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Malaria and its medicines with different targets

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Abstract:

This article will introduce global disease Malaria, introducing its history, distribution, mechanisms, and life cycle of its parasites plasmodium. Two antimalarial medicines will also be introduced in this paper about their histories, chemical properties and mechanisms of action. Finally, a comparison will be shown in the end of the paper.

Keywords:—Malaria, Plasmodium, Artemisinin

1. Introduction

The existence of Malaria on the planet is not only a simple disease but also a witness to human development of science and people's resilience in solving a problem. It is a complicated story showing the improvement of modern medical treatment. The first case that can be proved can be traced back to ancient Egypt. Archaeologists found Malaria antigens in Egyptian remains. In ancient Greece, the intensified Pontine Marshes and agricultural activities incurred new mosquito species from North Africa, which led to more cases. The Chinese medical canon called 'Nei Chin' proposed in 270BC first connected tertian and quartan to enlargement of the spleen (a typical symptom of Malaria). Three devils represent the symptoms of Malaria-a devil with a hammer represents a headache, one with a bucket represents coldness, with a stove represents fever.(Arrow & Peto, 2006) In the next 2000 years, in Europe, Everywhere that has crowded uptown and headwaters experienced serious threat of Malaria. Even in the 20th century, travelers still noticed the feebleness of the local residents and their awful agriculture.(Cartwright & Biddiss, 1991)

The progress on treating Malaria has no apparent improvement until a French military physician working in Algeria named Alphonse Laveran identified parasites in red blood cells are responsible for Malaria in November 1880. Then, in 1897, a British medical doctor Ronald Ross and Giovanni Grassi discovered a parasite of human Malaria in an Anopheles mosquito, solidifying that mosquitoes are transmitters of Malaria. (Beadle & Hoffman, 1993)

Throughout the 20th century, people spent lots of effort trying to eliminate Malaria. The comeout of chloroquine and other antimalarial drugs did help, but the tolerance of plasmodium brought challenges to scientists. To prevent the influence of Malaria, in 1955, WHO launched the Global Malaria Eradication Program aiming to eliminate Malaria. However, the scale and seriousness of Malaria were out of everyone's expectation; the program ultimately failed.

In recent decades, with the advent of ACTs and a series of mosquito control methods. Fewer cases appeared in cities, but in sub-Saharan Africa and Latin America, Malaria still prevailed. Nowadays, people are focusing on vaccine invention and plausible vector control in order to help more people get rid of Malaria.

Malaria is distributed in tropical and subtropical regions. Of an estimated number of about 247 million cases annually, 95% occur in Africa, where it is Malaria-endemic, in places like south-east Asia and the West-Pacific region. Malaria once prevailed in China.

In1970s, China reported 24million cases annually(Beadle & Hoffman, 1993). The turning point took place in 2010 when the Chinese government launched the National Malaria Elimination Programme, and with the introduction of artemisinin-based combination therapies(discovered by Chinese medical scientist Tu Youyou), Malaria cases gradually reduced. Finally, in 2021, WHO certificate China as a Malaria-free country, affirming the achievements China had made to overcome the disease.

The Malaria species in different regions are different. Humans typically infect five different types of plasmodium. (figure 1) Plasmodium falciparum and Plasmodium vivax are the most common and the hardest to cure. They were once vital for people who were infected. (Poespoprodjo et al., 2023)

