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***Corresponding author:**
Dr. Harveer Singh Cheema
College of Agriculture Sciences, Teerthanker Mahaveer University, Moradabad-244102, Uttar Pradesh, India
Email: harveersingh84@gmail.com,

Drug resistance in plasmodium, future malaria management strategies and importance of medicinal plants

Harveer Singh Cheema[1], Mitra Pal Singh[1]

[1] College of Agriculture Sciences, Teerthanker Mahaveer University, Moradabad-244102. Uttar Pradesh, India

ABSTRACT

Malaria, the most common and destructive parasite disease in humans, take the lives of 1-2 million people every year. With the exception of artemisinin, resistance to most of the existing antimalarial agent classes has arisen, resulting in a new spike in malaria-related mortality, particularly in Africa. Southeast Asia has been a focal point for the development of drug resistance in *Plasmodium falciparum* since the late 1950s, when the first example of chloroquine resistance was discovered along the Thai-Combodian border. Despite the fact that the first incidence of quinine resistance had been documented far earlier in South America, the emergence of chloroquine resistance in Southeast Asia signalled the beginning of a new era in malaria history. Following the development of chloroquine resistance, Thailand and African countries shifted to a sulphadoxine-pyrimethamine combination as their first-line medication (SP). SP was subsequently superseded by mefloquine. Because of the quick development of resistance to this new medicine, artemisinin was introduced as a combination drug in the mid-1990s. Artimisinin resistance has been identified in several parts of the world, and if it continues, malaria control initiatives could be jeopardised, as there is now no substitute antimalarial medicine available. The purpose of this review is to summarise the current state of knowledge about drug-resistant malaria and to sketch out the evolving trends of resistance to antibiotics, such as its causal factors, current situation in various geographical areas, molecular markers, consequences for preventing the emergence and spread of drug-resistant malaria, and the role of medicinal plants in the discovery of novel antimalarials.

Keywords: Artemisinin, Pfmdr1, Pfatp6, Gene Copy Number, Plasmodium Falciparum, Medicinal Plants.

INTRODUCTION

Malaria is a parasitic hematoprotozoan infection spread by several anopheline mosquito species. *Plasmodium falciparum*, one of four plasmodium species that typically infect people, is responsible for the majority of cases of morbidity and fatality [1]. Notwithstanding the incredible early successes of the malaria eradication campaign launched in the 1950s, many countries were unable to eradicate malaria due to technical, operational, and socio-economic challenges, resulting in malaria comeback in many regions of the world. The rise of drug resistance in pathogens and pesticide resistance in mosquito vectors has complicated the control programme [2]. Every year, an estimated 300–500 million people are afflicted with malaria, with 1.5–2.7 million people dying from it, including about one million children under the age of five. About 90% of global malaria cases and the vast majority of malaria-related demises occur in Sub-Saharan Africa and tropical Africa. Malaria incidence in India has fluctuated between 2 and 3 million cases each year during the last two decades [3,4]. Outside of Africa, India accounts for 40% of all instances. *Plasmodium falciparum* incidence was 9.3% in 1972, but it rose to 43.4 percent in 1991 [4]. In India, urban malaria is a challenging and serious problem, and the urban malaria control scheme covers more than 130 municipalities in 17 states. The spread of plasmodium species strains that are resistant to chloroquine and other antimalarial medications has complicated the problem even more.

Control of the anopheline mosquito vector has traditionally relied on two approaches: elimination of breeding places, usage of insecticides, stoppage of human contact (through the use of bed nets etc) and competent case supervision. A long-awaited 3rd support, an working malaria vaccine, has yet to appear and is unlikely to do so for another decade [1,2]. Antimalarials (mostly chloroquine, and sulfadoxine-pyrimethamine [SP]) have been used extensively in case management because they are affordable and readily available. Antimalarials, and antipyretics, are amongst the most frequently used drugs in tropical areas worldwide. Chloroquine concentrations in blood are measurable in the majority of the population in several parts of the tropics. In the last fifty years, the widespread use of these antimalarial medications has put immense pressure on human malaria parasites to acquire resistance mechanisms. In the last three decades, the evolution of resistance, notably in *P. falciparum*, has been a key factor to the worldwide rebirth of malaria disease [5,6]. The most plausible reason for a doubling of malaria-related child mortality in eastern and southern Africa is resistance [7]. In most malaria-affected areas, *P. falciparum* is now extremely resistant to chloroquine. SP resistance is also widespread and has grown at a considerably

faster rate. Mefloquine resistance is limited to zones where it has been widely used (Thailand, Cambodia, and Vietnam), yet it has emerged within 6 years of widespread usage [8]. The epidemiology of *Plasmodium vivax* resistance is less well understood; chloroquine resistance is only a severe problem in regions of Indonesia, Papua New Guinea, and surrounding countries [9].

