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## Review Article

# A systematic review on malaria

Rutuja R. Sumbe<sup>1,\*</sup>, Ganesh D. Barkade<sup>1</sup>

<sup>1</sup>Dept. of Pharmaceutical Chemistry, Dr. Vitthalrao Vikhe Patil Foundation's College of Pharmacy, Ahmednagar, Maharashtra, India



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### ABSTRACT

Millions of people die from the parasitic disease malaria each year. This illness is difficult to diagnose in a clinical environment and arises when the red blood cells in the blood are harmed. Malaria is caused by Plasmodium parasites, which are the main global cause of mortality and morbidity. Both in their hosts, the vertebrates, and their carriers, the mosquitoes, these parasites have a complicated life cycle.

The diagnosis is based on Plasmodium detected in a peripheral blood smear. The method of treatment and prevention depends on the species and drug sensitivity. The prevalence of the disease in places with low transmission rates and the therapeutic impact of artemisinin derivatives on the treatment of resistant falciparum malaria have both been important. The literature on biology, pathology, signs and symptoms, complications, diagnosis, treatment, method of transmission, and antimalarial medications is assessed in detail in the current study.

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## 1. Introduction

### 1.1. What is malaria?

*Plasmodium*, which causes malaria, is a mosquito-borne disease that is spread through the bite of an infected female *anophele's* mosquito. The word "malaria" is an Italian word that means "poor air." The disease malaria is well-known among humans. The Plasmodium parasite is spread from person to person by female *anophele's* mosquitoes. Two hosts: mosquito (sexual) and human or other organisms (asexual). The symptoms include chills, fever, sweat, exhaustion, splenomegaly and anemia. Malaria is both an acute and chronic condition. Humans and other animals can contract the infectious disease malaria, which is spread by mosquitoes. Frequent signs of malaria include fever, exhaustion, nausea, and headaches.<sup>1</sup> If the individual does not continue to be exposed to malaria, this partial resistance

vanishes over the course of months to years. *Plasmodium* group single-celled microbes are the primary cause of malaria. It only spreads by mosquito bites from infected *Anopheles* species.<sup>2,3</sup> The parasites from the mosquito's saliva enter a person's bloodstream through a mosquito bite. The liver is the destination of the parasites, where they develop and procreate. Humans are capable of transmitting five different *Plasmodium* species. *P. falciparum* is the most common cause of malaria-related mortality, but *P. vivax*, *P. ovale*, and *P. malariae* typically produce a milder version of the disease. Every year on April 25, there is a celebration known as World Malaria Day to bring attention to the global campaign to reduce and eventually eradicate malaria. Africa Malaria Day, which was commemorated by African countries since 2001, evolved into World Malaria Day, which was first celebrated in 2008.<sup>4</sup> Military physician Dr. Alphonse Laveran of France's Service de Sante des Armees (Health Service of the Armed Forces). The military clinic at Constantine, Algeria, where Laveran made his 1880

\* Corresponding author.

E-mail address: [ganeshbarkade7@gmail.com](mailto:ganeshbarkade7@gmail.com) (R. R. Sumbe).

discovery of the malaria parasite.<sup>5</sup> In July 2015, the RTS, S vaccine received a favourable scientific opinion with the recommendation that it be administered in Africa for infants who are at a higher risk of contracting malaria. The first malaria vaccine in the world to receive "approval" for usage was RTS, S.<sup>6</sup>

### 1.2. Etiology

Malaria is caused by the bite of an infected female *Anopheles* mosquito that introduces the sporozoites of the following:

1. *Plasmodium falciparum*
2. *Plasmodium vivax*
3. *Plasmodium ovale*
4. *Plasmodium malariae*

It can also be caused by blood transfusion in rare cases.

### 1.3. *Plasmodium falciparum*

1. It is believed that this species is responsible for 50% of all malaria cases.
2. It takes one to 3 weeks to incubate (average, 12 days).

### 1.4. *Plasmodium vivax*

1. This species, which accounts for around 40% of all malaria cases, is the second most prevalent species and can cause extremely chronic liver disease because it can re-infect liver cells.
2. It takes one to 4 weeks for incubation to occur (average, 2 weeks).

### 1.5. *Plasmodium malariae*

1. It only accounts for 10% of all cases of malaria; relapses are frequent. It takes two to four weeks for incubation to occur (average, 3 weeks).
2. This *P. malariae*-related RBC infection can persist for many years.