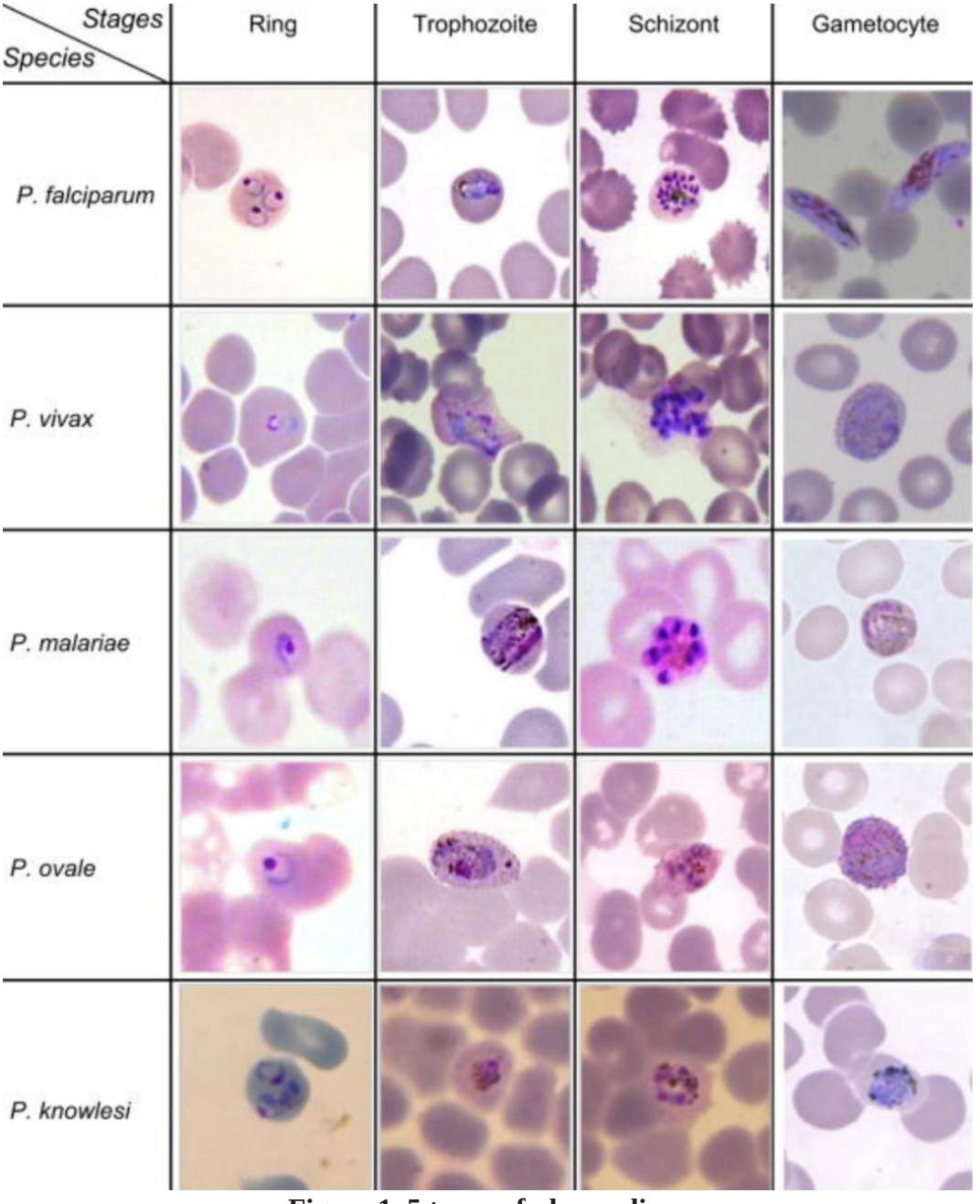

Figure 1. 5 types of plasmodium

In cases in Africa, 99% of them are caused by Plasmodium falciparum; in other regions like South-east Asia, Plasmodium falciparum and Plasmodium vivax are pandemic plasmodium, whereas other plasmodium species only account for 0.5 million cases and most of them are found accidentally. (Figure 2)

