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Plasmodium Falciparum ARTEMISININ DRUG RESISTANCE: A LEGITIMATE JUNCTURE TO DESIGN AND DISCOVER CONTEMPORARY ANTIMALARIAL MEDICAMENTS

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ABSTRACT

Malaria is a life-threatening infectious disease caused by parasitic single-celled microorganisms, mainly transmitted by the anopheles female mosquito of the plasmodium family. Artemisinin, an antimalarial agent, is one of the cheaper drugs available worldwide. It has been observed that resistance toward artemisinin and some other quinine derivatives developed in the southeast region of Asia like Cambodia, Thailand, Myanmar, and Vietnam since 1957. Since 1970, the exact resistance has been increased, and it has been developed in several regions of India. Consequently, it is necessary to create some potential antimalarial agents to overcome this kind of drug resistance and side effects. Here we have reviewed research articles by the researchers from various countries and executed an attempt to report Plasmodium falciparum artemisinin resistance as a result of mutations in pfcrt and pfmdr1 gene.

Keywords: Malaria, sepsis, gastroenteritis, Polymerase chain reaction, Resistance, Vacuolar transport

INTRODUCTION

Malaria is a life-threatening infectious parasitic disease caused by the anopheles female mosquito. Biting of the mosquito leads to the introduction of parasites from the mosquito's saliva into the host's blood. The parasites move to the liver of the infected host and perform the maturation and reproduction stage. Five species of Plasmodium have been reported that can infect and be spread by humans. P. falciparum can result in most death, whereas P. vivax, P. ovale and P. malariae broadly cause a benign form of malaria. The species P. knowlesi barely introduces disease to humans. These microorganisms can affect humans as well as other animals **(Figure 1)**.

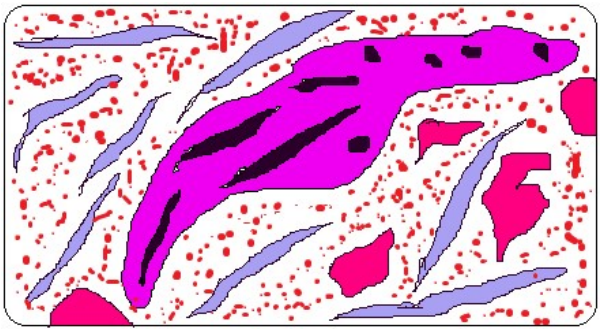

Figure 1: A Plasmodium From The Saliva of a Female Mosquito Moving Across a Cell Signs and symptoms

Malarial signs and symptoms can be seen in a human ten to fifteen days after being bitten by the mosquito. In typical cases, malaria causes symptoms like fever, a headache, tiredness, vomiting, shivering, joint pain, hemolytic anaemia, jaundice, and haemoglobin in the urine. But in an extreme situation, it can cause yellow skin, retinal damage, seizures, and coma, and if uncured, it may lead to death. Sometimes other conditions can be seen like sepsis, gastroenteritis and viral diseases. **(Figure 2)**.

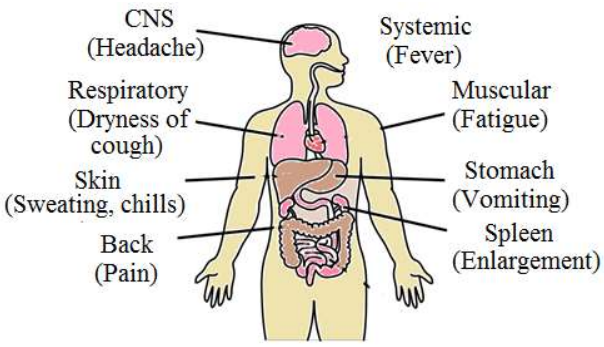

Figure 2: Signs and Symptoms of Malaria

Diagnosis

Malaria is typically diagnosed by microscopically examining blood using either blood films or antigen-based rapid diagnostic tests. Polymerase chain reaction methods have been developed that can be used to detect the DNA of the malarial parasite. Still, these methods are not widely used in areas where malaria is expected due to their cost and complexity.

