

**ANTI-MALARIAL AYURVEDA HERBAL DRUG DEVELOPMENT
WSR TO APPLICABILITY OF REVERSE PHARMACOLOGY*****¹Dr. Mukesh Kumar and ²Dr. Rajat Chaturvedi**

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ABSTRACT

Ayurveda, the ancient life science, has a history of over 4000 years of practice. It is a great living tradition that addresses health with a unique holistic approach. Currently, the Government of India has developed formal structures to regulate issues related to quality, safety, efficacy and practice of herbal medicines. Thus basic principle of Ayurveda is based on personalized approach can be used for creating personalized, customized or designer medicines. Therefore science of Ayurveda has the potential to revolutionize modern medicine and drug discovery processes. The credit for stimulating interest of Indian chemists and pharmacologists in medicinal plants should rightfully go to Sir Ram Nath Chopra who has been acclaimed as the ‘Father of Indian Pharmacology’. Gananath Sen laid the foundation of Reverse Pharmacology of medicinal plants by pursuing clinically documented

effects of Ayurvedic drugs. Reverse Pharmacology (RP), designed as an academic discipline to reduce three major bottlenecks of costs, time and toxicity. RP (Reverse Pharmacology) can be perceived to comprise of three phases. The scope of reverse pharmacology is to understand the mechanisms of action at multiple levels of biology and to optimize safety, efficacy and acceptability of the leads in natural products based on relevant science. In this approach as the candidate travels a reverse path from ‘clinics to laboratory’ rather than classical ‘laboratory to clinics. A wide array of modern drugs included the international pharmacopoeia have an origin in ethnopharmacology and traditional herbal medicine. Numerous plant extracts and their ingredients have unique pharmacological activities, such as

anti-inflammatory, anti-diabetic, anti-carcinogenic, vasodilatory, anti-bacterial, anti-viral, anticonvulsant, sedative and antipyretic effects. Recently, a study carried out in Kenya and has proved the applicability of R P for new drug discovery for the treatment of Malaria. However, very few randomized-controlled studies have been carried out to precisely evaluate their therapeutic efficacy and safety. Nonetheless, for some of the botanical materials, there are relatively well-organized database available describing the therapeutic potential, and their active ingredients can be tested by exploiting modern scientific methods. These desirable accidental discoveries are referred to as drug serendipity. There are many examples of medicinal plants and their constituents that have provided serendipitous bedside observations. Such clinical hits can be a basis of drug discovery and development. Advances in combinatorial chemistry and systems biology have created many drugable new entities. Reverse pharmacology integrates documented serendipitous clinical and experimental hits into leads that are further developed into drug candidates or formulations through more systematic and precisely designed preclinical and clinical research. A salient feature of this approach is the combination of knowledge learned from traditional or folk medicine and the modern technology to provide better and safer leads. RP is now getting formally established in India as an organized trans-discipline through efforts by the Indian Council of Medical Research (ICMR). Authors made an attempt to explore the Reverse Pharmacology applicability to the Ayurveda Herbal Drug for the Development of Anti-malarial drug.

KEYWORDS: Ayurveda, RP, Ethno-pharmacology, Pharmacoepidemiology, Phytomedicine, Transdiscipline.

INTRODUCTION

Knowledge about Indigenous / traditional medicinal practices and plants is currently transmitted from generation to generation principally by word of mouth. Large number of plant species has been identified as anti-malarial medicinal plants. Plants, as traditional medicine have been used for centuries as herbal remedies, and are still used up to this day, as they can be found to be non-narcotic, accessible and affordable.

