AYUSHDHARA
ISSN: 2393-9583 (P)/ 2393-9591 (O)
An International Journal of Research in AYUSH and Allied Systems

Research Article

RESEARCH ON AYURVEDA DRUGS TOWARDS THE DRUG DEVELOPMENT FOR PLASMODIUM VIVAX MALARIA

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KEYWORDS: Malaria, Plasmodium vivax, Ayurveda, *Vishamajvara, Kiratatikta, Saptaparna, Parijata.*

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ABSTRACT

Developing countries are more vulnerable to the Vector borne diseases, than developed countries. Incidence of Malaria is steadily increasing and number of deaths as well; is a serious problem in Africa; every five (20%) childhood deaths are due to the effects of the disease and every 30 seconds a child dies from malaria. The problem of Malaria acquired new dimensions such as resistance of vectors to chemical insecticides and drug resistance in strains of Plasmodium Vivax and Plasmodium Falciparum. These are the serious obstacles in the control of Malaria and hence there is a serious need to develop alternate strategies to control Malaria.

Central Council for Research in Ayurvedic Sciences is carrying out clinical trial on different Vector Borne Diseases like Malaria, Filariasis etc since seventies. Trial carried out with herbal and herbo-mineral drugs like AYUSH-64, *Saptaparnatwak ghanavati, Guduci satva, Spatika Bhasma, Kiratatiktadi* compound, *Parijatapatra ghanavati* etc. on Plasmodium Vivax Malaria. The present paper deals with the details of those drugs and concludes the best drug for control of Malaria.

INTRODUCTION

Malaria is one of the most prevalent and deadly infectious diseases in Asia, Africa and the America. All over the world, every year around 250 million cases are registered and nearly one million deaths are taking place. United Nations incorporated it as one of the Millennium Development Goals (6C) with the aim of combating Malaria. As per the World Malaria Report 2015[(1)], India accounts for 70% of the total malaria incidence in the South-East Asia Region and more than 80% of the global Plasmodium vivax burden is contributed by three countries including India. India alone contributes nearly half (46%) of the global population at risk and two thirds of those are at stable risk[(2)]. It is endemic across around 44 million km, approximately 1/3rd of earth land[(3)].

Malaria is caused by protozoa of the genus Plasmodium; species of falciparum, vivax, ovale, malariae. Plasmodium vivax malaria is found across a large area of the globe and potentially affects larger number of people than Plasmodium falciparum malaria.

Malaria description in Ayurveda

In Ayurvedic literature Malaria fever is known as *Vishamajwara* (intermittent fever). Since Vedic time references for fever is available and is known as *Takma* in Atharvaveda. Carakasamhita, the first detailed compendium of Ayurveda starts its therapeutics part with the treatment of *Jvara* (fever), shows the importance of treatment of fever in Ayurveda. There are numerous kinds of fevers described in Ayurveda, like *Santatajvara, Sannipatajvara, Vishamajvara, Abhishangajvara, Abhighatajajvara* etc[(4)].

Fever that manifests with irregular onset (*Vishama arambha*) and remission (*Visarga*) is called as *Vishamajvara* (intermittent fever). It is described in Kashyapasamhita that when all the three or two humours vitiate and reach *Rasavaha dhamani* (channels carrying rasa kind of tissue elements) produce *Vishamajvara*. This can be compared with malarial fever based on its irregular onset and remission. Clinical features of *Vishamajvara* (Malaria) are fever with irregular onset and remission, excessive thirst, heaviness in the body, generalized body pains, headache, rigors, nausea, vomiting etc.

Necessity of new, safe and effective drug

Incidence of Malaria is steadily increasing and number of deaths as well; the problem of Malaria acquired new dimensions such as resistance of vectors to chemical insecticides and drug resistance in strains

of Plasmodium Vivax and Plasmodium Falciparum. These are the serious obstacles in the control of Malaria and hence there is a serious need to develop alternate strategies to control Malaria. Very worrying reports from South East Asia is potential resistance to artemisinins which form the basis of first line anti-malarial treatment in many countries.