ANTIMALARIAL DRUGS USED IN MALARIA CONTROL

Chemotherapy has long been an important component of malaria management and treatment. The most effective malaria remedy is quinoline, which contains antimalarial ingredients [10]. This class of pharmaceuticals includes 4-aminoquinoline compounds like chloroquine and mefloquine, the former of which is a more effective, economical, safe, and widely accessible treatment [11]. Proguanil, chloroproguanil, pyrimethamine, and trimethoprime are dihydrofolate reductase inhibitors, as are sulfa medicines including dapsone, sulfalene, sulfamethoxazole, and sulfadoxine [12]. Sulphadoxine and pyrimethamine (SP) is a typical such combination that is utilised as a first-line medicine various areas of the globe. Tetracycline and its derivatives, such as doxycycline, are extremely effective antimalarials used for both treatment and prevention [13]. Tetracyclines are frequently used in conjunction with quinine to boost cure rates in areas where quinine response has declined. Artemisinin compounds, derived from the plant *Artemisia annua*, are another useful antimalarial. These antimalarials (artesunate, artemether, and arteether) are the most effective and appear to affect the malaria parasite's protein synthesis [14]. These are used to treat severe malaria and have proved to have a much faster parasite clearance rate than quinine compounds. In some Southeast Asian nations, where multidrug-resistant strains of *Plasmodium falciparum* are common, a combination of artemisinin and mefloquine is used to treat uncomplicated malaria [15].

THE CURRENT STATE OF DRUG-RESISTANT MALARIA

Malaria drug resistance has become a key problem in the fight against the disease. Except for Artemisinin and its derivatives, practically all antimalarial medicines have been shown to cause resistance *in vivo* [16,17]. Both *P. falciparum* and *P. vivax* have been found to be resistant to antimalarials.

A. Chloroquine

Except for Central America, Hisparivala Island in the Caribbean, and parts of the Middle East and Central Asia, chloroquine-resistant malaria has been found everywhere where falciparum malaria is present [18]. In the late 1950s, chloroquine resistance in *P. falciparum* arose almost concurrently in Southeast Asia and South America [19,20]. By 1970, chloroquine-resistant falciparum strains had spread throughout all of South America's endemic zones, and nearly all of Asia and Oceania by 1989 [21]. Chloroquine resistance first appeared in Africa in 1978, then extended to the central and southern regions before arriving in west Africa in 1983 [20-22]. Chloroquine resistance has become widespread in Sub-Saharan Africa by 1989 [21]. Resistance against chloroquine has since extended far beyond the original emphasis, and is today seen in every country where malaria is endemic. Resistance was less severe in west and central Africa than in east Africa, but even in West Africa, it ranges from an advanced stage with significant morbidity and mortality impacts in Senegal's target areas [23]. to a moderate degree in Ghana [24]. Cameroon [25]. and a low level in Mali [26].

Chloroquine resistance was first discovered in India in 1973 in Assam's Karbi-Anglong district and in 1974 in Assam's Nowgong district [27]. It gradually extended south west, eventually encompassing almost the entire nation [28]. CQ resistance is currently widespread in India's northeast and southeast, resulting in substantial morbidity and mortality. The north northwest and central regions of India are currently experiencing minimal resistance, while the southern part of India is experiencing moderate opposition [29]. There have been multiple instances of chloroquine resistance in *P. vivax* from India [30,31]. Resistance in *P. vivax* is more significant because hypnozoites cause resistant parasites to relapse, second it is a combination of different strains in terms of incubation length, relapsing pattern, and sensitivity to primaquine because sulpha medicines are ineffective in treating it [32].

B. Sulphadoxine-Pyrimethamine (SP)

Chloroquine resistance has been rising since the early 1960s, resulting in a large increase in mortality [33]. To treat chloroquine-resistant malaria, the sulphadoxine-pyrimethamine combination was the medication of choice. In the 1960s, resistance to SP was first documented on the Thai-Cambodian border [34]. Later, extensive areas of Southeast Asia, southern China, and the Amazon basin have shown SP resistance [18,35,36]. SP resistance was first discovered in Africa in the late 1980s, and it has since spread eastward rather than westward. In an endemic area of Tanzania, large fractions of R-II/R-III responses have been documented in kids [13]. Resistance to sulpha medicines has been found in *P. falciparum*-infested areas in India, such as the northeastern states and Orissa. In 1987, *P. falciparum* resistance to the SP recipe was originally discovered in Delhi [37]. If nothing is done to stop it, resistance will undoubtedly spread around the globe and intensify at an alarming rate.

C. Quinine

Nearly a century ago, the first case of quinine resistance was recorded from South America. In the mid-1960s, it was discovered near the Thai-Cambodian border. Diagnostic resistance to quinine chemotherapy has been recorded on an occasional basis in Southeast Asia and western Oceania. It is less common in South America [39]. as well as Africa [38]. The widespread usage of quinine in Thailand in the early 1980s may have contributed to the emergence of widespread resistance [40]. As a result, this medicine has been used in conjunction with tetracycline or doxycycline for the past two decades to improve its efficacy. In India, resistance to quinine has evolved in the northeastern regions and the Kolar area of Karnataka [41].

