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"Old" and Current Antimalarial Drugs, Mechanism of Action, Significance of Fever and Therapeutic Hyperthermia

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ABSTRACT

It is reported that according to WHO report (2020), more than 229 million people in 87 countries have malaria despite the use of antimalarial drugs. Moreover, modern combination therapy cannot exclude this disease either. The fact is that malaria pathogens, as well as pathogens of other infectious diseases, gradually acquire resistance to anti-infective drugs. And such resistance of parasites to antimalarial drugs increases with increasing duration of use of these drugs in the community. In other words, antimalarial drugs used in the treatment and prevention of malaria are not only factors in the treatment and prevention of malaria, but gradually acquire the role of factors affecting the "natural" selection of pathogens. It is with the help of applied antimalarial drugs that parasites gradually adapt to existence in the organism of malaria patients, trying to survive despite the availability of drugs. It is shown that the intensity of mutations of malaria pathogens in their population, parasite load, choice of antimalarial drugs, accounting and control of antimalarial activity of the drugs used, the effectiveness and safety of the drugs used, their single and course doses, the effectiveness of individual course antimalarial therapy and control of drug-parasite interaction are the main factors in the effectiveness of treatment and prevention of malaria, as well as the factors of drug resistance of parasites. The review reiterates the importance of knowledge of the basic metabolism and life cycle of both parasite and host in understanding the mechanism of drug action and drug resistance in parasites. This knowledge is very important for the selection of new drug targets for the search and development of new antimalarial drugs. It is reported that fever, diurnal rhythm of body temperature, and therapeutic hyperthermia are not only factors in preventing infection, keeping patients healthy, and the course of malaria, but also factors in the mechanism of action of antimalarial drugs, the efficacy of drug therapy for infection, and the resistance of malaria pathogens to antimalarial drugs.

Keywords: antimalarial drugs; plasmodium falciparum; heme ferriprotoporphyrin; apicoplast; resistance; temperature; fever; therapeutic hyperthermia.

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«Старые» и современные противомалярийные препараты, механизм их действия, значение лихорадки и терапевтической гипертермии

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АННОТАЦИЯ

Согласно отчету Всемирной организации здравоохранения (2020), более 229 млн человек в 87 странах мира болеют малярией, несмотря на применение противомалярийных препаратов. Более того, современная комбинированная терапия тоже не может исключить эту болезнь. Дело в том, что возбудители малярии, так же как и возбудители других инфекционных заболеваний, постепенно приобретают устойчивость к противоинфекционным препаратам. И такая устойчивость паразитов к противомалярийным препаратам повышается с увеличением длительности применения этих препаратов в обществе. Иными словами, противомалярийные препараты предназначены не только для лечения и профилактики малярии, но и постепенно приобретают роль факторов, влияющих на «естественный» отбор возбудителей болезни. Именно с помощью применяемых противомалярийных препаратов паразиты постепенно приспосабливаются к существованию в организме больных малярией, пытаясь выжить, несмотря на наличие лекарственных препаратов. Интенсивность мутаций возбудителей малярии в их популяции, паразитарная нагрузка, выбор противомалярийных препаратов, учет и контроль противомалярийной активности применяемых лекарств, эффективность и безопасность применяемых лекарств, их разовых и курсовых доз, эффективность проводимой индивидуальной курсовой противомалярийной терапии и контроль взаимодействия лекарств с паразитами являются основными факторами эффективности лечения и профилактики малярии, равно как и факторами лекарственной устойчивости паразитов. Обзор указывает на важность знаний основ метаболизма и жизненного цикла как паразита, так и хозяина для понимания механизма действия лекарств и лекарственной устойчивости паразитов к ним. Эти знания очень важны для выбора новых лекарственных мишеней с целью поиска и разработки новых противомалярийных препаратов. Лихорадка, суточный ритм температуры тела, а также терапевтическая гипертермия являются не только условиями для профилактики инфекций, сохранения здоровья пациентов и протекания малярии, но также факторами механизма действия противомалярийных препаратов, эффективности лекарственной терапии инфекции и устойчивости возбудителей малярии к противомалярийным препаратам.

