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AN EXTENSIVE REVIEW ON *PLASMODIUM FALCIPARUM* CHLOROQUINE DRUG RESISTANCE: A LEGITIMATE JUNCTURE TO INVENT AN ADVANCED ANTIMALARIAL DRUG AGENTS

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ABSTRACT

Malaria is a life challenging disease that occurred as a resut of infection by single celled parasitic microorganisms. Mainly, it is transmitted by female anopheles mosquito of plasmodium family. Chloroquine is the cheapest antimalarial drug candidate available worldwide. Since 1957, Chloroquine and some other quinine derivatives resistance has been observed by *P. falciparum* in the southeast Asia region like Cambodia, Thailand, Myanmar, and Vietnam country. The same resistance has been extended since 1970, and it has been emerged in several parts of India. Furthermore, chloroquine is having a far more adverse effects like nausea, vomiting, blurred vision, headache, abdominal cramp, deprivation of appetite, diarrhoea, hearing loss, baldness, change in skin color, decresed body weight, seizures. Further, this drug cannot be prescribed to the pregnant women. Accordingly, it is a necessary thing to invent some newer and potential antimalarial drug candidates so that the drug resistance along with side effects can be well overcome. In this present review, we have incorporated the essence of research articles by the research scientists from disparate countries and assassinated an endeavor to report *P. falciparum* chloroquine resistance developed as a result of mutations in pfcrt and pfmdr1 gene. Docking study revealed that NADP dependent *P. falciparum* glutamate dehydrogenase is a putative target enzyme for the design and development of contemporary antimalarial medicaments.

Keywords: Malaria, sepsis, gastroenteritis, Polymerase chain reaction, Resistance, Vacuolar transport, *Plasmodium falciparum* glutamate dehydrogenase

INTRODUCTION

Malaria is a life threatening infectious parasitic disease that caused by female anopheles mosquito. Mosquito biting results in incorporation of parasites from the mosquito saliva in to the host blood. The parasites travel to the infected host liver and executes stages of maturation and reproduction. Five *Plasmodium* species have been communiqued that can infect and spread by the humans. Death can also be possible by *P. falciparum* where as *P. vivax, P. ovale and P. malariae* mainly cause a benign form of malaria disease. The species *P. knowlesi* hardely incorporates disease in humans. These parasites can affect human as well as other animals.

Signs and symptoms of malaria disease can be seen in a human ten to fifteen days after mosquito biting. In normal cases, malaria can cause symptoms like fever, headache, vomiting, tiredness, joint pain, shivering, jaundice, hemolytic anemia, hemoglobin in urine. Whereas, in extreme condition, it can cause yellow coloration of skin, damage in retina, seizures, coma. If treatment has not been done it may lead to death, also. Sometimes, malaria can cause other conditions like gastroenteritis, sepsis, and viral diseases.

Typically, malaria can be diagnosed by microscopical examination of the blood using either blood films or with rapid diagnostic tests based on antigen. Polymerase chain reaction (PCR) methods have also been discovered that can be used to detect malarial parasite DNA. However, due to cost and complexity, these methods can not be used in the regions where malaria disease is common. Combination therapy can treat the malaria disease well. Combination of antimalarial medicaments include an artemisinin derivative. The second drug candidate may either be chloroquine, mefloquine, lumefantrine or sulfadoxine/pyrimethamine. Incase of unavailability of an artemisinin derivative, quinine along with doxycycline will be the drug of choice. **Figure 1** shows antimalarial drug candidates available in the market to treat the malaria disease **[1-3]**.

