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DESIGN OF ANTIMALARIAL DRUGS

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ABSTRACT

Malaria is an infectious disease that occurs due to the parasitic protozoan of genus Plasmodium. This parasite enters inside the blood of the person due to the bite of female Anopheles mosquito. Plasmodium then enters into the liver of the infected person. After being matured and reproduced, it infects the erythrocytes of the person. Symptoms of malaria develop at this erythrocytic stage only, in the form of fever, headache, fatigue, pain which may further lead to coma and death. Antimalarial drugs used to treat and prevent malaria, have both advantages and some limitations. These drugs act mainly on the erythrocytic stage and lesser on the liver stage. But because of the development of resistance against most of these drugs there is an urgent need for development of drugs that are free from resistance in future. ELQ 300 is the latest drug that is resistance free and has been produced, targeting Plasmodium at every stage.

Key Words: Anopheles, Antimalarial drugs, Life cycle, Malaria, Plasmodium.

I. INTRODUCTION

1.1 Malaria

Malaria is an infectious disease of humans which is caused due to the bite of female Anopheles mosquito carrying *Plasmodium*. The mosquito bite releases the parasitic protozoan of genus *Plasmodium* into the blood stream of the person.

Fig 1. Mosquito obtaining a blood meal from a human host [1]

Plasmodium is a large genus of parasitic protozoa. Protozoa are the group of eukaryotic organisms which are unicellular and mobile. *Plasmodium* consist of 200 species which are further divided into subgenera. Species of *Plasmodium* that are predominantly responsible for causing malaria are *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale*, *Plasmodium malariae* [2].

After being released into the blood stream *Plasmodium* enters the liver of that infected person and causes liver infection. This parasite after being matured and multiplied in the liver infects the blood cells, which is then called as erythrocytic stage of malarial infection in the person.

1.2 Malaria attack on humans : Global and India

1.2.1 Global level

Malaria is found to occur in more than 100 countries mainly in tropical regions. Among 3.4 billion people, half of the world population is at the risk of malaria. According to 2012 report, 207 million cases of malaria were discovered and approximately 627000 cases of death due to malaria. As noted from the prevalence of malaria in the world, Indian population is highly susceptible to the malarial attack [3].

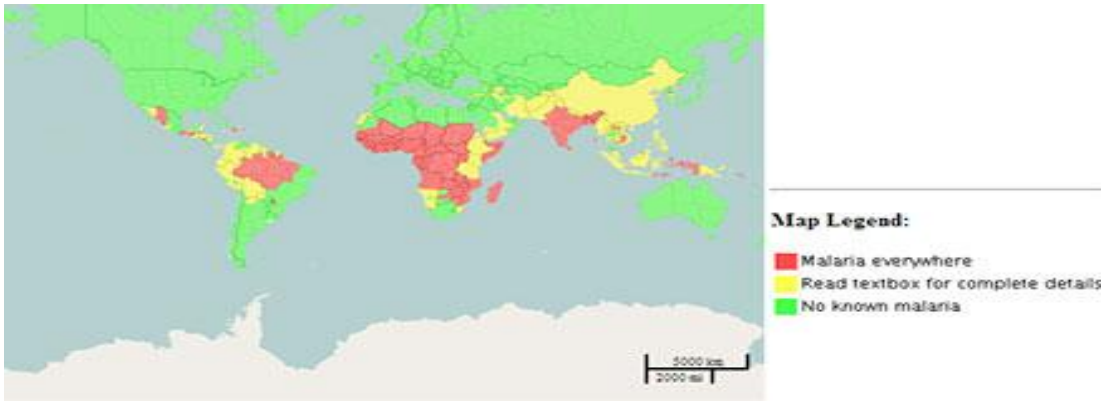


Fig 2. Map showing where malaria is widespread (red), present in selected areas (yellow), or not present (green) [4]

1.2.2 India

Endemic relates to the restriction of the infection to certain area, it is noted that most of the states of India are malaria endemic. Approximately, 15 lakh people are killed every year due to malaria in India. According to WHO report in 2013, in the coming next two years the cases of malaria will get reduced to 50%.