D. Mefloquine

Resistance against mefloquine was initially discovered near the Thai-Cambodian border in the late 1980s [42]. It is common in several parts of Southeast Asia, as well as in the Amazon region of South America and on rare occasions in Africa [43]. Resistance to mefloquine in *P. falciparum* has been discovered in Gujarat, India [44].

A. Artemisinin

The newest and most effective antimalarial medications are artemisinin and its variants. Artemisinins are one of the few pharmacological types that can be used to treat severe malaria after chloroquine is no longer effective [45]. Artemisinins kill parasites and limit their primary metabolic processes, such as glycolysis, nucleic acid, and protein synthesis, more quickly than other antimalarials [46]. Artemisinins also target parasites of all ages, from the tiny rings that have newly penetrated erythrocytes to more advanced stages such growing trophozoites and schizonts [46]. *Plasmodium falciparum* susceptibility to artemisinin derivatives has been demonstrated in the Cambodia–Thailand border region [47,48].

MECHANISMS OF ANTIMALARIAL RESISTANCE

Plasmodium parasites have an exceptionally heterogeneous genome and the ability to switch between micro habitats in different hosts and the metabolic alterations they require, making it challenging to examine the particular modes of action of antimalarial medications on parasite metabolism [49]. Resistance appears to develop as a result of spontaneous mutations conferring lower sensitivity to a specific medicine or family of drugs [36]. When a large population of parasites is exposed to pharmacological pressure, resistance develops more quickly because sensitive parasites are removed while resistant parasites survive. In order to understand the physical nature of resistance, greater research into the parasite's metabolism and the antimalarial medications' method of action is required.

Chloroquine

Chloroquine is the medicine which has been explored the maximum, despite the fact that its precise mechanism is unknown till now. Many researchers have looked into the mechanism of antimalarial effect of quinoline-containing medicines (such as chloroquine), and numerous targets have been proposed [50]. The majority of pharmacological targets are found in the parasite's acidic food vacuole [51]. Resistance to chloroquine in *P. falciparum* is thought to be related to the parasite's improved ability to excrete chloroquine at a rate that prevents chloroquine from reaching the levels essential for heamepolymerization inhibition [10]. Chloroquine efflux occurs 40 to 50 times faster in resistant parasites than in susceptible parasites [51]. The fact that medications that interfere with this efflux system can reverse chloroquine resistance [52]. adds to the evidence for this mechanism, but the molecular basis of this efflux is still a subject of contention. The molecular analysis of *P. falciparum* isolates reveals that only a limited gene loci are linked to *P. falciparum* chloroquine resistance. These genes are known as *pfmdr-1* and 2, as well as pfcrt. The *Pfmdr-1* gene, which codes for P-glycoprotein homologne-1 (Pgh-1) and is located on chromosome 5, has generated interest in antimalarial resistance. According to research undertaken in many parts of the world, the point mutation of aspartic acid to tyrosine at codon 86 (A-86 to T-86) is linked to chloroquine resistance [53,54]. Several other pfmdr-1 polymorphisms, including Phe 184, Cys 1034, Asp1042, and Tyr 1246, have been linked to chloroquine resistance to varied degrees. On chromosome 7, another locus influencing chloroquine resistance has been discovered, which encodes a transmembrane protein in a malaria parasite's digesting vacuole [55]. A series of point mutations in the pfcrt gene has been related to *in vitro* chloroquine resistance in *P. falciparum* from Africa, America, and Asia [56]. According to Djimde *et al*., the substitution of thyroxine (T76) to lysine (K76) at codon 76 was seen in all chloroquine resistant isolates but not in sensitive isolates [26].

Antifolate combination drug resistance

Sulphadoxine-pyrimethamine and other antifolate drugs inhibit dihydrofolate reductase (DHFR), though sulphones and sulphonamide substances impede dihydropteroate synthase (DHPS) [57]. Resistant cultures dihydrofolate reductase enzymes bind to pyrimethamine 400–800 times less readily than drug-sensitive strains' enzymes [58]. The molecular basis of SP resistance is the best understood. Resistance to DHFR and DHPS has been established as a result of specific gene mutations. Point mutations in the codons of the dhps gene are thought to provide resistance by lowering the enzyme's binding affinity [59-61]. A specific point mutation in the dhfr gene has been linked to pyrimethamine resistance due to a decrease in DHFR's drug binding affinity. Ala to val at codon 16, asp to isol at codon 51, cys to ar at codon 59, serine to asp at codon 108, thr and iso to leucine at codon 164, this combination of mutations has been observed in Thailand, where high level of SP resistance is well recognised. A crucial alteration for pyrimethamine resistance is a point mutation from serine to asparagine at codon 108. Additional point mutations in three more codons, ILe51, Arg59, and Leu164, have been shown to boost resistance [62]. It's unclear what role mutations in the dhfr and dhps genes play in clinical sulphadoxine-pyrimethamine resistance [21].

