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Preface

Malaria remains one of the deadliest infectious diseases globally, with *Plasmodium falciparum* being the most lethal of its causative agents. Despite significant advances in medical research and healthcare, the adaptation and resistance mechanisms of this parasite have continuously thwarted efforts to control the disease effectively. This book delves into the intricacies of the parasite's life cycle, its interaction with host mechanisms, and the evolving challenge of antimalarial drug resistance.

Each chapter in this book explores the critical aspects of malaria, from the basic biology of the parasite to the latest advancements in therapeutic interventions and drug resistance mechanisms. This book begins with an overview of malaria, its health impact, and the biological underpinnings of the Plasmodium species. Subsequent chapters delve into the pathogenesis of Plasmodium falciparum, detailing its mechanisms of host cell invasion, immune evasion, survival strategies, and identifying potential drug targets throughout its life cycle, highlighting crucial points for therapeutic intervention.

The discussion then advances to the development and challenges of antimalarial drugs. It examines the historical and current landscape of antimalarial treatments, the emergence of drug resistance, and the ongoing research into overcoming the resistance through innovative drug design and novel therapeutic targets. Special attention is given to metabolic pathways and enzyme targets within the parasite, highlighting recent discoveries.

Furthermore, this book addresses the critical role of novel drug delivery systems in enhancing the efficacy and specificity of antimalarial drugs. It also explores the potential of natural products and traditional medicine as complementary strategies in malaria treatment, which is particularly pertinent given the geographical overlap between malaria prevalence and traditional medicinal practices.

Delhi, India — Mohammed Tarique

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About the Author

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Introduction: An Overview of Malaria and Plasmodium

1

1.1 Introduction

1.1.1 The Struggle of Human Beings Against Malaria, Both in the Past and in the Present

Since ancient times, people have known that malaria is a major health risk. Plasmodium parasites are the causative agents of this illness—according to UNICEF (2023), WHO (2021), and the World Health Organization (2022). Human populations in malaria-endemic areas have likely evolved and been selected for some distinctive genetic variants due to the severe negative pressure of the disease. Malaria-resistant individuals have a genetic problem; especially those with thalassemia or sickle-cell disease, both of which have impaired RBCs found commonly in malaria-endemic prone regions. The people from Africa were found to have Duffy-negative blood type—this is another distinct difference of individuals from malaria prone regions (World Health Organization 2022). This provides a sort of protection especially against *Plasmodium vivax* infection. It was found that *P. vivax* malaria is uncommon; while *P. falciparum* malaria is most widespread in malaria epidemic areas. It is believed that the dissemination of this resistant trait in the population began roughly 42,000 years ago, even though effective antimalarial drugs and insecticide-treated bed nets (ITNs) have been developed in recent decades. Despite advances, large populations remain at risk due to the widespread prevalence of malaria. Still, huge populations live in danger because of the prevalence of malaria (Abdi et al. 2017). It is especially found in under developed and economically poor countries such as Africa, where *P. falciparum* is prevalent and causes huge mortality (Antinori et al. 2021).

Furthermore, worldwide, it has been challenging to roll out comprehensive and continuous programming to effectively control and develop awareness about malaria due to a shortage of funding (Arevalo-Herrera et al. 2014). In this context, during the year 2000, the United Nations decided and implemented worldwide program on

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health initiative to especially to "com-bat malaria" that was a crucial global target for the Millennium Development Goals. The goal of this international campaign was to reduce the disease burden, mortality rates, and ensure that all children under the age of five had access to ITNs and effective antimalarial drugs to prevent malaria (Arevalo-Herrera et al. 2022). National Malaria Control Programmes (NMCPs) contributed the majority of the projects of worth $960 million that spent worldwide on malaria prevention in 2005 (Bachmann et al. 2019). For malaria control the investments from other sources have been raised rapidly since 2006, while NMCP contributions have stayed flat. As a result, total global investment topped $2 billion in 2009 and has stayed relatively constant since then. Malaria prevention and treatment programs around the world have advanced significantly because of these additional funds and in 2000, it was projected that malaria was responsible for 839,000 deaths worldwide (between 653,000 and 1.1 million) and 694,000 deaths in Africa (between 569,000 and 901,000) (Bachmann et al. 2019). By 2015, these figures had dropped to 483; and there were an estimated 33 countries with fewer than 1,000 cases of indigenous malaria; additionally, six countries eliminated indigenous malaria cases for at least three consecutive years between 2000 and 2015, earning them WHO certification as malaria-free (Baer et al. 2007).

