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A review on an ayurvedic antimalarial drug: Ayush-64

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Abstract
Ayurveda is one of the oldest medicinal systems in the world, derived from ancient texts that emphasize a "natural" and holistic approach to physical and mental well-being. Ayurveda is still practiced in traditional Indian healthcare. A parasite that is prevalent in tropical regions is the cause of malaria. The kind of mosquito that spreads malaria from person to person is called *Anopheles*. Fever, chills, and a flu-like illness are common symptoms in those suffering from malaria. *Plasmodium falciparum, P. ovale, P. malariae*, and *P. vivax* are the four species that cause the disease. The latter three species may remain in the liver and can cause relapse many years after the initial infection, although they are not as harmful as *P. falciparum*. For thousands of years, people have been treating malaria with plants. Quinine was used as the dominant antimalarial medication for many years, but since the 1930s, several synthetic medications have essentially taken the position of these medications. The Ayurvedic formulation Ayush-64 was developed by the Central Council for Research in Ayurvedic Sciences (CCRAS), which is the highest authority for Ayurvedic research under the Ministry of Ayush. Since the 1980s, CCRAS peripheral institutes have been using it to treat a variety of illnesses, including inflammations, fevers, and joint difficulties. Its effectiveness in treating diseases including chikungunya, microfilaria, and the malarial fever has been documented. Ayush-64 is useful in treating asymptomatic, mild-to-moderate instances of COVID-19 illness, according to several trials. In short, Ayush-64 can be said addressed rightly as a miraculous boon from the field of Ayurveda to society.

Keywords: Anti-malarial, Ayush-64, Vishama jvara, Fever, Ayurveda

1. Introduction
Ayurveda is one of the oldest medicinal systems in the world, derived from ancient texts that emphasize a "natural" and holistic approach to physical and mental well-being. Ayurveda is still practiced in traditional Indian healthcare. Ayurveda is a science that uses various procedures for promoting and maintaining health along with treating and preventing disease [1].
A parasite that is prevalent in tropical regions is the cause of malaria. It is transmitted by biting of female Anopheles mosquito carrying the infection. Fever, chills, and a flu-like illness are common symptoms in those suffering from malaria. Based on estimates, 400 million people reside in nations where malaria is endemic, and 1,600 million people live in areas where malaria is capable of spreading. *Plasmodium falciparum, P. ovale, P. malariae*, and *P. vivax* are the four species that cause the disease. The latter three species may remain in the liver and can cause relapse many years after the initial infection, although they are not as harmful as *P. falciparum*. The deadly form of malaria, known as malignant tertiary malaria, is brought on by *P. falciparum* [2].
The medicinal properties of several plants have been known since ancient times. Due to their increased effectiveness, safety, and affordability, the use of plants as medicine has grown in popularity. Additionally, for thousands of years, people have been treating malaria with plants. Quinine was used as the dominant antimalarial medication for many years, but since the 1930s, several synthetic medications have essentially taken the position of these medications. This article attempts to succinctly explain how Ayush-64, an ayurvedic medicine, treats malaria. Since this essay is a literary review, the information was gathered from current and traditional ayurvedic textbooks, periodicals, and websites that are pertinent to Ayurveda [3].

2. Ayurvedic drug (Ayush-64)

The Ayurvedic formulation Ayush-64 was developed by the Central Council for Research in Ayurvedic Sciences (CCRAS), which is the highest authority for ayurvedic research under the Ministry of Ayush [4]. Since the 1980s, CCRAS peripheral institutes have been using it to treat a variety of illnesses, including inflammations, fevers, and joint difficulties. Its effectiveness in treating diseases including chikungunya, microfilaria, and the malarial fever has been documented. It was used to treat malaria, in 1994 and 1996, respectively, during the malaria epidemics in Rajasthan and Assam [4-7].

Four ingredients make up the formulation (Table 1). The majority of drugs are hot in potency (*usna virya*), pungent after biotransformation (*katu vipaka*), reduce *vata* and *kapha* in the body (*kaphavata hara*), boost digestive fire (*dipana*), aid in normal digestion (*pachana*), and clear blockages in the body's channels (*srotho shodhana*) (Table 2). The chemical compositions of plants used in this formulation are listed in Table 3 below.