Treatment

Malaria can be treated by combination therapy. A combination of antimalarial medications includes an artemisinin derivative. The second medication may be chloroquine, mefloquine, lumefantrine or sulfadoxine/pyrimethamine. If an artemisinin derivative is unavailable, then quinine and doxycycline may be used **(Figure 3) [1-4]**.

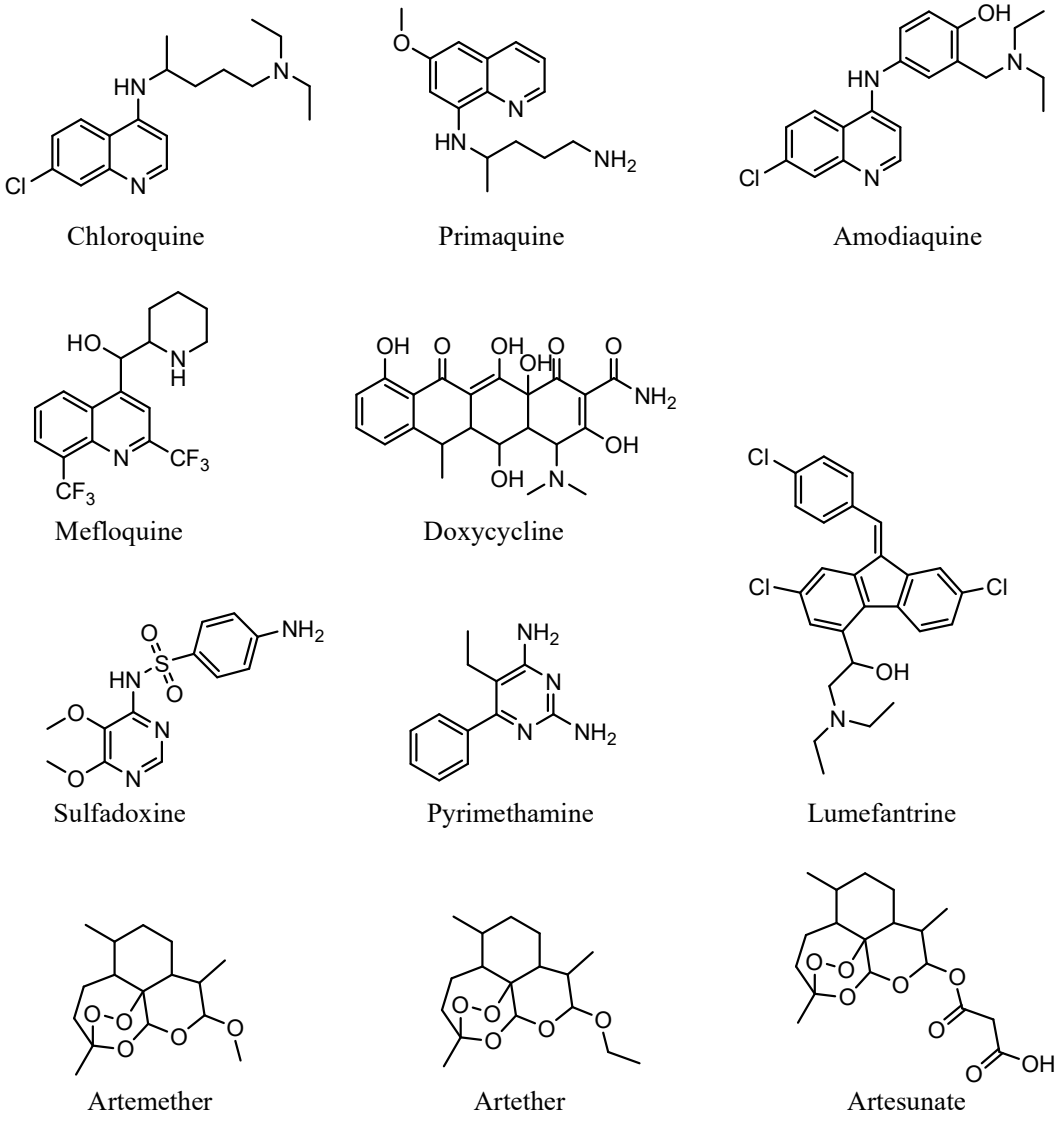

Figure 3: Currently available drugs used to treat malaria with their structure

The resistance of Plasmodium Falciparum to Chloroquine and Artemisinin derivatives.