Ключевые слова: противомалярийные препараты; плазмодий фальципарум; феррипротопорфирин гема; апикопласт; резистентность; температура; лихорадка; лечебная гипертермия.

Как цитировать

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INTRODUCTION

According to world malaria report (2020), 229 million malaria cases in 2019 with 87 countries listed in malaria endemic countries with a decline of 238 million cases in comparison to 2000 [1, 2]. Malaria is considered as a life-threatening disease caused by plasmodium sp. (in human by *Plasmodium falciparum* and *Plasmodium vivax*), which is transmitted through biting of infected female Anopheles mosquitoes [3]. Even though malaria is a preventable and curable disease but its control relies on effective antimalarial drug administration especially in children under the age of 5 years due to high morbidity and mortality rate [4]. The use of famous antimalarial drugs like quinolone, chloroquine, and sulfadoxine pyrimethamine are no more useful due to resistance developed for these drugs [5]. A lot of study now focuses on novel and effective antimalarial drug and their mechanism of action to reduce global malarial burden.

BASICS OF METABOLISM AND LIFE CYCLE OF PLASMODIUM SP. (*P. FALCIPARUM*)

The life cycle of *Plasmodium falciparum* is a complex and multistage cycle that completes in two living organisms (one vector and one host) [6], mosquitoes as vectors and human as hosts. *P. falciparum* can successfully survive in different cell types and organisms due to presence of 5,000 different genes and specialized protein [7]. The four different stages of parasite development includes; i) sporozoites — these are infectious spores injected by anopheles mosquitoes to human, ii) merozoites — stage in which meros invade erythrocytes, iii) trophozoites — stage in which parasite spores start multiplying in erythrocyte cells, and iv) gametocytes — its sexual stage with protein supplements [8].

The life cycle of *P. falciparum* startswith introduction of ***sporozoites*** to the gut of female anopheles mosquito during her bite for blood sucking. This is starting of sexual phase known as sporogony [9]. During this cycle the male and female **gametocytes** enter mosquito gut, where they fuse to form **zygote**. The zygote develops into motile **ookinetes** that dig into mid-gut wall to develop into **oocysts**. These oocysts divide and grow into haploid sporozoites, which are motile form and travel in mosquito body cavity to reach salivary gland and stay there until transferred to human bloodstream during biting of infected mosquito results in malaria infection in human host [10]. There are mutual benefits between mosquito and *P. falciparum* as one receive environment and nutrition to complete their sexual life cycle the other gets better survival and increased blood-feeding capacity from an infected host [10, 11].

Human is an intermediate host for *P. falciparum* in which asexual part of life cycle takes place [12]. When an infected mosquito bites a human, it releases hundreds of sporozoites some of which enters lymphatic system and reach lymph node, where they develop into exoerthrocyties. Some get entry into blood vessels and reach liver within some hours of entry and it lasts form 5–16 days [13]. These sporozoites travel by stick and slip motility method using TRAP (thrombospondin related anonymous protein) with actin-myosin motor. The sporozoites that succeed to reach hepatocytes multiply inside parasitophorous vacuoles and develop to more than 10,000 **merozoites**. The process of multiplication and growth of sporozoites inside a hepatocyte is facilitated by circumsporozoite protein present in the parasite [14]. The merozoites in liver cells are protected by merosomes (cell derived vesicles), which protects them from kuffer cells phagocytosis. Merozoites are then released to lung capillaries from their blood stage of malaria starts [15]. The life cycle of *P. falciparum* from infection to transmission is depicted in Fig. 1.