World Health Organization has advised to have a stock of other equivalent drugs for use when resistance occurs, as far as chloroquine is concerned. By this it appears that margin of security of malaria chemotherapy is very narrow and there is great need to develop new and better drugs. More over Malaria parasite develops resistance easily to allopathic ante-malarial drugs due to their simple chemical structure. As far as herbal and herbo-mineral drugs are concerns, it is highly difficult to develop resistance when given in the native dosage forms of Ayurvedic herbal drugs.

Central Council for Research in Ayurvedic Sciences is taken up clinical research in Malaria almost four decades ago with aim to develop a safe and effective new drug for Plasmodium Vivax malaria. It had also worked in association with National Malaria Eradication programme and Government of Haryana and carried out collaborative field trials at primary health centres of Gurgaon district. Observations of this trial have confirmed the effectiveness of the coded Ayurvedic drug AYUSH-64 in clearing the malaria parasite with 67-86% range of efficacy[5].

Dr. Achanta Laxmipathi Research Centre for Ayurveda, a peripheral unit of Central Council for Research in Ayurvedic Sciences (Ministry of AYUSH, Government of India), is carried out clinical research on effect of different herbal and herbo-mineral compounds of Ayurveda on Plasmodium Vivax malaria. The present article is aiming to review these studies to conclude the best drug for Plasmodium Vivax malaria.

MATERIALS AND METHODS

Malarial Patients positive for Plasmodium Vivax were selected from the Chennai Corporation Malaria clinic, located at Elephant gate area, Chennai city, Tamil Nadu, according to the selection criteria.

For Curative trials of Malaria

Criteria of inclusion

1. Positive cases of Malaria (Plasmodium vivax)
2. Periodic fever with chill and rigor

Criteria of exclusion

1. Age below 10 years and above 60 years
2. Pregnant woman
3. Malignant malaria
4. Malaria caused by other species

Criteria for withdrawal from the study

1. Patient who is not coming for regular follow up
2. Irregular drug intake

For Malaria prophylactic trials

Criteria of selection

1. Age above 15 years and below 60 years
2. History of frequent episodes of malarial fever with three or more attacks within one year period

Criteria of exclusion

1. Age below 15 years and above 60 years
2. Pregnant woman
3. Malignant malaria
4. Suffering with any other serious systemic illness

Criteria for withdrawal from the study

1. Patient who is not coming for regular follow up
2. Irregular trial drug intake

Study design and Trial Drugs

Study-I

Design: Randomized Double blind control trial

Trial drug: Ayush-64, 3gm/day in 3 divided doses for 4 days.

Control drug: Chloroquine 600mg + 30mg Primaquine – 1st Day,

Chloroquine 600mg+15mg Primaquine – next 3 days

Study-II

Design: Single blind comparative study

Trial drugs: Group-I: *Saptaparnatvak ghanavati* 1500mg TID for 10 days.

Group-II: coded drug AYUSH-64 3gm+ *Spatika bhasma* 500mg + *Guducisatva* 500mg: TID for 10 days.

Group-III: *Parijathapatra ghanavati* 1.5gm TID for 7 days.

Study-III

Design: Open trial

Trial drug: *Parijathapatra ghanavati* 1.5gm thrice daily with lukewarm water for 7 days.

Study -IV

Design: Open trial

Prophylactic study

Trial drug: *Indukanthaghritha* (a medicated ghee) 10 ml per day with lukewarm water for 28 days

Source of drug supply: For above studies 1 to 3, drugs are supplied by Central Research Institute (Ayurveda), Patiala (CCRAS, M/o AYUSH, Govt. of India).

Study –IV: IMPCOPS, Chennai.

Criteria for assessment of results

Study-I

Responded: Total disappearance of malarial parasites with clinical improvement after treatment i.e. on sixth day is considered as responded.

Not Responded: Non disappearance of parasite with or without clinical improvement.

Study-II and III

Responded: Blood smear negative for Malaria parasite Plasmodium vivax after treatment period till 29th day

Not Responded: Blood smear positive for Malaria parasite Plasmodium vivax after treatment period

Study-IV

Good response: Peripheral blood smear negative for plasmodium parasite till 360th day.

Fair response: 1). Peripheral blood smear negative for plasmodium parasite till 300th day in cases with history of previous 3 attacks of malaria fever.