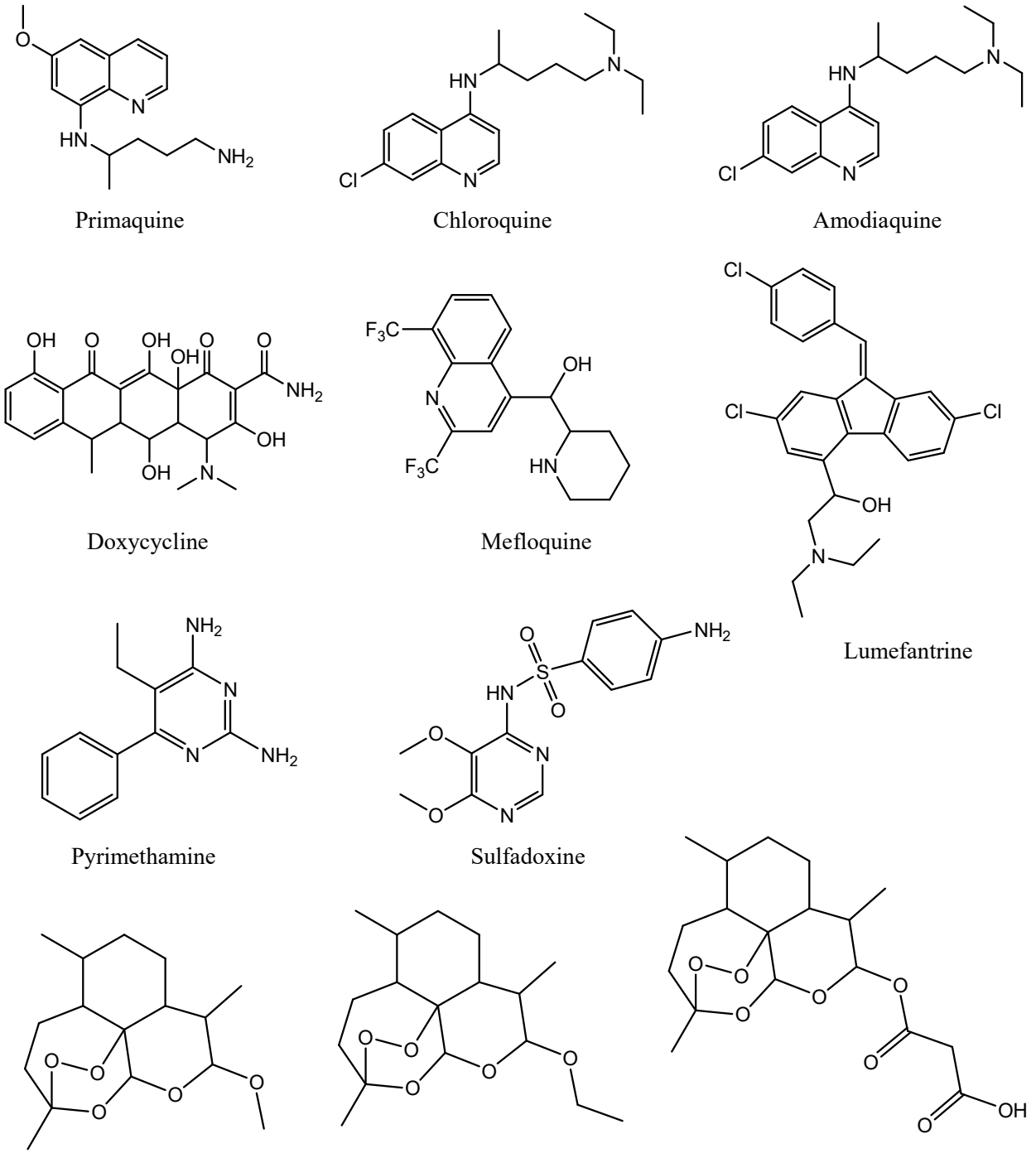

Figure 1: Currently available drugs with structure for the treatment of malaria disease

The purpose of the study

The cheapest drug Chloroquine was discovered in 1934 and used for prophylaxis and treatment of malaria disease effectively. It has been monitored that resistance has been developed in 1957 in border of Colombia-Thailand. The resistance has further boosted in Venezuela along with parts of Colombia

around 1960, in Papua New Guinea in the mid-1970s, and in Africa origin in 1978. Chloroquine resistance has further increased in Kenya, Tanzania, Sudan, Uganda, Zambia and Malawi. It has been confirmed that chloroquine resistance has been spread up to 40 different countries approximately **[4-7]**.

Intensive research that shows *Plasmodium falciparum* chloroquine resistance

Yeung S *et al.* have stated that Chloroquine and Sulfadoxine-pyrimethamine were used in the treatment of malaria due to high mortality. But due to development of drug resistance artemisinin-based combination therapy was used **[8]**. Cui L *et al.* have informed that *P. falciparum* strains are resistant to antimalarial drugs. To recover this resistance artemisinin-based combination therapies given mainly at Thia-Cambodian border which is epicenter of multidrug resistance **[9]**. Mekonnen SK *et al.* have communicated boost resistance to the antimalarial drug chloroquine and sulphadoxine-pyrimethamine by *P.falciparum* in Ethiopia. Escalated report of resistance and declined parasite clearance rate creates a new challenge in antimalarial therapy and since 2004 artemether-lumefantrine was used to treat uncomplicated *P. falciparum* **[10]**.