Malaria continues to be a major public health problem, affecting 36% of the world population in 107 tropical and sub-tropical countries. India alone contributes about 70% of the 2.5 million reported cases in the South East Asia.^[1] Malaria is caused by *Plasmodium* parasites. The parasites are spread to people through the bites of infected *Anopheles* mosquitoes, called "malaria vectors".^[2]

There are four parasite species that cause malaria in humans which are *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium malariae* and *Plasmodium ovale*.^[2] *P. falciparum* and *P. vivax* are the most common species clinically but *P. falciparum* is the most deadly leading to many fatal complications including cerebral malaria. More than two-third of Indian population lives in malaria zones. Overall, out of 4.2 million disability adjusted life years lost due to vector borne diseases, malaria alone accounts for estimated 1.85 million years loss per annum in India. Treatment strategies of malaria aim to terminate the acute blood infection, to cure the clinical symptoms, to clear hypnozoites from the liver to prevent future relapses and to prevent the spread of infection.^[3]

Radical treatment and curative treatment comprise main aspects of treatment. Various pharmacological options available for this purpose are *Chloroquine*, *Mefloquine*, *Quinine*, *Primaquine*, *Pyremethamine*, *Artemisinin derivatives like artesunate, artemether, arteether* and *amino alcohols like Lumefantrine* and *Halofantrine* along with *tetracycline*, *Doxycyclines* and *Sulfadoxime* etc.^[4] The greatest problem associated with this treatment is emergence of drug resistance which leads to treatment failure in significant number of cases.^[5]

AIM AND OBJECTIVES

- To review the literature for the applicability of Reverse Pharmacology for the development of Anti-malarial Herbal Drug.
- To prepare an update document regarding development of promising and potent natural anti-malarial herbal drug.

MATERIAL AND METHODS

Author made an attempt to review the available information on the Applicability of Reverse Pharmacology for the development of Anti-malarial Ayurveda Herbal drug. In depth study was done. The search words were used – Reverse Pharmacology, Ayurveda Herbal Drugs, Traditional Herbal Medicine. Major journals, PUBMED, TKDL, MEDLINE and other main online publications were searched. All information gathered and made fit for the achieving the aim and objectives of review article.

Uses of Medicinal Plants in the Treatment of Malaria

Apart from the pharmacological treatment, various options are being used since ancient times for many health ailments. Nearly 80 % of the global population still depends upon the herbal drugs for their health care. In India, the use of several medicinal plants to cure specific

ailments has been practiced since ancient times. Various cultural traditions are associated with use of wild plants as medicinal herbs. This medico-lore is passed over generations traditionally all over the world. Reliance on plants is primarily due to their safety, effectiveness, cultural preferences, inexpensiveness and abundant availability all the time. The medicinal virtues of plants are identified by instinct/intuition or by trial and errors. Globally, Ayurveda practitioners are using various medicinal plants for the treatment of malaria; however, this practice is not really completely recognized by modern medicine.

Plants, widely used as antimalarials by Ayurveda practitioners are significantly more active *in vitro* against *P. falciparum* as reported and represents a potential source for the discovery of lead molecules.^[6] Along with the Ayurveda the traditional herbal healers are also using herbs for the treatment of Malaria. Use of root powder of (**Shatavari**) *Asparagus racemosus* (Liliaceae) to cure Malaria by tribes of Rajasthan has been reported.^[7] while use of decoction of leaves and root of *A. zeylanica* ('Kawldawi', local name Mizoram) has taken orally for curing malaria. (Bora et al., 2007).^[8] Use of (**Mamajjak**) *Enicostema* plant to cure malaria by Ayurveda practitioners have been reported.^[9] Use of decoction of leaf of (**Karanj**) *Pongami pinnata* with black pepper is reported a better treatment for Malaria.

Some medicinal plants are being used by the tribes of Rajasthan for the treatment of Malaria. *Salvadora persica* is being used by *Gaduliya Luhar* local community of Rajasthan and Juice of fresh plant of *Datura innoxia* is in practice of *Sansi tribe* of Rajasthan while *Bhil tribe* are using decoction of *Fagonia indica* and *Evolvus alsinoides* used as anti pyretic and anti-malarial.^[10] The stem bark of *Ficus platyphylla* is used traditionally to treat malaria in Africa.^[11]