Quinine

It's possible that the pfmdr-1 mutation linked to chloroquine resistance is also responsible for lower quinine susceptibility [38]. The actual mechanism of resistance, however, is unknown.

Mefloquine

According to genetic studies, the copy number and variation of the pfmdr-1 gene are linked to mefloquine resistance. Research from Thailand suggested that having a larger copy number conferred mefloquine resistance [63]. but other studies from Brazil [38]. and Africa did not support that conclusion [64]. Some investigations have found that the pfmdr-1 Tyr86 mutation increases mefloquine sensitivity [63,64]. suggesting an inverse link between mefloquine and chloroquine sensitivity, while Ser1034, Asn1042, and Asp1246 mutations promote mefloquine resistance [65]. These findings support pfmdr-1's involvement as a major regulator of mefloquine resistance.

Artemisinin

Artemisinin resistance has no known molecular mechanism. *PfATP6* was thought to be a parasite SERCA-type calcium pump that could be a target for artemisinins a few years ago [66]. This idea had the consequence that mutations in *PfATP6* could affect susceptibility to artemisinins [67]. In some geographically and chronologically dispersed results, decreased *in vitro* susceptibility to artemisinins was later linked to mutations in pfatp6 (especially coding for a S769N change) [68,69].

Controlling Drug-Resistant Malaria In The Future

Antimalarial resistance in plasmodium parasites is a critical problem that has put most malaria control programs in jeopardy. The future of antimalarial drug resistance and efforts to counteract it is determined by a number of factors. To begin with, antimalarial drugs will be required indefinitely. Second, the longer the drugs are used, the greater the likelihood of resistance developing. Third, the discovery of new pharmaceuticals takes longer time than parasite resistance development. Fourth, any approach to combat drug-resistant malaria, particularly in Africa, must take affordability into account. Multidrug resistance is a disturbing trend that complicates the antimalarial control approach even more. The use of antimalarial medicines in combination for the treatment of multidrug-resistant malaria may be advantageous. For specific endemic areas, the benefits and downsides of each prospective regimen must be carefully assessed. Because the single most critical determinant in the development of resistance is assumed to be overall drug pressure, therapies aiming at preventing drug resistance often focus on lowering overall drug pressure. Drug use and prescribing practises that are more limited might be beneficial, if not necessary, in minimising the emergence, dissemination, and intensification of drug resistance. Several trials are presently underway to create a malaria vaccine, and work on this vital prospect has been ongoing for several years. Current malaria vaccine clinical trials (based on distinct stage specific antigens) appear to be promising. More understanding of drug resistance genetics will contribute in the development of new, improved molecular-based approaches for early diagnosis and therapies aimed at reducing existing multidrug resistance and preventing the establishment of new drug resistance foci.

MEDICINAL PLANTS AND DISCOVERY OF NEW ANTIMALARIAL DRUGS

The universe has been gifted by nature with the plant kingdom, and plants are one of the fundamental life-supporting systems. Medicinal plants are, without a doubt, the oldest kind of medicine for treating a wide range of human problems. They have been utilised by many societies throughout history and continue to be an important element of our current technological civilization [70]. Plants have been used to treat malaria since ancient times. Plant-based pharmaceuticals account for over half of all medications in clinical use today [71]. Many studies have been conducted to analyse plant extracts in the hunt for novel antimalarials, although the majority of these investigations have been limited to *in vitro* tests. Furthermore, the isolation of active compounds from plants has been a recent addition to the use of plants as medicines, beginning with the isolation of morphine from opium in the early nineteenth century and the subsequent discoveries of quinine from *Cinchona* and Artimisinin from *Artemisia anua*. Antimalarials derived from plants had previously been a huge success. There are numerous powerful natural compounds identified from plants that have antimalarial action in vitro. e.g. *Rosa damascene* [72]. *Lawsonia inermis* [73]. *Alnus nepalensis* [74]. *Pluchea lanceolata* [75]. *Christia vespertilionis* [76]. and *Conyza sumatrensis* [77]. as well as phytomolecule derivates including ursolic acid derivatives [78]. should also be evaluated in *in-vivo* models. Compounds with low activity should be produced logically to increase their activity. The inherent toxicity of certain strong families of chemicals, such as Quassinoids, is also a big worry [79]. The development of resistance towards the current therapies warrants for developments of new antimalarials. ACTs are now effective; however, they can only delay the emergence of resistance. The affordability of contemporary antimalarials is another challenge, despite the fact that WHO and other resources are already available. Due to a lack of investment, the pharmaceutical sector has neglected the development of antimalarial medications. Artimisinin resistance has been identified in numerous places of the world, and if it continues, malaria control initiatives may be jeopardised because there is no substitute antimalarial medicine available. As a result, ongoing efforts to create novel antimalarial medicines derived from plants are required to tackle malaria resistance.

