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Review Article

A SYSTEMATIC REVIEW ON MALARIA DISEASE AND ITS TREATMENTS FOCUS ON ARTEMETHER DRUG

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ABSTRACT

Malaria is one of the infectious illnesses of the highest scientific significance and importance to international health organizations. Plasmodium falciparum, the parasite responsible for a highly severe form of the disease in Africa, has traditionally received the most attention. However, in the last two decades, the Plasmodium vivax parasite, which is linked to a large number of cases in Latin America, the Middle East, South and Southeast Asia, the Horn of Africa, and Oceania, has sparked enormous interest, owing to published evidence that it can cause severe malaria, among other things. Malaria is a worldwide public health problem, with a saw 247 million cases recorded in 2021. African countries accounted for approximately 94% of all reported cases. So far, over 200 distinct varieties of protozoa have been discovered and identified, with at least 13 of them being pathogenic to humans. The malaria parasite's life cycle is a complex process involving a mosquito with the species Anopheles and a vertebrate host.

Artemether is a lipid-soluble artemisinin derivative. It is available in both oral and intramuscular forms. It is also available as a fixed-dose formulation with lumefantrine. Artemether-lumefantrine is one of the ACTs authorized by the WHO and is being used by the majority of countries transitioning from less effective medications to ACTs. However, the emergence of antimalarial medication resistance poses a significant challenge to malaria control. It works by killing the pathogenic organisms responsible for malaria. It is known as an antimalarial medication, and it is more effective than quinine therapies.

Keywords: Malaria, Artemether, Anopheles, Plasmodium falciparum, Mosquito, Fever etc

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INTRODUCTION

Malaria

Malaria is a potentially fatal disease caused by parasites transferred to humans by the bite of infected female Anopheles mosquitos. It is both preventable and treatable. Malaria is caused by five parasite species, two of which, Plasmodium falciparum and Plasmodium vivax, pose the greatest threat [1-3].

Almost half of the worldwide population was in danger of malaria in 2020. Sub-Saharan Africa has the highest number of cases and deaths. However, considerable numbers of cases and deaths have been reported in the World Health Organization's regions of South-East Asia, the Eastern Mediterranean, the Western Pacific, and the Americas [4, 5]. Children under the age of five are the most highly susceptible to malaria, accounting for over 80% of the deaths caused by malaria in the WHO African Region in 2021.

Despite diversions to prevention, diagnostic, and treatment operations during the epidemic, governments around the world have mostly held the line against additional setbacks to malaria control, according to the report's 2022 edition. In 2021, there are expected to be 619,000 malaria fatalities worldwide, compared with 625,000 in the very first year of the worldwide pandemic. Before the epidemic, the number of deaths in 2019 was 568,000 [6-8]. Malaria cases increased during 2020 and 2021, albeit at a lesser rate than from 2019 to 2020 [9]. Malaria incidences reached 247 million in 2021, up from 245 million in 2020 and 232 million in 2019 [10, 11].

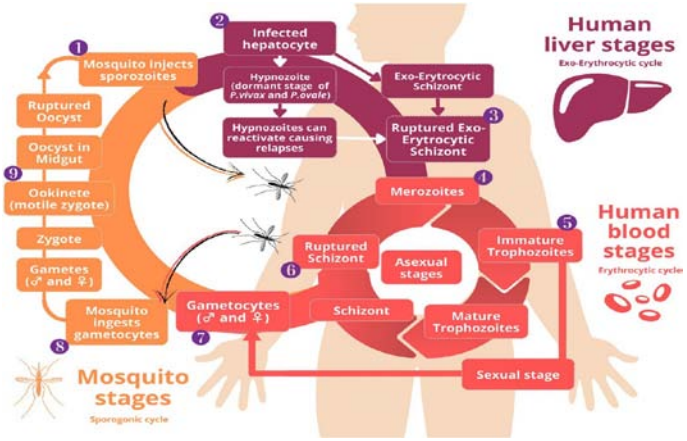

Fig. 1: Lifecycle of malaria [12, 24]

Malaria's life cycle is divided into two stages: sexual and asexual. The sexual stage takes place in an invertebrate host. The definitive host in malaria is a female a species of mosquito. The asexual stage takes place in a vertebrate intermediary host, the human [12-14].