Applicability of Reverse Pharmacology for New Drug Discovery for Malaria

Historically, drugs were discovered through identifying the active ingredient from traditional remedies or by serendipitous discovery. Later chemical libraries of synthetic small molecules, natural products or extracts were screened in intact cells or whole organisms to identify substances that have a desirable therapeutic effect in a process known as classical pharmacology. Modern drug discovery involves the identification of screening hits, medicinal chemistry and optimization of those hits to increase the affinity, selectivity (to reduce the potential of side effects), efficacy/potency, metabolic stability (to increase the half-life), and oral bioavailability. Once a compound that fulfills all of these requirements has been identified, it will begin the process of drug development prior to clinical trials. One or more

of these steps may, but not necessarily, involve computer-aided drug design. Though with the advanced technology and understanding of biological systems, drug discovery is still a lengthy, "expensive, difficult, and inefficient process" with low rate of new therapeutic discovery. At present, the research and development cost of each new molecular entity (NME) is approximately US\$1.8 billion.^[12]

Natural sources of drugs

Though, the rise of combinatorial chemistry as an integral part of lead discovery process, natural products still play a major role as starting material for drug discovery, but a lot of is to be done.^[13] A report was published in 2007,^[14] covering years 1981-2006 details the contribution of biologically occurring chemicals in drug development. According to this report, of the 974 small molecule new chemical entities, 63% were natural derived or semi-synthetic derivatives of natural products. For certain therapy areas, such as antimicrobials, anti-neoplastics, antihypertensive and anti-inflammatory drugs, the numbers were higher. In many cases, these products have been used traditionally for many years. Natural products may be useful as a source of novel chemical structures for modern techniques of development of antibacterial therapies.^[15]

India has a very long, safe and continuous usage of many herbal drugs in the officially recognized alternative systems of health viz. Ayurveda, Yoga, Unani, Siddha, Homeopathy and Naturopathy and have rightfully existed side-by-side with Allopathy and are not in 'the domain of obscurity'.^[16] The developer of potent natural product penicillin, Nobel-laureate Ernst Boris Chain wrote an inspiring article entitled "*The quest for new biodynamic substances*". In 1967, he wrote, "In China and India there has been an extensive drive aimed at the systemic study of medicinal plants traditionally used in these countries in folklore medicine; this has failed, so far, to bring to light new classes of compounds with interesting pharmacologic activities. As far as drug research is concerned, therefore, we cannot expect many major surprises to come from the study of plant constituents".^[17]

Ayurveda - the Ancient Science of Life

Ayurveda, the ancient life science, has a history of over 4000 years of practice. It is a great living tradition that addresses health with a unique holistic approach. Currently, with over 400,000 registered Ayurveda practitioners, the Government of India has formal structures to regulate issues related to quality, safety, efficacy and practice of herbal medicine^[18] (a,b). Thus basic principle of Ayurveda is based on personalized approach can be used for creating

personalized, customized or designer medicines. Therefore science of Ayurveda has the potential to revolutionize modern medicine and drug discovery processes.^[19] The systems biology approach based on Ayurveda knowledge will furnish two advantages: first, a systematization of very complex process of Ayurvedic therapeutics for uniform global clinical applications and second, an organized database of extract-activity libraries that will increase chances of better and functional leads. Current strategy of drug development of single target - single compound, is based on a super reductionism that involves molecular level assays.^[20] This approach is not suitable for studies on traditional medicines. A more holistic approach using systems biology seems much more suited to probe and confirm the efficacy and understand the mode of action.^[21]

Observational Therapeutics

India, having a pluralistic healthcare system, offers an unfettered choice for the quest for new clinical effects of traditionally used medicinal plants.^[22] (a,b) Roy Chaudhary coined a neologism for such a discipline named the Observational Therapeutics.^[23]

He expressed his hope that further research directed at a few of the chronic diseases against which more drugs are needed, such as diabetes, bronchial asthma, could lead to the discovery of new drugs for these conditions. Observational Therapeutics is an antecedent of the path of Reverse Pharmacology for new natural drug development. Reverse Pharmacology was proposed and initiated.^[24]

Reverse Pharmacology

The path of Reverse Pharmacology, arising from Observational Therapeutics is complementary to other approaches for natural drug development.^[25] Reverse Pharmacology is defined as the science of integrating documented clinical/experiential hits, into leads by transdisciplinary exploratory studies and further developing these into drug candidates by experimental and clinical research. The identification of structures with novel biodynamic effects can also lead to new chemical entity path for drug development.

