of neonatal sepsis and necrotising enterocolitis in preterm babies [62].

2. Oligosaccharides in Human Milk

Oligosaccharides from human milk are used as food sources for prebiotics that provide protection against infectious diseases. Human milk oligosaccharides (HMOs) also inhibit the adhesion of pathogenic microorganisms to cells in the intestinal epithelium and stimulate the growth of beneficial intestinal microbiota, including Bifidobacteria. The use of HMOs has a significant impact on reducing gastrointestinal infections and fostering the development of the immune system through their many beneficial effects [63].

3. Lysozyme

Lysozyme is another antimicrobial enzyme found in high concentrations in breastmilk. This enzyme breaks down the peptidoglycan layer of the bacterial cell wall (especially in Gram-positive bacteria). Together with lactoferrin, lysozyme helps to make up a large portion of the antimicrobial activity associated with human milk [64].

4.Plant Based Essential Oils

A number of compounds sourced from plants, exhibit antimicrobial properties against pathogens that infect children. Essential oils from thyme, cinnamon, clove, mint, fennel and oregano all have active components, including thymol, eugenol, carvacrol, and cinnamaldehyde, that disrupt microbial cell membranes resulting in the inhibition of the growth of bacteria [65,66].

5. Polyphenols and Flavonoids

Natural polyphenolics that are extracted from pomegranate peels, olives, cocoa, and berries are able to demonstrate both antioxidant and antimicrobial activity. Flavonoids have been shown to act at

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Volume 11, Issue 4, Jul.-Aug.2026, pp:1572-1580 www.ijprajournal.com ISSN:2456-4494

different sites by inhibiting microbial enzymes, interrupting nucleic acid synthesis, and reducing oxidative stress. The dual anti-inflammatory and antimicrobial activity of flavonoids makes them highly regarded for use in pediatric medicine [67,68].

6.Chitosan (Chitin-Derived Polysaccharide)

Chitosan is a naturally-occurring polysaccharide made from chitin. Chitosan has a wide range of antimicrobial activity against bacterial cells because it interacts with the negatively charged membrane of the bacteria, causing leakage of intracellular contents. Baby-safe antimicrobial formulations that contain chitosan are currently being researched [65].

7. Bacteriocins (Antimicrobial Peptides)

Bacteriocins are antimicrobial peptides produced by some types of 'good' bacteria. One bacteriocin studied the most is nisin, which exhibits antimicrobial activity against several food-borne and neonatal pathogens. Bacteriocins are regarded as being safe in humans and as a possible substitute for antibiotics [65,69].

X. Discussion

Artemisinin-based therapies have significantly improved malaria management in infants by providing rapid reduction of parasite burden and faster symptom resolution compared with conventional antimalarial drugs such as quinine [35,39,40]. Their unique endoperoxide bridge enables generation of reactive radicals inside infected erythrocytes, leading to irreversible parasite damage and death [35-38]. This mechanism makes artemisinin highly effective against multiple developmental stages of malaria parasites.

The use of artemisinin-based combination therapies (ACTs) is especially crucial in infants, as treatment with artemisinin alone may result in therapeutic failure and contribute to the development of drug resistance due to its short elimination half-life of approximately one hour [35 , 41-49].Combining artemisinin derivatives with longer-acting partner drugs, such as lumefantrine or amodiaquine, enhances treatment efficacy, increases cure rates, and minimizes the risk of parasite recrudescence. Furthermore, the World Health Organization (WHO) recommends child- friendly dispersible formulations, which improve medication adherence and therapeutic outcomes in paediatric patients [29,30].

Dose optimization remains challenging in infants, especially in malnourished children. Physiological factors such as immature hepatic metabolism, reduced gastrointestinal absorption, and altered pharmacokinetics influence drug exposure and treatment success [50]. Although weight-based WHO dosing is commonly used, interpatient variability suggests the need for more pharmacokinetic studies specifically in neonates and infants.

A Significant challenge in malaria management is the emergence of artemisinin resistance, particularly in regions of Southeast Asia. Resistance is primarily linked to mutations in the PfK13 gene, which decrease the parasite susceptibility to artemisinin during the ring stage of development, thereby compromising the effectiveness of ACTs [50-54]. Therefore, continuous monitoring of resistance patterns, prompt diagnosis, and the development of novel antimalarial therapies are crucial for maintaining the long-term efficacy of malaria treatment.

Beyond malaria treatment, artemisinin derivatives have shown promising anti-inflammatory, antiviral, and antiparasitic activities, suggesting broader clinical potential [18]. Future research should focus on improving bioavailability, reducing toxicity, and developing novel formulations suitable for infant use.

XI. Conclusion

Artemisinin and its derivative continue to be among the most effective antimalarial drugs for infants, providing rapid clearance of parasites and improving survival rates in both uncomplicated and severe malaria. Owing to their excellent efficacy and favourable safety profile, artemisinin-based combination therapies (ACTs) have become the foundation of malaria treatment in pediatric patients. However, challenges such as short drug half-life, dosing variability in infants, and emerging resistance continue to limit long-term effectiveness. Continued pharmacokinetic research, resistance monitoring, and development of improved pediatric formulations are necessary to ensure sustained success of artemisinin-based therapies in infant malaria management.

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Volume 11, Issue 4, Jul.-Aug.2026, pp:1572-1580 www.ijprajournal.com ISSN:2456-4494

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