Falciparum malaria has the potential to be fatal. Severe falciparum malaria can cause liver and renal failure, convulsions, and coma. Infections with P. vivax and P. ovale, while rarely severe, normally produce less significant sickness; nonetheless, the parasites can remain inactive in the liver's cells for many months, causing symptoms to appear again months or even years later [15-17]. There are mainly Five species of Malarial parasites that cause malaria-like Plasmodium falciparum (P. falciparum), Plasmodium malariae (P. malariae), Plasmodium vivax (P. vivax), Plasmodium ovale (P. ovale), Plasmodium knowlesi (P. knowlesi) these all has different structure at different stages of erythrocytes as shown in fig. [18].

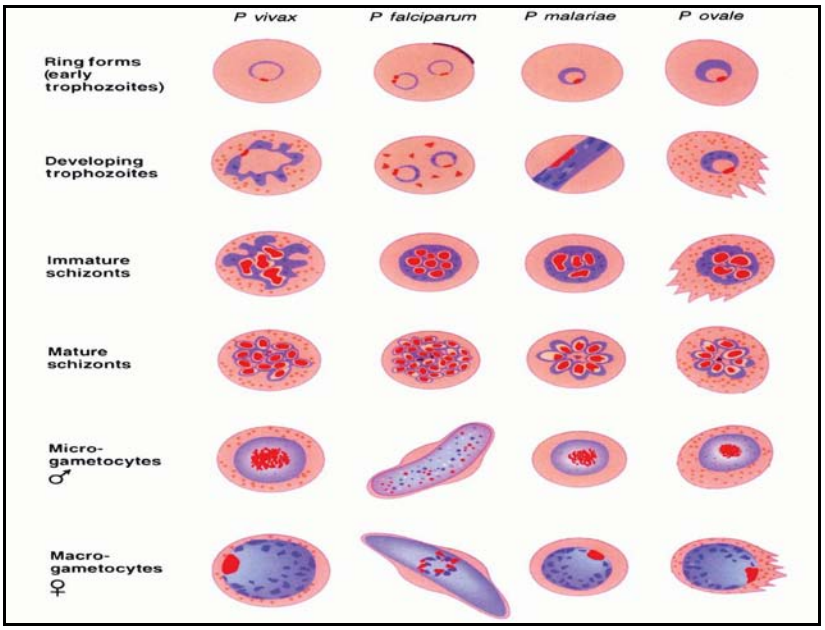

Fig. 2: Appearance of stained intraerythrocytic parasites [18]

Each of the four plasmodia species that infect people has a distinct look that allows them to be distinguished in stained smears. In P. vivax and P. ovale infections, the parasitized erythrocyte appears pale, swollen, and covered in Schüffner's spots. Several asexual stages (trophozoite, schizont, merozoite) can be observed together [19, 20]. P. ovale-infected cells have elongated shapes and are frequently irregular or fimbriated. RBCs in P. malariae infections are not swollen and do not contain granules. Trophozoites are frequently seen in "band" shapes, while merozoites are grouped in rosettes around a cluster of central pigments. The rings in P. falciparum infections are relatively tiny and may have two chromatin spots rather than one [21, 23].