Djimde A *et al.* have picturized Sub-Saharian African country where chloroquine resistance is a primary healh issue. Mutations in two genes PFCRT and PFMDR 1 that codes for *P. falciparum* transmembrane proteins PfCRT and Pgh1 were responsible for chloroquine resistance **[11]**. Djimde A *et al.* have addressed on African countries where drug-resistant falciparum malaria was boosted. Djimde A *et al.* have reported PFCRT T76 can be used for surveillance of clinical resistance of chloroquine. Widespread of chloroquine resistance, PFCRT T76 and drug failure were employed to calculate genotype-resistance indices (GRIs) and genotype-failure indices (GFIs) in Mali, West Africa that models were used to map chloroquine resistance **[12]**.

Talisuna AO *et al.* have stated that the mutant genotype at codon 76 was used as a molecular marker of the PFCRT gene (T76) for control of chloroquine resistance *P.falciparum* in Uganda **[13]**. Warhurst DC has informed about the development of resistance in Southeast Asia and South America at 1950s and in Africa at the 1970s. Further, Warhurst DC has assessed that mutation in pfmdr1 (DR like gene) on chromosome 5 that codes Pgh1 protein was responsible for chloroquine resistance **[14]**. Venkatesan M *et al.* have communicated

mutations in gene PFCRT (*P.falciparum* chloroquine resistance transporter were associated with chloroquine resistance. As a result at codon 76 lysine was changed by threonine. Chloroquine resistance was developed by point mutations at codon 86 in gene pfmdr1 (*P. falciparum* multidrug resistance transporter 1) and mutations in positions 184, 1034, 1042, and 1246 **[15]**. Ndiaye M *et al.* have summarized the development of chloroquine resistance in *P. falciprum* in many parts of the African country including Senegal. Mutations in gene PFCRT and pfmdr1 were related to chloroquine resistance. To overcome that resistance Sulfadoxine–pyrimethamine (SP) plus amodiaquine (AQ) were employed as the first line drug **[16]**. Hien TT *et al.* have broadcasted the most resistant *P.falciparum* parasites were found in Southeast Asian countries that decline the options of treatment. Artemisinin-based combination therapy should be employed to treat chloroquine resistance *P. falciparum* **[17]**.

Trape JF *et al.* have performed a complete examination for 12 years, from 1984 to 1995 and concluded that development of chloroquine resistance in the Savana, Sahel and some forest locations of Senegal resulted inthe risk of death among 0-9 years oldchildren **[18]**. Martin SK *et al.* have informed that likewise cancer cells, *P. falciparum* cells produce resistance. Martin SK *et al.* have described that chloroquine resistance can be comprehensively reversed by use of verapamil, a calcium channel blocker as that can reverse the resistance of anticancer drugs also. This resistance can be overcome in Southeast Asia and Brazil where chloroquine resistance has been reported **[19]**. Krogstad DJ*et al.* have given an overview on chloroquine-resistant *P. falciparum* parasites that acquired less chloroquine than the susceptible parasites by an unknown mechanism. Verapamil and two other calcium channel blocker, as well as vinblastin and daunomycin, can boost that accumulation and reverse the chloroquine resistance **[20]**.

Martin RE *et al.* have informed that mutation in *P. falciparum* chloroquine resistance transporter (PfCRT), an integral membrane protein located at parasite's internal digestive vacuole was responsible for chloroquine resistance. This resistance can be reversed by verapamil **[21]**. Trape JF, has reported boosted resistance of *P. falciparum* to chloroquine in all African countries in between 1978 and 1988. After the 1980s resistance has been developed followed by 2-3 times enhanced death.Trape JF has informed about the routine treatment of malaria should be changed on anurgent basis **[22]**. Sidhu AB

et al. have reported point mutation in *P. falciparum* chloroquine resistance transporter (PFCRT) was responsible for chloroquine resistance and less accretion of chloroquine by a parasite. Use of verapamil and some other drugs can raise this accretion so reverse that resistance **[23]**. Baird JK has informed that chloroquine was used as first-line treatment for *P. falciparum*. The resistance of *P.falciparum* to chloroquine was reported in the 1950s. The resistance of *P. vivax* to chloroquine was reported in Indonesia, Myanmar, India, Guyana and South America after 1989. Baird JK has reported that alternative therapies should be developed and employed to treat *P. falciparum* **[24]**.