CONCLUSION

Resistance to widely used antimalarials has hampered malaria control efforts over the past 50 years, at significant cost to human health and life. Antimalarial medication resistance seemed almost inevitable. Given that most nations have accepted ACT as an antimalarial treatment method, the establishment and dissemination of artemisinin resistance is expected. To avoid this, a detailed understanding of the problems that underpin safe ACT use is essential, as well as increased antimalarial resistance monitoring. To summarise, significantly reducing drug pressure by more selectively using drugs, trying to improve how drugs are being used, prescribing follow-up procedures, or incorporating drugs that are inherently less likely to facilitate resistance or have properties that do not facilitate the development or spread of resistant parasites is required to control drug resistance in malaria parasites. We will only be able to extend the life of ACT and retain the advances made in malaria reduction in current years if we make these important steps.

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Conflict of Interest

None declared.

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REFERENCE

1. White NJ. Antimalarial drug resistance. J Clin Invest. 2004;113(8):1084-92.
2. Ballou WR, Hoffman SL, Sherwood JA, Hollingdale MR, Neva FA, Hockmeyer WT, *et al*. Safety and efficacy of a recombinant DNA Plasmodium falciparum sporozoite vaccine. Lancet. 1987;1(8545):1277-81.
3. Weekly Epidemiol Rec. Geneva: World Health Organization. 1996;71:25–32.
4. World malaria situation in 1994. Weekly Epidemiol Rec. Geneva : World Health Organization. 1997;72:285–92.
5. World malaria situation in 1992. Weekly Epidemiol Rec.Geneva : World Health Organization. 1994;69:309–14.
6. Marsh K. Malaria disaster in Africa. Lancet. 1998;352(9132):924.
7. Korenromp EL, Williams BG, Gouws E, Dye C, Snow RW. Measurement of trends in childhood malaria mortality in Africa: an assessment of progress toward targets based on verbal autopsy. Lancet Infect Dis. 2003;3(6):349-58.