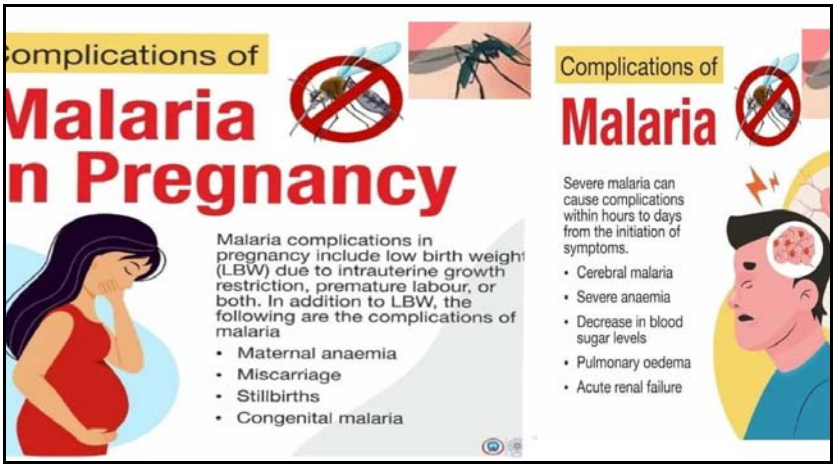

Fig. 3: Complications in malaria [24, 25]

Symptoms

Malaria is a contagious febrile sickness. Symptoms usually emerge 10-15 d after the infectious mosquito bite in a non-immune person. The earliest signs of malaria, such as fever, headache, and chills, could be mild and difficult to identify. Plasmodium falciparum malaria may lead to severe disease and death unless it's treated within 24 h [1, 25, 27].

Severe malaria frequently causes one or more of the following symptoms in children: severe anemia, for instance, respiratory distress due to metabolic acidosis, or brain malaria. Adults are also

prone to multi-organ failure [28]. People in malaria-endemic areas may develop some immunity, which facilitates asymptomatic infections. Some groups of people are at a far higher risk of catching malaria and developing severe sickness than others [29, 30]. Infants, children under the age of five, pregnant women, HIV/AIDS patients, non-immune migrants, mobile groups, and travelers are among them. National malaria control programs must take additional precautions to safeguard these populations from contracting the disease, taking into account their unique conditions [31].

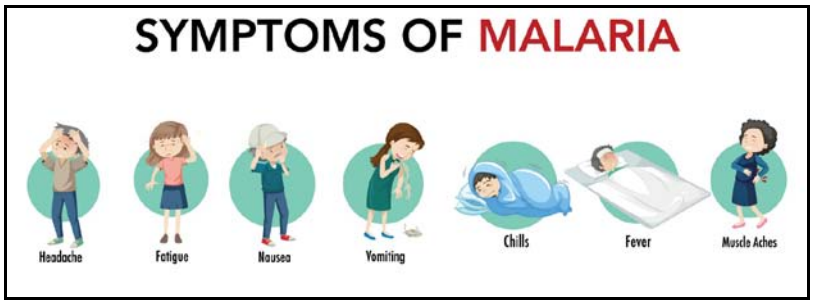

Fig. 4: Symptoms of malaria [31, 32]

Diagnosis of malaria

Malaria diagnosis that is timely and accurate not only decreases suffering but also reduces community transmission [33]. Malaria is diagnosed in the laboratory using a variety of techniques, including traditional microscopic diagnosis by staining thin and thick peripheral blood smears, other concentration techniques, such as the quantitative buffy coat (QBC) method, rapid diagnostic tests, such as OptiMAL, ICT, Para-HIT-f, ParaScreen, SD Bioline, Paracheck, and molecular tests for diagnosis, such as polymerase chain reaction (PCR) [34, 35]. Some advantages and disadvantages of these technologies, such as specificity, sensitivity, accuracy, precision, time utilized, cost-effectiveness, labor intensiveness, the requirement for competent microscopists, and the issue associated with inexperienced technicians, have also been described [36, 38].

Prevention

Take precautions to avoid mosquito bites. The only way to avoid the spread of this disease is to protect yourself from mosquito bites [40, 41]. Furthermore, the likelihood of severity varies from person to person according to their physical state and health history. Here are some preventive actions you may take to keep malaria at bay and prevent it from spreading faster [43, 44]. Use insect repellent on any exposed skin [45, 46]. The repellent advised comprises 20-35% N,N-Diethyl-meta-toluamide (DEET). If you are going to be outside at night, wear long-sleeved apparel and long pants [47, 48].