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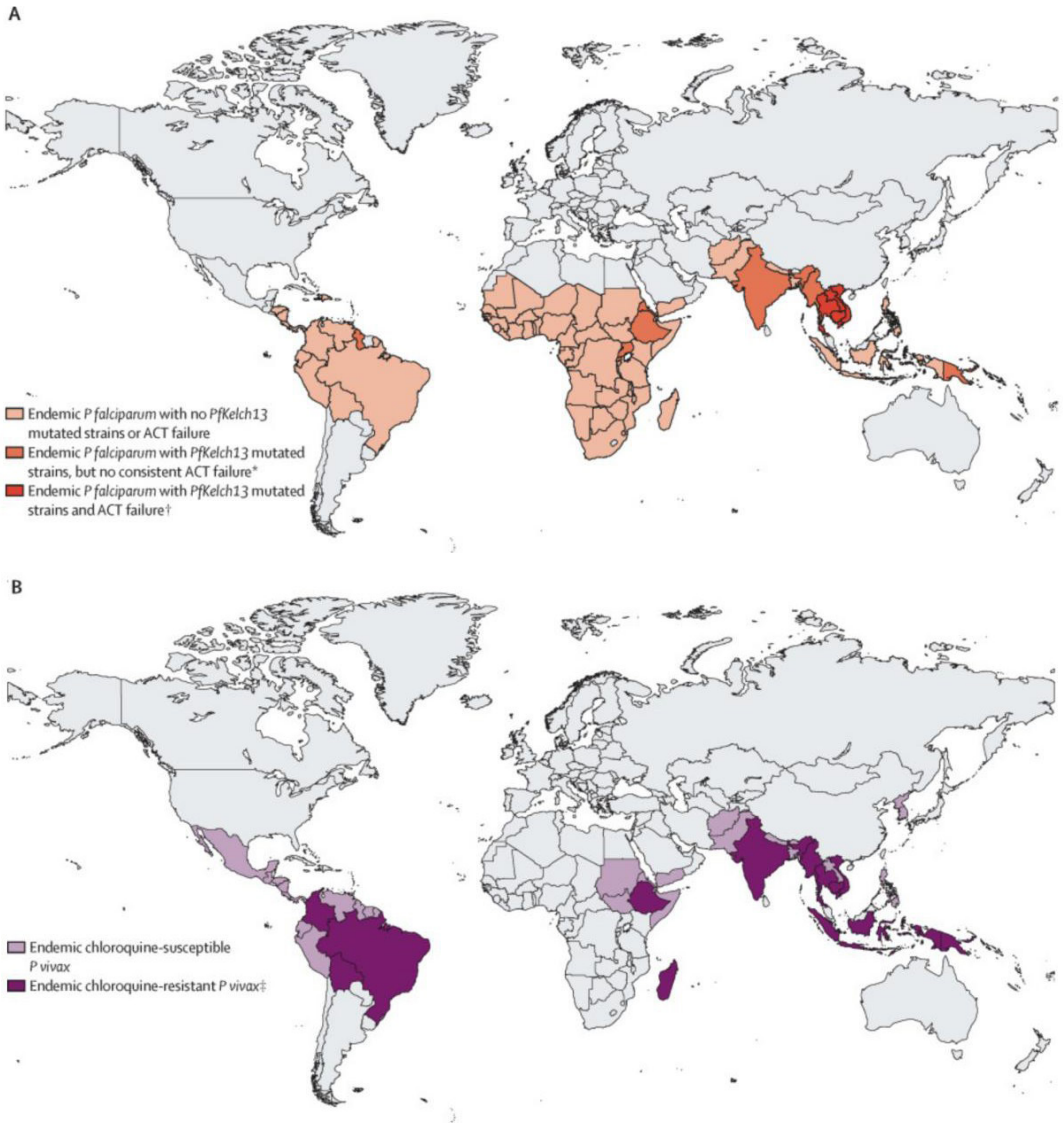

Figure 2. Map of Plasmodium falciparum (A) and Plasmodium vivax (B) endemicity and antimalarial drug resistance

This paper aims to talk about plasmodium falciparum about its causes, mechanisms, effects, and so on. Also, introducing two drugs that have different targets but both can effectually help infected people with their mode of action, their history, and their limitations.

2. Malaria

2.1 Plasmodium lifecycle

Malaria is caused by plasmodium, as we know, but how do plasmodium actually enter and grow in order to affect human bodies? The whole process can be divided into several stages for the plasmodium to mature. It starts when a female Anopheles mosquito bites a human, injecting Plasmodium sporozoites into the bloodstream. The sporozoites will quickly invade the liver and occupy the liver cells. In this stage, there's no typical symptoms, which lasts about 1-2 weeks. In the liver stage, the sporozoites that parasitize in liver cell will change into schizonts that contain thousands of merozites. When the liver cells are broken, the merozoites will be released into the bloodstream. Some plasmodium species like P. vivax and P. ovale, the sporozoites can hide in liver cells for weeks, months even years. That may lead to the recurrence of Malaria. The reasons for sporozoites to mature in liver cells are interesting as well. The liver is a relatively safe place for the sporozoites to grow since liver cells have no defence system and the immune system usually will not immediately find parasites and destroy them(Sixpence et al., 2020). In addition, metabolism is frequent in liver, providing ample nutrition for the sporozoites, supporting

their growth and replication. So the choice of sporozoites is a result of evolutionary adaptation.