8. Nosten F, van Vugt M, Price R, Luxemburger C, Thway KL, Brockman A, *et al*. Effects of artesunate-mefloquine combination on incidence of Plasmodium falciparum malaria and mefloquine resistance in western Thailand: a prospective study. Lancet. 2000;356(9226):297-02.
9. Resistance of malaria parasites to drug. WHO Tech Rep Ser. Geneva: World Health Organization. 1965;296:29.
10. Foley M, Tilley L. Quinoline antimalarials: mechanisms of action and resistance. Int J Parasitol. 1997;27(2):231-40.
11. Vandekerckhove S, D'hooghe M. Quinoline-based antimalarial hybrid compounds. Bioorg Med Chem. 2015;23(16):5098-119.
12. Ferone R. Dihydrofolate reductase from pyrimethamine resistant P. berghei. J Biol Chem. 1970;245(4):850–4.
13. Rønn AM, Msangeni HA, Mhina J, Wernsdorfer WH, Bygbjerg IC. High level of resistance of Plasmodium falciparum to sulfadoxine-pyrimethamine in children in Tanzania. Trans R Soc Trop Med Hyg. 1996;90(2):179-81.
14. Chawira AN, Warhurst DC, Robinson BL, Peters W. The effect of combinations of qinghaosu (artemisinin) with standard antimalarial drugs in the suppressive treatment of malaria in mice. Trans R Soc Trop Med Hyg. 1987;81(4):554-8.
15. White NJ, Nosten F, Looareesuwan S, Watkins WM, Marsh K, Snow RW, *et al*. Averting a malaria disaster. Lancet. 1999;353(9168):1965-7.
16. Zucker JR, Campbell CC. Smear-negative cerebral malaria due to mefloquine-resistant Plasmodium falciparum acquired in the Amazon. J Infect Dis. 1992;166(6):1458-9.
17. Talisuna AO, Karema C, Ogutu B, Juma E, Logedi J, Nyandigisi A, *et al*. Mitigating the threat of artemisinin resistance in Africa: improvement of drug-resistance surveillance and response systems. Lancet Infect Dis. 2012;12(11):888-96.
18. The use of antimalarial drugs. Report of an informal consultation. Geneva: World Health Organization 2001. WHO/CDS/RBM/2001.33.
19. Spencer HC. Drug-resistant malaria--changing patterns mean difficult decisions. Trans R Soc Trop Med Hyg. 1985;79(6):748-58.
20. Wernsdorfer WH, Payne D. The dynamics of drug resistance in Plasmodium falciparum. Pharmacol Ther. 1991;50(1):95-121.
21. Roux AT, Maharaj L, Oyegoke O, Akoniyon OP, Adeleke MA, Maharaj R, *et al*. Chloroquine and Sulfadoxine-Pyrimethamine Resistance in Sub-Saharan Africa-A Review. Front Genet. 2021;12:668574.
22. Wongsrichanalai C, Pickard AL, Wernsdorfer WH, Meshnick SR. Epidemiology of drug-resistant malaria. Lancet Infect Dis. 2002;2(4):209-18.
23. Trape JF. The public health impact of chloroquine resistance in Africa. Am J Trop Med Hyg. 2001;64(1-2 Suppl):12-7.
24. Landgraf B, Kollaritsch H, Wiedermann G, Wernsdorfer WH. Plasmodium falciparum: susceptibility in vitro and in vivo to chloroquine and sulfadoxine-pyrimethamine in Ghanaian schoolchildren. Trans R Soc Trop Med Hyg. 1994;88(4):440-2.
25. Ringwald P, Same Ekobo A, Keundjian A, Kedy Mangamba D, Basco LK. Chemoresistance of P. falciparum in urban areas of Yaounde, Cameroon. Part 1: Surveillance of in vitro and in vivo resistance of Plasmodium falciparum to chloroquine from 1994 to 1999 in Yaounde, Cameroon. Trop Med Int Health. 2000;5(9):612-9.
26. Djimdé A, Doumbo OK, Cortese JF, Kayentao K, Doumbo S, Diourté Y, *et al*. A molecular marker for chloroquine-resistant falciparum malaria. N Engl J Med. 2001;344(4):257-63.
27. Pattanayak S, Roy RG, Phukan D, Barkakuty BN. Chloroquine resistance in P. falciparum in Assam State. Indian J Med Res. 1979;70:14-9.
28. Shah NK, Dhillon GP, Dash AP, Arora U, Meshnick SR, Valecha N, *et al*. Antimalarial drug resistance of Plasmodium falciparum in India: changes over time and space. Lancet Infect Dis. 2011;11(1):57-64.
29. Verma SC, Mahajan RC, Prasad RN, Kumari S, Ganguly NK, Sharma BK, *et al*. Chloroquine-resistant falciparum malaria in Punjab (northern India). Trans R Soc Trop Med Hyg. 1986;80(3):489.
30. Rieckmann KH, Davis DR, Hutton DC. Plasmodium vivax resistance to chloroquine? Lancet. 1989;2(8673):1183-4.