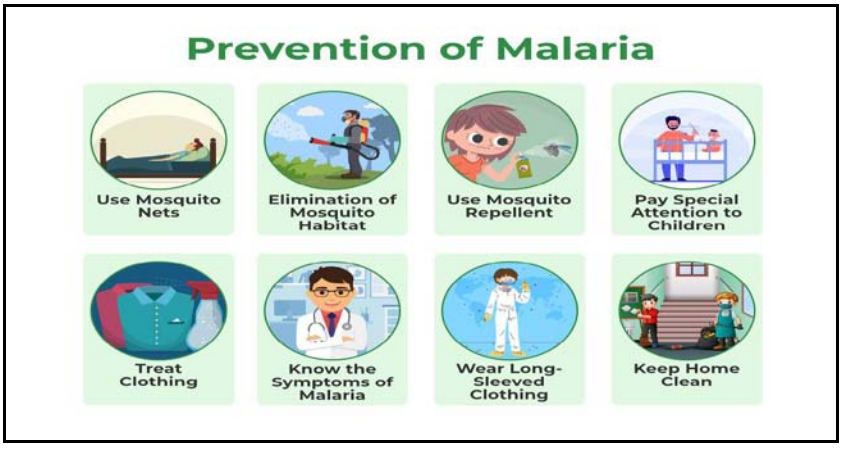

Fig. 5: Prevention from malaria [49-51]

Treatments

Malaria is a disease that can be avoided and treated. Early malaria diagnosis and treatment minimize sickness and fatalities while also helping to reduce transmission [52-55]. Artemisinin-based therapy in combination (ACT) is the most effective treatment available, especially when treating Plasmodium falciparum malaria [56]. Malaria can also be prevented with antimalarial medications [57-59].

Malaria can be avoided by using chemoprophylaxis, which lowers the blood levels of malaria infections and thereby prevents malaria illness [60, 61]. Persons should speak with their national disease control centers or other agencies offering travel advice before traveling to malaria-endemic countries or regions for information on the preventative actions that should be taken [62, 65].

There are four therapeutic options for P. falciparum infections acquired in chloroquine-resistant areas. Artemether-lumefantrine (Coartem®), which is the recommended combination if available, and atovaquone-proguanil (MalaroneTM) are two examples [66, 67]. These are fixed-dose combination medicines for young children weighing less than 5 kg. Quinine sulfate in combination with doxycycline, tetracycline, or clindamycin, is another therapy option. Quinine sulfate plus whether doxycycline or tetracycline is often chosen over quinine sulfate plus clindamycin because there is more data on the effectiveness of quinine sulfate plus doxycycline or tetracycline [68-70]. Except for illnesses acquired in Southeast Asia, which require seven days of treatment, quinine should be administered for three days. Mefloquine, the fourth alternative, has been linked to uncommon but possibly severe neuropsychiatric responses [https://www.cdc.gov/malaria/diagnosis_treatment/clinicians1.html]