2). Peripheral blood smear negative for plasmodium parasite till 270th day in cases with history of more than 3 previous attacks of malaria fever.

Poor Response: Peripheral blood smear negative for plasmodium parasite till 240th day.

No response: Appearance of plasmodium parasite in the blood before 90 days.

Follow-up

Curative trials

Study-I: Follow-up was carried out for three months

Study-III and III - drug intake for 7 days, there after weekly follow up for up to 29th day.

Prophylactic trial:

Study-IV: drug intake for 29 days, there after weekly follow up for up to 360th day.

i.e. on 8th, 15th, 22nd, 29th, 36th, 43rd, 50th, 57th, 64th, 90th, 120th, 150th, 180th, 210th, 240th, 270th, 300th, 330th and 360th days.

Statistical analysis: Applied student's 't' test for assessment.

Ethical issues: Voluntary informed consent was obtained from all the subjects who participated in the study, before starting clinical trial.

DISCUSSION

In spite of advanced chemotherapy and development of new plant based drugs like artemisinins and vigorous attempts of vector control, between 2000 and 2015, the substantial expansion of malaria interventions led to only 58% decline in malaria mortality rates globally. This shows the necessity of invention as well as adoption of anti-malarial drugs from indigenous systems of medicine world-wide. Keeping this and national priority of malaria control in view the Central Council for Research in Ayurvedic Sciences, the apex body for research in Ayurvedic system of medicine has taken up the job of development of safe and effective anti-malarial drugs. As a part of that programme, Dr. A. Lakshmipathi Research Centre for Ayurveda, Chennai, one of the peripheral institutes of Central Council for Research in Ayurvedic Sciences, Ministry of AYUSH, Government of India, has carried out series of clinical trials with herbal as well as herbo-mineral drugs on Plasmodium Vivax malaria for around three decades. The present article is written to review/judge the best anti-malarial herbal or herbo-mineral drug after analyzing the studies carried out at the Achanta Laxmipathi Research Centre for Ayurveda, Chennai and corresponding author is one of the investigators of Study-III and IV.

Study-I was carried out on Randomized Double blind basis with trial and control groups; trial drug Ayush-64 was given to 29 subjects and standard modern anti-malarial drugs Chloroquine + Primaquine to 30 subjects as control drug. Besides clinical response (absence of fever), absence of malaria parasite after treatment period was taken as the criteria for assessing the efficacy of the drug. Out of 29 cases who received Ayush-64, 21 cases responded well to the treatment and the other eight were declared as failure. So far the disappearance of Malaria parasite was concerned nearly 95% cases in the control group and 90.5% in Ayush-64 group become free from parasites on fourth day respectively. In this study it was concluded the trial drug Ayush-64 was found to possess good anti-malarial property with positive result in 72.41% as compared to 100% in control group (Table-I). The follow-up study carried out for three months indicate that there was no relapse in any of the case in both the treated groups [6]. Before initiating the study toxicity studies of the drug was conducted by the Achanta Laxmipathi Research Centre for Ayurveda, Chennai, and found that the drug did not possess any toxicity at the dose of 500mg/kg when fed orally to rats for a period of four weeks. There was no side effect or toxic manifestation worth considering during the course of the study and follow-up in any of the treated groups.

Study II was carried out under three trial groups – Group-I with *Saptaparnatvak ghanavati* (49 subjects), Group-II with tab. Ayush-64, along with *Spatika bhasma* and *Guducisatva* (100 subjects) and Group III with *Parijatapatra ghanavati* (114 subjects). Positive response was observed in 23 (47%) numbers in Group-I, 50 (50%) in Group-II and 78 (68.4%) in Group-III (Table II).

Among the above three groups in study-II, group-III i.e. single herbal drug *Parijatapatra ghanavati* was found more efficacious. Based on the encouraging results of Group-III, next trial i.e. study-III was taken up with the single drug *Parijatapatra ghanavati* and successfully completed on total 31 subjects. This study was a open label study and shown highly positive response in 28 cases of Plasmodium Vivax Malaria with 90.32% of cure rate. These 28 cases did not show any relapse till day 29th. Remaining 03 cases had shown relapse, in 01 case smear was positive on day 15, in 02 cases smear was positive on day 22 [7] (Table –III).

