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Mechanisms of antimalarial activity and drug resistance : Indian antimalarial medicinal plants

Shilpa Valiyaparambil[1], Muddukrishnaiah Kotakonda[1]*, Selvaraj Palanisamy, Natarajan Ashokkumar[2], Rameswari Shanmugam[3], Poornima Marimuthu[4], Samuel Thavamani B[5], Sirajudheen Mukriyan Kallungal[1]

1 Department of Pharmaceutics, Jamia Salafiya Pharmacy College, Pulikkal, Malapuram District, Kerala, India.
2 Department of Biochemistry and Biotechnology, Annamalai University, Annamalainagar 608002. Tamil Nadu, India.
3 Department of Pharmaceutical Chemistry, Sree Sastha Pharmacy College, Chembarambakkam, Tamil Nadu, India.
4 Department of Pharmaceutics, Tagore College of Pharmacy, Rathinamangalam, Melakotayur, Chennai, Tamil Nadu, India.
5 Department of Pharmacognosy, Ahalia School of Pharmacy, Kozhippara, Pudussery East, Palakkad, Kerala, India.

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*Corresponding author:

Email : krishna123muddu@gmail.com
Phone : +91-9633291641

ABSTRACT

Malaria is generally controlled through pharmacological therapy and is preventable to a certain extent. Most antimalarial drugs that have been in use for decades are now limited owing to the emergence and spread of drug resistance. Mechanisms of antimalarial activity and drug resistance: Indian antimalarial medicinal plants. A thorough search for antimalarial drugs was conducted in several databases, including Scopus, Embase, Cochrane, and PubMed. The keywords used for the search were antimalarial drugs, mechanisms of action, antimalarial resistance, and Indian medicinal plants. This study included all publications in English. Studying the method of action of drugs and the mechanism of drug susceptibility is critical for optimising their benefits and developing novel therapies with new targets. Little is known about the function of antimalarial medications and development of resistance. Many chemicals used for antimalarial activity have developed resistance. The demand for new antimalarial medicines has prompted significant efforts to develop novel antimalarial drugs from plants. Information from different Indian tribal communities and research publications was collected and compiled. The mechanisms of action, drug resistance, and antimalarial agents of Indian medicinal herbs have been documented in this study. This would aid future research on the antimalarial activity in plants.

INTRODUCTION

Plasmodium, a single-celled protozoan parasite transmitted to humans by the Anopheles mosquito, causes malaria. Malaria is one among the most prominent illness in tropical regions worldwide. It is endemic to many nations, placing more than 50% of the nation's population at risk, with exceptionally high death rates among young children [1]. Each year, the WHO (World Health Organization) assesses that between three hundred and five hundred million new malaria cases are diagnosed throughout the world, with the majority of cases occurring in Asia, Africa, South America and the South Pacific Islands [2]. According to WHO estimates, malaria is responsible for at least one million deaths annually. Despite efforts to control the disease, only modest improvements have been observed in many countries. Infections can reduce labour productivity and result in economic and human losses, depending on the severity of the infection [3]. In recent years, malaria control has become more challenging owing to the emergence of drug-resistant Plasmodium strains and the discovery that humans can become infected with similar Plasmodium species. Anopheles mosquitoes develop resistance to a wide range of insecticides. *Plasmodium falciparum* is the most potent parasite responsible for the highest rates of malaria and mortality, particularly in pregnant women and children. As per World Health Organization data, 228 million malaria cases were reported in 2018, with an estimated 405,000 fatalities linked to the disease [4, 5].

Malaria can be treated with chemotherapy; however, it is resistant to several medications. Artemisinin resistance was originally detected in Cambodia in 2006, and has since spread across Southeast Asia. The safety of chemoprophylaxis is also a

key problem because Doxycycline, Primaquine and Atovaquone are contraindicated in pregnant women and children. These flaws must be rectified and new medicines to combat malaria must be discovered [6].

Herbs and extracts are extensively used for the management and treatment of malaria in various parts of the world because they are inexpensive, readily available, and effective. Herbal medicine has become increasingly popular worldwide as a therapeutic option. Over 80% of the world's population relies on herbs for their primary health ailments [7]. Most people use traditional herbal medicines because of their proven therapeutic effectiveness. Researchers' interest in herbal plants as viable alternatives to more effective antimalarial medications is encouraged by an increased preference for herbal therapies combined with pathogenic strains resistant to contemporary drugs, especially Plasmodium species [8].