### 1.6. *Plasmodium ovale*

1. This species is the least common.
2. It takes 9 to 18 days for incubation to occur (average, 14 days).
3. People who have been exposed to this plasmodium have been documented to experience relapses.<sup>7</sup>

### 1.7. Pathogenesis

When a person is bitten by an infected female *Anopheles* mosquito, sporozoites of the *Plasmodium* species, which cause malaria, are released into the bloodstream. In the following 7–10 days, the sporozoites multiply asexually in the liver.<sup>8</sup> No symptoms are present at this time. The

parasites, which have changed into merozoites, release from the liver cells in vesicles and go through the digestive tract to the lungs' capillaries. The merozoites are finally released from the vesicles and enter the bloodstream. The erythrocytes they penetrate, where they grow. More erythrocytes are invaded by the parasites when the cells burst. The onset of clinical symptoms, such as fever, coincides with the rupture of infected erythrocytes and the subsequent release of parasite and erythrocyte debris, such as malarial pigment (hemozoin) and glycoposphatidylinositol, the purported "malaria toxin," as well as the malarial pigment (hemozoin).<sup>8,9</sup> In some infected blood cells, the merozoites develop into sexual forms (gametocytes), which circulate in the bloodstream and are swallowed during mosquito bites, as opposed to reproducing asexually. In the mosquito, the ingested gametocytes mature into adult sex cells (gametes), which then transform into ookinetes, which actively borrow through the mosquito's midgut wall to create oocysts, during which hundreds of active sporozoites develop. The oocyst eventually bursts, releasing sporozoites that visit the salivary glands of the mosquito. The cycle of human infection begins again when the mosquito bites another person.<sup>10</sup>

## 2. Mode of Transmission

### 2.1. Mother to the growing foetus (congenital malaria)

Congenital malaria, also known as transmission of parasites from an infected mother's red blood cells to her child during labour or trans placentally, can cause malaria in the newborn. Congenital malaria appears to be uncommonly documented, and it has traditionally been assumed that non immune people experience it more frequently than people in endemic locations. All four of the *Plasmodium* species that typically infect people have been linked to congenital malaria cases, however the majority of these occur when the mother has *P. falciparum* or *P. vivax* malaria.<sup>11,12</sup> Due to *P. malariae*'s extended host persistence, congenital malaria cases may be disproportionately more common in non-endemic regions. During the initial pregnancy, congenital malaria develops more frequently.<sup>11</sup> Figure 1

## 3. Transfusion Malaria

The most common way that blood transfusions from infected donors spread malaria is transfusion-transmitted malaria is one of the most prevalent illnesses nowadays and was first described in 1911.<sup>13,14</sup> In nonendemic nations like the United States, the risk of contracting transfusion malaria is quite low (1 case per 4 million), whereas it is substantially greater (>50 cases per million donor units) in endemic nations.<sup>15</sup> Following a malaria infection, a person may continue to be contagious for weeks, months, or even years if only *P. malariae* is present. As a result, people who carriers should never give blood. Just in the case of

transfusions of plasma, plasma components, or derivatives devoid of intact red blood cells, the danger of transmission is incredibly low.<sup>16</sup> Malaria infection is challenging to detect in donated blood samples. assays.<sup>17,18</sup> Just in cases of infection, particularly in nonimmune patients, the infection can advance quickly into a deadly sickness in addition to the usual symptoms of fever, and headache.<sup>19,20</sup> exoerythrocytic phase.<sup>14,21–23</sup>

### 3.1. Injury from needles

Cases of malaria transmission by needle-stick injuries, unintentionally among medical personnel (some even deadly), or because drug addicts share needles have also been documented.<sup>13,14,24</sup> Figure 2

