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Abstract

A fact which favors the increase in morbidity and mortality of malaria cases in the world is the resistance to chemotherapeutic agents that the parasite presents. Therefore, it is necessary to identify new potential targets specific to the parasite in order to be able to perform a rational planning. One target for the evaluation of potential antimalarial compounds is isoprenoid synthesis, which occurs via the 2-C-methyl-d-erythritol-4-phosphate pathway in *Plasmodium falciparum*. Several intermediaries and final products of this pathway were identified in the parasite and lead us to the conclusion that it is different from the vertebrate host. In this chapter, we describe the effect of some monoterpenes and sesquiterpenes on *Plasmodium falciparum* and *Plasmodium berghei* as potential antimalarial drugs.

Keywords: terpenes, malaria, *Plasmodium falciparum*, *Plasmodium berghei*, isoprenoid

1. Introduction

Malaria is one of the major threats to human health, affecting an estimated number of 216 million peoples in 2016 all over the world, leading to 445,000 deaths, mainly in the African continent [1]. The human malaria is caused by six different species of the genus *Plasmodium*, which are *P. falciparum*, *P. vivax*, *P. ovale*, *P. malariae*, *Plasmodium knowlesi* and *P. simium*, where the last one is exclusive to the Brazilian Atlantic Forest [2].
Plasmodium was first described in 1880 by Laveran, who observed it in human erythrocytes. In human Plasmodium genus, the life cycle is very similar between species, being characterized by a sexual phase in vector Anopheles and an asexual phase in the human host that can be divided into liver phase and intraerythrocytic phase [3] (Figure 1).

The cycle begins with the injection of infective sporozoites of salivary glands of Anopheles into the human host bloodstream. Once there, the sporozoites make their way into the liver, where they infect hepatocytes to start the first massive replication, an asexual process, known as exo-erythrocytic schizogony. After 9–16 days, those new-formed merozoites are then released into the bloodstream in hepatocyte-derived vesicles [4], called merosomes, to avoid its capture by Kupffer cell. This liver endures this phase differently across different species which can last an average of 6 days (P. falciparum), 10 days (P. vivax), or 15 days (P. ovale and P. malariae) [5].

In the bloodstream, the merosomes are then disrupted liberating the merozoites, each merozoite infecting a single red blood cell (RBC). The process of invasion is complex, relying on diverse cell machineries, which permit the parasite to attach, reorientate, and invade, forming the parasitophorous vacuole [6]. Once in the erythrocyte, the parasite starts its asexual division, passing through different stages. The early trophozoite, called “ring stage”, starts to develop, enlarging to a mature trophozoite that has a high metabolic index. In the late stage, multiple nuclear divisions

![Figure 1. Malaria parasite life cycle. Schematic life cycle of P. falciparum in the invertebrate (left) and vertebrate hosts (right). 1. Hepatocytes invasion and exo-erythrocytic schizogony to merozoites formation. 2. Release of merosomes in the blood stream. 3. Intraerythrocytic phase. 4. Parasite differentiation to gametocytes which ones could be ingested by invertebrate host. 5. Sexual phase in the midgut of invertebrate host. 6. Migration of sporozoites into salivary glands. 7. Injection of sporozoites during the blood meal.](image-url)
are triggered without cytokinesis, forming schizonts. Each schizont holds an average of 32 merozoites (10 merozoites in average for *P. knowlesi* [7]) that are unleashed upon the RBC lysis. The whole process can take about 36–48 h in *P. falciparum*, 48 h in *P. vivax* and can reach even 72 h in *P. malariae*, but in *P. knowlesi* the cycle is 24 h, which is one factor that leads to its high virulence in humans [8]. Cell lysis coincides with fever symptoms, a response of immune system to the liberation of hemozoin and other parasite products into the bloodstream [9].

Within the red blood cells, the parasite can follow another path of development, differentiating into gametocytes. During a blood meal in an infected individual, the *Anopheles* female ingests those gametocytes. In the female of the *Anopheles* mosquito the parasite undergoes a meiotic division. Inside the mosquito gut, the gametocytes mature to form male and female gametes. The gametes undergo fertilization, forming the zygote, which transforms into an ookinete. The ookinete then penetrates the midgut and installs itself developing into oocyst. Under multiple cellular divisions, thousands of sporozoites are formed, which migrate to the salivary glands of the mosquito, to get expelled with anticoagulant factor contained in saliva during the next blood meal, restarting the cycle [10] (Figure 1).

Although *P. vivax* is the most prevalent parasite in the world, *P. falciparum* is responsible for most cases of severe malaria, being the most prevalent malarial parasite in the African continent, which accounts for 80% of the global disease burden. The groups with higher risk of malaria disease includes pregnant women, patients with HIV/AIDS, infants and children under 5 years old, whereas *P. falciparum* is responsible for about 70% of the malaria-related deaths. Although a lot of efforts have been made aiming to eradicate malaria, the World Health Organization (WHO) strives to reduce the mortality rates and malaria cases in 90% up to the year of 2030 [11]. The acquired drug resistance of the parasite continues to be a struggle in the fight against the disease, which led to rising of malaria-related death.