31. Potkar CN, Kshirsagar NA, Kathuria R. Resurgence of malaria and drug resistance in plasmodium falciparum and plasmodium vivax species in Bombay. J Assoc Physicians India. 1995;43(5):336-8.
32. Adak T, Sharma VP, Orlov VS. Studies on the Plasmodium vivax relapse pattern in Delhi, India. Am J Trop Med Hyg. 1998;59(1):175-9.
33. Winstanley P. Modern chemotherapeutic options for malaria. Lancet Infect Dis. 2001;1(4):242-50.
34. Björkman A, Phillips-Howard PA. The epidemiology of drug-resistant malaria. Trans R Soc Trop Med Hyg. 1990;84(2):177-80.
35. Vasconcelos KF, Plowe CV, Fontes CJ, Kyle D, Wirth DF, Pereira da Silva LH, *et al*. Mutations in Plasmodium falciparum dihydrofolate reductase and dihydropteroate synthase of isolates from the Amazon region of Brazil. Mem Inst Oswaldo Cruz. 2000;95(5):721-8.
36. Bloland P. Drug resistance in malaria. Geneva: WHO 2001.WHO/CDS/CSR/DRS/2001.4.
37. Choudhury DS, Sinha S, Ghosh SK, Devi CU, Sharma VP. Report of a case of P. falciparum malaria resistant to chloroquine and combination of sulfalene and pyrimethamine in Delhi. Indian J Malariol. 1987;24(1):95-6.
38. Zalis MG, Pang L, Silveira MS, Milhous WK, Wirth DF. Characterization of Plasmodium falciparum isolated from the Amazon region of Brazil: evidence for quinine resistance. Am J Trop Med Hyg. 1998;58(5):630-7.
39. Jelinek T, Grobusch MP, Löscher T. Patterns of Plasmodium falciparum drug resistance in nonimmune travellers to Africa. Eur J Clin Microbiol Infect Dis. 2001;20(4):284-6.
40. Wernsdorfer WH. Epidemiology of drug resistance in malaria. Acta Trop. 1994;56(2-3):143-56.
41. Mishra SP. In vivo resistance to chloroquine and sulphapyrimethamine combination in P. falciparum in India. Proceedings of National Academy of Sciences, India. 1996;66:123–8.
42. Wongsrichanalai C, Sirichaisinthop J, Karwacki JJ, Congpuong K, Miller RS, Pang L, *et al*. Drug resistant malaria on the Thai-Myanmar and Thai-Cambodian borders. Southeast Asian J Trop Med Public Health. 2001;32(1):41-9.
43. Mockenhaupt FP. Mefloquine resistance in Plasmodium falciparum. Parasitol Today. 1995;11(7):248-53.
44. Sharma VP. Re-emergence of malaria in India. Indian J Med Res. 1996;103:26-45.
45. Krishna S, Bustamante L, Haynes RK, Staines HM. Artemisinins: their growing importance in medicine. Trends Pharmacol Sci. 2008;29(10):520-7.
46. Ter Kuile F, White NJ, Holloway P, Pasvol G, Krishna S. Plasmodium falciparum: in vitro studies of the pharmacodynamic properties of drugs used for the treatment of severe malaria. Exp Parasitol. 1993;76(1):85-95.
47. Noedl H, Se Y, Schaecher K, Smith BL, Socheat D, Fukuda MM, *et al*. Artemisinin Resistance in Cambodia 1 (ARC1) Study Consortium. Evidence of artemisinin-resistant malaria in western Cambodia. N Engl J Med. 2008;359(24):2619-20.
48. Dondorp AM, Nosten F, Yi P, Das D, Phyo AP, Tarning J, *et al*. Artemisinin resistance in Plasmodium falciparum malaria. N Engl J Med. 2009 Jul 30;361(5):455-67. doi: 10.1056/NEJMoa0808859. Erratum in: N Engl J Med. 2009;361(17):1714.
49. The biology of malaria parasites. Report of a WHO Scientific Group. WHO Tech Rep Ser 1987.
50. Yamada KA, Sherman IW. Plasmodium lophurae: composition and properties of hemozoin, the malarial pigment. Exp Parasitol. 1979;48(1):61-74.
51. Krogstad DJ, Gluzman IY, Kyle DE, Oduola AM, Martin SK, Milhous WK, Schlesinger PH. Efflux of chloroquine from Plasmodium falciparum: mechanism of chloroquine resistance. Science. 1987 Nov 27;238(4831):1283-5. doi: 10.1126/science.3317830. PMID: 3317830.
52. Martin SK, Oduola AM, Milhous WK. Reversal of chloroquine resistance in Plasmodium falciparum by verapamil. Science. 1987 Feb 20;235(4791):899-901. doi: 10.1126/science.3544220. PMID: 3544220.
53. von Seidlein L, Duraisingh MT, Drakeley CJ, Bailey R, Greenwood BM, Pinder M. Polymorphism of the Pfmdr1 gene and chloroquine resistance in