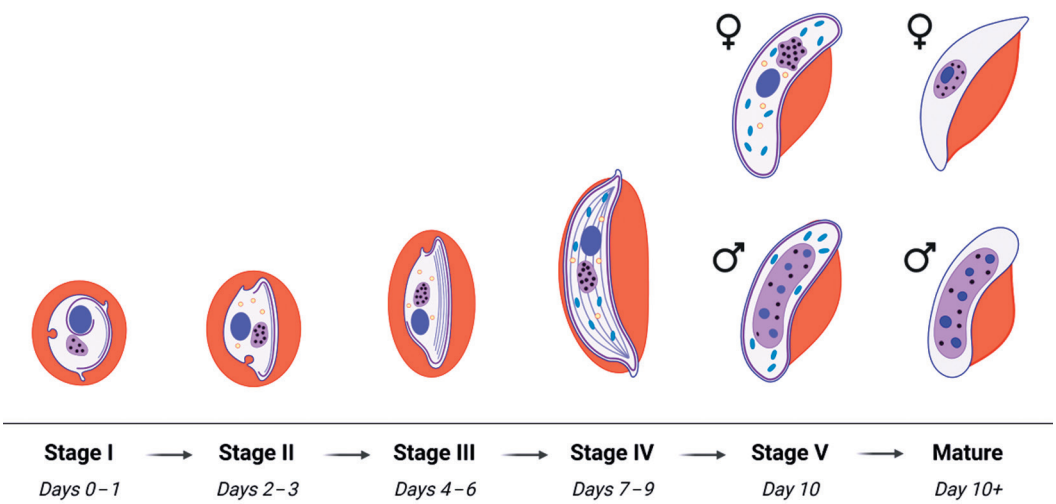

Fig. 1. Life cycle of *Plasmodium falciparum* from infection to transmission.
Рис. 1. Жизненный цикл *Plasmodium falciparum* от заражения до передачи.

In red blood cells (RBC) the processes of division and growth is repeated many times that results in numerous daughter cells which further invade more RBC [16]. The identification and attachment to RBC cells is carried out with the help of receptors ligand binding within 60 second of merozoites release from liver [17]. The invasion to RBC and attachment to the cell is facilitated by organelles present at the tip of *P. falciparum* known as apical complex [18]. During invasion these apical organelles enter RBC first and disappear once invaded. The speed of invasion not only increases the chances of survival of parasites but also save them from host immune response. The attack of merozoites in RBC is assisted by molecular connections between different ligands and receptors present on the membrane of both merozoite and host [6]. *P. falciparum* contains numerous receptors and many alternate pathways for invasion. Duffy binding — like (DBL) homologous protein of *P. falciparum* with reticulocyte binding — like (RBL) homologous protein can identify different RBC receptors due to presence of four gene signaling for DBL binding protein in comparison to other plasmodium species which carry single gene for DBL receptor binding protein receptor. Erythrocytic cycle in *P. falciparum* occurs in48 hours and during each cycle every merozoite divides and grows in to 8–32 new merozoites, and through ring stages they develop to trophozoite and schizont inside the vacuole [19]. On completion of cycle the RBC ruptures and release merozoites, which further infect more RBCs. Some merozoites do not undergo shizogony and undergo differentiation into sexual gametocytes [20]. Male and female gametocytes are non-pathogenic in nature and only spread infection to other by female anopheles mosquitoes [21].

The process of feeding in *P. falciparum* starts with ingestion of erythrocyte cytosol with the help of cytostome. Cytostome creates a membrane bounded vacuole and release a mixture of digestive enzyme [22]. The digestion of hemoglobin by *P. falciparum* takes place with the help of enzyme proteases and cathepsin D, and any other parasite with fails to develop these trophozoites are unable to survive and die [23]. Some recent studies on *P. falciparum* discovered some other enzymes like cysteinyl proteinase and aspartyl proteinase. Some host enzyme like leupeptin can block hemoglobin digestion by reversing cysteinyl protease and suspends growth of parasite but it's an irreversible process that which resume after removing the inhibitor even after long time incubation. These enzymes can be considerable target for antimalarial drug [24]. Digestion of hemoglobin leaves an insoluble complex known as hemozoin that containsheme. After entry in RBC, in effect of parasite intercellular metabolism of host increases due to requirement of nutrient movement from outside to inside of the cell and waste product should be disposed of outside the cell [24]. The RBC cell membrane also adjusts its capacity as per the increased demandof essential amino acids, lactate, nucleosides, and fatty acids [25]. This increased permeability allows numerous substances like hexitols, amino acids, inorganic, and organicacids to enter the infected cell which is not allowed in general condition. All these changes in metabolism takes place due to remodeling of cell by parasite protein that either attaches with host membrane components, or adhering to the inner membrane and sometime directly penetrating to the membrane [26].

