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Review Article

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A COMPREHENSIVE REVIEW ON MULTIDISCIPLINARY APPROACH TO STUDY ANTIMALARIAL REMEDIES

Harsha Pawar[1]*, Mayur Joshi[2], Dipti Masram[3] and Nikita Dhake[4]

[1]Assistant Professor, Department of Pharmacognosy, Trinity College of Pharmacy, Pune.
[2]Assistant Professor, Department of Pharmaceutics, Rastriya College of Pharmacy, Hatnoor, Sambhajinagar.
[3]Assistant Professor, Department of Pharmacognosy, Shree Sainath College of Pharmacy, Nagpur.
[4]Department of Pharmacognosy, Shree Gulabrao Deokar Institute of Pharmacy and Research, Jalgaon.

***Corresponding Author: Harsha Pawar**

Assistant Professor, Department of Pharmacognosy, Trinity College of Pharmacy, Pune.

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ABSTRACT

Malaria is a serious health issue in tropical and developing countries in Sub-Saharan Africa, Southeast Asia, and India. Malaria is a leading cause of morbidity and mortality in many countries due to the failure of therapy and its rapid spread globally. Pharmacotherapy is the most prevalent therapeutic approach for the condition. The most significant challenge is the evolution of resistance to multiple drugs. In order to solve this issue, herbal medicinal herbs have been used for centuries worldwide. Plasmodium falciparum resistance to chloroquin has been observed in numerous countries. Mankind is blessed with a wide range of herbal plants for various ailments, with a lot of those useful for malaria treatment as well. This review discusses the safety and efficacy of herbal plants, since there is often insufficient data to ensure their quality, efficacy, and safety. Herbal remedies are not always safe and may include toxins due to their complex composition. Biotechnological research and genetic enhancement of herbal medicinal plants are becoming more prevalent. Utilizing high-quality, uniform raw materials over wild-harvested plants can improve the efficacy and safety of herbal medicines. This article focuses on multidisciplinary approaches for curing malarial threats in order to sustain healthy life.

KEYWORDS: Herbal formulation, Plasmodium falciparum, Safety, Efficacy, etc.

INTRODUCTION

The term "malaria" comes from the Italian phrase "*mala-aria*," which means foul air. The protozoal blood infection is caused by a mosquito-borne apicomplexan parasite that is transferred to humans during the bite of an infected female Anopheles mosquito species. Malaria is the leading cause of mortality globally, and early diagnosis and treatment may prevent adverse outcomes. It is prevalent in Africa and Asia but can be brought into developed countries from endemic places.

In China, sweet sagewort has been used to treat malaria f ever since the second century BC. Quinine was later utilized as an antimalarial drug. The global fight against malaria began in 1955, with Croatia declaring 1964 as the year of eradication. The World Health Organization's global malaria control campaign promotes local primary health care, early diagnosis, treatment, and prevention. Malaria frequency has decreased globally compared to a decade ago. Malaria cases have increased globally in recent years. The progress towards WHO targets has slowed. Malaria affected an estimated 219 million people causing 435,000 deaths in 2017 globally. Over a century of global research has improved malaria prevention, diagnosis, and treatment, resulting in reduced morbidity and mortality.(Nureye *et.al.*, 2020; Thalapko *et.al.*, 2019)

Natural remedies for the treatment of malaria

Family	Species
Annonaceae	Annona muricata
Anacardiaceae	Mangifera indica
Crassulaceae	Kalanchoe pinnata Lam
Cucurbitaceae	Momordica charantia
Euphorbiaceae	Jatropha curcas, Ricinus communis
Fabaceae	Senna occidentalis Link, Senna tora
Malvaceae	Sida rhombifolia
Menispermaceae	Cissampelos pareira
Zingiberaceae	Zingiber officinale Roscoe

The proportion of patients using traditional herbal remedies for malaria varies widely. A meta-analysis of 28 studies investigating the behavior of people seeking therapy revealed that 307 out of 315 458 respondents participated in these therapies. Although the range varied significantly from 0% to 75%, the overall figure of 20% is misleading. Many factors affect the way traditional remedies have been employed for the treatment of malaria. Until now, 1277 plant species from 160 families have been utilized to treat fever or malaria. In all three of the tropical continents, eleven species were utilized as antimalarial or antipyretics, and in two of the continents, comparable uses were made of 47 species. The majority of the 1213 plant species are not included on the World Conservation Union's (IUCN) red list of threatened species; of those that are, 5 have been categorized as "endangered," 13 as "vulnerable," and 3 as "near threatened."(Willcox *et.al.*, 2004)

Clinical safety and efficacy of herbal formulations

Herb-drug interactions may result from the biologically active phytocompounds obtained from various plants, corresponding adverse effects, and adulteration with various pollutants.