The scope of Reverse Pharmacology is to understand the mechanisms of action at multiple levels of biological organization and to optimize safety, efficacy and acceptability of the leads in natural products, *based on relevant science*.^[26] Reverse Pharmacology (RP), designed as an academic discipline to reduce three major bottlenecks of costs, time and toxicity. RP can be perceived to comprise of three phases.

First, the experiential phase that includes robust documentation of clinical observations of the biodynamic effects of standardized Ayurvedic drugs by meticulous record keeping. Second, the exploratory studies for tolerability, drug-interactions, dose-range finding in ambulant patients of defined subsets of the disease and para-clinical studies in relevant *in vitro* and *in vivo* models to evaluate the target-activity. Third phase refers experimental studies, basic and clinical, at several levels of biological organization, to identify and validate the reverse pharmacological correlates of herbal drug safety and efficacy.

The scope of reverse pharmacology is to understand the mechanisms of action at multiple levels of biology and to optimize safety, efficacy and acceptability of the leads in natural products based on relevant science. In this approach as the candidate travels a reverse path from ‘clinics to laboratory’ rather than classical ‘laboratory to clinics.’^[27]

Reverse Pharmacology is possible only in those countries with pluralistic healthcare and where robust clinical and laboratory documentation of novel human, pharmacodynamic effects are possible by inter-system collaborative teamwork.^[28] India, at the national level, has adopted this approach of Reverse Pharmacology and also the golden triangular research for correlating the three fields by R & D network viz. modern medicine, Indian systems of medicine, and life and pharmaceutical sciences.^[29] (a,b)

The science has to integrate documented clinical and experiential hits into leads by interdisciplinary exploratory studies on defined targets *in vitro* and *in vivo* and conducting the gamut of developmental activities.

Recently, India has amended the Drug Act to include a category of phytopharmaceuticals to be developed from medicinal plants by Reverse Pharmacology, with evidence of quality, safety and efficacy. These drugs will be distinct from traditional medicines like Ayurvedic, Unani or Siddha. India with its pluralistic health care system offers immense opportunities for natural product drug discovery and development based on traditional knowledge and clinical observations.^[30] There is a need to develop an academic niche for Reverse Pharmacology in medical and pharmaceutical sciences colleges and drug R & D centers. Linkages must be established with Observational Therapeutics and Ayurvedic Pharmacoepidemiology to identify clinical hits. In India, major endeavors in this direction have been initiated already, both in the private and the public sectors of pharmaceutical R & D.^[31]

Ayurveda and Reverse Pharmacology

RP is now getting formally established in India as an organized trans-discipline through efforts by the Indian Council of Medical Research (ICMR) Advanced Centre of RP in Traditional Medicine under Medical Research Centre-Kasturba Health Society (MRC-KHS).

However, perception of RP appears to be mystifying. The recent article of Lele - “Beyond Reverse Pharmacology Mechanism based Screenings of Ayurveda Drugs” emphasizes a need of approach for mechanism-based screening of Ayurvedic drugs.^[32] The Willcox *et al* have used the term RP for their work on traditional herbal medicine but it may be exemplified for Ayurveda-through RP for further studies for malaria to highlight the differences in the study by Willcox *et al*. Such communications are necessary for expanding the understanding of RP. Apart from it, in recent, a national was conducted by MRC-KHS titled “ICMR workshop for Training in RP” and state-level research fellowships in RP announced by the Maharashtra University of Health Sciences (MUHS) will certainly help to appropriately comprehend and further develop this trans-discipline of RP for Ayurveda and Traditional medicine.^[33]