Artemisinin derivatives like Artemether, Artether, and Artesunate consist of artemisinin and dihydroartemisinin that employed to prevent and treat malaria effectively. It has been monitored that resistance to Chloroquine and Artemisin derivatives have been emerged in 1957 on the Colombia-Thailand border. In Venezuela and parts of Colombia around 1960, in Papua New Guinea in the mid-1970s and in Africa origin in 1978 in Kenya and Tanzania and prevalence by 1983 in Sudan, Uganda, Zambia and Malawi. It has been confirmed that this resistance has been spread up to 40 different countries **[5-9]**.

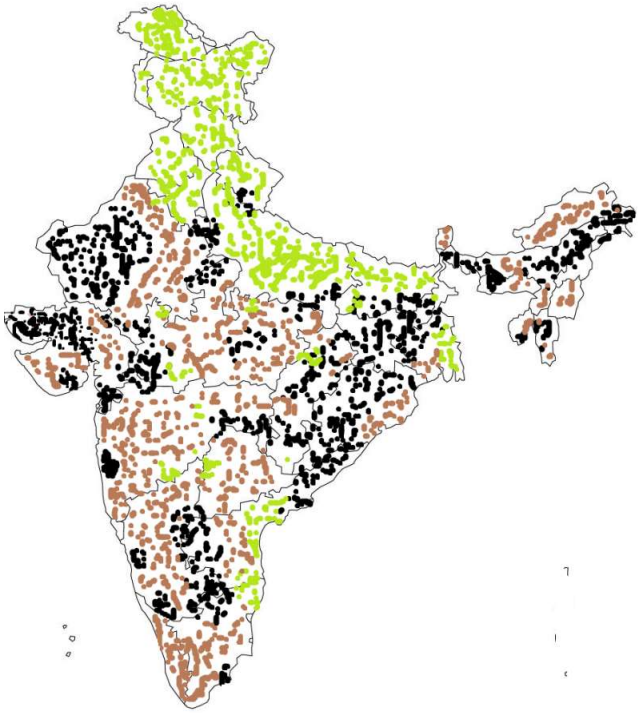

Figure 4: Study between 1978 and 2021. The black region indicates districts of 10% or more chloroquine and Artemisinin derivatives resistance. Brown region indicates Plasmodium Falciparum endemic areas and green region indicates districts without Plasmodium transmission

An intensive research that shows Plasmodium Falciparum artemisinin resistance

Dondrop AM *et al*. have pondered 40 patients in Pailin, western Cambodia and Wang Pha, Northwestern Thailand. The patients were delivered an oral artesunate dose of 2 mg per kg of body weight per day. In the second case, patients were administered 4 mg per kg of artesunate for three days, followed by mefloquine at 25 mg per kg. Dondrop*et al*. Meditated in vitro and in vivo on Plasmodium

falciparum susceptibility, artesunate pharmacokinetics and molecular resistance and reported that artemisinin-based combination therapies have abstained on the Thai–Cambodian border **[10]**.

Amaratunga C *et al*. have assessed 26 Plasmodium falciparum parasites. Among them, four gave better results, 13 were fast clearing parasites, but the resistant stage was developed with three parasites. In the Lancet Infectious Diseases, they have documented that the endurance of Plasmodium falciparum contradicted between fast clearing and slow clearing parasites of artemisinin treated malaria patients in Western Cambodia **[11]**. Ashley EA *et al*. have matriculated 1241 adults and children with acute and uncomplicated falciparum malaria in the open-label endeavour at 15 sections in 10 countries (seven Asian and three African countries) between May 2011 and April 2013. Patients were orally administered artesunate 2 mg per kg according to the patient's weight or 4 mg per kg for three days, ensured by three days of artemisinin combination therapies. Blood samples were assessed every six hours. They reported declined clearing infections correlated with single point mutations in the propeller domain of the P. falciparum kelch protein gene present on chromosome 13 (Kelch 13) was observed in Southeast Asia from southern Vietnam to central Myanmar **[12]**.