Table 1: Ingredients of the Ayurvedic drug (Ayush-64) [8]

S. No.	Botanical name	Drug	Part used	Proportion
1.	*Alstonia scholaris* R.	*Saptaparna*	Bark aqueous extract	1 part
2.	*Picrorhiza kurroa Royle* ex. Benth	*Katuki*	Root extract	1 part
3.	*Swertia Chirata* Pexbex. Karst	*Kiratatikta*	whole-plant extract	1 part
4.	*Caesalpinia crista* L.	*Kuberaksha*	seed powder	2 part

Table 2: Pharmacodynamics properties of ingredients [9]

S. No.	Drug	Taste (*Rasa*)	Quality (*Guna*)	Potency (*Virya*)	Biotransformation (*Vipaka*)	Indication (Roghannata)
1.	*Saptaparna*	Bitter, Astringent	Light, Unctuous	Hot	Pungent	Pain, wormicidal, bloating, cardiac tonic, asthma, blood-related diseases, wound antihelminthic, fevers pacifies *kapha*, *pitta* and *vata* disorders,
2.	*Katuki*	Bitter	Light, Dry	Cold	Pungent	Purgative, cardiac tonic, improves digestion recurrent fevers urinary disorders, diabetes, pacifies *kapha* and *pitta*, burning sensation, asthma, cough, skin disorders
3.	*Kiratatikta*	Bitter	Light, Dry	Cold	Pungent	Asthma, useful in chronic and recurrent fevers, blood related diseases, pacifies *kapha* and *pitta*, burning sensation, cough, thirst, inflammation, skin disorders, wormicidal, wound
4.	*Kuberaksha*	Pungent, Bitter, Astringent	Light, Dry	Hot	Pungent	Improves digestion, pacifies *kapha* and *vata* bloating, pain, wormicidal, urinary disorders, diabetes, skin disorders, antiemetic, haemorrhoids, cough useful in recurrent fevers

Table 3: Chemical composition of ingredients [10]

S. No.	Drug	Chemical constituents
1.	*Alstonia scholaris*	Alpha-amyrin, alstonides, echitamidine N-oxide, echitaminic acid, akuammicine N-oxide, and akuammiginone
2.	*Picrorhiza kurroa*	Kutkoside, vanillic acid, ferulic acid, cinnamic acid, apocynin, amarogentin, saptoparna, eufoliatorin, kutkin, and picroside I and II
3.	*Swertia Chirata*	Flavonoids, iridoid glycocide, triterpenoid, anthine, and Xanthine glycoside
4.	*Caesalpinia crista*	Diterpenoids, casalmin, noncasalpine-E, diterpines, and caesalpinins

3. Method of preparation of the Ayurvedic drug (Ayush-64)

To prepare the Ayush-64 formulation, all elements are taken according to Table 1 composition and prepared using the CCRAS technique. All three ingredients were prepared into a separate kashaya (decoction), from which ghanasatva (concentrated extract) was derived. Weighing each component precisely allowed us to formulate the Ayush-64 pill. Two parts of *Caesalpinia bonducella* powder (100 mesh) were combined with one part each of ghansatva (concentrated extract). The ingredients are mixed in the exact ratio specified, along with a few additions like sodium benzoate, starch, gum acacia, *etc*. A ball mill is filled with prescribed amounts of powdered herbal extracts and additives for even mixing and fine grinding. After that, the whole thing is granulated. Using a hot air drier, the granules are dried at 70 °C. Finally, 500 mg tablets were made using the technique of wet granulation and 10 mm round punches. They are packed in strips to shield the pills from moisture in the air [11].