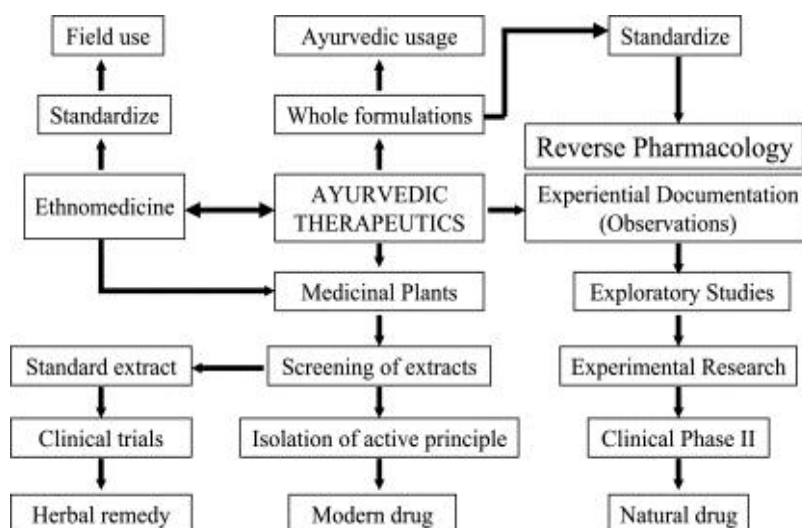


Fig 1: Ayurveda and Reverse Pharmacology – An Illustrated View.

Courtesy: Bhushan Patwardhan, *et al*, *Current Bioactive Compounds* 2008, 4, 201-212

New Herbal Drug Discovery for Malaria

A “reverse pharmacology” approach to developing an anti-malarial phytomedicine was designed and implemented in Mali, resulting in a new standardized herbal anti-malarial after six years of research.^[34] The first step was to select a remedy for development, through a retrospective treatment-outcome study. The second step was a dose-escalating clinical trial that showed a dose-response phenomenon and helped select the safest and most efficacious

dose. The third step was a randomized controlled trial to compare the phytomedicine to the standard first-line treatment. The last step was to identify active compounds which can be used as markers for standardization and quality control. This example of “reverse pharmacology” shows that a standardized phytomedicine can be developed faster and more cheaply than conventional drugs. Even if both approaches are not fully comparable, their efficiency in terms of public health and their complementarity should be thoroughly considered.^[35] Above said recent issue of the Malaria Journal has been dedicated to the research and development of natural products for treatment of malaria. The article on Reverse Pharmacology (RP) by Willcox *et al* is of particular interest, which suggested that this transdiscipline of RP has global appeal. The RP path, as Willcox *et al* have rightly mentioned in their article, has originated in India for new drug discovery and is based on Ayurveda, India's ancient traditional system of medicine. However, the statement of Willcox *et al* supported by the reference of Patwardhan and Mashelkar that “RP still involves classical pathway of isolating compounds for further development” is true only to a certain extent.^[36]

Reverse Pharmacology (R P) in India focuses mainly on the development of Ayurveda-inspired standardized formulations, the safety, and activity of which is implied through its long history of usage. Several other paths may be considered for the development of drugs from Ayurvedic therapeutics and natural products, one of them is isolation and identification of active compounds.^[37] (a,b)

Ayurvedic approach to Malaria makes use of diagnostic components and Ayurvedic Pharmacology of Medicinal plants.^[38] (a,b) Classical Ayurvedic descriptions of ailments and their management besides a long tradition of usage of medicines by Ayurvedic physicians form a basis for the selection of the medicine for evaluation through RP. Willcox *et al* evolved a standard score system to prioritize a plant from folklore practices. This includes meticulous analysis and scoring of ethnobotanical data for (i) frequency of citation of a plant, (ii) efficacy *in vitro* and *in vivo*, and (iii) safety and activity based on Retrospective Treatment Outcome (RTO) study.^[39] Ayurveda-inspired RP on the other hand provides foundation of long-term experience of clinical usage, Ayurvedic-pharmacodynamic rationale and evidence generated through current biomedical integration for the development of drugs.