It was found that the life cycle of all Plasmodium species infecting human starts from liver and continues with rapid multiplication in the host blood. Similarly, the resistance to antimalarial drugs was also observed due to susceptibility of drugs like quinine, chloroquine, and artemisinin (Baird 2019; Baird 2013). The anopheline mosquitoes were found responsible for the transmission of disease, however, 8-aminoquinolines like primaquine is very effective for prevention of *P. vivax* malaria, in comparison to drugs which eliminate parasites exclusively at the intraerythrocytic (infective stage in RBCs) growth stage. So, systematic control procedures with the right measures in place are essential (Battle et al. 2019). In addition to effective mosquito management, chemotherapy, such as the treatment by primaquine in infected patients with *P. vivax* malaria, was found to reduce total count of malaria cases by any of the Plasmodium species (Beeson et al. 2019).

Malaria in humans is caused by many Plasmodium species, which typically infect hosts other than human beings (Bennett et al. 2016). Pig-tailed macaques from Southeast Asia and long tailed macaques—a **cercopithecine primate** of Southeast Asia were found as natural hosts of Plasmodium parasite, especially *P. knowlesi*. In humans the *P. knowlesi* caused infection since from 1960s, but until recently were considered as an outlier among zoonotic malarias (Burns Jr et al. 2016). But, till late 1990s, and early 2000s, the total count of infected individuals from *P. falciparum* and *P. vivax* from Malaysian regions had declined abruptly, the credit of that went to NMCP implemented in Malaysia during 1960s (Chang et al. 2021). In contrast to this, there appears to have been an increase in the prevalence of *P. malariae* that is otherwise uncommon from Malaysian. The parasites from blood films were examined under the microscope to determine the type of Plasmodium present in Malaysian (Sarawak) patients (Chavatte and Snounou 2021). In Malaysia, the maximum of malaria cases found were caused by *P. malariae*; however it was found by using microscopy, PCR and DNA sequencing that actual

causal organism is *P. knowlesi*. In Human the first ever instances of infection by *P. knowlesi* were first discovered in Sarawak Malaysia and later more cases were discovered from Sabah state and from other peninsular regions of Malaysia. Further, the *P. knowlesi* malaria is ranked at 5th position among all parasites causing human malaria with clear examples from South East Asian especially Vietnam and Thailand (Chi et al. 2021). Also, the gametocyte production by *P. knowlesi* were recovered and proven from individuals infected naturally; however the human tot human transmission of parasite (*P. knowlesi*) were not yet confirmed. Due to the hard work of NMCP all Plasmodium species causing disease in human from Malaysia had got eradicated, however, the infection *P. knowlesi* malaria had remained significant in that country (Childs and Buckee 2015). The most dominant cause of malaria in Malaysia is *P. knowlesi* and zoonotic risks from disease caused by this pathogen has remained constant infecting primates were examined thoroughly by scientists. In Malayia almost six Plasmodium species such as *P. knowlesi*, *P. inui*, *P. cynomolgi*, *P. coatneyi*, *P. fieldi*, and *P. simiovale* were recorded from macaques of Sarawak, and natural infection from *P. cynomolgi* were recorded too. Even though *P. cynomolgi* and *P. inui* seldom exhibited clinical cases of zoonotic malaria, but they have a strong potential to emerge next infection cause of malaria that can impact human being to significant level (Clyde et al. 1973; Collins et al. 2020).

1.2 Life Cycle of *Plasmodium*

The life cycles of all Plasmodium species were remarkably similar, with two distinct stages of infections (Cox 2010; Dejon-Agobe et al. 2019). At first stage the parasite attacks the human or other vertebrate host (primates); while at second stage the insect vector carries the infection across different hosts. Anopheles mosquitoes are the primary vectors for the transmission of the all five human-infecting Plasmodium species. Other mammalian Plasmodium species are likewise transmitted by the same mosquitoes, but birds and reptiles require insects from a different genus or subfamily of Plasmodium (Di Santo and Apetrei 2017). Parasites called sporozoites develop in the anopheles mosquito who work as insect vector and make an entry into blood of host while it bite. The infection causing sporozoites get deposited in the skin, which later make a quick entry into liver of host. In liver the parasite cause infection of hepatocytes and later proliferate into millions through a process known as schizogony (Dudley et al. 2019). The merozoites infect RBCs once in circulation and each merozoite produce about 8–64 additional merozoites via asexual schizogony occurring in RBCs. At intervals of 24, 48, and 72 hours, the parasites *P. knowlesi*, *P. falciparum*, *P. ovale*, *P. vivax*, and *P. malariae*, respectively, produce and release new merozoites into the bloodstream, initiating a new cycle of infection (Enserink 2019; Evans et al. 2015). Merozoites progress to the gametocyte stage of development, used for sexual reproduction; and differentiation of gametocytes (gametocytogenesis) is species-specific character (Flanagan et al. 2017). However, *P. vivax* make new gametocytes at the initial stage of intraerythrocytic propagation cycles; which is unlike to *P. falciparum* that first complete its cycles of