P. falciparum single cell can produce 10 billion new copies of itself so the most important requirement is to supply glucose to support the growth of large number of new organisms and to support the process of reproduction. If sugar is replaced from galactose, mannose, ribose, or any other form other than glucose and fructose, the parasite is not able to survive *in vitro* [27, 28]. According to flawed model if any other form of sugar is provided the malarial parasites like *P. gallinaceum*, *P. berghei*, *P. knowlesi* and *P. lophurae*-acquire amino acids produced from digestion of hemoglobin, but this hypothesis is not supported by biochemistry of *P. falciparum. P. falciparum* culture shows production of 13 amino acids by digesting erythrocyte cytosol and the rest 7 should be obtained from outside RBC, whereas the other species of plasmodium shows no growth when glutamine is replaced with other metabolite [29]. So, glutamine and glutamate should not be less or replaced with other forms for continuous culture of plasmodium (Fig. 2).

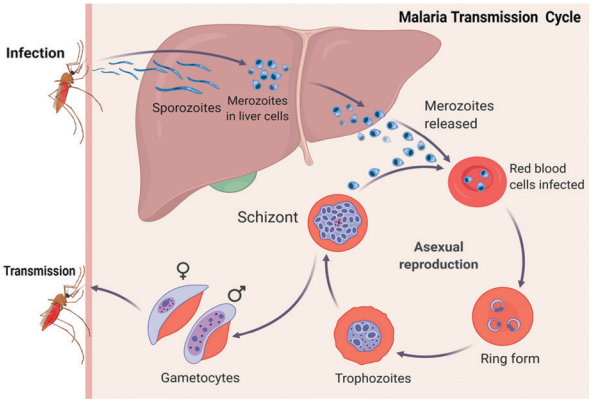

Fig. 2. Different developmental stages of *Plasmodium falciparum* in red blood cells. Image adapted with modifications from [DOI: https://doi.org/10.3390/pathogens12060791]. © Kartal L. et al. 2023. Distributed under CC BY 4.0 license.
Рис. 2. Различные стадии развития *Plasmodium falciparum* в эритроцитах. Изображение адаптировано с изменениями из [DOI: https://doi.org/10.3390/pathogens12060791]. © Kartal L. et al. 2023. Распространяется на условиях лицензии CC BY 4.0.

Many studies on malarial parasite confirm the requirement of calcium pantothenate as essential for survival [24]. The culture media study of parasites shows the need of para-aminobenzoic acid and folic acid provided by RBC cells [30]. Sulfonamides are for this reason in use as potential antimalarial drug due to their inhibition of folic acid synthesis. Malarial parasites can synthesize pyrimidine's but purines are to be supplied from outside [31]. The kinetic study of DNA synthesis in *P. falciparum* shows integration of labeled purines takes place after 30 hour of merozoite invasion to RBC and its multiplication in next 14–18 hours, when schizogony development is completed [32].

MECHANISM OF ANTIPARASITIC ACTION OF "OLD" ANTIMALARIAL DRUGS

As several studies shows during their invasion to RBC *P. falciparum* ingest up to 80% of hemoglobin through cytostome [33]. Cytostome transports this hemoglobin to acidic digestive vacuole, where proteolytic enzyme breaks down it in to small peptides that are used as nutrients by growing merozoites [34]. Breaking down of one hemoglobin releases up to 4 heme molecules that are toxic in Free State to plasmodium so they must rapidly converts it to an intermediate product with the help of heme oxygenase [35]. Most of Hematophagouse organisms like plasmodium, *Boophilus* sp. and *Schistosome* do not contain heme oxygenase, instead they follow an alternate pathway to crystalize heme to hemozoin (a non-toxic biomineral). Hemozoin is a 5 coordinate Fe (III) PPIX connected to reciprocating monodentate carboxylate linked to protoporphyrin IX's propionate moieties [36]. More than 1% concentration of Fe (III) PPIX is toxic to plasmodium. On the basis of long investigation researchers are able to explain the mechanism of formation of hemozoin [37]. Theories proposed contains different enzyme — catalyzed heme polymerases, lipid and protein mediation, and combination of both. The most recent studies shows neutral lipid as effective mediates in formation of hemozoin. Some illustrations from TEM (transmission electron micrograph) show presence of lipid non-spheres surrounds hemozoin crystals [38]. These nano-spheres are recorded as the blend of monostearic, diplamitic, monopalmitic, dilinoleic, and dioleic which are mono and di-glycerols in the ratio of 4:2:1:1:1. Kinetic study of β-Hematin under *in vitro* condition facilitated by neutral lipids is competent to hold the essential flux of monomeric Fe(III) PPIX so it can be maintained at low toxicity level [39]. After degradation of hemoglobin when heme starts to accumulate in parasites organelles, the acidic environment of organelles containing neutral lipids starts detoxification of toxic molecules. Lipid based hemozoin construction was found more effective in comparison to autocatalysis, as vacuole membrane can function as nucleation site for the growth of crystal [39].