Study-IV was a prophylactic trial taken up to evaluate the efficacy of a medicated ghee

Indukanthaghrita, which is popularly used in Kerala state. Study carried out on total 67 patients, of which, 35 (74.46%) showed Good response, 11 (23.40%) showed Fair response but, 01 (02.12%) cases did not show any response; 09 patients were dropped out from the study due to irregular drug intake[8] (Table IV).

Details of Drugs used in these formulations

Study-I

Herbal compound drug Ayush-64 contains *Alstonia scholaris* (L.) R. Br., *Swertia chirata* Bunch Ham. [*Swertia chirayayita* (Roxb .ex flem) Karst.], *Caesalpinia Crista* Linn. [C. bonduc (L) Roxb.] and *Picrorhiza kurroa* Royle ex Benth.

Central Council for Research in Ayurvedic Sciences, Ministry of AYUSH, Govt. of India carried out a series of experimental and pharmacological studies on Ayush-64. This drug at doses of 100, 250, 500 and 750 mg/kg body weight administered orally showed an appreciable anti-malarial property when tested on Plasmodium berghei infected albino mice.

Experimental studies carried out with Ayush-64 for its anti-malarial effect on albino rats and the study shows that it is not effective against Plasmodium berghei in experimental animals[9].

The above council also carried out experimental studies to assess the anti-malarial activity of active principles Echitamine chloride from *Alstonia scholaris*, Swerchirin from *Swertia chirata* and β-Caesalpin from *Caesalpinea bonducella* in rats. Echitamine chloride had shown anti-malarial activity at the dose of 320micro gram/K.g. (sub-cutaneous route) and 1.6 mg/kg (Oral route). Swerchirin had shown anti-malarial effect at the doses of 320 micro gram/K.g. and 1.6 mg/kg in both the oral as well as sub-cutaneous routes. Whereas β-Caesalpin was found to have anti-malarial effect at the dose of 1.6 mg/kg in both oral as well as sub-cutaneous routes [10].

LD $_{50}$ value of Ayush-64 in mice by oral route is more than 2gm/kg while in rats it was more than 4gm/kg. In subacute studies the drug in the dose of 500mg/kg orally for a period of 12 weeks was considered absolutely safe. In acute toxicity studies, it was found to be non-toxic up to the dose of 10g/kg, when given orally to mice [11].

Study II

Group-I: single herbal drug *Alstonia scholaris* (L.) R. Br.

Group-II: Herbal drugs: Ayush-64 (*Alstonia scholaris* (L.) R. Br., *Swertia chirata* Bunch Ham. (*Swertia chirayayita* (Roxb .ex flem) Karst., *Caesalpinia Crista* Linn. [*C. bonduc* (L) Roxb.] and *Picrorhiza kurroa* Royle ex Benth) + water extract of *Tinospora cordifolia* (Willd.) Miers. + Mineral drug: *Spatika bhasma* (Alum)

Group-III: single herbal drug *Nyctanthes arbortristis* Linn.

Study-III: single herbal drug *Nyctanthes arbortristis* Linn.

Main anti-malarial drugs evaluated in these trails are - Tab. Ayush-64, *Kiratatikta* (*Swertia chirayita* (Roxb. Ex Flem.), *Latakaranja* (*Caesalpinia bonducella*), *Saptaparna* (*Alstonia scholaris* R.Br.) and *Parijata* (*Nyctanthes arbor-tristis* Linn.), remaining drugs of the above formulations are supportive only. Hence the main drugs are discussed below for their comparative effect.

***Kiratatikta* (*Swertia chirayita* (Roxb. Ex Flem.)**

The chiretta is much prized in India as a tonic and bitter without aroma or astringency. It possesses the property of bitter tonic but unlike most other bitters it does not constipate the bowels. Instead it tends to produce a regular action and causes a free discharge of bile. In Indian medicine, chiretta is prescribed in a variety of forms and combinations in chronic fevers.