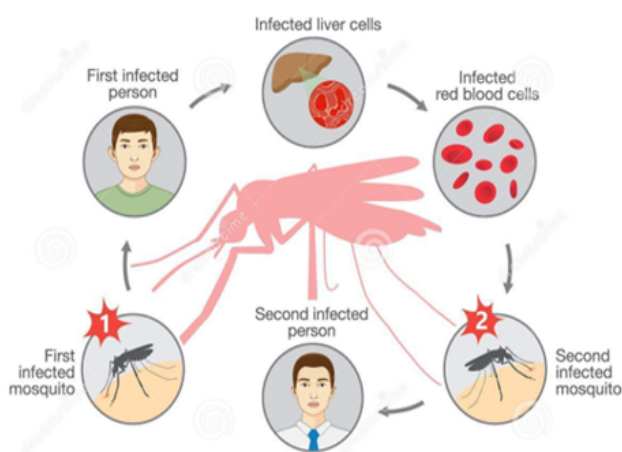


Fig. 1: Transmission of malaria<sup>25</sup>

## 4. Life Cycle of Malaria

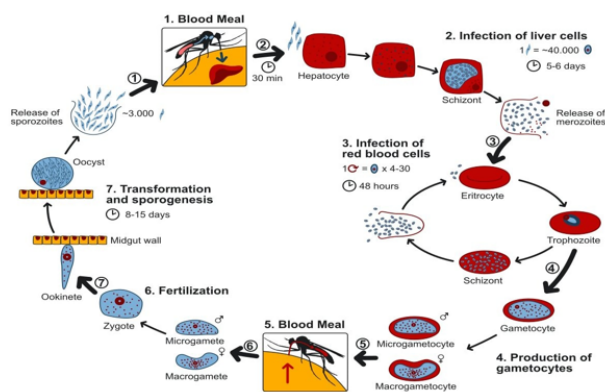


Fig. 2: Life cycle of malaria<sup>26</sup>

A female *Anopheles* mosquito injects sporozoites of the *Plasmodium* parasite into the bloodstream when she bites a person who has malaria. The sporozoites are quickly

absorbed by the human liver. The sporozoites develop asexually in the liver cells over the next 7 to 10 days without causing any symptoms. The parasites are ejected from the liver cells in vesicles in an animal model in the form of merozoites. Before being lodged inside lung capillaries, merozoites travel to and from the heart and lungs. The ruptured vesicles were finally opened, and the merozoites started to grow in the blood phase. Invading erythrocytes in the bloodstream, the merozoites flourished there until the cells ruptured. The invasion of erythrocytes then continues. Fever results from the cycle being repeated each time the parasites escape and enter the blood cells. A small number of the infected blood cells stop multiplying in an asexual manner. Instead of replicating, the merozoites in these cells undergo transformation into gametocytes, the sexual forms of the parasites that move through the blood stream. When a mosquito bites a person who is infected, it ingests gametocytes, which develop into gametes, which are mature sex cells, later. After fertilization, the female gametes develop into moving ookinets that puncture the mosquito's midgut wall and produce oocysts on the outside.<sup>27</sup>

## 5. Global Statistics Table 1

### 6. Symptoms

Malaria symptoms include fever and flu-like symptoms such as shaking chills, headache, muscular aches, and fatigue. There may also be nausea, vomiting, and diarrhea. Because of the loss of red blood cells caused by malaria, anemia and hostility (unheroic coloration of the skin and eyes) may develop. If the infection is not treated right away, it may become serious and result in seizures and organ failure. Generally after biting of infected mosquito signs and symptoms of malaria observed in patients in few weeks.<sup>29</sup>

### 7. Complications

Malaria can be fatal, especially if it is brought on by a *Plasmodium* species that is widespread in Africa. 94% of all malaria-related deaths, which primarily affect young children under the age of 5, occur in Africa, according to the World Health Organization.

1. **Cerebral malaria:** Brain swelling or injury could result from blood cells with parasites inside that obstruct small blood arteries to the brain (cerebral malaria).
2. **Breathing problems:** Breathing might be challenging if you have pulmonary edema, which is a buildup of fluid in your lungs.
3. **Low blood sugar:** Quinine, a common malaria treatment drug, as well as severe forms of the disease can both result in low blood sugar (hypoglycemia). A coma or death may arise from extremely low blood sugar.

**Table 1:** Global Statistics of malaria<sup>28</sup>

| Year | Rates of incidence and mortality are based on the population. | Cases   |          |          | Deaths |       |         |
|------|---|---------|----------|----------|--------|-------|---------|
|      |   | Lowest  | Point    | Highest  | Lowest | Point | Highest |
| 2016 | 1237628916  | 8897000 | 12431896 | 18160000 | 1500   | 22437 | 44300   |
| 2017 | 1250859601  | 6897000 | 9339370  | 13290000 | 1190   | 16296 | 31500   |
| 2018 | 1263908968  | 4656000 | 6768155  | 9506000  | 940    | 9664  | 18400   |
| 2019 | 1276780904  | 3697000 | 55488478 | 7891000  | 770    | 7701  | 14700   |
| 2020 | 1289475946  | 2738000 | 4148253  | 5971000  | 510    | 7341  | 14500   |
| 2020 | 1289475946  | 2738000 | 4148253  | 5971000  | 510    | 7341  | 14500   |