In 1940 and up to next 40 years chloroquine was considered as the most effective antimalarial drug against *P. falciparum* until all endemic regions developed resistance against it. Even after its low efficacy hemozoin was the most suitable target for antimalarial drugs [40]. Drug resistance develops due to mutations in expression of different membrane proteins present in digestive vacuole in *P. falciparum* PfCRT found to work in chloroquine resistance and Pf PGH1 work in mefloquine resistance. This protein work by reducing the concentration of drug in digestive vacuoles [40]. Fe (III) PPIX is part of host response system which is not affected by pathogen gene mutation and present in large amount in environment due to which parasite have to produce hemozoin that becomes a definite drug target [41].

Quinine, CQ and related drugs (quinoline based)

Quinoline based Quinine are weak bases that can easily pass through digestive vacuoles membrane and accumulate inside due to low intravacuolar pH [42]. After accumulatin inside the vacuole it binds with heme to make heme ferriprotoporphyrin IX [Fe (III) PPIX]-drug complex that successfully inhibiting formation of hemozoin resulting in free heme release which is toxic to parasite and causes their death [43]. High non- physiological concentration 4-aminoquinoline are also reported to damage parasite lysosome functioning, and attaches with parasitic DNA [44]. Point mutation and occurrence of halotype in PfCRT (*P. falciparum* Chloroquine resistance transporter) and PfMDR1 (*P. falciparum* multi-drug resistance 1) are related to resistance against quinine in *P. falciparum* [44, 45]. PfCRT are reported to be located on chromosome number 7 and resistance results from replacement in an amino acid lysine (K) with threonine (T) at 76th codon (K76T) [45]. This replacement promotes drug efflux from digestive vacuoles by active or passive transport, which decreases collection of drug in digestive vacuoles. K76T is also found responsible for conformational changes in wild type PfCRT in active transporter of protonated CQ across digestive vacuoles into cytosol [46]. Recent studies of PfMDR1 identified 5 prevalent amino acid polymorphisms namely: N86Y, Y184F, S1034C, N1042D, and D1246Y which can generate susceptibility for Artemisinins and quinolones [47]. In silico study of these SNPs are found capable of drug resistance modulation by allelic exchange during crossing over. Some researchers also consider ms476o alleles as competent biomarkers for QN resistance whereas some still found it specific to some geographical locations [48].

Artemisinin and related drugs

Artemisinin (ART) is a phytochemical derived from leaves of wormwood Artemisia annua from China [49]. It is a sesquiterpene trioxane lactone and its chemical variation will results in formation of Dihydroartemisinin semi-synthetic derivative that can serve as a template for Artesunate synthesis [50]. ART are effective against all stages of plasmodium including gametocytes, also considered as uncomplicated therapy for malaria [51]. The antiplasmodial activity of

ART is due to ring structure of 1,2,4-trioxane endoperoxide, which induce oxidative stress on interacting with heme and produce a protein alkylation and toxin free radical which results in a permanent damage to malaria parasite [52]. SERCA (sarco endoplasmic reticulum membrane calcium ATPase) is a potential biomarker for ART resistance which can decrease the ART responsiveness [53]. Studies on whole genome sequencing of *P. falciparum* showed a correlation ship between non-synonymous SNPs like PfK13 and kelch13 gene in an *in vitro* study. The disadvantage of using ARTs is their short half-lives that areabout 1–3 hours. Its working can be extended using ACTs along with ARTs, as it can prevent denial and recrudescent infections associated with multiple dose monotherapy. WHO qualified ACT treatment as first line drug for treatment of *P. falciparum* malaria [54].