Wellems TE *et al.* have given information that development of chloroquine-resistant *P. falciparum* strains played a major role in the survival rate of humans. Drug resistance was related to multiple mutations in PFCRT, an integral membrane protein **[25]**. Price RN *et al.*, after a deep study from Indonesia, Papua New Guinea, Thailand and India, have addressed though *P. falciparum* cause severe disease than *P. vivax*, *P. vivax* can cause severe disease and drug-resistant *P. vivax* may also be produced **[26]**. Padua RA has announced chloroquine resistance has been developed in the malarial parasite, *P. chabaudi* that was stable and genetically multigenic. Padua RA has informed Chloroquine resistance was the division of pyrimethamine resistance and enzyme markers **[27]**. Babiker HA *et al.* have examined polymorphism in *P.falciparum* gene in samples of eastern Sudan villages. They report the relation between PFCRT-T76 allele and resistance further they included relation between *pfmdr1-Y86* and *pfcrt-T76* was clear among resistant samples, that indicates an association of the two genes that shown boosted chloroquine resistance **[28]**.

Schueler FW *et al.* have examined the antimalarial action of chloroquine in mice infected with P.berghei. After the experimental work Schueler FW *et al.* have concluded that metabolite of hemin, known as ferrihemic acid converted into hematin that was responsible for chloroquine resistance **[29]**. Bray PG *et al.* after experimenting, reported that binding of chloroquine to hematin reduces the accumulation of chloroquine by *P. falciparum* due to reduction in chloroquine binding sites in parasites. This reduction in the accumulation of chloroquine creates resistance **[30]**. Johnson DJ *et al.* have addressed *P. falciparum* chloroquine resistance was due to PFCRT mutation. That resistance can show hypersensitivity to other antimalarials. Verapamil, a calcium channel blocker can reverse that resistance **[31]**. Chen

N *et al.* have accounted for ten mutations in PFCRT and five mutations in pfmdr1 in *P.falciparum* were responsible for chloroquine resistance in South America, Southeast Asia and Papua New Guinea. Chen N *et al.* have examined chloroquine resistance in samples from Morong, Philippines, and compared them **[32]**. Djimde AA *et al.* have reported that chloroquine resistance was developed due to mutation in K76T in PFCRT gene. Djimde AA *et al.* have investigated decline in parasite clearance rate that was because of *P. falciparum* resistance to chloroquine **[33]**.

Beshir K *et al.* have pondered pre and post genotype treatment in amodiaquine failure patients in Afghanistan. They reported PFCRT codon 72 to 76 haplotypes present in isolates. Beshir K *et al.* have concluded that mutation in PFCRT gene was associated with amodiaqine resistance **[34]**. Mayengue PI *et al.* have pored over examination in malaria hyperendemic town of Brazzaville (republic of Congo, Central Africa) and assessed 50 children with uncomplicated malaria. Mayaguez PI *et al.* have reported that chloroquine resistance was related with a mutation in PFCRT gene at 76th codon **[35]**. Lehane AM *et al.* have accounted that mutation in PFCRT resulted in decline accumulation of chloroquine in the *P.falciparum* parasite that related to resistance. In chloroquine-resistant allele due to less accumulation of chloroquine, there was excessive leakage of H^+ ions from the digestive vacuole of the *P.falciparum* parasite **[36]**. Baro NK *et al.* have studied *Saccharomyces cerevisiae* model system and reported that the *P. faciparum* chloroquine resistance transporter gene mutation was associated with *P. falciparum* resistance to chloroquine **[37]**.