4. The pharmacological activity of the ingredients

4.1. *Alstonia scholaris*

The *Alstonia scholaris* bark methanolic extract was shown to have more promising antiplasmodial action. However, compared to *Alstonia macrophylla*, *Alstonia scholaris*'s antiplasmodium effectiveness was not as strong. In India, *Alstonia macrophylla* is commonly misidentified as *Alstonia sholaris*. From *Alstonia macrophylla*, four novel alkaloids, alstiphyllanines A-D (1–4), were extracted, and 2D NMR and MS studies were used to determine their structures. Alkaloids 1-4 exhibited vaso relaxant efficacy against phenylephrine-induced constriction of the isolated rat aorta and mild antiplasmodial activity in malaria caused by *Plasmodium falciparum* [12, 13]. *Alstonia scholaris* has potent schizonticidal and antiplasmodial properties against *P. falciparum*, which help it to reduce malarial fever [14]. It reduced the inflammation in the rat paw edema study model that was caused by carrageenan. Indole alkaloids derived from the leaves of *Alstonia scholaris* exhibit substantial inhibitory effects against both adenovirus and herpes simplex virus (HSV). Alkaloids inhibited inflammatory mediators (5-LOX, COX-1, and COX-2) in *in-vitro* study [15, 16].

4.2. *Picrorhiza kurroa*

Picrorhiza kurroa suppresses *Plasmodium falciparum* growth

[17]. It is noteworthy that l3-adrenergic inhibition has an anti-inflammatory impact [18]. In animals used for experiments, it stimulates phagocytosis as well as the humoral and cell-mediated aspects of immunity. It also increases lymphocyte proliferation, cytokine levels in serum (IL-4 and IFN-gamma), hemagglutinating antibody (HA titre), phagocytic index, delayed-type hypersensitivity (DTH), PFC, and CD4/CD8 population, all of which contribute to an improvement in the immune system [19, 20]. An additional investigation showcases the plant's leaf extract's capacity to scavenge free radicals and antioxidant activity [21].

4.3. *Swertia chirata*

The medication has encouraging results because of its antimalarial and antipyretic properties (Bhargava, 2009). Three secoiridoid glycosides (amaroswerin, amarogentin, and sweroside) were obtained by fractionating a methanol extract of *Swertia chirata*, which was discovered to inhibit the catalytic activity of topoisomerase I in *Leishmania donovani*. Amarogentin interacts with type I DNA topoisomerase from *Leishmania* to effectively limit its activity and stop the production of binary complexes. Additionally, in HeLa cells carrying the TREx plasmid encoding full-length Vpr (TREx-HeLa-Vpr cells), it suppresses the expression of viral protein R, an appealing target for HIV infection [22]. In another study, it prevented HSV-1 from spreading and causing plaque formation at a level higher than 70% [23]. According to a study on rats with arthritis, the plant's leaves showed an immunomodulatory impact by reducing inflammatory and oxidative stress [24]. Following treatment with the *Sweetie chirata* leaves in the animal subjects showed a significant reduction in inflammation. By preventing the production of COX-2 and the activation of Akt, MAPK, IKK-β, and NF-κB phosphorylation in LPS-stimulated macrophages, it also demonstrated suppressive effects on inflammatory mediators [25].

4.4 *Caesalpinia crista*

Methylene chloride extract from *Caesalpinia crista* seed kernels, which showed a promising antimalarial activity against *Plasmodium berghei* infected mice, seven new furanocassane-type diterpenes [caesalpinins C-G and norcaesalpinins D and E] were isolated, in addition to norcaesalpinins A–C and 11 known compounds (norcaesalpinins A-C, 2-acetoxy-3-deacetoxycaesaldekarin E, caesalmin B, caesalpin F, caesalmin G, 14(17)-dehydrocaesalpin F, 2-acetoxycaesaldekarin E, and 7-acetoxybonducellpin C). The structures of these were ascertained using spectroscopic investigation. Significant dose-dependent inhibitory effects on *Plasmodium falciparum* FCR-3/A2 growth were demonstrated by the isolated diterpenes *in vitro*. The most powerful inhibitory effect was demonstrated by norcaesalpinin E, whose IC50 value was 90 nM. Their values varied from 6.5 micro M to 90 nM [26].

Both hepatoprotective and antimalarial properties are present in this plant [27]. It reduced DNA damage and red blood cell hemolysis (RBC) [28]. After being challenged with *Pseudomonas aeruginosa* for two weeks, the animals treated with *Caesalpinia* exhibited a notable reduction in lung abscess incidence and bacterial clearance from the lungs [29]. Shown protection against the vaccinia virus. Positive activation of immune modulation was shown in an *in-vivo* investigation, hemagglutinating antibody (HA) titre, neutrophil adhesion test, delayed-type hypersensitivity (DTH) reaction, phagocytic activity, and cyclophosphamide-induced myelosuppression [30].