multiplication and intraerythrocytic propagation before it begins differentiating into gametocytes (Galinski and Barnwell 2012). While all gametocytes are alike during first glance, they are genetically programed to eventually grow into either of sex gametes (gametogenesis, sexual commitment). This concludes the phase of the Plasmodium life cycle from human host (Galinski et al. 2018). After full development of infection from blood meal, both male and female gametes merge in the mosquito midgut lumen, allowing for further development into sever form of malaria. Rarely, however, the male gametes which are of exflagellated form from *P. falciparum* have been reported inside the human body; and by entry of gametocyte-rich blood from an infected vertebrate host, the insect vector enters the next phase of its life cycle (Garrido-Cardenas et al. 2019). After being subjected to the proper stimuli from receptors of blood, the next phases of gametocytes become active and infection progress and symptoms appear (Galinski et al. 2013) (Fig. 1.1, Table 1.1).

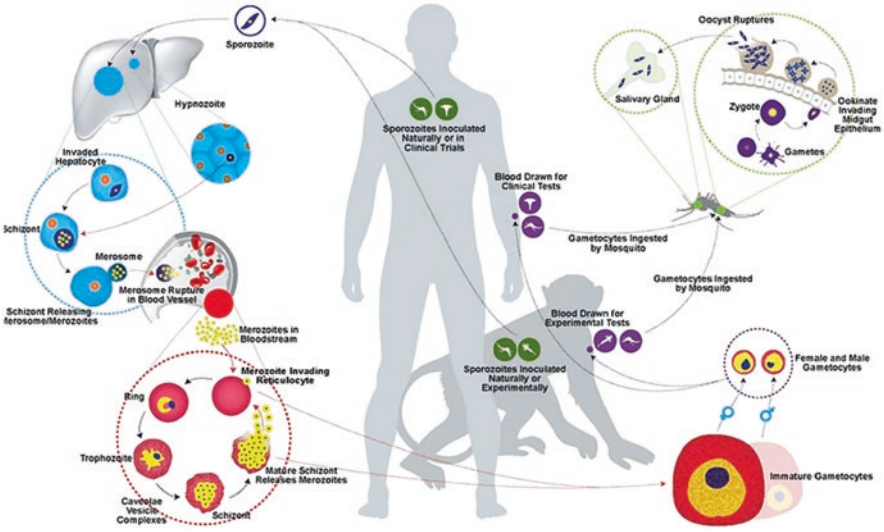

Fig. 1.1 Figure illustrates the distinct biological properties of Plasmodium species (monkey malaria), throughout the life cycle of monkey malaria species and the necessity of clinical and experimental therapies. Here we show a schematic illustrating the life cycle of *Plasmodium vivax* and related sibling simian species. The purple and green icons represent potential sites for natural occurrences and manipulated experiments, respectively. Green mosquitoes represent sporozoite inoculation through biting, whereas the purple mosquitoes represent both biting and natural inoculation. Mosquitoes of the genus Anopheles spread the disease by sucking blood with contaminated gametocytes. The inoculation is represented with a green medical emblem. Transmission of sporozoites into human and non-human primate hosts, respectively, denotes the potential for challenging these hosts following vaccination. The availability of sporozoites for in vitro and in vivo studies of infection: Biological characteristics that set *P. vivax* apart from other similar species caveolae vesicle complexes (CVCs), the hypnozoite, and merozoite invasion of reticulocytes preferentially diseased red blood cells take on a mottled appearance, and gametocytes form and circulate very quickly. Actions are indicated by the red arrows, pertaining to areas where more study is urgently needed. Source: Galinski (2023)

Table 1.1 The beginning of gametocyte production and the reoccurrence of malaria in humans