After the merozites being released into the bloodstream, The merozites will intrude Red Blood Cells (RBC) where they transform into ring-stage trophozoites. The trophozoites will consume hemoglobin in the RBCs to grow bigger. During this process, the trophozoites will metabolize hemoglobin to transfer into amino acids, which is a complicated process. Once the parasites enter the RBC, they engulf parts of the cytoplasm, forming digestive vacuoles to concentrate hemoglobin. Then, the hemoglobin is resolved by proteolytic enzymes, which are primarily proteases, cysteine proteases, and metalloproteases (Musyoka et al., 2019). They sequentially cleave the hemoglobin into peptide fragments and eventually into free amino acids that is needed by parasites. Once the parasites achieve adequate nutrition from degraded amino acids, they undergoes a nuclei division to form schizont. During this stage, the parasite has already occupied 75% of the space of RBC until the schizont ruptures along with RBC and releases 16-32 new schizont to repeat this action again. That is the reason for anemia and fever of Malaria patients. Especially for the Plasmodium falciparum, they will modify the host's RBC by exporting proteins like PfEMP1 (figure 3) that enable RBC to adhere to the blood vessels, which will prevent blood from flowing to the brain, causing serious neurological symptoms.

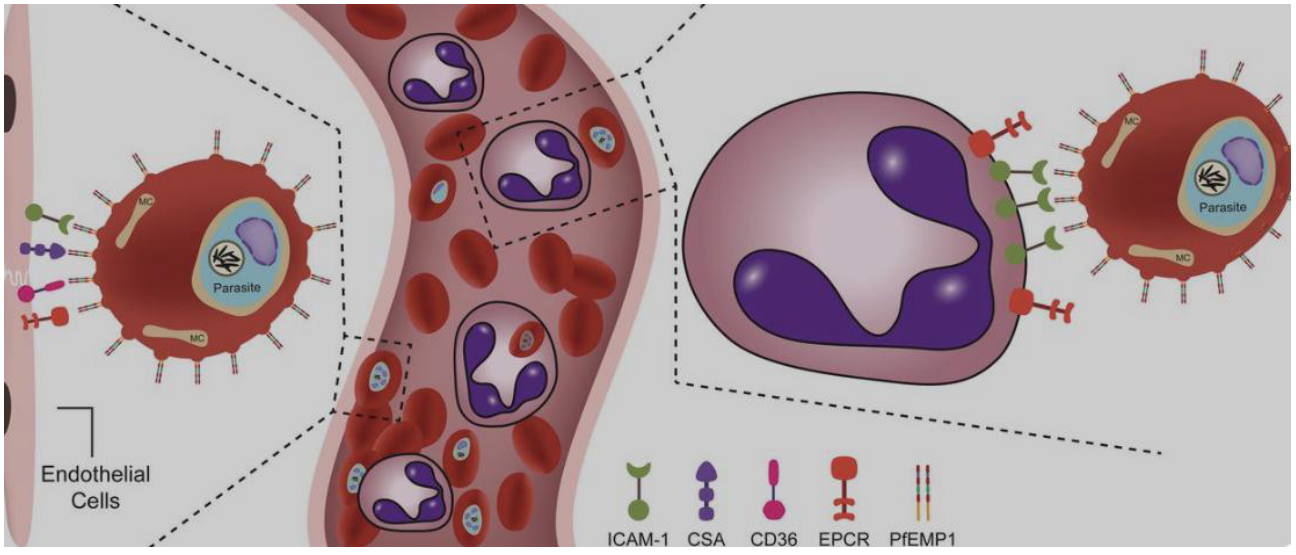

Figure 3. PfEMP1 does to the RBC

After that, some merozoites grow into gametocytes, which are the sexual forms. The bone marrow is the prime place for the sexual stage. The gametocytes will enter circulation in 9-12 days. When another mosquito bites the person that has gametocytes in the bloodstream, the gametocytes will mature in the mosquito's gut, which divides the male and female gametes and finally develops into ookinetes. The ookinetes gather to form oocysts that produce sporozoites. At last, the sporozoites move to the salivary glands of the mosquito, starting a new round of infection.