Warhurst DC *et al.* have stated chloroquine was a cheap and nontoxic drug used to treat malaria. Warhurst DC *et al.* have reported resistance has been developed in *P.falciparum* in southeast Asia and South America in the 1970s as well as in West African countries in 1985 lead to the boosted mortality rate in African children **[38]**. Das A *et al.*have detailed that drug pressure was responsible for *P. falciparum* drug resistance. Das A *et al.*have picturized that amino acid mutation K76T in PFCRT gene in the digestive vacuole of *P. falciparum* was pledged for *P. falciparum* to chloroquine resistance **[39]**. Happ CT *et al*. have scrutinized 101 samples of children suffering from malaria in an African country. They were treated with amodiaquine which was followed up by 28 days. Happ CT *et al*. have declared relation between PFMDR Y86

alleles and PFCRT T76 with amodiaquine resistance. In addition to this Happ CT *et al*. have summarized that PFMDR Y86 alleles and PFCRT T76 could be used a molecular marker to monitor the origin as well as the prevalence of amodiaquine resistance in Africa **[40]**. Chaijaroenkul W *et al.* have audited total of 95 blood samples of patients suffering from malaria of Thailand and announced *P. falciparum* chloroquine resistance transporter protein mutation was responsible for *P. falciparum* resistance to chloroquine. Chaijaroenkul W *et al.* have demonstrated a strong link between PFCRT mutation and chloroquine resistance **[41]**.

Ross LS *et al.* have performed genomic analysis that showed boosted widespread of mutation in PFCRT gene that resulted in chloroquine resistance. To overcome that resistance usage of combination therapy dihydroartemisinin and piperaquine were employed. Ross LS *et al.* have reported that dihydroartemisinin and piperaquine combination therapy has been failed in Cambodia. Ross LS *et al.* have summarized that H97Y, F145I, M343L, or G353V mutations were bonded with amodiaquine resistance **[42]**. Bennett TN *et al*. have developed some newer methods to assess digestive vacuolar (DV) pH under continuous administration of chloroquine in Southeast Asia and South America. Bennett TN *et al*. have addressed that mutation in PFCRT to Southeast Asia Dd2 and South America 7G8 strain declined the pH of the digestive vacuole that boosted the pH of the vacuole. Bennett TN *et al*. have concluded that there was a strong alliance in between changed in physiology in the digestive vacuole and PFCRT alleles. Further, they have added that the resistance could be overcome by the use of verapamil **[43]**.

Young MD *et al.* have pondered seven patients from South America and Colombia and observed relation of chloroquine to the strain of *Plasmodium falciparum* . Young MD *et al.* have summarized no clearance or declined clearance of chloroquine from the parasite that showed chloroquine resistance. Further, they have reported the prevalence of chloroquine resistance **[44]**. Hess FI *et al.* have performed a case-control study on school children infected with *P. falciparum* for 7 days in North Guadalcanal, the Solomon Islands to detect chloroquine resistance. Their investigation aimed to study patient-related risk factors of chloroquine resistance **[45]**. Alene GD *et al.* developed a newer strategy to treat *P. falciparum* malaria patients that were not cured by chloroquine announced. The failure of chloroquine effect was associated

with the resistance that was mainly observed in Shewa and Arsiprovinces **[46]**. Nkhoma S *et al.* have examined 178 *P.falciparum* infections in three different locations of Malawi and confirmed that chloroquine and sulphadoxine-pyrimethamine resistance was rare in Malawi. Further Nkhoma S *et al.* have reported that mutations in a set of three dihydrofolate reductases and two dihydropteroate synthases were correlated with sulphadoxine-pyrimethamine treatment failure **[47]**.

Sanchez C *et al.* have reviewed on pros and cons of the carrier and transporter models to explain *P. falciparum* resistance to chloroquine. Sanchez C *et al.* have communicated that chloroquine resistance is due to K76T mutation in PFCRT, that present on membrane digestive vacuole of the parasite **[48]**. Carlton JMR *et al.* have announced that mutations in novel vacuole transporter PFCRT have resulted in *P. falciparum* chloroquine resistance. Carlton JMR *et al*. have declared that there was no kind of relation between chloroquine resistance and codon mutations in *P. vivax* gene **[49]**. Daily JP *et al.* have announced that *P. falciparum* chloroquine resistance was associated with mutations in PFCRT K76T in Senegal. In addition to that Daily JP *et al*. have also informed that polymorphism in codon A220S, Q271E, N326S and R371I were also pledged for chloroquine resistance **[50]**. Fidock DA *et al.* have informed about verapamil reversible chloroquine resistance cross designs to a 36 kb portion of chromosome 7 which docks a 13 exon gene point mutation in PFCRT in Asia, South America and Africa. Further Fidock DA *et al.* have declared a mutation in novel K76I gene resulted in declined pH, boosted acidification of digestive vacuole in *P.falciparum* parasite that was the major cause for chloroquine resistance **[51]**.