Mbengue A *et al*. have argued that artemisinin derivatives are potent inhibitors of Plasmodium falciparum phosphatidylinositol-3-kinase (PfPI3K). They have affirmed that *P.falciparum* Kelch 13 (PfKelch13) was a primary marker of artemisinin resistance. As a consequence of the mutation of PfKelch13, poubiquitation and artemisinin binding to PfKelch13 were lessened. As a result, the kinase level and PfPI3K level were boosted. Transgenic expression of an additional kinase brainstormed resistance **[13]**. Saralamba S *et al*. evolved a mathematical model depicting the intrahost parasite stage-specific pharmacokinetics-pharmacodynamics relationships. Thirty-nine patients from Pailin and 40 patients from Wang Pha were treated with artesunate. In vivo study was carried out. The parameters demonstrated the best results for the trophozoite and schizont stages but a wavering relationship for the ring stages. The model advocated the development of artesunate resistance by the ring stage of *P.falciparum* **[14]**. O'Brien C *et al*.have executed artemisinin resistance during in vitro study of short-term exposure artemisinin to ring-stage intra-erythrocyte *P.falciparum* parasites. That was eventuated by curtailing

the haemoglobin degeneration rate, the crucial step for artemisinin bioactivation **[15]**.

Witkoski B *et al*. have enforced in-vitro and ex-vivo phenotypic artemisinin assays and broadcasted artemisinin-resistant Plasmodium falciparum malaria in Cambodia **[16]**. Straimer J *et al*. have genetically mutated the *P.falciparum* K13 locus by applying zinc-finger nuclease enzymes. They unmasked ring-stage parasites to the artemisinin in vitro and computed the survival rates. They abolished mutated K13 and recognised dwindling survival rates of parasites from 13 to 49 % to 0.3 to 2.4 % in Cambodia. Likewise, they examined to deepen survival rates from ≤0.6% to 2 to 29% after infusion of K13 mutations. They concluded that K13 mutations were dominant in artemisininresistance **[17]**. Cheng Q *et al*. have proposed that 3-50% of non-immune patients decline treatment when artemisinin is administered singly. This breakdown in medicine results from the shorter treatment span of 3 to 5 days. This failure was reduced when the treatment span was increased from 5 to 7 days. Artemisinin derivatives have a shorter half-life, so they destroy all *P.falciparum* . This is a significant reason for artemisinin resistance **[18]**.

Amaratunga C *et al*. have surveyed 3504 individuals from different six districts of Pursat and concluded input of two genetics and host factors to the artemisinin-resistance phenotype in Pursat, Western Cambodia **[19]**. Breman JG *et al*. have reported lengthened clearance time of P. falciparum in Cambodia, Thailand, and nearby patients and decreased effectiveness of artemisinin derivatives. They announced the main factors for the drug resistance were drug pressure, parasite selection and mutation **[20]**. Ariey F *et al*. have accomplice mutations in the PF3D7_134700Kelch propeller domain (K13-propeller) and the artemisinin resistance in vivo and in vitro. They communicated a forceful alliance between the presence of a mutated genome within Vitro endurance rates and in vivo parasite clearance rates. They firmly concluded that k13-propeller mutations are the crucial stimulus for artemisinin resistance **[21]**. Miotto O *et al*. have assessed genetic differentiation in 825 Asian and African *P.falciparum* samples and marked Western Cambodia as an epicentre of artemisinin resistance **[22]**.

St. Laurent B *et al*. have apprised that artemisinin resistance parasites were repeatedly present in gametocytaemia and also suggested that transmission of artemisinin-resistant parasites has been boosted. They further pondered resistance of artemisinin in the ring stage of parasites, and

it is because of Kelch13 mutations **[23]**. Miotto O *et al*. have investigated 20 mutations in Kelch13 (PF3D7_1343700) across 15 locations in Southeast Asia that decline clearance of *P.falciparum* parasite. They summarised nonsynonymous polymorphisms in ferredoxin (Fd), apicoplast ribosomal protein S10 (arps10), multidrug resistance protein 2 (mdr2) and chloroquine resistance transporter (CRT), further parade heavy correlation with artemisinin resistance **[24]**. Amaratunga C *et al*. have addressed where chloroquine resistance has not been developed; it can be used to treat P.vivax. Artemisinin-based combination therapy can be used where artemisinin resistance has not been produced. They pictured that chloroquine adequately treatsP.vivax in Pursat Province, West Cambodia **[25]**. Mishra N *et al*. have analysed Pfk-13 mutations that effectively correlate with artemisinin resistance in India. PCR amplified samples were arranged from codon 427 to 727. They assessed 384 samples in India and concluded nonsynonymous mutations in northeastern states **[26]**.