Natural chemicals, such as plant products, play a significant role in medication development and have benefited the pharmaceutical industry. Many pharmacological classifications have been developed based on active chemicals. For example, those from plant sources have helped in therapies for many infectious diseases, such as cancer, and other incurable diseases caused by various metabolic problems [9]. Furthermore, plant-derived compounds, such as Artemisinin and Quinine, and their synthetic analogues are the mainstays of antimalarial treatment. Many people in malaria-endemic areas, particularly in African countries, depend only on herbal treatments as an initial line of defense. The expense of mainstream treatments, accessibility, apparent effectiveness, fewer side effects, and great faith in traditional therapies are all prominent reasons for their preference [10].

Reviews of the antimalarial activity of medicinal plants are required to promote the discovery and manufacture of new antimalarial medications. Only a few reviews of plant-based antimalarial effectiveness have been published in scientific journals. Only studies on phytocomponents with antimalarial activity and their mechanisms of action were included in these reviews. The aim of the present study was to investigate medicinal herbs that exhibit moderate-to-excellent antimalarial properties.

METHODS

Scientific studies documenting the antimalarial actions of medicinal plants and mechanisms of antimalarial activity have been reported in the literature. Preferred Reporting Items for Systematic Reviews were used in this study. Publications between 1990 and 2021 were based on computer-based data from PubMed and ISI Web of Knowledge using the key phrases antimalarial activity, medicinal plants, plant extracts, active chemicals, and modes of action. The present review was primarily based on articles found in these databases.

Mechanism of antimalarial agents

Drugs presently in use target several steps of the malaria parasite life cycle, most of which act on the intra-erythrocytic development of the parasite (Figure 1).

Antimalarial drugs have been recognised because of significant metabolic pathway variations between Plasmodium species and their hosts [11]. A few novel areas for new drug design include the major metabolic processes of the parasite, such as haeme detoxification, fatty acid synthesis, nucleic acid synthesis, fatty acid synthesis, and oxidative stress. Although most antimalarial drugs have been in use for many years, their use is currently limited because of drug resistance. According to this study, no antimalarial medication has been found to block a recognised drug target.

Inhibitors of nucleic acids

The folate antagonist class of drugs includes a few of the most frequently used antimalarial medicines, although their usefulness in the control of malaria is limited by the swift establishment of resistance under pharmacological pressure. Inhibiting folate pathway enzymes reduces pyrimidine synthesis. All levels of the asexual erythrocytic cycle and juvenile gametocytes are active [12].

Haem detoxification

Chloroquine, a 4-aminoquinoline, is widely used for malaria treatment. Chloroquine is thought to get stuck in the parasite-feeding vacuole, where it prevents haematin from crystallising.

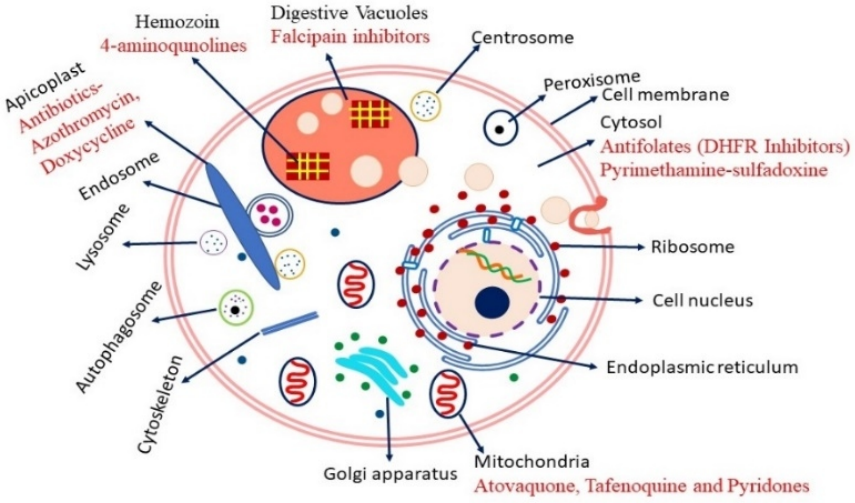

Figure 1: Antimalarial drugs are effective by interfering with metabolic pathways in several intracellular organelles