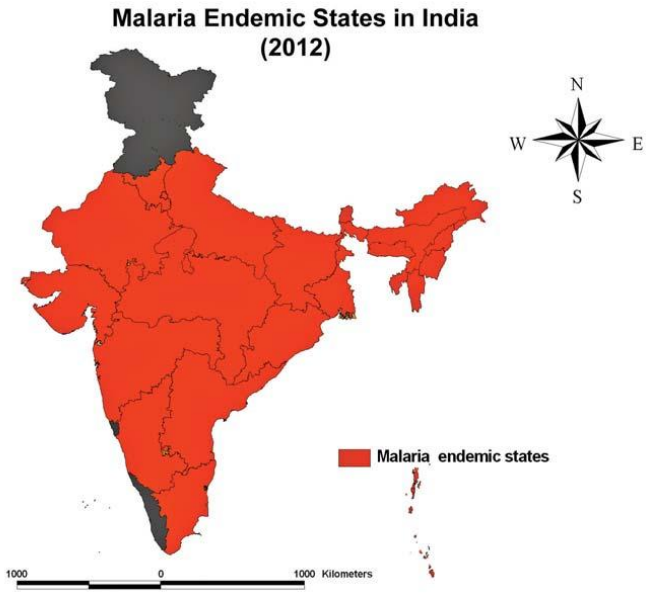


Fig 3: The malaria endemic states / UTs in India [5]

1.3 Malaria Symptoms

The symptoms of malaria takes nearly 8–25 days to develop after the infection. The symptoms develop in the form of fever, headache, fatigue, pain which may further lead to coma or death.

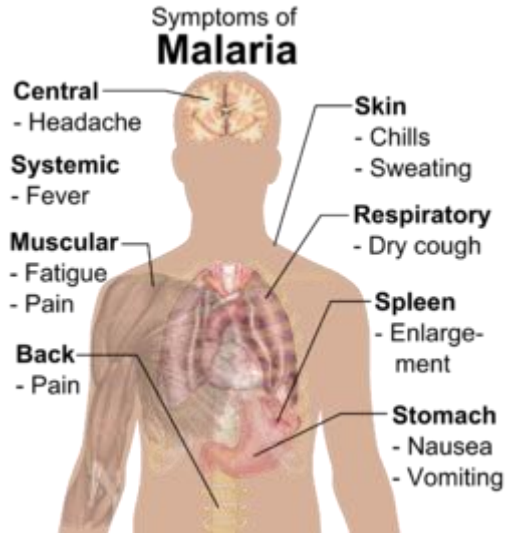


Fig 4. Main symptoms of malaria [6]