R P Studies on Anti-Malarial Ayurveda Herbal Medicine and Potent Ayurveda Herbs

In India, pharmacology of medicinal plants from Ayurveda has evolved during the last century. The pioneering work by Sir Ramnath Chopra, an experimental pharmacologist, and

Gananath Sen, an eminent Ayurvedic clinician, through thorough observations indicated the need for organized research efforts.^[40]

The plant, referred in Ayurveda for the treatment of Malaria is used by Ayurvedic physicians for recurrent fevers and hepatosplenomegaly.^[41] A study was carried out on the *Nyctanthes arbor-tristis* Linn. (**Parijat**), through the three stages of RP (experiential, exploratory, and experimental) as defined by Vaidya ADB in 1990s.^[42] The experiential study of the paste of leaves of *N. arbor-tristis* in 120 patients showed ~80% clinical and parasite cure.^[43] Detailed biochemical investigations for organ function safety and for the mechanism of action were done in these 20 patients. Early clinical response was associated with increase in platelet count, decrease in lactic acid; the key markers of severity of malaria. There was also a significant reduction in circulating TNF- α and other pro-inflammatory cytokines with the given fixed dose of the paste. In this study at very early stage of RP sophisticated science was used as the disappearance of the malarial parasite was confirmed by the polymerase chain reaction for parasite DNA and early in vitro study conducted concomitantly during the exploratory phase showed anti-parasitic activity against drug sensitive (3D7) and drug-resistant (Dd2) *Plasmodium falciparum* strains with non-polar extracts of leaves at minimum inhibitory concentration (MIC₅₀ 25–35 μ g/mL).^[44]

As referred above, there is possibility to find out promising and potent anti-malarial herbs for new drug discovery, with application of the R P. Some of medicinal plants are reported with the potential of anti-malarial activity. Their, efficacy, safety and Phytochemical observation studies may open new path for finding new anti-malarial herbal remedy.

Table 1: Ayurveda Plants may be selected for the study for anti-Malarial property using with R P.

S. No.	Scientific name	Hindi name	Part used	Scientific validation
1	<i>Andrographis paniculata</i>	Kalmegh/ Chirayta	Whole plant	Anti malarial, ^[45] (Kirti Mishra, <i>et al</i> , 2009)
2	<i>Bixa orellana</i>	Sinduri	leaf	Anti-malarial ^[46] (Fernández-Calienes Valdés A, <i>et al</i> , 2011)
3	<i>Clerodendrum viscosum</i>	Bhati, Vaita	Whole plant	Anti-malarial ^[47] (KD Tripathi-2006)
4	<i>Capparis zelanica</i>	Nahar-kanta	Leaf, flower	Anti pyretic, Analgesic ^[48] (Lather Amit, <i>et al</i> , 2010)
5	<i>Enicostemma littorale</i>	Nahi/mamajjak	Whole plant	Anti diabetic and anti-pyretic. ^[49] (Samir Tanna, <i>et al</i> , 2010)

CONCLUSION

Plant-derived substances have recently become of great interest owing to their versatile applications. Medicinal plants are the richest bio-resource of drugs of traditional systems of medicine, modern medicines, nutraceuticals, food supplements, folk medicines, pharmaceutical intermediates and chemical entities for synthetic drugs.

Reverse pharmacology offers a major paradigm shift in drug discovery. Instead of serendipitous findings pursued randomly an organized path from clinical observations and successes is established.

Reverse Pharmacology is possible only in those countries with pluralistic healthcare and where robust clinical and laboratory documentation of novel human, pharmacodynamic effects are possible by inter-system collaborative teamwork. Reverse Pharmacology (R P) in India focuses mainly on the development of Ayurveda-inspired standardized formulations, the safety, and activity of which is implied through its long history of usage.

The article on using Reverse Pharmacology (RP) by Willcox *et al* for finding anti-malarial herbal medicine suggests that this trans-discipline of RP has global appeal. Willcox *et al* evolved a standard score system to prioritize a plant from folklore practices. Classical Ayurvedic references of ailments and their management used by Ayurvedic physicians is based on the selection of the medicine for evaluation through RP, besides a long tradition of usage of medicines. There is possibility to find out promising and potent anti-malarial Ayurveda herbs for new drug discovery, with application of the R P.

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