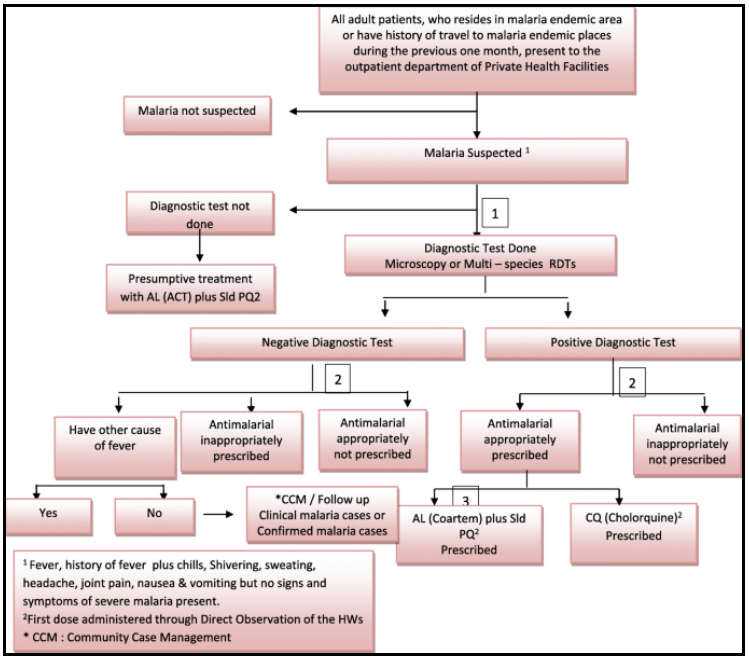

Fig. 6: Malaria diagnosis and treatment under standard guidelines [60]

Artemether drug

Artemether is a lipid-soluble artemisinin derivative. It is available in both oral and intramuscular forms. It is also available as a fixed-dose formulation with lumefantrine [71-73]. Artemether-lumefantrine is one of the ACTs authorized by the WHO and is being used by the majority of countries transitioning from less effective medications to ACTs., which is artemisinin with the lactone changed to the lactol methyl ether. It is used as an antimalarial in combination with lumefantrine to treat multi-drug resistant forms of falciparum malaria. It acts as an antimalarial [74, 75]. It's a sesquiterpenoid, cyclic acetal, organic peroxide, artemisinin derivative, and semisynthetic derivative all rolled into one [76, 77].

Artemether is an antimalarial medication used to treat uncomplicated acute malaria [79]. It is given in conjunction with lumefantrine to increase efficacy [80]. This combination medication is effective against Plasmodium spp. erythrocytic stages and may be used for the treatment of infections caused by P. falciparum and unidentified Plasmodium species, including infections acquired in chloroquine-resistant areas [81-83].

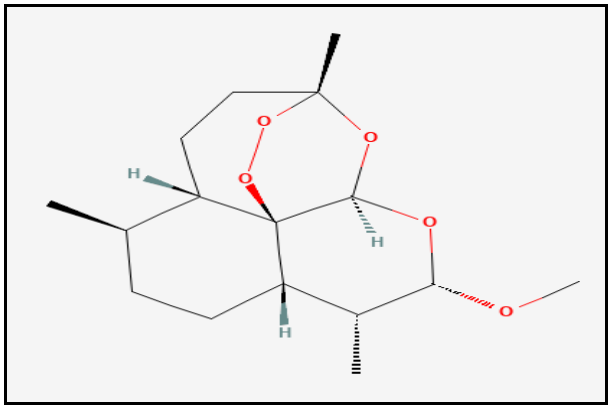

Fig. 7: Structure of the artemether

- **IUPAC name-** (1R,4S,5R,8S,9R,10S,12R,13R)-10-methoxy-1,5,9-trimethyl-11,14,15,16 tetraoxatetracyclo [10.3.1.04,13.08,13] hexadecane.
- **Molecular formula-**$C_{16}H_{26}O_5$
- **Molecular weight-**298.37g/mol
- **Melting point-**86-90 °C
- **Solubility-**Artemether is insoluble in water but soluble in organic solvents like ethanol, DMSO, and dimethyl formamide (DMF), which must be purged with an inert gas before use. Artemether is soluble in these solvents at around 16, 10, and 20 mg/ml, accordingly. Artemether is only somewhat soluble in aqueous buffers [84, 85].
- **Appearance-**White Crystalline powder with having Bitter taste
- **Dose**: An injectable dose of 3.2 mg/kg is given first, followed by 1.6 mg/kg daily for a maximum of 7 d before switching to oral administration. Capsule formulation: 160 mg the first day, then 80 mg per day for the next four years.