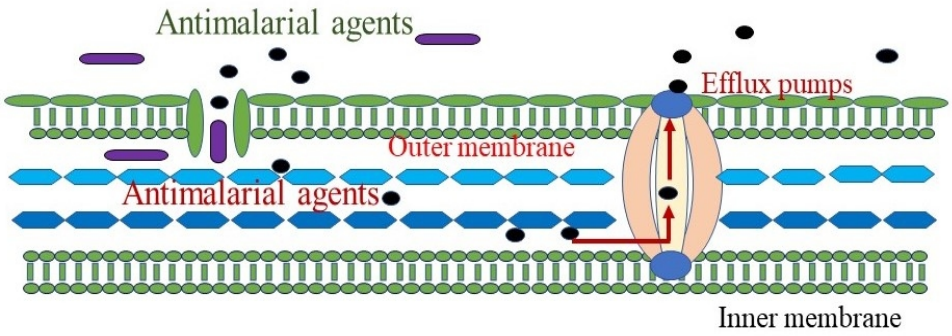

Figure 2: Elimination of drug molecules by efflux pump

Because of the acidic environment of the vacuole, chloroquine becomes 'imprisoned' in its membrane-impermeable, doubly protonated form. Chloroquine then forms a compound with free haem, causing haem to accumulate and the parasite to die [13].

Antibiotics

Antimalarial agents, such as tetracyclines and macrolides, are well known; however, additional antibiotics should also be examined. Chemical changes in older compounds with antiplasmodial characteristics could lead to breakthroughs.

The cost is low for the clinical development of antimalarial medications such as doxycycline, tigecycline, clindamycin, azithromycin, and co-trimoxazole. Furthermore, most of the approved antibiotics are inexpensive and widely available. Another advantage of antibiotics is that their mechanisms of action differ from those of most commonly used medications. Antibiotics and typical antimalarial medications have different modes of action; thus, there was no cross-resistance. Antibiotics can be used in areas where the parasites are resistant to antimalarial drugs. They are excellent companions of combination therapy because of their different modes of action. The WHO recommends the use of clindamycin and quinine to cure uncomplicated malaria in pregnant women during their first trimester [14].

Antimalarial resistance

Resistance develops because of spontaneous mutations that lower drug sensitivity. Some medications only require a single-point mutation to confer resistance, whereas others require numerous mutations. Drug pressure eradicates vulnerable parasites, whereas resistant parasites remain alive if mutations do not harm the survival of the parasite. Individual malaria isolates have been found out to form heterogeneous parasite populations with varied treatment response characteristics, ranging from highly resistant to entirely responsive. Malaria infections also exhibit various medication susceptibilities in geographical areas [15]. Resistance develops in the community over time and can persist long after specific medication pressure has been eliminated.

Drug accumulation mechanisms are altered by lowering the drug concentrations in the digesting vacuole.

The assumption that accelerated drug efflux mediates resistance to quinoline-containing antimalarials was based on similarities between the multidrug-resistant phenotype of tumour cells and resistance to quinoline containing anti-malarials [16, 17]. This occurs at the food vacuole membrane, which is mediated by increased expression of P-glycoprotein, an ATP-dependent efflux pump. pfmdr1 and pfmdr2 are MDR-like gene homologues found in Plasmodium falciparum plasmodia (Figure 2). pfmdr1 is linked to mefloquine resistance and halofantrine cross-resistance. The link between pfmdr1 and chloroquine resistance has yet to be proven.

Changes in parasite cytoplasmic membrane transport

Chloroquine-resistant parasites have been found to discharge pre-accumulated chloroquine approximately 50 times faster than chloroquine-sensitive parasites. The dynamics of accumulation in resistant parasites indicates a transient yet rapid increase in chloroquine accumulation, which leads to less or no accumulation within minutes. In contrast, chloroquine accumulation in chloroquine-sensitive parasites continues to climb and reaches a plateau significantly higher than that of chloroquine-resistant parasites [18]. The initial chloroquine