Das S *et al*. have pondered 136 patients infected with uncomplicated *P.falciparum* . Das S *et al*. have executed an ex-vivo survival assay at 0-3 hours after ring-stage parasites violation to Red Blood Cells. They deliberated parasite clearance half-life, kelch13 mutations, and parasites survival of parasites from April 2013 through March 2014 **[27]**. Mishra N *et al*. have Collected 254 samples during 2014-2015 from Indian Northeast region states Tripura, Mizoram and Arunachal Pradesh. Mishra N *et al*. have said that three non-synonymous mutations in the K13 propeller gene (k13) are responsible for artemisinin resistance. Among these three codons, 446 and 578 are present in the propeller region, whereas codon 189 is present in the nonpropelledregion **[28]**. Valderramos SG *et al*.have reported that artemisinin can inhibit the *P.falciparum* ortholog of the ER calcium pump PfATP6 SERCA, PfATP6. Valderramos SG *et al*.have stated mutation in the genome can create resistance of *P.falciparum* to artemisinin and decrease the clearance rate of *P.falciparum* in vivo **[29]**.

Conrad MD *et al*. have described that haemoglobin degradation is required for potent artemisinin drug activity. In addition, Conrad MD *et al*. have addressed that mutation in *P.falciparum* genome Kelch13(PF3D7_1343700), and bared mutation in FP2 gene in parasites were pledged for artemisinin resistance **[30]**. Imwong M *et al*. have pored over gens like *P.falciparum* mdr1 (Pfmdr1), *P.falciparum* ATPase6 (PfATPase6), 6-kb mitochondrial

genome and ubp-1 of ART resistant strain from Cambodia and compared it with sensitive strains from Thailand. They concluded that *P.falciparum* resistant phenotype was not associated with any other gene described above **[31]**. Klonis N *et al*. have administered *P.falciparum* with artemisinin to check the activity. They found that the drug can decline the uptake of haemoglobin and the growth of the parasite. Klonis N *et al*. have summarised that inhibition of hemoglobinase activity by cysteine protease inhibitors, expunction of cysteine protease falcipain-2, and direct destitution of host cell lysate downturn artemisinin sensitivity **[32]**.

Tucker MS *et al*. have stated intermediate resistance levels in *P.falciparum* that were engendered in vitro for artelinic acid and artemisinin. The addressed parent clone (D6) can be recovered by 1,500 ng/ml artemisinin, whereas the resistant parasite can be recovered by 2,400 ng/ml artemisinin. Tucker MS *et al*. have documented that three resistant parasites, D6, W2 and TM91c235, show three-fold resistance to artemisinin **[33]**. Menard D *et al*. have assessed 14,037 samples from 59 countries and observed kelch k-13 propeller sequence polymorphism. Menard D *et al*. have mentioned that 36.5% of the K13 mutations were reported within two areas of Asia- One in Laos, Cambodia, and Vietnam, while the other was in Myanmar, China, and Thailand. This mutation is responsible for the delayed clearance of parasites **[34]**. Kamau E *et al*. have analysed 1212 *P.falciparum* samples collected from 12 countries. They found a mutation in the Kelch-13 propeller domain. They summarised widespread K13-propeller polymorphism around sub-Saharan Africa and detected 22 unique mutations containing seven nonsynonymous mutations **[35]**. Mohon AN *et al*. have collected *P.falciparum* infected malaria patients from seven endemic districts of Bangladesh between 2009 and 2013, including Bandarban (Lama Upazila health complexes(UHC)), Netrokona (Durgapur and Kalmakanda UHC), Rangamati (Rajasthali UHC), Moulvibazar (Sreemangal and Kamalganj UHC), Khagrachari (Matiranga UHC), Cox's Bazar (Ramu and Ukhia UHC) and Mymensingh (Haluaghat UHC). They wrapped up that artemisinin-based combination therapy remained fruitful in Bangladesh. In contrast, a mutation in the K13 propeller gene (PF3D7_1343700 or PF13_0238) has emerged in Thai-Myanmar and Thai-Cambodian borders, leading to artemisinin resistance **[36]**.