The resistance to antimalarial drugs is due to the indiscriminate use of the drugs and its incorrect use in treatment of malaria cases, such as wrong dosage, drug quality problems, erroneous diagnosis, not sticking to treatment, and others. These are characterized as treatment failure but can lead to a strong selective pressure in parasites, resulting in drug resistance. In recent years, with the emergence of artemisinin derivatives, resistance has allowed the number of cases to grow fast, especially in East Asia. Artemisinin, a sesquiterpene lactone, and its derivatives were adopted in the early 2000s as a first-line treatment in combined therapy for *P. falciparum* [12]. Artemisinin and its derivate can clear early trophozoites (ring stage), but the drug has a short span in vertebrate organisms, making it necessary to combined it with other drugs. In countries where *P. vivax* is the main malaria transmitter, the first-line treatment remains using chloroquine and primaquine, although WHO suggests that changes must be made to artemisinin-based combined therapy (ACT) when the rate of chloroquine resistance have reached more than 10%. Some strategies have been adapted to control malaria, such as vector control; insecticide-treated bed nets, indoor residual spraying, preventive treatment for pregnant women, and rapid diagnosis and treatment of infected individuals [1, 12, 13]. But considering the fast acquirement of resistance by parasites and vectors to drugs and insecticides, respectively, the development of an effective vaccine turns out to be an important issue. However *Plasmodium* species, especially *P. falciparum*, has a highly variant antigen pool, responsible for the adhesion
of infected red blood cells (RBCs) to small vessels, which causes aggregation that leads to severe stage of the disease, making difficult advances in this area of interest [9]. The pathogenesis of *P. falciparum* relies on a complex interaction of RBC alterations, microcirculatory anomalies, and immune response. The infected RBCs start to agglomerate in small vessels by action of adhesins expressed by the parasite on the surface of infected RBCs. Those adhesins are capable of interacting with endothelial cells of small vessels, to avoid the clearance of infected RBCs by the spleen, leading to a sequestration in diverse organs, such as brain, lungs, and placenta. This, together with other factors, causes the severe forms of malaria [9].

The increasing resistance of the parasite to practically all current medications, such as artemisinin in five countries in Asia, Southeast Asia and probably South America [1], calls for the use of combination drug therapy, as well as for the identification of new targets [12, 13]. Targets targeting the parasite for the development of new therapies for the treatment of malaria encompass both cellular functions, such as detoxification of heme or ferrirhopsophyrin IX (Fe (III) PPIX), and folate metabolism, already explored for drugs established as antimalarial, as well as other metabolic pathways, such as fatty acid synthesis, and isoprenoid biosynthesis, both of which are found in the apicoplast [14].

The apicoplast, an organelle originating from a secondary endosymbiotic origin of red algae, has lost its photosynthetic function in the course of evolution [15], and speculations have demonstrated its importance in the formation of essential components incorporated into the membrane of the parasitophorous vacuole [16]. Recently, it has been shown that isoprenoid biosynthesis is not only essential for the parasite but, in fact, is the only function of the apicoplast during blood stage growth [17] and sexual forms [18]. Parasites that lacked apicoplast can be chemically rescued by addition of isopentenyl pyrophosphate (IPP) to the growth media [17].

2. Isoprenoids in *Plasmodium* spp

All isoprenoids are derived from a common precursor, IPP and its dimethylallyl pyrophosphate isomer (DMAPP) [19] (Figure 2). The identification and characterization of farnesyl pyrophosphate (FPP) in *P. falciparum* [20], as well as the presence of proteins covalently modified by isoprenoids [21, 22] and dolichols [23], were the first evidence for the study of isoprenoid biosynthesis in *Plasmodium*. In the last decade, there has been a broad characterization of isoprenoid biosynthesis products in the parasite [22–27] resulting from the alternative route 2-C-methyl-4-erythritol-phosphate (MEP) [28, 29] (Figure 2). The essential and important step in the metabolism of the biosynthesis of all isoprenoids is the elongation of the isoprene chain by enzymes called prenyltransferases. These enzymes are classified according to the chain length of the final product and the stereochemistry of the double bond formed by condensations, with FPPS (farnesyl pyrophosphate synthase) and GGPPS (geranylgeranyl pyrophosphate synthase) being the most studied prenyltransferases [30]. FPPS catalyzes the condensation of IPP with DMAPP and geranyl pyrophosphate (GPP) to form the 15-carbon isoprenoid compound, farnesyl pyrophosphate (FPP). FPP is the substrate that catalyzes the first step in the biosynthesis of ubiquinone, carotenoids, dolichols, and protein prenylation. FPP can also be condensed with an additional molecule of IPP by the enzyme GGPPS to form the 20-carbon isoprenoid, geranylgeranyl pyrophosphate (GGPP), also essential in protein isoprenylation [30] (Figure 2).
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splicing present in the FPPS/GGPPS from *Plasmodium falciparum*. Scientific Reports. 2016;5:18429. DOI: 10.1038/srep18429


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