II. LIFE CYCLE OF MALARIAL PARASITE

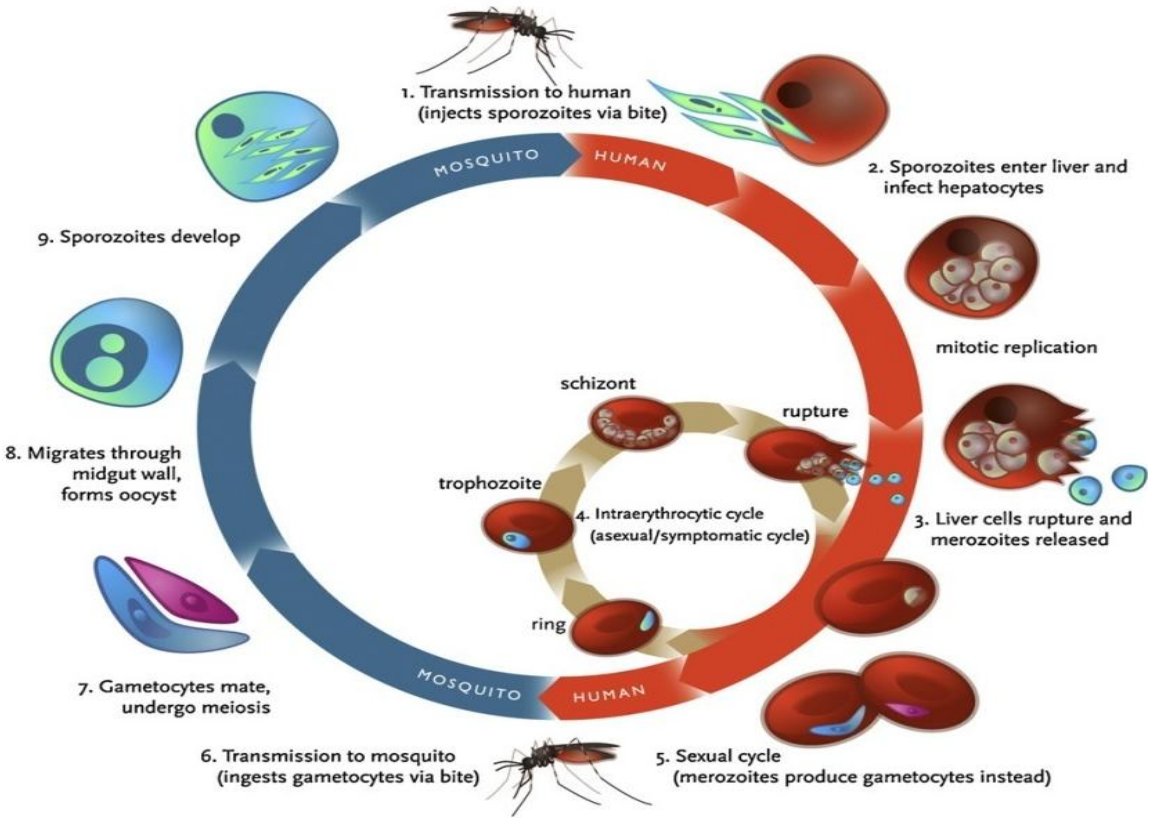


Fig 5. Life cycle of malarial parasite [7]

Life Cycle of malarial parasite

Transmission to humans- The plasmodium parasite gets entry inside the circulatory system of humans due to the bite of female Anopheles mosquito.

↓

Sporozoites (haploid) enter liver and infect hepatocytes- Sporozoites which are the infectious form of the malarial parasite enter into the liver and infect the cells of liver (hepatocytes).

↓

Liver cells rupture and merozoites released- After 5-16 days sporozoites start multiplying mitotically and dividing to form haploid merozoites. The liver cells then get ruptured and the parasite is released to invade the red blood cells.

↓

Intraerythrocytic cycle- It relates to the time during which infection is spread in the RBCs. When merozoites enter the RBCs they are called as trophozoites which grow mitotically (asexual) inside the red blood cells to form schizonts. Mitotically grown mass of trophozoites are called schizont, which divide inside the red blood cells and produce more merozoites that are released to infect more red blood cells. This asexual multiplication results into development of illness and other symptoms of malaria [8].

↓

Sexual cycle- Merozoites infecting some of the RBCs behave then as gametocytes, which at later stages develop into gametes.

↓

Transmission to mosquito- When again the mosquito comes to bite the infected person, the gametocytes are taken up by the mosquito along with the blood of infected person.

↓

Gametocytes mate, undergo meiosis- Inside the mosquito's midgut, the gametocytes develop into gametes.

↓

Migrates through midgut wall, form oocyst- Male and female gametes of malarial parasite fuse to form oocyst (diploid) in the mosquito midgut [9].

↓

Sporozoites develop- Motile zygotes (oocyst) undergo growth and meiotic division and form haploid sporozoites [10], which after 8-15 days get released from the oocyst and move to the salivary glands of mosquito. These sporozoites are then injected from the salivary glands of mosquito into the next human host of the mosquito, infecting and restarting its life cycle.

III. APPROACHES FOR CONTROL AND TREATMENT OF MALARIA

- Inhibit breeding of Anopheles mosquito
- Treatment of patient after infection

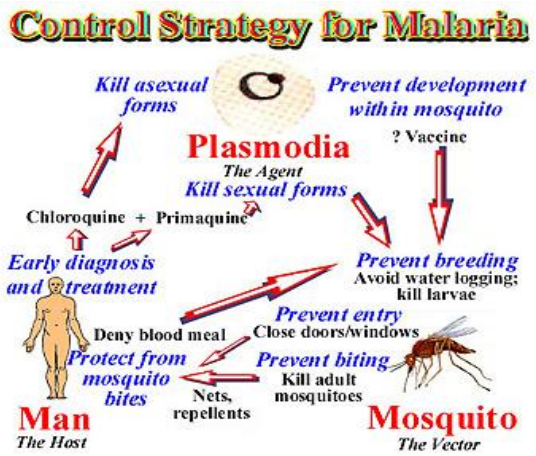


Fig 6. Control strategy for malaria [11]

3.1. Inhibit breeding of Anopheles mosquito

Since prevention is always better than cure so appropriate measures must be taken to inhibit the breeding of mosquito population and prevent human beings from mosquito bite. These measures include-

- Avoid stagnant water which are the places of Anopheles mosquito breeding
- Larvae of mosquitoes are also killed by methoprene which behaves as a hormone interfering with the growth and development of the insect.
- Use insecticides
- Use mosquito repellants
- Use window screens
- Use bed nets

3.2.Treatment of patient with Antimalarial drugs

Antimalarial drugs are used to treat and cure malarial infection. Antimalarial drugs target at-

- Liver stage- Few drugs target at liver stage of malarial infection. Example-Decoquinate.
- Erythrocytic stage- Most of the antimalarial drugs target at erythrocytic stage of malarial infection. Examples- Chloroquine, antifolates.