Year of Discovery and First report of resistance of antimalarial

Drug	Discovered in year	First year Resistance reported	References
Quinine	1632	1910	Wongsrichnalai et.al 2002
Chloroqine	1945	1957	Wongsrichnalai et.al 2002
Proguanil	1948	1949	Wongsrichnalai et.al 2002
Sulfadoxinepyrimethamine	1967	1967	Wongsrichnalai et.al 2002
Mefloquine	1977	1982	Wongsrichnalai et.al 2002
Atovaquone	1996	1992	Carter et.al 2015
Artemisnine	1971	1971	Hurst et.al 2012

Ethical framework

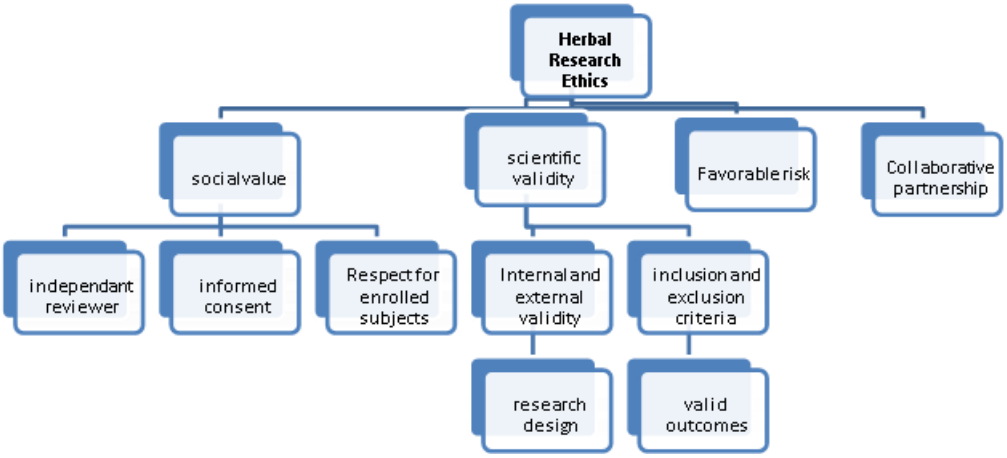

Fig. 1

Steps to ensure Safety and Efficacy of herbal formulation

- Plant material selection, Authentication and preparation of crude extracts
- Patient selection
- Preparation of formulation
- Treatment and sampling of patients
- Acute and sub-chronic sampling, activation studies in animals and sampling
- Malaria parasite count
- Biochemical assay
- Aspects of utilizing traditional medications over allopathic approaches

Natural products and traditional medicines have a range of unique advantages, including extensive clinical experience, a broad range of chemical structures and biological processes, and the sensible and rational development of novel drugs.

Recent advances in conventional medicines used in treatment of Malaria.

- Artemisinin and Its Derivatives
  - 4-Aminoquinolines
  - Chloroquine Resistance Reversal Agents
  - 8-Aminoquinolines
  - Quaternary Ammonium
  - Iron Chelators
  - Target-Based Antimalarial Agent
- Combination therapy
  - Artemisnine based combination therapy
  - Artemether lumefantrine combination therapy
  - Artesunate-chlorproguanil dapsone combination therapy [Vangapandu *et.al.*, 2017]