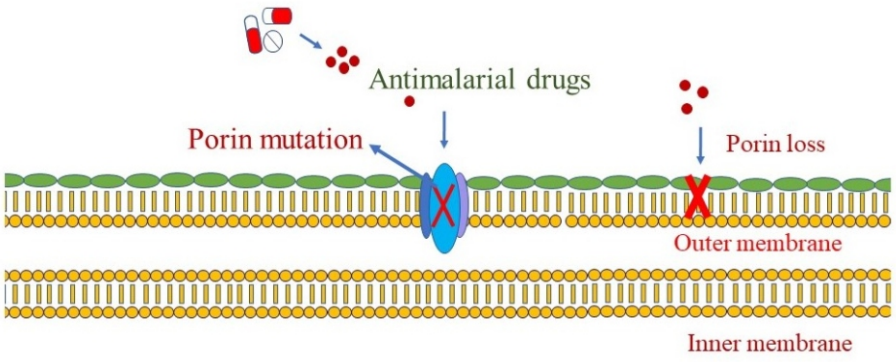

Figure 3: Porin mutation: Inhibition of Antimalarial drug entry inside the cells

absorption in all parasites was the highest at 3740 °C, implying that uptake is a temperature-dependent active process. The inclusion of glucose significantly increased chloroquine accumulation in the chloroquine-sensitive parasites. However, chloroquine accumulation steadily decreased in chloroquine-sensitive parasites, implying energy-coupled mechanisms for chloroquine uptake and efflux in sensitive and resistant parasites, respectively.

Mutation

Antimalarial resistance is caused by spontaneous and infrequent genetic processes that are unrelated to the medication used (Figure 3). These mutations affect antiparasitic medication concentrations by altering the number of gene copies that encode the drug parasite targets. A single genetic event may be sufficient; however, numerous unrelated events may be involved. Because the likelihood of multigenic resistance is the product of the probabilities of the individual components, it is uncommon. Southeast Asian *Plasmodium falciparum* parasites are at high risk of developing treatment resistance.

Chloroquine resistance in *Plasmodium falciparum* may be multigenic, with changes in transporter genes initially conferring resistance. Changes in a second transporter regulate the level of resistance [19]. However, the function of *P. falciparum* in regulating the therapeutic response to chloroquine treatment remains unknown.

Antimalarial compounds derived from plants

The rise in resistance to many antimalarial drugs has underlined the importance of creating future medicines with different mechanisms of action than those of the present treatments. Compounds produced by plants play important roles in antimalarial drug development (Table 1) [20].

Multiple novel chemotypes are undergoing clinical development, thanks to the development of high-throughput screening methods that evaluate their efficacy against liver and asexual blood stage parasites and gametocytes. Drugs for malaria ventures have played a critical role in several initiatives, ranging from drug development to clinical effectiveness trials and drug registration. The rise in resistance to many antimalarial drugs has underlined the importance of creating future medicines with different mechanisms of action than those of the present treatments.

CONCLUSION

The present survey has produced data on the antimalarial activity of antimalarial medicines, the mechanism of antimalarial agent resistance development, and the spectrum of plant species used to treat malaria in India. Understanding the processes causing antimalarial drug resistance will also aid in preventing the development of resistance to new antimalarial drugs in the near future. It creates an excellent opportunity for those in the field of

Table 1 : Some of the Indian plats have the antimalarial properties

S.NO	Medicinal plant	Part of the plant	References
1	*Tagetes erecta*	Leaf and roots	[21]
2	*Zingiber zerumbet*	Rhizome	[22]
3	*Piper nigrum*	seed	[23]
4	*Solanum trilobatum*	Leaf	[24]
5	*Phyllanthus amarus*	leaf	[25]
6	*Nelumbo nucifera*	Leaf	[26]
7	*Momordica charantia*	Leaf	[27]
8	*Eclipta prostrata*	Leaf	[28]
10	*Aegle marmelos*	Leaf	[29]
11	*Adhatoda vasica*	Leaf	[30]
12	*Cassia fistula*	Flower	[31]
13	*Cocculus hirsutus*	Leaf	[32]
14	*Acacia concinna*	Seed	[33]

pharmaceuticals to produce novel medicines for malaria by integrating anti-Plasmodium pharmaceuticals and providing chemical analysis, pharmacological action, and *in vitro* investigations using traditional information. Traditional healers in the most isolated areas of the region have devoted close attention to the treatment of various diseases. When it comes to using herbs for treatment, some people are more focused on the therapeutic approach, whereas others are more focused on how to use them. Solid scientific data are required to evaluate whether plants currently used to treat malaria are effective. In the long run, this should assist in preventing deaths caused by ignorance and misuse of plants for self-medication, without medical advice. Plants are rarely used on their own. It will always be challenging to determine which plant is most likely to be useful, and should be investigated to isolate pure active chemicals. Antimalarial herbs are used to prepare baths and inhalants.

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CONFLICT OF INTEREST

Nil

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