3.2.1. Structure of Antimalarial Drug: An antimalarial drug has a chemical group which is a peroxide group or any other related group that react with heme's Fe(II).“Head” that has hydrophobic alkyl/aryl groups surrounds the reactive hydrophilic center to protect it when the drug floats inside the body. A “tail” is attached to the reactive "head" of the drug and enhances its activity.

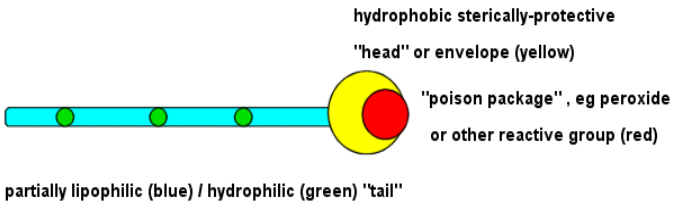
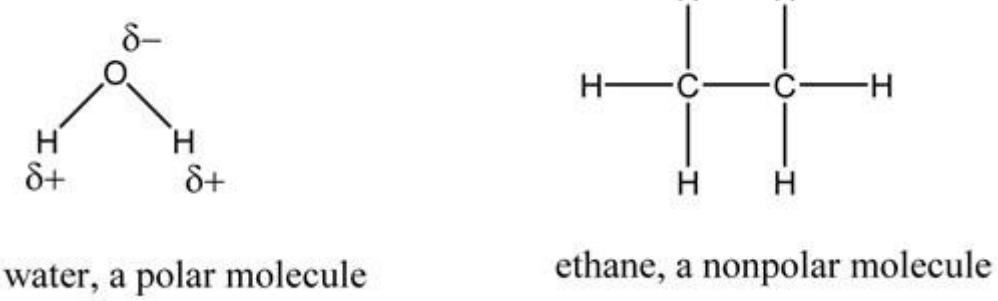


Fig 7. Idealised structure of antimalarial drug [12]

3.2.2. Concept behind designing hydrophilic and hydrophobic ends for a drug: Electronegative elements like nitrogen, oxygen and fluorine have a strong tendency to pull the shared electrons after covalent bonding towards their nucleus, thereby developing a partial negative charge on itself and a partial positive charge on the bonded atom. As shown in the covalent bonding of water molecule, oxygen develops a partial negative charge and hydrogen develops a partial positive charge on itself. So water molecule exists as a polar structure. Hydrogen bonding which is a weak electrostatic linkage, is thus possible in only those structures which contain an electronegative element.



water, a polar molecule ethane, a nonpolar molecule

However, when hydrogen is bonded to carbon, the possibility of hydrogen bonding does not exist because carbon is weakly electronegative and it does not pull the shared electrons towards its nucleus after covalent bonding. Thus, there is equal distribution of charge. So hydrocarbons exist as non polar structures and are therefore incapable of forming weak electrostatic linkages to form hydrogen bonding.

For designing an antimalarial drug, it is therefore required to include an electronegative element like (N,O, F, etc) for creating the hydrophilic ends (water loving) of the drug and incorporate weakly electronegative element like carbon to develop hydrophobic end (water hating) of the drug. Since the drug has to reach the target by passing through the aqueous medium, the reactive part of the drug must be protected from its dissolution in aqueous blood medium. Hence, a hydrophobic (lipophilic) surrounding protects the structural integrity of the reactive part of the drug.