Current approaches for developing malaria vaccine

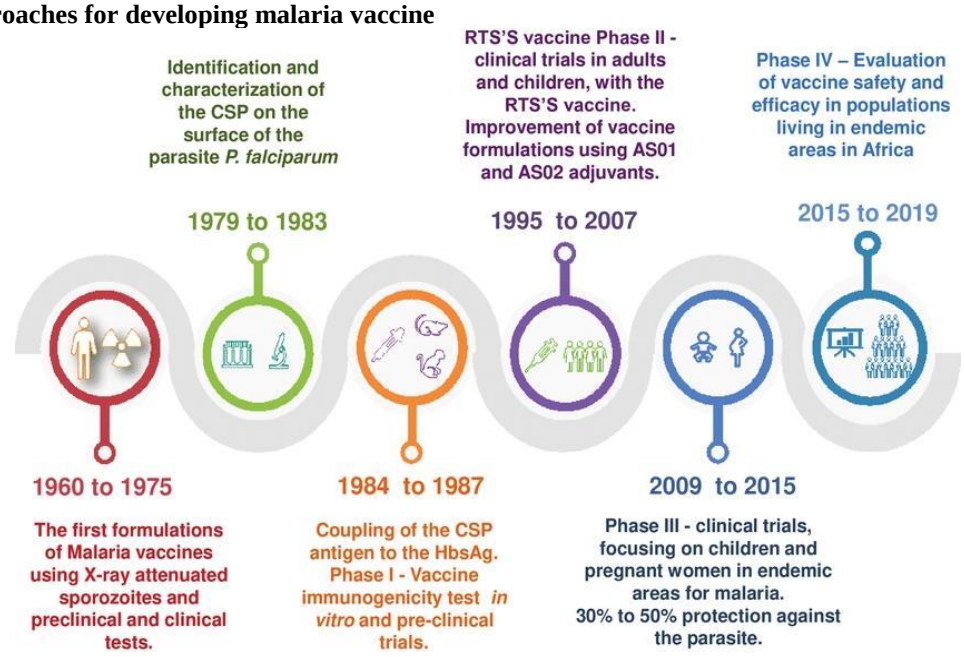

Fig. 2

There is plenty of data available to suggest that humans are capable of getting a malaria vaccine. Those who are born in endemic areas and survive the first few years of exposure still develop parasitic infection when exposed naturally, but they first develop resistance to severe, potentially lethal malaria and then to clinical disease. It takes numerous exposures to sustain this condition of immunity against infection. The development of a highly effective malaria vaccine that drastically lowers transmission could be an important breakthrough that allows for the disease's ultimate eradication. (Frimpong *et.al.*, 2018)

Vaccine targets

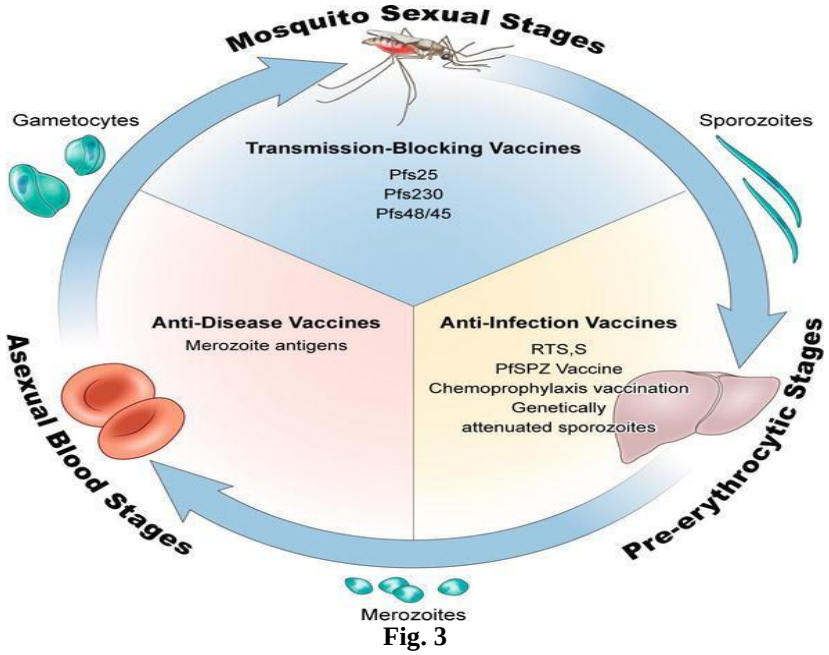

Fig. 3

- The first target of vaccine development is the pre-erythrocytic stage.
- The second target for malaria vaccine candidate design is the blood-stage of the parasite.
- The third malaria vaccine candidate target is the sexual parasite forms or gametocytes.

- **Safety and Efficacy of malaria vaccination**

➢ Reactogenicity is higher with water-in-oil emulsions (e.g. ISA 720) when compared to marketed adjuvants (alhydrogel) or a marketed virosomal platform.