2.2 Malaria in pregnancy

Malaria in pregnancy is fatal to both the mother and the fetus. Since the disease may cause anemia, Malaria is life-threatening to maternity. According to Poespoprodjo et al., in sub-Saharan regions, Plasmodium falciparum is a key factor of 75 000–200 000 infant deaths (2023). Also, the plasmodium will affect the infant's health, triggering low birthweight, small for gestational age, or even stillbirth. Therefore, the attention on pregnant women should be more in order to ensure the health of both the mother and the fetus.

3. Medicines

3.1 Artemisinin

Artemisin is a strong antimalarial drug that can kill 90% of the plasmodium of the host within 24 hours. The discovery of Artemisinin is attributed to Chinese medical the winner of the 2015 Nobel Prize Youyou. In the 1960s, North Vietnam soldiers were plagued by Malaria during the Vietnam War. Many of the soldiers died before they went to the battlefield. Chinese premier Zhou Enlai then launched a '523 program' aiming to find new antimalarial drugs. When choosing ingredients, Tu Youyou and her team decided to use indigenous herbs called Artemisia annua L. In Ben Cao Gang Mu written by Li Shizhen, it mentions that it can mitigate the fever of Malaria. And

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after several experiments on mice and monkeys, it was proven to be 100% cured against parasitemia in 1971(Ma et al., 2020). She and her team's achievements have saved millions of lives in the past decade.

Artemisinin has a sesquiterpene lactone structure with an endoperoxide bridge. It is crucial for the activity of Artemisinin. (figure 4)

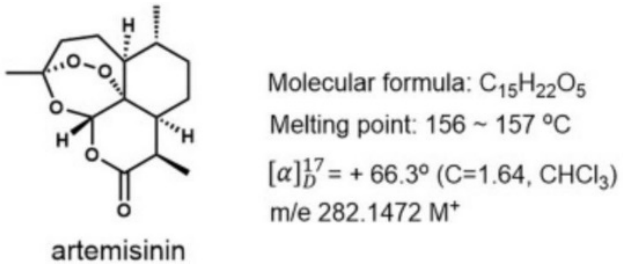

Figure 4. Chemical structure of artemisinin

Besides, the molecule has a three-dimensional configuration due to its several chiral centers. The methods used to determine the structure of Artemisinin are primarily X-Ray Crystallography (Woodley et al., 2021). The X-Ray will be directedly exposed to the crystal of the substance. By analyzing the diffraction pattern to exactly know the atoms involved in Artemisinin. This is especially important for investing synthesizing artemisinin derivatives and developing artemisinin-based combination therapies.

When Artemisinin comes to the bodies, it will invade infected RBC by the parasites. As I mentioned in the previous paragraph, parasites will digest hemoglobin and release heme which is a byproduct. The endoperoxide bridge in the artemisinin can react with heme, cleaving the endoperoxide bridge and creating reactive oxygen species (ROS) and carbon-centered free radicals. These two are highly reactive and cause damage to the cells of parasites. This oxidative stress changes the proteins and lipids within the cell so that the cells are disrupted. Specifically, When reactive oxygen species (ROS) and carbon-centered radicals are produced, they will interact with proteins, leading to oxidative modifications, including carbonylation, nitrosylation, and the formation of disulfide bonds(Wicht et al., 2020). After all, the structure and function of the original proteins have been changed. The oxidative damage of proteins may induce degradation, misfolding, and aggregation since proteins are critical for enzyme activity, structural integrity, and signaling pathways. The oxidative stress also impairs parasites' mitochondrial function, which can impede their energy production. Apart from that, artemisinin restrains the conversion of toxic heme into hemozoin from parasites' activities. When parasites resolve hemoglobin, hemoglobin will produce reactive oxygen species, which is toxic to parasites(Mishra & Das, 2008). Therefore, they have to find a way to detoxify. Artemisinin disrupts the cells of proteins, interfering with this detoxification process and contributing to the deaths of parasites. Artemisinin is effectual to many stages of plasmodium including asexual blood stages, gametocytes (the sexual forms responsible for transmission), and early ring stages. This can rapidly eliminate the parasites in blood cells so as not to infect other people. To prevent the resilience of parasites, ACTs is used widely by all over the world, which means a combination of artemisinin and other antimalarial medicines. This can make sure that all of the parasites in the host are eliminated so that the probability of resilience will decrease. Till now, this therapy is still the most effective way of treating malaria.