4. *Anemia*: Malaria may prevent you from producing enough red blood cells to ensure your body's tissues receive a proper amount of oxygen (anemia).
5. *Organ failure*: Malaria can harm the liver, kidneys, or spleen, or even rupture them. Any of these ailments has the potential to be fatal.<sup>29</sup>

## 8. Diagnosis

### 8.1. Microscopy

1. Peripheral blood smears- gold standard
2. Thick and thin smear

### 8.2. Advantages

1. Sensitivity is high
2. Detects parasites even at low densities
3. Quantify the load
4. Requires skills to identify.

### 8.3. Rapid diagnostic Test

1. Dipstick test Immuno chromatographic test for detection of malarial antigens (monoclonal/ polyclonal antibodies).
2. Detection of antigens –HRP2, Aldolase, pfLDH

### 8.4. Other tests

1. QBC
2. Serological test
3. Parasite F, Optimal assay
4. PCR
5. Radioimmuno assays, Immuno fluorescence.<sup>29,30</sup>

### 8.5. Treatment

Malaria is treated using antimalarial medications, however which ones are utilised depending on the type and severity of the disease.<sup>31</sup> Although fever-relieving drugs are frequently prescribed, their effects on outcomes are unclear. When used properly, giving free antimalarial drugs to households may lower childhood mortality.

### 8.6. Uncomplicated malaria

Oral drugs can be used to treat malaria that is simple or uncomplicated. Drugs containing artemisinin are efficient and secure for treating simple malaria. Artemisinin-combination treatment (ACT), which combines artemisinin with additional antimalarials, is around 90% successful in treating uncomplicated malaria.<sup>32</sup> The most successful treatment for *P. falciparum* infection is the use of ACT, which lowers resistance to any one medicine component.<sup>33</sup> The six-dose artemether-lumefantrine regimen is more effective at treating *falciparum* malaria than the four-dose artemether-lumefantrine regimen or other regimens that do not include artemisinin derivatives. Another potential combination is piperazine and dihydroartemisinin.<sup>34,35</sup> Artemisinin-naphthoquine combination therapy demonstrated encouraging outcomes in the treatment of *falciparum* malaria. Amodiaquine plus sulfadoxine-pyrimethamine may result in fewer treatment failures as compared to sulfadoxine-pyrimethamine alone in uncomplicated *falciparum* malaria. There are insufficient evidence on the use of chlorproguanil-dapsone to treat uncomplicated *falciparum* malaria.<sup>36</sup> Primaquine, when used in combination with an artemisinin-based therapy, lowers *falciparum* malaria transmission on days 3–4 and 8 after infection. In terms of preventing treatment failure at day 28, sulfadoxine-pyrimethamine plus artesunate performs better than sulfadoxine-pyrimethamine with amodiaquine. However, the latter outperforms the former in reducing gametocyte levels in blood at day 7. In order to treat malaria during pregnancy, the WHO recommends quinine plus clindamycin in the first trimester and ACT in the second and third.<sup>37,38</sup>

### 8.7. Severe and complicated malaria

Infection with *P. falciparum* is almost always the cause of severe and complex malaria cases. The only disease caused by the other species is often febrile.<sup>39</sup> Due to the significant (10% to 50%) mortality rates associated with malaria, severe and complex cases are considered medical emergencies.<sup>40</sup> The intravenous administration

of antimalarial medications is advised as a treatment for severe malaria. In a different systematic study, quinine and the artemisinin derivatives Arteether and artemether were equally efficacious at treating pediatric cerebral malaria.<sup>41</sup> For the treatment of severe malaria in both children and adults, parenteral artesunate proved more effective than quinine.<sup>42</sup> However, giving rectal artesunate prior to hospital transfer may lower the mortality rate for children with severe malaria. Intrarectal quinine is equally effective in treating uncomplicated and complicated falciparum malaria as intravenous or intramuscular quinine. The most severe neurological symptoms of malaria, known as cerebral malaria, are present in this form of the disease.<sup>43</sup> The effectiveness of osmotic medications for cerebral malaria, including mannitol or urea, is unknown due to a lack of data. Steroid use does not appear to improve cerebral malaria treatment outcomes.<sup>44</sup>