- Safety and reactogenicity in semi-immune populations living in endemic areas has not been higher than in naïve populations, and is often lower.
- Safety and reactogenicity in young children has not been worse than in adult populations.
- Only RTS, S-based vaccines have repeatedly shown efficacy to reduce morbidity in endemic areas.
- Highly polymorphic blood-stage antigens have tended to lead to allele-specific efficacy, but poor efficacy against the population of circulating strains.
- Multiple episodes of malaria takes priority over time to first episode for public health assessment in clinical malaria vaccine trials (Calixto *et.al.*,2000)

Promising approaches to malaria vaccine development

The Parasite-Focused Approach

- Reverse Vaccinology
- Structural Vaccinology
- Immunoinformatics Based Approach to Vaccine Design

Vaccine name	Target protein	Vaccination protocol	Clinical phase	Antigen force
Pre-erythrocytic stage:				
RTS,S/AS01E	Pf CSP (207–395) and HepBsAg	IM	IV	*S. cerevisiae*
ChAd63/MVA ME-TRAP	TRAP + ME epitopes (CS, LSA1, LSA3, STARP, EXP1, pb9)	IM	IIb	Simian adenovirus ChAd63, MVA
ChAd63/MVA ME-TRAP + Matrix M™	TRAP + ME epitopes (CS, LSA1, LSA3, STARP, EXP1, pb9)	IM	I	Simian adenovirus ChAd63, MVA
PfSPZ	ND	DVI	ND	Simian adenovirus ChAd63, MVA
R21 (RTS,S-biosimilar)/ME-TRAP	CSP	SC, ID, IM	IIa	P. pastoris
Blood stage:				
GMZ2	GLURP, MSP3	IM	II	L. lactis
SE36	N-terminal of serine repeat antigen (SERA5)	SC, IM	Ib	E. coli
PfPEBS	ND	ND	II	E. coli
PRIMVAC	VAR2CSA	IM	Ia/b	E. coli
Sexual stage:				
Pfs25 VLP	Pfs25	IM	I/IIa	N. benthamiana
Pfs230D1M-EPA/Alhydrogel and/or Pfs25-EPA/Alhydrogel	Pfs25M, Pfs230D1M	IM	I	P. pastoris
Pfs230D1M-EPA/Alhydrogel and Pfs25-EPA/AS01	Pfs25M, Pfs230D1M	IM	I	P. pastoris
ChAd63 Pfs25-IMX313/MVA Pfs25-IMX313	Pfs25	IM	Ia	Chimpanzee Adenovirus 63, MVA

(Salamanca *et.al.*, 2019;[8])

RESULT AND DISCUSSIONS

Herbal medications are the most extensively used form of disease management around the globe. In contrast to herbal plants, potential medicinal products that have the potential to be recruited as medications must undergo clinical studies to ensure total safety and efficacy. Initially, safety and efficacy clinical data are inadequate. Second, there's no consensus, not even among traditional

healers, about the most effective herbs, preparations, and dosages. Depending on a number of variables, a plant species' concentration of active chemicals varies greatly. A further challenge is the fact that even though there are many herbal and botanical dietary products available, the majority of them tend to be of lower quality and dubious efficacy, even though studies using high-quality products have demonstrated the herb's influence. There is a belief that herbs, being natural products, are completely safe and have no negative effects, and that their effectiveness may be achieved at a wide range of concentrations. Even though herbs may have adverse side effects, there are no set doses but interactions for both herbal and herbal medicines are possible. There is no defined dosage for herbs, but interactions between herbs and herbal medications are possible even though they may have adverse side effects.

CONCLUSION

It is imperative that malaria be controlled and eradicated since it continues to be a burden on humanity. For millions of years, the multistage, complex malarial parasite has coevolved in both mosquitoes and their human hosts. The treatment of malaria with herbal medicine is common in today's globe. In order to develop a vaccine to treat malaria, one would need to have a detailed understanding of the biology of this parasite. Plants are the only realistic approach for discovering a lead compound. Multiple studies have verified the efficacy of specific herbal products in treating malaria through in vitro and in vivo experiments involving animals, as well as clinical trials. Herbal medicine may appear promising, but its sustainability and future will only be realized if standard procedures are supported in order to increase the products' safety and efficacy through clinical trials and to empower herbal practitioners to maintain professional ethics and ensure product quality through good manufacturing practices. Numerous plant species may have the potential to treat malaria, however this has not been thoroughly investigated.

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