Ozonide series of endoperoxidase antimalarial drugs are low cost drugs with improved bio-pharmaceutical properties and enhanced effectiveness in comparison to Artemisinin derived drugs [55]. This category include OZ277 AND OZ439 constructed on 1,2,4-trioxolane in place of Artemisinin 1,2,4-trioxane core lined with spiroadamantane, and spirocyclohexane group [53]. OZ277 is currently in use with combination of Piperaquine in countries like India against all asexual stages of *P. falciparum* with a half like double of DHA. OZ277 is also associated with low concentration of drug in patient's plasma in comparison to uninfected people [56]. The cis-8-phenyl moiety group of OZ277 is replaced with cis-8-alkyl to produce OZ439 which can overcome the challenge of low dose concentration and it is more susceptible to heme degradation that makes it more bioavailable. OZ439 is in phase II of human trial [57].

Antifolates

Two subclasses of antifolates which are used as antimalarial drugs are DHPS (class I antifolates), and DHFR (dihydrofolate reductase, class II antifolates) in combination as effective treatment against malaria [58]. The first antifolate that was used as antimalarial agent was Proguanil during rigorous British research programme [59]. Comparative studies between quinine and Proguanil in animal model reported Proguanil with better therapeutic index against avian malaria. Malarone is a combination of Proguanil and atovaquone that are used to inhibit electron transport system of coenzyme Q (cytochrome bc1 complex), also it is synergistic, prophylactic against malaria [60]. The other antifolate drugs used against malaria are Pyrimethamine (PRY) that is metabolized as cycloguanil (CG), sulfadoxine, sulfonamide, and sulfa drugs. In 1940s the studies shows PRY and CG acts on DHFR and DHFR-thymidylate synthetase protein, on the other hand sulfa drugs works as competitive inhibitor of natural substances [61]. The effective functioning of these drugs in synergistic combination with sulfa drugs initiates rapid resistance. SDX-PYR was the first combination used in 1960, was a cheap alternative to CQ-resistant plasmodium found in African countries [62].

Halofantrine

Halofantrine and Lumefantrine are two schizontocide-which are used to activate both chloroquine sensitivity and chloroquine resistance against *P. falciparum.* Non-comparative clinical trials and dose designing based studies established the efficacy of both these drugs in chloroquine and pyrimethamine resistance in falciparum and vivax both type of malaria parasites [63]. Studies oneffect ofHalofantrine on mefloquine- resistant *P. falciparum* showed poor results in patients who failed mefloquine prophylaxis indicate halofantine is not effective against mefloquine resistant *P. falciparum* [64].

Resistance to Halofatrine in parasite is predictable especially with cross resistance of mefloquine, so Halofantrine should be used in patients with chloroquine and sulfonamide resistance to preserve and sustain efficacy [65]. *In vitro* study of Halofantrine confirmed activity against strains of *P. falciparum* with chloroquine-sensitive and chloroquine- resistant [66]. *In vivo* study of Halofantrine in mice infected with *P. berghei*showed three time greater activity in comparison to chloroquine with a dose in 250 mg confirmed activity against both chloroquine-sensitive in every 6 hours for 3 days [67]. Like other blood schizontocide Halofantrine is also effective against Erythrocytic stage of different *Plasmodium sp.*by inhibiting the proton pump at host-parasite interface [68]. Most of the malaria endemic countries are now affected by Plasmodium sp. with chloroquine resistance and susceptibility of *P. falciparum* for Halofantrine has been verified by both *in vivo* and *in vitro* studies [69]. It was also documented that Halofantrine is poorly and variably absorbed and it can be improved by food control [70].

