Review Article

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Potent future antimalarials from Indian indigenous plants: a systematic review

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ABSTRACT

Malaria has a global impact due to development of resistance against the frontline anti-malarial drugs which include artemisinin and its derivatives. According to the ancient Indian system of medicine, the Ayurveda, several Indian indigenous plants have been used for treating various ailments. The use of Indian indigenous plants for treatment of malaria is proving to be quite effective and also offers as a cheaper alternative. The purpose of this review is to obtain knowledge about the different Indian indigenous plants that have antimalarial and antiplasmodial biological activities. Literature suggests that many indigenous Indian plants have shown good antiplasmodial and antimalarial activity with effects like decrease in anaemia, weight loss and pyrexia. Hence the Indian indigenous plants have a vast scope to be used as potent future antimalarials.

Keywords: Malaria, Indian indigenous plants, Ayurveda, Reverse pharmacology

INTRODUCTION

Malaria remains an important public health concern in countries where transmission occurs regularly, as well as in areas where transmission has been largely controlled or eliminated. The development and spread of drug-resistant strains of malaria parasites has been identified as a key factor in this resurgence and is one of the greatest challenges to malaria control today. The malaria parasites have demonstrated some level of resistance to almost every antimalarial drug currently available, significantly increasing the cost and complexity of achieving parasitological cure. ¹

Since ancient times, people have been exploring the nature particularly plants in search of new drugs. Nearly 80% of the world's population relies on traditional medicines for primary health care, most of which involve the use of plant extracts.² In 2013, WHO (World Health

Organization) developed and launched 'WHO Traditional Medicine Strategy 2014–2023'and emphasized to integrate traditional and complementary medicine to promote universal healthcare and to ensure the quality, safety and effectiveness of such medicine. Therefore, the world is looking for cost effective, easily available, better physiological compatible traditional systems of medicine and holistic approach to avert such problem and provide the basic healthcare to all.³

The use of plant-derived drugs for the treatment of malaria has a long and successful tradition. The first antimalarial drug was quinine, isolated from the bark of *Cinchona* species (*Rubiaceae*) in 1820. It is one of the oldest and most important antimalarial drugs, which is still used today. In 1940, another antimalarial drug, chloroquine, was synthesized and is being used for the treatment of malaria. Unfortunately, after an early success, the malarial parasite, especially *Plasmodium falciparum* (*P. falciparum*), also became resistant to

chloroquine. Treatment of chloroquine-resistant malaria was done with alternative drugs or drug combinations, which were rather expensive and sometimes toxic. ⁴

In Ghana, several plant species like *Nyctanthes arbortristis* and *Tinospora cordifolia* are used in the treatment of malaria. The extract of the bark and leaves of *Azadirachta indica* has also been used in Thailand and Nigeria as an antimalarial for a long time. Charaka in 300 BC and Susruta in 200 BC reported the antimalarial and antipyretic activity of this species. Hence, it is clear that the main drugs developed for malaria and used until now (quina alkaloid derived drugs and artemisinin) were discovered based on traditional use and ethnomedical data.⁴

The diverse climates of India flourish huge diversity of medicinal plants and the use of plants for treating ailments traces back to ancient Indian system of medicine -the Ayurveda. The term Ayurveda means 'knowledge of life, which comprises two Sanskrit words, Ayu (life) and Veda (knowledge or science). Four Vedas, considered as the oldest Indian literature (5000–1000 BC) contain information about natural remedies.³

The purpose of the study is to obtain knowledge about the different Indian indigenous plants that have antimalarial

and antiplasmodial biological activities. Reverse pharmacology of Ayurvedic drugs and the practice of traditional healers in India, which uses indigenous Indian plants for treatment of malaria is proving to be quite effective and also offers as cheap alternative treatment. Hence intensive new drug discovery by reverse pharmacology of Ayurvedic drugs to develop more effective, affordable and accessible anti-malarial agents possessing novel modes of action is required and for this the Indian indigenous plants offer a huge scope.

METHODOLOGY

A literature search was conducted in the electronic databases (PubMed and Google Scholar) to identify publications from the years 2001 to 2017. The search identified 30 papers; 26 were excluded and 4 papers were included (Figure 1). The studies included for the review were laboratory culture tests against *P. falciparum* cultured on human erythrocytes- in vitro studies, randomized control trials (RCT) and open-labelled observational studies. The study participants were Indian population provided that they did not have any systemic disorder. The exclusion criteria were animal experimental studies and qualitative studies.

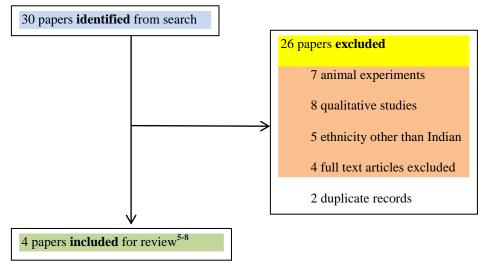


Figure 1: Identification and study selection.