Kublin JG *et al.* have declared for the replacement of chloroquine antimalarial drug with sulfadoxine-pyrimethamine in Malawi in 1993 due to the increased rate of *P.falciparum* chloroquine resistance because of pfcrt mutation. Kublin JG *et al.* have announced decline chloroquine resistance from 1992 to 2000 and concluded that chloroquine could be reintroduced in combination with another antimalarial drug **[52]**. Cooper RA *et al.* have studied on the molecular basis of *P.falciparum* chloroquine resistance and announced that chloroquine resistance is as a virtue of PFRCT mutation that resulted in a change of amino acid K76T **[53]**. Hatabu T *et al.* have exercised on *P.falciparum* parasite isolates from three different regions of Philippines (Kalinga, Palawan and Mindanao). Hatabu T *et al.* have

found mutations in PFCRT K76T amino acid and detected two newer pfcrt 72-76 allelic types CVMDT and SVMDT. In addition to that, they also found mutations in pfmdr1 N86Y. Hatabu T *et al.* have announced mutations in PFCRT and pfmdr1 were the pledged for *P. falciparum* chloroquine resistance **[54]**.

Osman ME *et al.* have investigated parasite samples obtained from 50 patients suffering from uncomplicated *P.falciparum* in rural Eastern Sudan country. Osman ME *et al.* have reported that mutations in pfcrt gene on chromosome 7 and mutations in pfmdr1 on chromosome 5 performed a major role in chloroquine resistance. Further Osman ME *et al.* have added mutations of PFDHFR on chromosome 4 and PFDHPS on chromosome 8 werepledged for sulphadoxine-Pyrimethamine resistance **[55]**. Nsobya SL *et al.*have pondered malaria suffering patients of Toroyo, Uganda with artesunate-amodiaquine. Nsobya SL *et al.*have reported that mutations in PFCRT as well as mutations in pfmdr1 in 86Y and 1246Y allele were the major reason for the amodiaquine resistancethat was associated with the decreased response of *P. falciparum* to amodiaquine **[56]**. Naude B *et al.* have examined *P. falciparum* isolates in Southeast Asia and informed that PFCRT was a member of the unique transporters family that present in apicomplexan parasites as well as Dictyosteliumdiscoideum. Naude B *et al.* have reported that mutations in the PFCRT gene were directly associated with the *P. falciparum* chloroquine resistance **[57]**.

Docking is the inventive technique that can be used to design and discover some new drug candidates with potential medicinal value. Badeliya SN *et al.* have performed docking study of 1-Azetidinone substituted benzimidazole and benztriazole derivatives and reported that Glutamate dehydrogenase is really a potential target enzyme to design and discover some newer antimalarial drug agents. 1-Azetidinone substituted benzimidazole and benztriazole are the putative pharmacophore that can well inhibit NADP dependent *P. falciparum* glutamate dehydrogenase enzyme **[58-60]**.

CONCLUSION

The mutation in PFCRT and PFMDR1 are amenable for chloroquine and other quinine resistance whereas polymorphism in the Kelch13 (K13) propeller domain is pledged for the artemisinin resistance. This resistance is associated with a declined clearance rate of the parasite from the human that often lead to the death of a human in the southeast region of Asia like Cambodia, Thailand, Myanmar and Vietnam. NADP dependent *P. falciparum*

glutamate dehydrogenase enzyme is the accepted pharmacophore for the design and development of newer antimalarial agents. Furthermore, 1-Azetidinone substituted benzimidazole and benztriazole derivatives has shown their effectiveness in inhibiting this *P. falciparum* glutamate dehydrogenase enzyme. So, it is an authentic time to design and discover newer antimalarial medicaments that overcome the mutation, boost the parasite clearance rate with minimal or no side effects, and help the society.

List of Abbreviations

Pfcrt = *Plasmodium falciparum* chloroquine resistance transporter

Pfmdr = *Plasmodium falciparum* multidrug resistance transporter

GFI = Genotype-failure indices

K13 = Kelch13 propeller domain

PFDHFR= *Plasmodium falciparum* dihydrofolate reductase

PfPI3K = Phosphatidylinositol-3-kinase

SNP = Single nucleotide polymorphism

Humans and Animal Rights

No any human or animal were employed for the course.

Consent for Publication

Not applicable.

Availability of Data and Materials

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