Atovaquone

Atovaquone is a fixed dose composition used with Malarone for treating adults and children with uncomplicated malarial condition and as chemoprophylactic agent to control malaria in travelers [71]. The research and development of Atovaquone began during World War II when malarial outbreak and shortage of quinine produced the need to develop compound which can be used as antimalarial in place of quinine [72]. USA led researcher's derived more than 300 hydroxynapthoquinones, which when tested on ducks infected with *Plasmodium lophurae* demonstrated great activity in comparison quinones but when tested on human patients the assay showed poor result due to low absorption and fast metabolism [73]. Atovaquone acts asubiquinol inhibitor in mitochondrial electron transport chain at bc_1 complex as it results in loss of mitrochondiral functioning. Parasite mitochondria play a key role in providing orotate during pyrimidine biosynthesis catalyzed by dihydroorotate dehydrogenase (DHODH) [74]. Effect of Atovaquone on blood-stage parasite results in death of parasite but the effect is slow as compared to other drugs like chloroquine and Artemisinin [75]. Atovaquone shows better result with liver stage parasites utilized as prophylactic drug, whereas it is not effective on dormant hypozoites [76].

Atovaquone shows high affinity to human serum albumin and bounds to plasma protein with >99.5% affinity. The affinity of Atovaquone decreases when taken with other antibiotics. Recent studies also indicate that Atovaquone can also inhibit cytochrome P450 enzyme, sulfamethoxazole metabolism by CYP2C9, and 7-benzyloxy-4-(trifluoromethyl) coumarin (BFC) [77].

Other drugs

Pyronaridine4-[(7-chloro-2-methoxybenzob[1,5]naphthyridin-10-yl)amino]-2,6-bis[(pyrrolidin-1-yl)methyl]phenol) was first synthesized in Chinese Parasitic Diseases and used in China for more than three decayed for malarial treatment against *P. falciparum* for chloroquine-resistant strains [78]. Early studies around 1970s found pyronaridine resistance against antimalarial strains showing resistance for chloroquine but resistance to pyronaridine when it was used in combination with other antimalarial drugs, especially with Artesunate [79]. Pharmacokinetical clinical data of pyronaridine specifies its elimination half life time ranges between 9.6 to 13.2 days in adults and children with acute uncomplicated *P. falciparum* and *P. vivax* malaria in patients with Artemisinin combination based therapies [80]. Pyronaridine fixed dose combination therapy includes treatment with Artesunate in a ratio of 3:1 for acute uncomplicated *P. falciparum* and for *P. vivax* blood stage malaria [80]. Pyronaridine affects the food vacuoles of *P. falciparum* in early stages of infection whereas inerythrocytic stage it bringsalterations to food vacuoletailed by multilameliate whorls in complex of trophozoites [81].

In vitro studies state pyronaridine as inhibitor for β-haematin when given in ration of 1:2 with chloroquine enhance blood cell lysis induced by haematin [82]. Some studies reported pyronaridine as inhibitor of decatenation activity of *P. falciparum* DNA topoisomerase II [83]. The mechanism behind pyronaridine resistance is not clear whereas the *in vitro* studies indicate cross resistance with chloroquine inconsistent and *in vivo* studies indicate the activity against chloroquine- resistant Plasmodium species. This conflict between *in vitro* and *in vivo* indicates presence of more than one mechanism works to overcome the resistance mechanism and high potency in *P. falciparum.* In study by D. Wu et al., demonstrated increase in number of food vacuoles in *P. berghei* trophozoites and decrease in malaria pigment containing digestive vesicles ultimately reduction in haemozoin grains [84]. These results summaries the direct effect of pyronaridine on these ultrastructure may be the cause of development of resistance in these species. A similar study by F. Liu et al. [85] relate them with overexpression of 54 kDa protein and alternation in parasite polyamine metabolism.

PROBLEM OF RESISTANCE OF ANTIMALARIAL DRUGS

Antimalarial drug research and need for novel targets are important for reducing the burden of malaria. A routine monitoring in malaria endemic countries with antimalarial drug efficacy helps to control treatment responses with follow- ups on each 28 to 42 days [86]. To identify antimalarial drug targets it is important to identify major metabolic pathway differences between host and parasite. Some of key metabolic pathways for drug target discovery are heme detoxification, nucleic acid synthesis, oxidative stress, and fatty acid synthesis [87]. Most of the antimalarial drugs in the past and present face drug resistance as none of the antimalarial agents focused on antimalarial drug target [88].

Protein kinases are involved in many metabolic activities of plasmodium parasite life cycle including protein degradation, phosphorylation, transcriptional control, and post-transcriptional control that can make it good target for drug discovery [89]. In *P. falciparum*the most studied kinase arecycline dependent kinase, protein kinase 5 (PfPK5), and mitogen related kinase (PfMRK). PfPK5 play significant role in controlling RNA synthesis and reducing DNA synthesis in *P. falciparum* [89].