Tun MD KM *et al*. have amassed 940 samples of different 26 countries and did a

cross-sectional survey at malaria treatment centres at other 55 locations in Myanmar and some nearby borders in Thailand and Bangladesh between January 2013 and September 2014 that 371 among them parade K13-propeller mutation. This mutation was associated with artemisinin resistance **[37]**. Isozumi R *et al*. have compiled 539 samples from islands in Kenya and Lake Victoria in 2012-2013. Isozumi R *et al*. established mutation in the *P.falciparum* K13 propeller gene. Further, they announced five new types of synonymous and four new types of nonsynonymous mutations associated with artemisinin resistance **[38]**. Wang Z *et al*. studied 191 parasite clones from the China-Myanmar area between 2007 and 2012. They scrutinised K13 polymorphisms in Plasmodium falciparum parasites and concluded that the K13-propeller gene (K13), PF3D7_1343700 was correlated with artemisinin resistance **[39]**. Ouattara A *et al*.have addressed those molecular markers are the primary tool for the prevalence of artemisinin resistance. They pictured that single nucleotide polymorphisms (SNPs) in the PF3D7_1343700 Kelch13 propeller were correlated with artemisinin resistance **[40]**. Lu F *et al*. have performed a ring-stage survival assay of *P.falciparum* strains and documented nonsynonymous single nucleotide polymorphism (SNP) followed by moving from methionine to isoleucine at amino acid position 579, which correlates with artemisinin resistance **[41]**.

Fairhurst RM *et al*. have given information that artemisinin, chemically, sesquiterpene lactones, are potent inhibitors of almost all blood stages of *P.falciparum* . This includes the ring, trophozoite and schizont like asexual stages and immature gametocytes like asexual stages **[42]**. Huang B *et al*. has examined 207 *P.falciparum* affected blood samples from Comoros Island and communique that artemisinin-based combination therapy can treat uncomplicated *P.falciparum* because of mutation in the K13-propeller gene in *P.falciparum* strain in GrandeComrore Island, Union of Comoros that was correlated with artemisinin resistance **[43]**. Hott A *et al*. have reported artemisinin derivatives can be used to treat multidrug-resistant malaria. In Southeast Asia, due to mutation in the Kelch13 domain gene (Pf3D7_1343700) declined clearance rate of ring-stage *P.falciparum* parasites **[44]**.

Grigg MJ *et al*. have analysed oral artesunate study daily for three days of patients with uncomplicated malaria in 3 adjacent district hospitals in Sabah, East Malaysia. Patients were given a split dose of mefloquine on days 3 and 4 (total dose of 25

mg/kg), followed for 28 days. They observed and concluded that Kelch13 polymorphism was correlated with artemisinin resistance **[45]**. Takala-Harisson S *et al*. have performed trials on *P.falciparum* from artesunate efficacy in Laos, Myanmar, Bangladesh, Cambodia and Vietnam and were genotyped at 33716 genome-wide single-nucleotide polymorphisms (SNPs). They informed that Kelch13 mutations were responsible for the decline clearance of *P.falciparum* **[46]**. Dondrop AM *et al*. have announced artemisinin combination therapies were the first-line treatment of uncomplicated *P.falciparum* malaria. Artemisinin resistance decreases the parasite clearance rate. They communicated about various strategies to treat malaria. This includes early diagnosis, appropriate treatment, decline in drug pressure, vector control optimisation, population targeting, strong management, surveillance systems, and operational research **[47]**.