RESULTS

A summary of the studies included in this review are discussed and presented as Tables 1 and $2.^{6-8}$

In one of the studies included for review, chloroquine (CQ)-sensitive strain 3D7 and CQ-resistant strain INDO of *P. falciparum* were cultured in vitro on O+ve human erythrocytes and the toxicity with HeLa cells tested. The extracts of experimental plants were evaluated for their antiplasmodial activity against the culture. *Aerva lanata* [whole aerial parts-EAE (ethyl acetate extract)],

Anisomeles malabarica (Leaf-EAE), Anogeissus latifolia (bark-EAE), Cassia alata (leaves-EAE), Glycyrrhiza glabra (root-EAE), Juglans regia (seed-ME), Psidium guajava [leaf-ME (methanol extract) and EAE] Solanum xanthocarpum (Whole aerial parts-EAE) showed promising antiplasmodial activity (IC50Pf3D7 ≤20 μg/ml). EAEs from leaves of Couroupita guianensis, Euphorbia hirta, Pergularia daemia, Tinospora cordifolia, Tridax procumbens and Ricinus communis (ME from leaf and seed) showed good antiplasmodial activity (Pf 3D7 IC50 21-40 µg/ml). Leaf EAEs of Cardiospermum halicacabum and Indigofera tinctoria showed moderate activity (Pf 3D7 IC50: 40 $60 \,\mu g/ml$). The promising extracts showed good resistance indices (0.41–1.4) against the chloroquine resistant INDO strain of *P. falciparum* and good

selectivity indices (3 to >22.2) when tested against the HeLa cell line.⁵

Table 1: Distribution according to the Indian indigenous plant used (*Nyctanthes arbor-tristis* and *Aloe vera*), methodology and result.

Indian plant used	Methodology	Result
Nyctanthes arbor-tristis ⁶ (Parijat)	 Administration of a paste of 5 fresh leaves, thrice a day for a week in patients with moderate to mild fevers and chills; patient aged 15-55 years and having haemoglobin value >8 gm % and absence of cerebral or renal complications. Sample size of 20 	 Early amelioration of disease severity Decline of TNF-α (tumor necrosis factor alpha) Good clinical tolerability Improvement in organ function markers
Aloe vera ⁷	O+ human erythrocytes culture of <i>P</i> . <i>falciparum</i> & HPTLC (high performance thin layer chromatography) analysis	 EC50 (Effective concentration at 50%) values of aloin and aloeemodin was 67 μg/ml and 22 μg/ml Positive correlation was reported between aloin and aloe-emodin Antiplasmodial activity was increased with increase in the concentration of aloin and aloeemodin. North Indian Aloe vera samples are more potent against malaria parasite as compared to south Indian samples

Table 2: Distribution according to the Indian indigenous plant used (*Carica papaya* and *Swertia chirata*), methodology and result.

Indian plant used	Methodology	Result
Carica papaya ⁸ (petroleum ether extract of the rind)	Human red blood cells (blood type O) culture of <i>P. falciparum</i>	 High antimalarial activity Inhibitory concentration- value that inhibits 50% (IC50) of 15.19 μg/ml Delay in development of ring stage
Swertia chirata ⁸ (ethanolic extract of leaves and stem)	Human red blood cells (blood type O) culture of <i>P. falciparum</i>	 IC50=21.69 μg/ml Trophozoites were smaller in size compared with controls, failing to develop into schizonts.

DISCUSSION

Drug discovery is no longer a game of chance or just limited to the availability of new technology. Reverse pharmacology approach, inspired by the ancient Indian traditional medicine- Ayurveda, can offer a smart strategy for developing new drugs from botanical formulations to overcome drug resistance and toxicity. Development of standardized, synergistic, safe and effective traditional herbal formulations with robust scientific evidence can also offer faster and more economical alternatives. Ayurveda is a comprehensive scientific medicinal system indigenous to India. Ayurveda was established as a fully grown medicinal system. Charaka Samhita (focussing on internal medicine) and Susruta Samhita (focussing on surgery) were written systematically and considered as classical text of Ayurveda. Introduction of allopathic drug during British era and neglecting Indian traditional

medicine by British rulers were responsible for significant erosion of Indian traditional medicine. High scientific progress in allopathic medicine and modern facilities also resists the growth of traditional medicine. Still, about 70% rural populations of India believe in traditional medicine for primary healthcare. Ayurvedic texts include thousands of single or polyherbal formulations. These have been rationally designed and have been in therapeutic use for many years. Sufficient pharmacoepidemiological evidence, based on actual clinical use, can be generated to support their safety and efficacy. Despite the vast potential and possibilities, till now, very few success stories have emerged from Ayurveda. This may be because most of the work in this field has remained within the clinics of traditional practitioners or confined to academic research laboratories and not taken seriously by industries that are strong in research and development.^{9,3}

CONCLUSION

Many indigenous Indian plants have shown good antiplasmodial and antimalarial activity with effects like decrease in anaemia, weight loss and pyrexia. The Indian indigenous plants have a vast scope to be used as potent future antimalarials, of which many are becoming rare and some of them are critically endangered. Hence steps should also be taken to preserve them and use them in a sustainable manner.

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