### 9. Taking Care of Cerebral Malaria

Testing for other locally prevalent causes of encephalopathy, such as bacterial, viral, or fungal infections, should be carried out when the exact reason of a patient's coma is unknown. Cerebral malaria typically renders a patient unconscious. Treatment may begin without a test in regions with a high prevalence of malaria infection (such as tropical regions). When cerebral malaria is identified, the following can be done to manage it:

1. Patients who are in comas should receive attentive nursing care (monitor vital signs, turn patient every 2 hours, avoid lying the patient in a wet bed etc.)
2. When convulsions occur, a benzodiazepine injection is given slowly intravenously.<sup>45</sup>

The assertions that blood transfusions can decrease fatalities in kids with severe anemia or raise their haemoglobin levels over the course of a month are unproven.<sup>46</sup> There are four possible sites for drug therapy:

1. Destroy the sporozoites the mosquito injected or prevent them from doing so.
2. Destroy the schizonts found in hepatocytes or prevent them from maturing into merozoites.
3. Destroy the blood merozoites or prevent them from maturing into gametocytes.
4. Get rid of the gametocytes before they can enter the mosquito and mature into zygotes.<sup>47</sup>

### 10. Classification of Antimalarial Drugs<sup>48</sup> Table 2

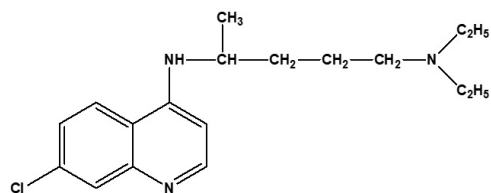


Diagram 1: Table 2+ Structure+ S N 1

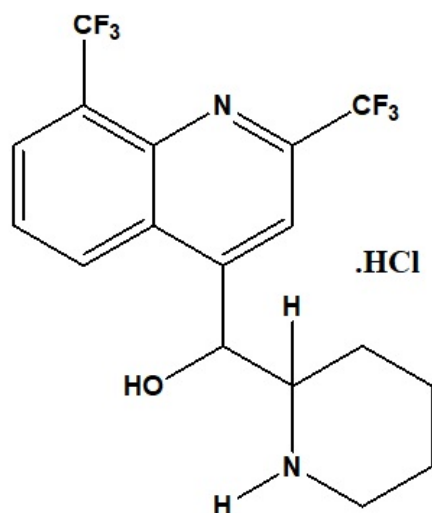


Diagram 2: Table 2+ Structure+ S. N. 2

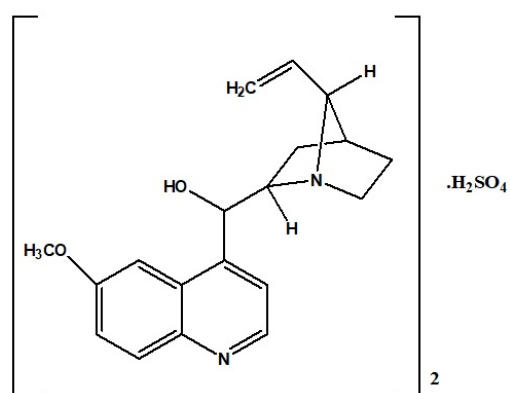


Diagram 3: Table 2+ Structure+ S. N. 3

**Table 2:** Classification of antimalarial

| Sr. No. | Antimalarial Drugs | Examples                                 | Structure                         | Mechanism   | Uses  |
|---------|--------------------|--|-----------------------------------|---|---|
| 1.      | 4-Aminoquinolines  | Chloroquine, Amodiaquine, Piperaquine.   | Structure of Chloroquine          | By blocking the polymerization of toxic heme produced during haemoglobin proteolysis in the digestive vacuole of Plasmodium, chloroquine is able to exert its antimalarial action. There is no known mechanism for this blockage. | Treatment and prevention of malaria. Additionally, it works well as an anti-inflammatory medication for the treatment of lupus erythematosus and rheumatoid arthritis, as well as extra intestinal amebiasis.             |
| 2.      | Quinoline-Methanol | Mefloquine                               | Structure of Mefloquine           | Mefloquine selectively inhibits protein synthesis at the Plasmodium falciparum 80S ribosome, which has schizonticidal effects.  | Used to treat and prevent malaria caused by P. falciparum. It's contraindicated in patients with active depression  |
| 3.      | Cinchona Alkaloids | Quinine, Quinidine                       | Structure of Quinine Sulphate     | Quinine inhibits nucleic acid synthesis, protein synthesis, and glycolysis in Plasmodium falciparum and can bind with hemazoin in parasitized erythrocytes.   | It is also a mild antipyretic and analgesic. To the treat chloroquine – resistant strains of P. falciparum  |
| 4.      | Biguanide          | Proguanil                                | Structure of Proguanil            | Inhibiting the enzyme, dihydrofolate reductase, which is involved in the reproduction of the parasite.  | • •   |