Witkowski B *et al*. have cultured 20 isolates from Pailin and Ratanakiri and performed comparative in-vitro activity of dihydroartemisinin to ring-stage *P.falciparum* parasite. They addressed the survival rate of the ring-stage parasite is 17 fold higher in isolates of Pailin than in the isolates of Ratanakiri **[48]**. Rogers WO *et al*. have studied 51 samples having uncomplicated *P.falciparum*. They were given therapy with 12 mg/kg up to a maximum of 600 mg of artesunate and 25 mg/kg of mefloquine up to 1000mg. Polymerase chain reaction genotyping of msp1, msp2 and glurp was employed for the treatment failure from new infections. They concluded that artesunate-mefloquine combination therapy failed in Southern Cambodia due to the resistance **[49]**. Taylor *et al*. have analysed the *P.falciparum* K13-propeller gene in 22 parasites from the *P.falciparum* strain 3D7 (ATCC, Manass, VA) and AnlongVeng, Cambodia. Taylor *et al*. have described polymorphism and mutation in the Kelch13 propeller gene have been detected more in southeast Asia than among African people. Taylor *et al*. have concluded that artemisinin resistance is more in Southeast Asia than in Africa **[50]**.

Tilley L *et al*. have addressed a rationale for resistance: a slower rate of parasite clearance in artemisinin administered malarial patients. The slower release was related to a boosted survival rate of ring-stage parasites. Tilley L *et al*. have further pictured that K13 mutation was a molecular marker that exhibited a significant role in artemisinin resistance **[51]**. Dogovski C *et al*. have described that mutation of Kelch13 in *P.falciparum* was responsible for artemisinin

resistance. Dogovski C *et al*. have announced that this increases the survival rate of a ring-stage parasite and enhances the cell stress response that proteasome inhibitors can target. Dogovski C *et al*.have addressed that proteasome inhibitors exhibit a synergistic effect on artemisinin that resulted in declined artemisinin resistance as well as enhanced activity of artemisinin towards *P.falciparum* **[52]**. Leang R *et al*. have briefed that Western Cambodia was considered as an epicentre for multidrug resistance of *P.falciparum* , WHO approved artemisinin-based combination therapies. Due to mutation in Kelch13, antagonism has been developed to artemisinin **[53]**.

Imwong M *et al*. have examined isolates of *P.falciparum* for Pfkelch13 mutations and Pfplasmepsin2 gene amplification from northeastern Thailand, Western Cambodia, Southern Laos and Myanmar. Imwong M *et al*. have compiled blood samples and insured uncomplicated *P.falciparum* malaria. Mutation in Pfkelch13 results in artemisinin resistance in *P.falciparum* across the Greater Mekong subregion **[54]**. Phyo AP *et al*.have pondered parasite count six-hourly in patients on the northwestern border of Thailand who has given artesunate. Phyo AP *et al*. have pored over parasite clearance half-lives, and parasites were genotyped for 93 single nucleotide polymorphisms. They point out their study to examine if artemisinin resistance has prevalence on the Thailand–Myanmar (Burma) border **[55]**. Noedl H *et al*. have described that artemisinin was a potent drug to treat *P.falciparum* , but due to its prevalence, it cropped up the resistance. Noedl H *et al*. have declared that artemisinin monotherapy cannot be employed where malaria was endemic. Artemisinin-based combination therapy can be used to overcome that resistance **[56]**.

Chenet SM *et al*. have scrutinised 98 samples from Guyana and investigated polymorphisms in Kelch13 (Pfk13) propeller domain. Chenet SM *et al*. have informed that in Guyana and nearby countries, continued molecular supervision and routine checkup of the therapeutic efficacy of artemisinin-based combination therapy were sanctioned **[57]**. Talundzic E *et al*. pursued 417 patient blood samples in 2007 in Thailand. They used K13 as a molecular marker and found seven different K13 mutant alleles (N458Y, R539T, E556D, P574L, R575K, C580Y, S621F) across the Thai-Cambodia and Thai-Myanmar borders. Talundzic E *et al*. have declared that K13 mutations are responsible for artemisinin resistance **[58]**.

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 leads to the death of a human in the southeast region of Asia like Cambodia, Thailand, Myanmar and Vietnam. So, it is an exact time to design and discover newer antimalarial medicaments that overcome the mutation, boost the parasite clearance rate 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.

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