3.2 Chloroquine

Another drug that can cure Malaria is chloroquine. The history of chloroquine can be traced to the 17th century when Spanish adventurers learned the function of cinchona bark from South American natives that can cure fever. German scientists first synthesized chloroquine in 1934, but it was not until the American scientists studied Sontochin captured in the war they found a tight correlation between chloroquine and Sontochin. Conducting several experiments afterward, chloroquine was eventually proved to be one of the antimalarial medicines(Hemingway, 2019). In 20th century, chloroquine was widely used due to its cheap price and helpful effect, becoming one of the prime antimalarial drugs.(Meshnick & Dobson, 2003)

Chloroquine is a 4-aminoquinoline compound, including a quinoline core with a chlorine atom at the 7-position and a diethylaminoethyl side chain at the 4-position(Figure 5). The molecular formula is C18H26ClN3. Chloroquine can store in the red blood cells of liver, spleen and kidneys. Besides, This compound is lipophilic, making it easily combine with plasma proteins. It primarily goes through N-dealkylation by cytochrome P450 enzyme in the liver, to form active metabolites.(Vincent et al., 2005).

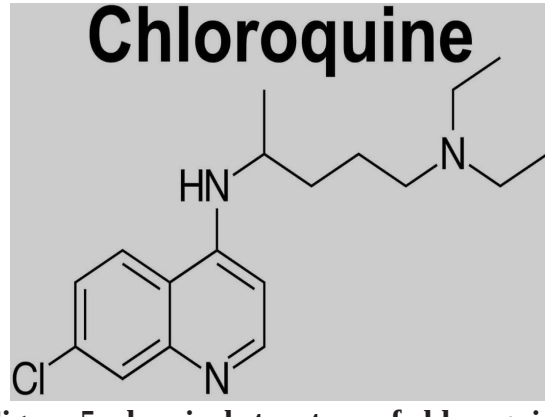

Figure 5. chemical structure of chloroquine

Similar to artemisinin, chloroquine can combine with

free heme, preventing it to converse to hemozoin. In turn, the free heme will generate the ROS that can cause harm to the parasites' cells. Eventually, the parasites' cells' membranes will break down, leading to the death of the parasites. Therefore, chloroquine targets the red blood cell stage of parasites, preventing plasmodium from breeding and infecting other people. Additionally, according to research also found that chloroquine can also interfere with the DNA process of parasites.

Chloroquine can intercalate into a parasite's DNA, particularly between the base pairs of the parasite's DNA strands. That will disrupt the normal unwinding and separation of the DNA strands by physically damaging the DNA structure. While the parasites are going to replica, they have to duplicate their DNA to their daughter cells. Since chloroquine has already distorted the DNA structure, the parasites' ability to multiply will be reduced. (Płusa et al., 2020)

Even though the chloroquine is useful, it still can not completely deal with Plasmodium falciparum and its drug-resistant strains. So humans have to learn more about the mechanisms of chloroquine to overcome the situation.

3.3 Comparison

Chloroquine primarily interferes with heme detoxification within the parasite's food vacuole in the asexual blood stage of plasmodium, causing oxidative damage to the parasite's cellular structures. On the other hand, when artemisinin encounters iron in the parasite, its endoperoxide bridge will cleave(Oke & Mugweru, 2021), producing free radicals that will destroy the proteins and lipids within the parasites. Artemisinin especially targets the asexual blood cycle and also has some activity against sexual forms. Chloroquine was once used for the first-line treatment of Malaria due to its cheap price, but the emergence of chloroquine-resistant strains of Plasmodium falciparum caused the mutation of the parasite's chloroquine resistance transporter (PfCRT) so that chloroquine accumulated in the food vacuole will reduce, diminishing its curative effect(Pulcini et al., 2015). Compared to the uncertainties of chloroquine, artemisinin, along with ACTs, is well established. it is highly effective even against chloroquine-resistant strains of Plasmodium falciparum. So, the ACT is still widespread in the world.

4. Conclusion

Malaria still prevails in the world, afflicting millions of people each year. Fortunately, Many antimalarial drugs have been invented, like artemisinin and chloroquine, that have saved countless lives. However, the plasmodium's drug resilience capacity is also increasing, which means scientists have to make more efforts on antimalarial studies.

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