Plasmodium falciparum in The Gambia. Trans R Soc Trop Med Hyg. 1997 Jul-Aug;91(4):450-3. doi: 10.1016/s0035-9203(97)90281-9. PMID: 9373652.
54. Duraisingh MT, Jones P, Sambou I, von Seidlein L, Pinder M, Warhurst DC, *et al*. The tyrosine-86 allele of the pfmdr1 gene of Plasmodium falciparum is associated with increased sensitivity to the anti-malarials mefloquine and artemisinin. Mol Biochem Parasitol. 2000;108(1):13-23.
55. Fidock DA, Nomura T, Talley AK, Cooper RA, Dzekunov SM, Ferdig MT, *et al*. Mutations in the P. falciparum digestive vacuole transmembrane protein PfCRT and evidence for their role in chloroquine resistance. Mol Cell. 2000;6(4):861-71.
56. Durand R, Jafari S, Vauzelle J, Delabre JF, Jesic Z, Le Bras J, *et al*. Analysis of pfcrt point mutations and chloroquine susceptibility in isolates of Plasmodium falciparum. Mol Biochem Parasitol. 2001;114(1):95-102.
57. Bruce -Chwatt LJ. Chemotherapy of malaria. Geneva: World Health Organization 1986.
58. Ferone R. Dihydrofolate reductase from pyrimethamine-resistant Plasmodium berghei. J Biol Chem. 1970;245(4):850-4.
59. Nagesha HS, Din-Syafruddin, Casey GJ, Susanti AI, Fryauff DJ, Reeder JC, *et al*. Mutations in the pfmdr1, dhfr and dhps genes of Plasmodium falciparum are associated with in-vivo drug resistance in West Papua, Indonesia. Trans R Soc Trop Med Hyg. 2001;95(1):43-9.
60. Plowe CV, Cortese JF, Djimde A, Nwanyanwu OC, Watkins WM, Winstanley PA, *et al*. Mutations in Plasmodium falciparum dihydrofolate reductase and dihydropteroate synthase and epidemiologic patterns of pyrimethamine-sulfadoxine use and resistance. J Infect Dis. 1997;176(6):1590-6.
61. Urdaneta L, Plowe C, Goldman I, Lal AA. Point mutations in dihydrofolate reductase and dihydropteroate synthase genes of Plasmodium falciparum isolates from Venezuela. Am J Trop Med Hyg. 1999;61(3):457-62.
62. Mawili-Mboumba DP, Ekala MT, Lekoulou F, Ntoumi F. Molecular analysis of DHFR and DHPS genes in P. falciparum clinical isolates from the Haut--Ogooué region in Gabon. Acta Trop. 2001;78(3):231-40.
63. Price RN, Cassar C, Brockman A, Duraisingh M, van Vugt M, White NJ, *et al*. The pfmdr1 gene is associated with a multidrug-resistant phenotype in Plasmodium falciparum from the western border of Thailand. Antimicrob Agents Chemother. 1999;43(12):2943-9.
64. Basco LK, Le Bras J, Rhoades Z, Wilson CM. Analysis of pfmdr1 and drug susceptibility in fresh isolates of Plasmodium falciparum from subsaharan Africa. Mol Biochem Parasitol. 1995;74(2):157-66.
65. Reed ME, Saliba KJ, Caruana SR, Kirk K, Cowman AF. Pgh 1 modulates sensitivity and resistance to multiple antimalarials in Plasmodium falciparum. Nature. 2000;403:906–9
66. Eckstein-Ludwig U, Webb RJ, Van Goethem ID, East JM, Lee AG, Kimura M, *et al*. Artemisinins target the SERCA of Plasmodium falciparum. Nature. 2003;424(6951):957-61.
67. Uhlemann AC, Cameron A, Eckstein-Ludwig U, Fischbarg J, Iserovich P, Zuniga FA, *et al*. A single amino acid residue can determine the sensitivity of SERCAs to artemisinins. Nat Struct Mol Biol. 2005;12(7):628-9.
68. Jambou R, Legrand E, Niang M, Khim N, Lim P, Volney B, *et al*. Resistance of Plasmodium falciparum field isolates to in-vitro artemether and point mutations of the SERCA-type PfATPase6. Lancet. 2005;366(9501):1960-3.
69. Jambou R, Martinelli A, Pinto J, Gribaldo S, Legrand E, Niang M, *et al*. Geographic structuring of the Plasmodium falciparum sarco(endo)plasmic reticulum Ca2+ ATPase (PfSERCA) gene diversity. PLoS One. 2010;5(2):e9424.
70. Cheema HS, Singh MP. The Use of Medicinal Plants in Digestive System Related Disorders: A Systematic Review. J Ayu Herb Med. 2021;7(3):182-87.
71. Cheema HS, Prakash O, Pal A, Khan F, Bawankule DU, Darokar MP, *et al*. Glabridin induces oxidative stress mediated apoptosis like cell death of malaria parasite Plasmodium falciparum. Parasitol Int. 2014;63(2):349-58.
72. Khare S, Gupta M, Cheema HS, Maurya AK, Rout P, Darokar MP, *et al*. Rosa damascena restrains Plasmodium falciparum progression in vitro and impedes malaria pathogenesis in murine model. Biomed Pharmacother. 2018;97:1654-1662.
73. Singh DK, Cheema HS, Saxena A, Jyotshana, Singh S, Darokar MP, *et al*. Fraxetin and ethyl acetate extract from Lawsonia inermis L. ameliorate oxidative stress in P. berghei infected mice by augmenting antioxidant defence system. Phytomedicine. 2017;36:262-272.
74. Saxena A, Yadav D, Mohanty S, Cheema HS, Gupta MM, Darokar MP, *et al*. Diarylheptanoids Rich Fraction of Alnus nepalensis Attenuates Malaria Pathogenesis: In-vitro and In-vivo Study. Phytother Res. 2016;30(6):940-8.
75. Mohanty S, Srivastava P, Maurya AK, Cheema HS, Shanker K, Dhawan S, *et al*. Antimalarial and safety evaluation of Pluchea lanceolata (DC.) Oliv. & Hiern: in-vitro and in-vivo study. J Ethnopharmacol. 2013;149(3):797-802.
76. Harish C, Upadhyaya, Brijesh S, Sisodiab, Harveer S, Cheemab, *et al* Darokarb and Santosh K. Srivastava, Novel Antiplasmodial Agents from Christia vespertilionis. 2013;8(11):1591–94.
77. Boniface PK, Verma S, Shukla A, Cheema HS, Srivastava SK, Khan F, *et al*. Bioactivity-guided isolation of antiplasmodial constituents from Conyza sumatrensis (Retz.) E.H. Walker. Parasitol Int. 2015;64(1):118-23.
78. Kalani K, Yadav DK, Singh A, Khan F, Godbole MM, Srivastava SK, *et al*. QSAR guided semi-synthesis and in-vitro validation of anticancer activity in ursolic acid derivatives. Curr Top Med Chem. 2014;14(8):1005-13.
79. Negi AS, Gupta A, Hamid AA. Combating malaria with plant molecules: a brief update. Curr Med Chem. 2014;21(4):458-500.

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