| 5.      | Diaminopyrimidine  | Pyrimethamine                            | Structure of Pyrimethamine        | Because pyrimethamine only inhibits the plasmodial form of dihydrofolate reductase, the malarial parasite produces less folic acid, which is necessary for the synthesis of nucleic acids.  | The protection against severe P. falciparum and P. vivax assaults. As an immunosuppressant and treatment for toxoplasmosis, it is also employed.  |
| 6.      | 8-Aminoquinolines  | Primaquine, Tafenoquine                  | Structure of Primaquine Phosphate | Primaquine eliminates the intrahepatic forms of Plasmodium vivax and Plasmodium ovale, which stops the erythrocytic forms from developing and causing relapses.   | Primaquine, an aminoquinoline, has been used for more than 50 years to treat and prevent malaria.   |
| 7.      | Sulphone           | Dapsone, Sulfadoxine, Sulfamethopyrazine | Structure of Dapsone              | By competing with para-aminobenzoate for the active site of dihydropteroate synthase, dapsone prevents bacteria from synthesizing dihydrofolic acid, which prevents the formation of nucleic acids.                               | • • It is also having a role as an antimalarial, an anti-infective agent and an anti-inflammatory drug  |
| 8.      | Antibiotics        | Clindamycin, Doxycycline                 | Structure of Doxycycline          | Doxycycline has been seen to inhibit the expression of apicoplast genes in P. falciparum, resulting in nonfunctional apicoplasts in successive progeny and preventing the growth of viable parasites.                             | Doxycycline is broad-spectrum antibiotic. It is used to treat adult periodontitis, non-gonococcal urethritis and cervicitis, as well as bronchitis flare-ups in people with chronic obstructive pulmonary disease (COPD). |

Table 2 Cont...

|     |                        |   |                           |   |  |
|-----|------------------------|---|---------------------------|---|--|
| 9.  | Sesquiterpine-lactones | Artesunate, Artemether, Arteether, Arterolane | Structure of Artesunate   | In all erythrocytic stages of the Plasmodium parasites, the endoperoxide bridge of DHA combines with heme to produce free radicals that prevent the parasites from synthesizing proteins and nucleic acids.                           | • It also has anti-schistosomiasis, antiviral, and potential anti-neoplastic activities  |
| 10. | Amino-alcohols         | Halofantrine, Lumefantrine                    | Structure of Halofantrine | Halofantrine's mechanism of action may be similar to those of chloroquine, quinine, and mefloquine in that it also damages the parasite's membrane by generating toxic complexes with ferritoporphyrin IX.                            | Is effective against both chloroquine-sensitive and chloroquine-resistant Plasmodium falciparum infections and is beneficial for the treatment of uncomplicated malaria. |
| 11. | Naphthoquinone         | Atovaquone                                    | Structure of Atovaquone   | Atovaquone is a ubiquinol competitor that particularly inhibits the bc1 complex of the mitochondrial electron transport chain.  | Atovaquone is used in combination with proguanil for prevention and treatment P. falciparum malaria.   |
| 12. | Naphthyridine          | Pyronaridine                                  | Structure of Pyronaridine | An agent that prevents the biopolymerization of -hematin, allowing poisonous hematin to accumulate in the parasite's digestive vacuole. Hemozoin is a biomineral malaria pigment that is a byproduct of the digestion of haemoglobin. | When used with artesunate, the medication is used to treat both adults and children with uncomplicated P. falciparum malaria. <sup>48</sup>                              |