5. Probable mode of action in the management of fever as per Ayurveda

The primary treatment of jvara (fever) is to digest *ama* (which is partially digested metabolic waste), by means of langhana, (which is fasting or calorie restriction), and formulations, which are polyherbal medicines made of components with anti-inflammatory qualities such *tikta rasa*, *ushna virya*, *katu vipaka*, and *amapathaka*.

6. Research studies on ayurvedic medicine (Ayush-64)

6.1. Anti-malaria studies

Patients with *P. vivax* malaria participated in a phase II prospective comparative randomized clinical trial to evaluate the effectiveness of Ayush-64 vs chloroquine. The patients were administered a total of 1500 mg of chloroquine over three days, or 1 g of Ayush-64 three times a day for five to seven days. According to the study's findings, at day 28, just 23 out of 47 patients (48.9%) in the Ayush-64 group and all 41 patients in the chloroquine group had recovered ($p < 0.05$). The Ayush-64 group's 23 patients had a parasite clearance time that was longer than that of chloroquine (3.16 vs 1.5 days). In general, both regimens were highly received. In summary, normal chloroquine therapy is more successful in treating *P. vivax* malaria than Ayush-64 at a dose of 1 g three times a day for 5-7 days [31]. The medication has an 81% curative effect on *P. vivax*; it works better in the ring stage than in the gamete stage. It was discovered that after extended medication, the cure result in cases of mixed *P. vivax* and *P. falciparum* infection was 75% [32]. Ayush-64 was found to be safe, non-toxic, and to have good anti-malarial action in a study group comprising 4500 people. When Ayush-64 was used in conjunction with anti-mosquito measures, a significant decrease in the infectivity rate was detected in cases of fever. Ayush-64 was found to be more effective than chloroquine/primaquine, the conventional contemporary control, in double-blind research including sixty patients of *P. vivax* malaria. In pilot research with 112 participants, preventive therapy resulted in 97.14% of cases of *P. falciparum* malaria cases [33, 34].

6.2. Other studies

It was established that Ayush-64 had a positive clinical impact on the treatment of microfilariasis and microfilaraemia [35, 36]. A one-week intervention of "Ayush-64" at a dose of 3 g/day effectively helped to recover from influenza-like illnesses and also the quicker return to normal life with reduced frequency of usage of acetaminophen/antihistaminic drugs in a prospective, open-label, nonrandomized, single group, single-center pilot study with pre-test and post-test design. Throughout the trial, no negative impacts were discovered [37]. Between January 2022 and March 2022, clinical research was carried out at the Government Ayurvedic Hospital in Patiala to assess the safety and effectiveness of Ayush-64 in patients with influenza-like symptoms who had received a clinical diagnosis. When Ayush-64 was given to patients as an adjuvant to usual care, it was noted that the patient's symptoms significantly improved. In mild to severe cases, it slowed the disease's course and none of the patients needed to be admitted to the hospital. Within two to three days of

medication, the symptoms started to go away [39]. A two-arm, multi-centric, randomized (1:1) experiment comparing standard of care (SOC) with Ayush-64 plus SOC (Ayush plus); the trial was open-label (assessor blind). When used with SOC, Ayush-64 accelerated recovery, decreased hospital stays, and enhanced health in COVID-19 patients. It was deemed secure and well-absorbed [40].

6.3. Toxicological studies

Ayush-64 was the subject of numerous pre-clinical investigations to examine both its safety and effectiveness. The main research, which focused on the anti-malarial properties in albino mice, discovered that a dose of 500 mg/kg of body weight for 12 weeks was both safe and non-toxic [41].

7. Conclusion

Ayush-64 is an amazing polyherbal formulation from Ayurveda, which is applied in the treatment of a wide range of disorders by clinicians all over the country in their daily clinical practice. It is available in the market from various pharmacies across India due to its wide utility. The formulation has previously been used to treat several illnesses, including influenza, joint discomfort, chikungunya, and malaria. Ayush-64 is also useful in treating asymptomatic, mild-to-moderate instances of COVID-19 illness, according to several trials. In summary, Ayush-64 is appropriately regarded as a miracle gift from Ayurveda to society.

8. Conflicts of interest: Nil.

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