Causal organisms	Onset of gametocyte production	Recurrence
P. falciparum	Relapse recrudescence. Following the number of cycles of asexual reproduction within the erythrocytic compartment ("gametocytes may make their appearance in small numbers on or about the 10th day following the first day of fever, and their numbers increase rapidly day by day for 2 or 3 weeks)	Unknown (there have been no observations of hypnozoites so far). Known to occur (latent Period usually <2 months, but can be >2 years)
P. vivax	The process begins with initial rounds of intraerythrocytic asexual reproduction. Sexual forms may appear as early as the 6th or 7th day and typically reach their maximum number around the 10th day	It has been shown time and again (the lag period can range from <2 weeks to >1 year and varies systematically by geographic region hypnozoites in liver observed)
P. malariae	The process continues from the earliest stages of intraerythrocytic asexual reproduction. Following a prepatent period ranging from 16 to 59 days, gametocytes emerge in the patient's blood alongside other intraerythrocytic forms	Unknown (hypnozoites have not yet been observed) but known to occur, with a latent period that can extend beyond 40 years
P. ovale	The process continues from early rounds of intraerythrocytic asexual reproduction, with gametocytes appearing in the peripheral blood slightly earlier than in benign tertian malaria	Clinical cases reported molecular evidence for a causal relationship between dormant liver stages and subsequent relapses unavailable hypnozoites not observed yet
P. knowlesi	Unknown (gametocytes identified in some of the naturally infected malaria patients)	Unknown (hypnozoites not observed)

Both microgametes and macrogametes are produced from gametocytes of male and female, respectively, in the mosquito midgut lumen (Grifn et al. 2016). The zygote is the only diploid stage of parasite life cycle which is created when a microgamete fertilizes a macrogamete. The gametocytes from two *P. falciparum* clones include different allelic variations which exhibited recombination that take place at the zygotic stage. After meiosis of the zygote, differentiating into the ookinete takes place, producing a motile stage with four haploid genomes. The ookinete makes its way through the mosquito's midgut wall, emerging from the other side to produce an oocyst. Multiple mitoses occur in the oocyst, and sporogony results in the production of many sporozoites.

The adult oocyst bursts in hemolymph and release huge count of sporozoites which later enter into salivary glands and gain the high virulence potential to infect human cells before being discharged into the body of a vertebrate host (Hanboonkunupakarn and White 2020). The 2nd stage of life cycle commencing from gametocytes to sporozoites are very much ready to infect the next human host for completion of next 2–3 weeks of (13–21 days) of life cycle in human beings. Plasmodium cells have two distinct organelles, the mitochondrion and the

apicoplast, each of which contains its own genomic DNA in addition to the nucleus. It has been found experimentally that the mitochondrial genomic DNA of *P. falciparum* is passed on to each developing oocyst in the mosquito from the female gamete in a process called uniparental inheritance. *P. gallinaceum* is a species that infects hens, and a further investigation showed that genetic material from both organelles were found female gametes only. In other words, macrogamete which is a female gamete is capable enough to pass on to apicoplast as well as to mitochondrion of Plasmodium species (Hang et al. 2021).

1.3 Recurrence of Malaria and the Hypnozoite

Plasmodium species reappear in patients infected with malaria disease, and even after the disease has been treated. Either a recrudescence or a relapse can cause a recurrence; however, the relapse is caused by hidden, latent cells called as hypnozoites which remain in liver of patent. The recrudescence is caused by a small count or parasite load of parasites that remained undiscovered in the blood. Only sporozoites can differentiate into hypnozoites; merozoites, another type of the parasite found in the bloodstream (Jakeman et al. 1999). Antimalarial drugs like chloroquine or quinine can clear the blood of the parasites while as parasite *P. vivax* were found to make a dominant but very infectious form called hypnozoites that cause relapses and recurrence; and in this context study found that parasite genotype is different at initial relapse stage compared to the acute episode that came before it. Possible explanations of this finding include the following: infection with *P. vivax* sporozoites from more than one genotype; differentiation of sporozoites into hypnozoites in the liver; and relapse and recurrence caused by a single hypnozoite. Although the mechanism is unclear, but it has been hypothesized that exposure to other illnesses, such as *P. falciparum malaria*, can trigger a recurrence of *P. vivax malaria*. For instances, the recurrence of conditions after first infection and no susceptibility to second infection by species *P. ovale* were assumed to produce a dominant parasite hypnozoite (Chen et al. 2014). This is unlike to other human malaria parasites. It was found that hypnozoites from the liver has recently called this query into question. Although hypnozoites are thought to formed by *P. falciparum* and have never been seen to form in *P. malariae*; however, these species are enough capable to induce a chronic infection without causing any symptoms to appear for a very long time. A *P. falciparum* infection were found to have a lain dormant in a human host for an additional 13 years while as *P. malariae* infection due to blood donation of donor is likely to contract the disease more than 40 years ago (Chew et al. 2022).