Chiretta is reported to contain a yellow bitter acid, ophelic acid ($C_{15}H_{20}O_{13}$), two bitter glucosides, chiratin ($C_{26}H_{48}O_{15}$) and amarogentin ($C_{32}H_{38}O_{16}$), xanthone, swerchirin ($C_{25}H_{13}O_6$). Amarogentin is one of the bitterest substances known. [12]

***Latakaranja* (*Caesalpinia bonducella*)**

The three new cassane furanoditerpenoids (1-3) together with known cassane diterpenes were isolated from the seed kernels of Caesalpinia bonduc compound 1-3 exhibited good anti-malarial activity against multi drug resistant K1 strain of Plasmodium falciparum[13]. Kalauni et al has reported antimalarial activity of cassane and norcassane type of diterpenes from Caesalpinia crista and their structure activity relationship [14]. Linn et al has reported cassane and norcassane type diterpene from Caesalpinia crista of Indonasia and their antimalarial activity against the growth of plasmodium falciparum[15].

***Saptaparna* (*Alstonia scholaris* R.Br.)**

Commonly known as Devil's tree. The bark is regarded as bitter tonic and a mild febrifuge, and possesses astringent, anthelmintic and galactogogue properties. The total alkaloidal content in the Indian bark is reported to be 0.16-0.27%, with echitamine as the chief constituent, and echitamidine in small quantities. The total alkaloids and the tincture made from the bark showed little or no demonstrable action on malaria; also no synergistic action with quinine was observed [16]. Gandhi and Vinayak reported the antimalarial activity of this drug [17].

***Parijata* (*Nyctanthes arbor-tristis* Linn.)**

It is commonly known as Night Jasmine. Among all the drugs discussed in this paper, the drug *Parijata* is found most efficacious among all. Leaves of this plant contain tannic acid, methyl salicylate, an amorphous glycoside, mannitol, an amorphous resin

and a trace of volatile oil. They also contain ascorbic acid (30mg/100g.) and carotene [18].

Parijata is found to have anti-malarial and antipyretic and antimicrobial properties on pharmacological screening [19]. Fresh paste of leaves of this plant also tried clinically for its safety and anti-malarial efficacy in around 120 patients, 92 (76.6%) patients had shown complete relief [20]. Aminuddin et al [21] and Badam L Rao et al [21] are also reported the anti-malarial activity of *Parijata*.

Prophylactic study

Study-IV: Compound herbal ghee preparation contains *Caesalpinia Crista Linn*. [*C. bonduc* (L) Roxb.], *Cedrus deodara* (Roxb.) Loud are main ingredients. In this study a medicated ghee *Indukantaghrita* evaluated for its prophylactic activity against Malaria. Main ingredients of trail drug *Indukanthaghrita* are *Devadaru, Putikaranja* etc. *Devadaru* (*Cedrus deodara*) is having *Krimighna* (anthelmintic) property. The bark is said as useful in remittent and intermittent fevers. *Putikaranja* or *Latakaranja* the other main drug is already discussed above.

CONCLUSION

1. From 17th century onwards treating of Malaria is started with Cinchona bark. After successful invention of chemotherapy, the world was relaxed about Malaria. But after observing resistance to chemotherapy drugs, big question arouse about the eradication of Malaria.
2. World started looking after alternate systems of medicine, and artemisinins created a ray of hope.
3. Now it is very shocking to know about the resistance to artemisinins in South East Asia region.
4. It is the peak time to go for new, alternative, effective and safe drugs from traditional systems of medicine.
5. This paper too have worked on the aim of finding a new, safe, effective plant based drug, based on the drugs of Ayurvedic pharmacology and clinical studies done on Vivax Malaria.
6. An elaborative analysis done on the studies carried exclusively by Dr. Achanta Laxmipathi Research Centre for Ayurveda, Chennai, is one of units of the Central Council for Research in Ayurvedic Sciences, worked extensively on Vivax Malaria.
7. Drugs reviewed for Anti-malarial effect are Tab. Ayush-64, *Kiratatikta (Swertia chirayita (Roxb. Ex Flem.), Latakaranja (Caesalpinia bonducella), Saptaparna (Alstonia scholaris R.Br.)* and *Parijata (Nyctanthes arbor-tristis Linn.)*.
8. Among these drugs, *Parijata* (*Nyctanthes arbor-tristis Linn*.) was found highly effective as well safe drug (Chart-I).
9. This article concludes that the pharmaceutical form used in administering *Cinchona officinalis* and *Artemisia ammua*, should not be done with *Parijata*, the new world scientists must evaluate *Parijata* in the traditional form prescribed by the Ayurvedic system of medicine like paste of the leaf, or tablets made of water extract of the leaf. By this only drug resistance to Malaria can be avoided.