Mechanism of action

Endoperoxide bridges are present in artemether compounds. In the parasite, an endoperoxide bridge binds with heme (Fe2+) [87]. This

endoperoxide bridge is cleaved by heme iron. Highly reactive free radicals are produced, which cause parasite membrane damage by covalently attaching to membrane proteins. The enzyme P. falciparum adenosine triphosphatase is being proposed as the likely route of action [88-90].

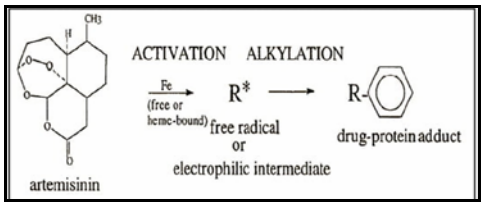

Fig. 8: MOA of artemether [90]

Pharmacokinetics

When administered orally, artemether absorbs quickly, reaching its maximum concentration within 2 h and undergoing extensive first-pass metabolism [90, 91]. DHA is its main active metabolite. Artemether has a high protein binding affinity (>90%) for 1-acid glycoprotein, albumin, and lipids. The process of elimination half-life is between 2 and 4 h. Artemether absorption from the intramuscular route is very poor and extremely variable in malaria patients, can take many hours to achieve peak concentrations, and has been linked to reduced parasite clearance [92]. Various hepatic and intestinal CYP enzymes, including CYP3A4, 2C11, and 2B6, are likely to metabolize artemether. It is most likely a substrate of intestinal CYP3A4, as evidenced by an increase in artemether bioavailability when combined with grapefruit juice [93-95].

Pharmacodynamics

Artemether is converted in the body to the active metabolite dihydroartemisinin. The medication works against P. falciparum erythrocytic stages by blocking nucleic acid and protein production. Artemether is given in conjunction with lumefantrine to increase efficacy [95-98] Artemether has an immediate start of the action and is quickly eliminated from the body. Artemether is supposed to provide quick symptom relief by lowering the quantity of malarial parasites. Lumefantrine has a substantially longer half-life and is thought to kill any remaining parasites [99, 100].

Fig. 9: Marketed formulations of artemether (Injections, tablets, syrup)

Table 1: List of medicines used in the treatment of malaria.

Drugs	Treatment pattern of IPD complicated cases out of 100 % probability
Artesunate	(80%)
Chloroquine	(72.30%)
Artemether	(55%)
Primaquine	(25%)
Doxycycline	(11.71%)
Quinine	(56.31%)

For all-over medicines used in the treatment of Malaria, we just give the probability of the drug used to treat Malaria (Percentage may be±)

CONCLUSION

Malaria is one of the world's biggest health challenges today, both in terms of its scope and the priority attention it has gotten from public and commercial health organizations.

The study discovered that Artemether had a good therapeutic efficacy for the therapy of uncomplicated falciparum malaria, with a high elimination of parasites rate and a rapid resolution of fever. AL was also effective against the parasite's transmissible sexual phase (gametocytes). The overall rate of high malaria success rate for artemether-lumefantrine, artesunate-amodiaquine, and dihydroartemisinin-piperaquine is greater than the WHO threshold value, implying that there is no need for an alteration in treatment policy in Sub-Saharan Africa. However, there is a desire to increase molecular producers' monitoring for resistance to artemisinin compounds and their partner medications.

Malaria is a fatal illness that affects millions of people around the world. Despite current therapies, antimalarial drug resistance has increased. Nanotechnology advancements for the creation of new medication delivery methods are promising and are increasingly being examined in preclinical experiments, with significant and motivating findings. This helps in the treatment of complicated malaria conditions like cerebral malaria.

ABBREVIATIONS

Artemisinin-based combination treatments (ACTs).

FUNDING

Nil

AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICTS OF INTERESTS

The authors declare no conflicts of interest.

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