The development rate of Plasmodium parasites and immunity from susceptible host are in a delicate balance, and the parasites remain in human blood for extended long time at love quantity.

Disruption of the equilibrium is thought to mark the start of the recurrence (recrudescence) and there is compelling indication that hypnozoites induce relapses in *P. vivax malaria.* In human malaria non-hypnozoite cells were responsible for some relapses (Jao et al. 2020). Furthermore, it was found that some neurosyphilis

patients (brain and spinal cord infection) received blood of *P. vivax* malaria patient for malariotherapy (malaria inoculation) were found a return of parasitemia. No hypnozoite could have formed in the receivers as parasite species *P. vivax* did not survive in the sporozoite form in human blood; however, research showed that *P. vivax* malaria can recur in the absence of hypnozoites (Kavanaugh et al. 2021).

1.4 Gametocytes

Plasmodium cells from all susceptible vertebrate hosts exist in the form of haploid genome genetic status throughout their development. In the vertebrate host, the gametocytes are produced by a cloned line of Plasmodium that is originated from a single cell, and literature showed that sex of Plasmodium gametocytes is decided epi-genetically rather than chromosomally. It appears that environmental influences impacts the sex ratio of gametocytes that improve the efficiency of parasite transmission (Kitchen 1938). Antimalarial drugs which target parasites during their asexual intraerythrocytic development, including artemisinin and chloroquine, which are ineffective against gametocytes from human Plasmodium species. However, it was found that 8- aminoquinolines especially primaquine are effective against gametocytes; therefore the transfer of gametocytes in the blood might cause malaria in other people even after the parasites in their asexual intraerythrocytic growth cycle; was eradicated by therapy made by use of antimalarial drugs (Kraft et al. 2019). The asexual blood stage parasites have been eliminated with drug treatment, such as artemisinin-combination therapy. The gametocytes of *P. falciparum* have been known to survive for weeks; and gametocytes with 50% survival rate from 2.6 to 6.5 days, and signs of survival were found visible for about 2 months after initial infection. Multiple factors, including the type of treatment, execution, and host immunity influence how quickly gametocytes are cleared from the body and how quickly gametocyte infectivity declines (Lefebvre and Harty 2020). Similar to patients with malaria symptoms, the asymptomatic infections have a substantial count of gametocytes circulating in blood. Therefore, asymptomatic Plasmodium carriers get gametocytocidal treatment alongside symptomatic malaria patients in order to stop the spread of the parasite (Loiseau et al. 2020).

1.5 Asymptomatic Carriers

Many people in malaria-endemic regions have Plasmodium parasites in their bodies without being ill from infections (Mallapaty et al. 2021). Microscopy and rapid detection tests (RDTs) were used for malaria infected individuals for determining infections in body in the form of presence of parasites. However, the ultrasensitive versions of RDTs and molecular analysis for detection using PCR and LAMP were found efficient for infection detection (Malleret et al. 2015). It was found that when total count of gametocytes from blood is less, the possible infection transfer of asymptomatic type of malaria in the community is modest or nonexistent. Moving

to a malaria-free environment, where they will not be exposed to fresh Plasmodium infections to maintain immunity, is one example of how carrier of asymptomatic type acquire an episode of malaria in humans (Martinelli and Culleton 2018). Thus, asymptomatic carriers may contribute to the spread of malaria in other countries. They can spread malaria through blood transfusions or organ transplants even if the recipient has never had malaria before. Today, more than ever, it is crucial to eliminate asymptomatic malaria parasite carriers. It is mainly because technological and economic advancements have made travel considerably more convenient for people than in the past. More people are fleeing their homes due to various conflicts and most of them reside in malaria hotspots. To stop the spread, and reintroduction of disease into safer areas, it is important to identify carrier of asymptomatic type from all migrants from endemic and infected areas; which provide them with the same level of care as patients with clear malaria symptoms (McCarthy et al. 2013).