Table -I: Results of Study-I

	Responded	**Not responded**
Trial group (n=29)	21 (72.41%)	08 (27.59%)
Control group (n=30)	30 (100%)	00

Table-II: Results of Study-II

	Responded	**Poor response**
Group-I (n= 49)	23 (47%)	26 (53%)
Group-II (n=100)	50 (50%)	50 (50%)
Group-III (n=114)	78 (68.4%)	36 (31.6%)

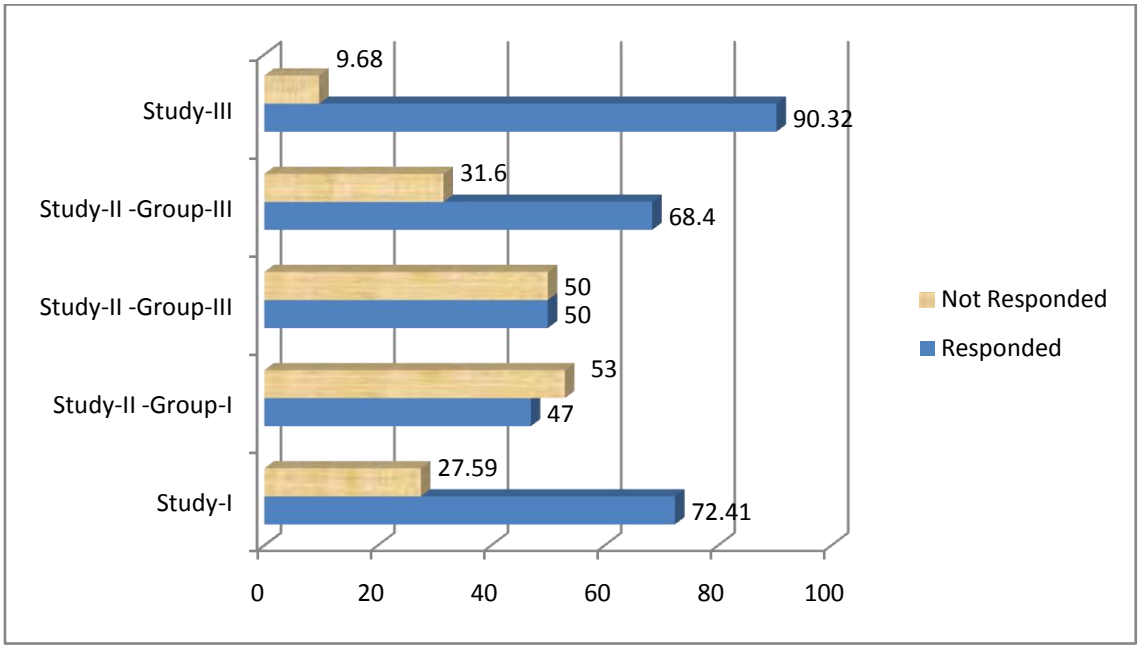
Table-III: Results of Study-III

	Responded	**Not responded**
Parijatapatra ghanavati (n=31)	28 (90.32%)	03 (09.68%)

Table-IV: Results of Study-IV

	Good response	**Fair response**	**Poor response**	**No response**
Indukanthagrutha (n=47)	35 (74.46%)	11 (23.40%)	00	01 (2.12%)

Chart-I: Comparison of Results of Malaria curative trails



ACKNOWLEDGEMENTS

Authors are grateful to the Dr. K.S. Dhiman, Director General, Central Council for Research in Ayurvedic Sciences, New Delhi for his financial support and encouragement.

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Cite this article as:
K. Bharathi, G. P. Prasad, T. Maheswar, G. Babu. Research on Ayurveda Drugs Towards the Drug Development for Plasmodium Vivax Malaria. AYUSHDHARA, 2016;4(2):1100-1106.
Source of support: Nil, Conflict of interest: None Declared