As we know glucose is main source of energy not only for the host but also for the parasites like plasmodium. Malarial parasite infected RBC consume large amount of energy in comparison to normal erythrocytic cell and in case of *P. falciparum*it completely depends on glucose for its energy need [90]. Glucose from host erythrocyte is transferred via GLUT1 transporter to parasitized erythrocyte. *P. falciparum* hexose transporter (PfHT) is crucial for its growth and survival and for glucose transport as it can transport both D-glucose and D-fructose as compared to GLUT1 which can transport only D-glucose [91]. Due to difference in their substrate interaction PfHT is a potential target for antimalarial drug discovery [92].

Recent studies on *P. falciparum* ribosomal blockage and other protein kinase blockage are promising targets for the novel antimalarial drug targets [93]. Plasmodium species carry 3 types of genomenamely Apicoplast, nuclear, and mitochondrial genome. Apicoplasts are similar to chloroplast in apicomplexan plasmodium. It originates as a result of endosymbiosis and helps to maintain many functions like metabolism of heme, fatty acids and amino acid [94]. Apicoplast is plastid with non-photosynthetic involved in many metabolic activities which make it vital for survival of *P. falciparum* and ideal as drug target [95]. From the small genome of 32-kb DNA of *P. falciparum*, 3 gene codes for oligomeric RNA polymerase, 1 gene for PfTu (elongation factor), and one for Fe-S pathway. As Apicoplast have unique pathway for isoprenoid–heme synthesis, and fatty acid synthesis which are not found in human so it can be a potential target for antimicrobial drug discovery [96].

Despite the continuing potential of chemotherapeutic therapy for many infectious diseases, including malaria, the increasing prevalence of multidrug-resistant pathogens justifies the search for non-pharmacologic treatments. In recent years, it has been shown that therapeutic hyperthermia has been successfully used in the treatment of infections in the past [97]. In addition, there are emerging reports that

therapeutic hyperthermia and fever in infectious diseases play a positive role in contrast to hypothermia [98, 99]. Indeed, since fever in malaria and other infections develops as part of the physiologic response of humans and warm-blooded animals to infectious disease, which is anchored by evolution, fever cannot play a negative role. A detailed study of the role of temperature in the maintenance of health in malaria and other infections is therefore required. In doing so, it is very reasonable to abandon the strategy of using antipyretic drugs and adopt the strategy of using controlled therapeutic hyperthermia in the medical treatment of infectious diseases. It may very well be that the febrile response represents an important means of helping the body fight infection. Therefore, the prescription of antipyretic drugs and physical cooling measures for patients with fever and infectious diseases is questioned [100].

In addition, it has been reported that human and animal body temperature is not constant even in normals. Moreover, there is a circadian rhythm that needs to be considered in medicine because the metabolism of biological substances and the mechanism of action of drugs are temperature dependent [101–104]. It follows that fever, diurnal rhythm of body temperature and therapeutic hyperthermia are important factors affecting patient health and the course of infectious diseases including malaria. In addition, local and general temperature are important factors in the mechanism of action of all drugs, including antimalarial drugs, the efficacy of drug therapy for infectious diseases, and the resistance of malaria pathogens to antimalarial drugs. Undoubtedly, the unconditional temperature dependence of all living things holds great potential for the pharmacology and drug therapy of many diseases, including malaria. In the future, we will have to look more closely at the potential of temperature pharmacology to better utilize antimalarial drugs and therapeutic hyperthermia in the treatment of malaria.

CONCLUSION

Malaria disease is a burden on world economy and many countries like Africa, Asia, and South America. The emergence of resistance to antimalarial drugs around the globe creates pressure on scientists to search and discover new antimalarial drugs or combination therapies to control the problem of resistance from *P. falciparum* and *P. vivax.* The study on novel biochemical pathways as targets can provide new opportunity for antimalarial drug agents. The future studies must concentrate on novel target identification and medicines with distinguishing mechanism of action to deal with resistance against antimalarial drugs.

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ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

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