1.6 Apicoplast and Plant-Like Metabolism

The superfamily Alveolata includes dinoflagellates and ciliates, while members of the genus Plasmodium, which are classified as protozoans, are all obligate parasites (Milne et al. 2021; Minassian et al. 2021). Many are apicomplexan species, including Plasmodium itself. The Plasmodium is a non-photosynthetic plastid containing organism containing apicoplast in their cells. Apicoplast is the smallest known plastid genome and is a secondary plastid surrounded by four layers of membrane with many species having photosynthetic plastid (Mo et al. 2020). These newly discovered species known as chromerids are able to grow via photosynthesis rather than by parasitizing other organisms. Like all photoautotrophic alveolates, chromerid plastids also possess chlorophyll a, however, they are deficient in chlorophyll c. Similar to the apicoplast, chromerid photosynthetic plastids are secondary plastids whose genome composition reveals similarities to apicomplexan plastids, suggesting evolution from a common ancestor (Moormann et al. 2019). Unlike plant plastids, the apicoplast lacks photosynthesis and the tiny organelle DNA is thought to be responsible for transcription and translation (Moormann 2009).

At the discovery of plastid from Plasmodium, it was unclear why parasitic apicomplexans Plasmodium contain a non-photosynthetic plastid. However, got later clear that the Plasmodium apicoplast participates in plant-type metabolic pathways (Mueller et al. 2013). The important pathways are comprised of isoprenoid biosynthesis, type II fatty acid biosynthesis, and haem biosynthesis; further, more and more genetic information encoded in parasites nuclear genome has become available making Plasmodium an important organism (Muller et al. 2020). It has been hypothesized that Plasmodium relies on apicoplast and on various other biosynthetic pathways comprised of apicoplast in order to mature, particularly in dipteran insects such as mosquitoes and in the liver where organism complete maximum part of life cycle. It is demonstrated that Plasmodium in the intraerythrocytic cycle in vitro culture lost the apicoplast. For media culturing the sufficient amount of isopentenyl pyrophosphate (IPP) is given, indicating that apicoplast is not necessary

for the parasites at this stage other than for the production of IPP (Naung et al. 2022). Plasmodium requires IPP for survival which is synthesized exclusively via the plant-type methylerythritol phosphate (MEP) route in apicoplast (Neal et al. 2022).

The growth of parasite (*P. falciparum*) were found suppressed through fosmidomycin both in vitro and in vivo (Nelson et al. 2020). The fosmidomycin is known as a selective inhibitor of 1-deoxy-D-xylulose-5-phosphate reductoi-somerase (DXR). The DXR enzyme is an important component involved in the MEP pathway; however, *Toxoplasma gondii* also rely on IPP from apicoplast is not significantly inhibited by fosmidomycin. Studies into cellular mechanisms underlying *T. gondii* resistance to fosmidomycin have pointed inadequate ability of parasite to take up the drugs through its plasma membrane. According to another study it was found that *P. falciparum* induces a novel permeability channel responsible for absorption of fosmidomycin by infected erythrocyte (RBCs) (Niemuth et al. 2021). It was found that Plasmodium have potential to developed resistance to fosmidomycin using mutation in unanticipated genes (Njue et al. 2018). The apicoplast is not present in all apicomplexans, also apicomplexan species that lack the apicoplast typically lack all the genes designating the enzymes needed for plant-like metabolism of the apicoplast in lower organism. Enzymes from organelle encoded in the nuclear genome, compared to apicomplexans having an apicoplast. Further the genetic information from Cryptosporidium species are encoded with an exceptionally huge count of putative amino acid transporters intracellularly. Without an apicoplast, the organisms must acquire the compounds normally synthesized by apicomplexans from their hosts (Obaldia 3rd et al. 2018).

1.7 Antimalarial Drugs and Resistance

Malaria has been treated with plant-based metabolites/medicines since ancient times. In South American the quinaquina trees (*Cinchona* spp.) having red bark, native of Andes, were found to have an antimalarial chemical component in its red bark, that was found first time during seventeenth century (Obiero et al. 2019). Since then, quinine has been employed in the therapy of malaria, and biochemical synthesis of pure compounds with antimalarial activity began in the 19th century. By the end of 1930s, an antimalarial compound like chloroquine were ready for use in clinical practice (Pasini and Kocken 2020). The Artemisinin is a natural chemical obtained from plants were used traditionally in China and is effective against malaria which was found during 1972.

Clinically effective antimalarial medicines can be categorized into five groups according to their molecular structure and mechanism of action. These include (1) endoperoxides, such as artemisinin and its closely associated compounds such as 4-aminoquinolines (a precursor for synthesis of various compounds), such as chloroquine (effective against malaria, rheumatoid and lupus erythematosus); (3) antifolates, especially pyrimethamine (effective against **toxoplasmosis** and **cystoisosporiasis),** proguanil (prevents malaria), and sulfadoxine (prevents malaria