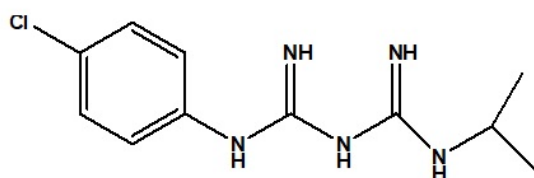


Diagram 4: Table 2+ Structure+ S. N. 4

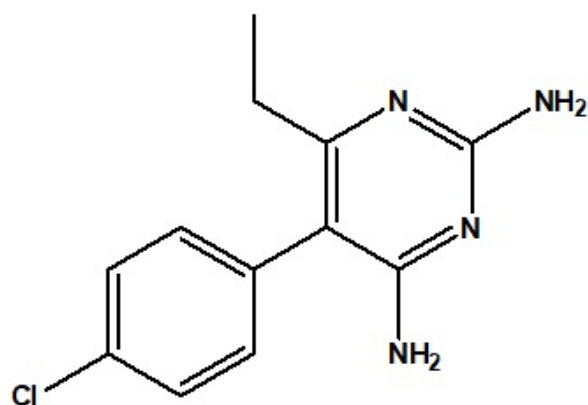


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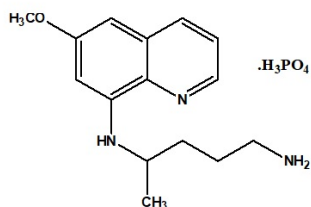


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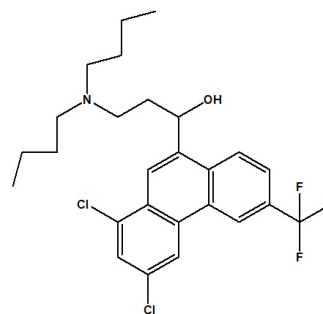


Diagram 10: Table 2+ Structure+ S. N. 10

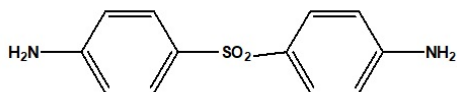


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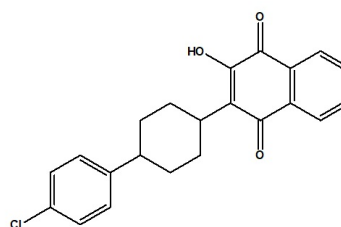


Diagram 11: Table 2+ Structure+ S. N. 11

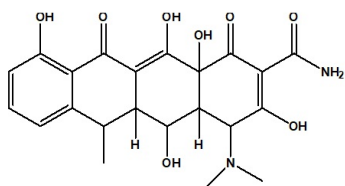


Diagram 8: Table 2+ Structure+ S. N. 8

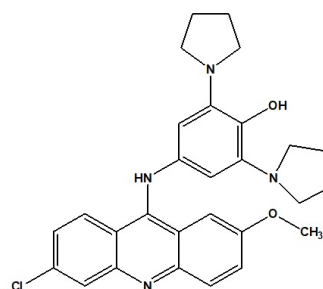


Diagram 12: Table 2+ Structure+ S. N. 12

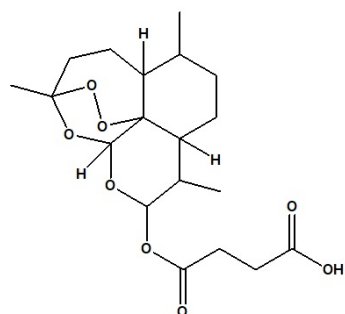


Diagram 9: Table 2+ Structure+ S. N. 9

## 11. Conclusion

Malaria may be serious life-threatening diseases that lead to millions of deaths yearly. But malaria is often prevented and treated. Malaria kills thousands of individuals unnecessarily. With immediate and proper treatment people are able to recover from these diseases with no problem. The commonly used anti-malarial drug Chloroquine, Quinine within the case of vivax and Quinine or Artemether in falciparum malaria are helpful in more cases. Malaria



and the resulting morbidities and fatalities can be reduced by raising awareness of malaria prevention strategies and encouraging early use of prenatal care services. In present study, intimately literature of biology, pathology, signs and symptoms, complications, diagnosis, treatment, mode of transmissions, Antimalarial drugs are evaluated during this Malaria project report.

## 12. Conflict of Interest

Authors Declares no Conflict of Interest.

## 13. Source of Funding

None.


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### Author biography

**Rutuja R. Sumbe**, Research Scholar

**Ganesh D. Barkade**, Assistant Professor  <https://orcid.org/0000-0003-3836-3125>

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