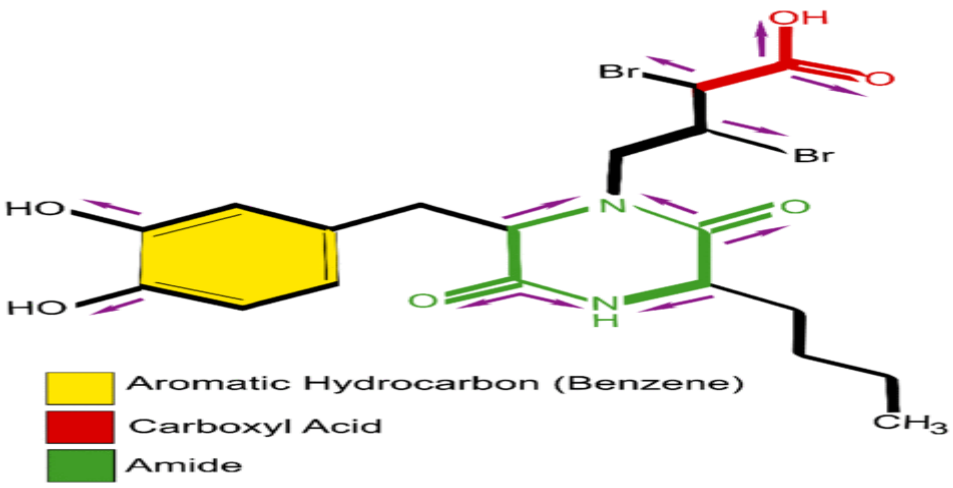


Fig 8. Example of an antimalarial drug specifying its hydrophilic and hydrophobic structure [13]

- Aromatic Hydrocarbons (yellow) non polar in nature.
- Carboxyl Acid (red) Strongly polar in nature (hydrophilic).
- Amides (green) Amides are the derivatives of an acid with ammonia or the derivative of an amine.
- The arrows show the strong polarity of each of the functional group.

3.2.3. Mode of function of peroxide in destroying malarial infection: Peroxides are the common sources of reactive oxygen species (ROS), so antimalarial drugs initiate oxidative stress of malarial parasite and decrease the levels of reduced glutathione (GSH) and antioxidants in the parasite and thus cause the death of malarial parasite.

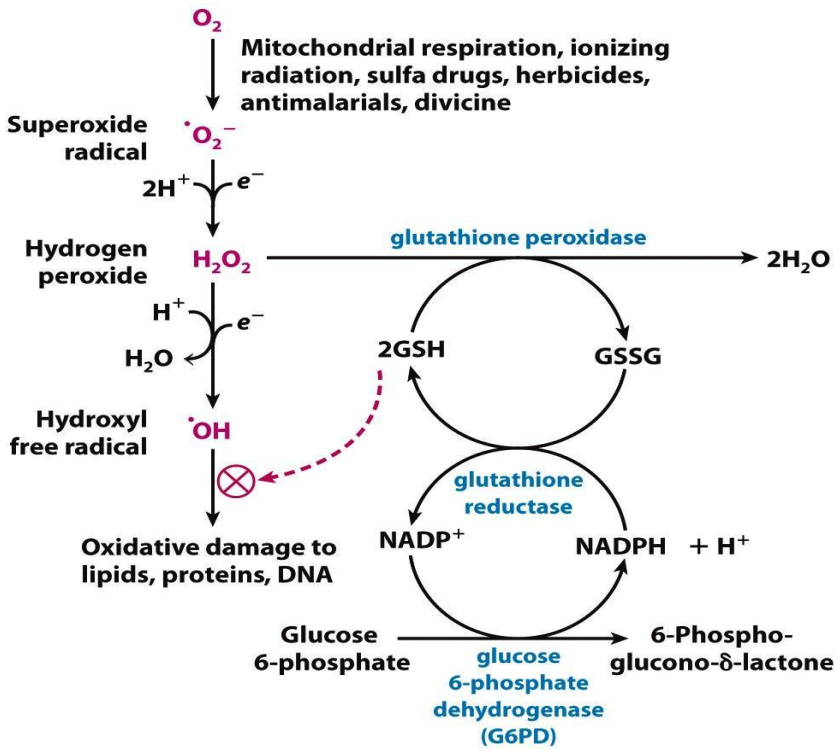


Fig 9. Mode of action of antimalarial drugs [14]

3.2.4. Mode of action of antimalarial drugs: Antimalarial drugs target the glucose 6- phosphate dehydrogenase (G6PD) of *Plasmodium falciparum*. As described in Figure 8,G6PD is an important enzyme in pentose phosphate pathway of carbohydrate metabolism. It plays an important role in scavenging of superoxide radicals. In the absence of this enzyme, NADPH is not formed which inhibits the conversion of oxidized glutathione GSSG into reduced GSH. Hence hydrogen peroxide and hydroxyl free radical are not scavenged in presence of antimalarial drugs leading to the death of the malarial parasite due to the oxidative damage to lipids, proteins, DNA.

IV. FUTURE ASPECTS

Since antimalarial drugs are boon for the infected persons, the development of resistance against most of these drugs become a challenge and require innovation of new drugs free from resistance. ELQ 300 is a drug that is resistance free and has been produced that targets *Plasmodium* at every stages [15].

V. ACKNOWLEDGEMENT

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