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Study of the development of anti-malarial compounds derived from Indian medicinal plant

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ABSTRACT

Malaria is most dangerous parasite in many tropical and subtropical countries such as India, America, China etc due to increase resistance of plasmodium falciparum. There is widely available anti-malarial drug. Sixty-eight plant species used for the treatment of malaria in the north-east India. These are following plant are used in the treatment of the malaria such as Coptisteeta, Crotolariaocculata, Ocimum sanctum, Alstoniascholaris, Vitex peduncularis. Antimalral plant leaves 33%, root 31%, bark 12% and whole plant 12% are used. These review present information on alkaloids, natural compound, anthraquinone sesquiterpene, xanthones, flavonoids, coumarin and related compounds which has antimalarial properties. Malaria is currently a public health concern in India due to poor hygienic condition, drug resistance, lack of vector control program and no approved vaccine.

The anti-malarial products are discovered in vitro, in-vivo assay as well as bio-guided isolation of active compound. The final product of antimalarial chemical compound would bepotentiated new drug for the development and standardised of antimalarial extract. Which are used for pre-clinical and clinical studies. It is very effective for the development of safe and effective phytomedicine.

Key word: -anti-malarial plant, alkaloids, anthraquinone, malaria, medicinal plant

I. INTRODUCTION

The first antimalarial drug was quinine, isolated from the bark of Cinchona species (Rubiaceae) in 1820. Malaria is caused by single-celled protozoan parasites called Plasmodium and transmitted to man through the Anopheles mosquito. Control of malaria is complex because of the appearance of drug resistant strains of Plasmodium and with the discovery that man becomes infested with species of simian (monkey) malaria. At the same time, the Anopheles mosquitoes have developed resistance to many insecticides. Unfortunately, after an early success, the malarial parasite, especially Plasmodium 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. 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 [1]. Quinine, an aminoquinoline alkaloid isolated from the bark of Cinchona species (Rubiaceae) in 1820 by Pelletier and Caventou, is one of the oldest and most important antimalarial drugs and is still used today. The appearance of drug-resistance P. falciparum strains since 1960, in particular to chloroquine, has made the treatment of malaria increasingly problematic in virtually all malarious regions of the world. Several researchers have dedicated efforts to the development of new active compounds, especially from artemisinin, as an alternative to chloroquine. Currently no single drug is effective for treating multi-drug resistant malaria, and effective combination therapy includes artemisinin derivatives such as artesunate (5), or mixtures with older drugs such as the atovaquone, proguanil combination Malarone[2]. Malaria remains one of the most prevalent infectious disease in the world. In 2006, there were approximately 247 million cases of malaria and 3.3 billion people that were at risk of the disease. Nearly 1 million deaths, mostly of children under the age of 5, were caused by malaria. There are currently 109 malarious countries and territories, of which 45 are within the World Health Organization (WHO) African region (WHO 2008). Although malaria is a curable and preventable disease, its prevalence increased in the 1980s and 1990s as the parasites developed resistance to the most frequently used antimalarial drugs and the vectors became resistant to insecticides. Four species of malaria parasites are pathogenic to humans: P. falciparum, P. vivax, P. ovale, and P. malariae. P. ovale seems to be limited to sub-Saharan Africa and some islands of the western Pacific, whereas P. falciparum and P. vivax are prevalent in endemic malarial countries, such as

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Brazil. Most of the antimalarial drugs that are currently in use belong to the classes of aminoquinolines (chloroquine, amodiaquine, primaquine), quinolinomethanol derivatives (quinine, mefloquine, halofantrine), diaminopyrimidines (pyrimethamine), sulfonamides (sulfadoxine, sulfadiazine), biguanides (proguanil and derivatives), antibiotics (tetracyclines, Doxycyclin, clindamycin), sesquiterpenes (artemisinin, dihydroartemisinin, artemether, artesunate) and naphtoquinon (atovaquone) [3].

Table 1: List of antimalarial plants reported from northeast India

Name of the plant	Family	Vern. name	Parts used	Methodology
Acacia farnesiana (L.) Willd	Mimosaceae	*Tarua kadam* (Ass)	Bark	
Acorus calamus L.	Araceae	*Bach* (Beng), Sweet flag (Eng)	Rhizome	If taken with quinine, stops remittent fever
Adhatoda zeylanica Medicus	Acanthaceae	*Kawldai* (Mi)	Leaf	The leaves are boiled and the water is used for bathing and the leaf paste is applied on the whole body as an effective cure for chronic fever/malaria
Alstonia scholaris R.Br.	Apocynaceae	*Tun tong* (Khamti), *Chatiana* (Assamese), *Thamrita* (Mi)	Bark	Bark infusion is given once a day
Andrographis paniculata Wall. Ex Nees	Acanthaceae	*Gokur* (Beng), *Kalmegh* (S), *Hnakapui* (Mi), *Vubati* (Man)	Leaf	Crushed raw leaves are taken orally for 2 days twice with half glass of milk
Artemisia nilagirica (C.B. Clarke) Pamp.	Asteraceae	*Koken* (Nyishi), *Sai* (Mi), *Laibakngou* (Man), *Nagdona*, *Tongloti* (Ass)	Leaf	Decoction of leaves is given
Asplenium adiantoides C. Chr.	Aspleniaceae	*Ruimangma* (Man)	Plant	
Aster amellus L.	Asteraceae		Root	
Berberis aristata DC.	Berberidaceae	*Daru Haridra* (S), *Drauhaldi* (Beng)	Root	The root bark is used as tonic
Betula alnoides Buch.-Ham	Betulaceae	*Hriang* (Mi), *Bhujpattra* (Hi)	Bark	Decoction is taken
Brucea javanica (Linn.) Merr.	Simaroubaceae	*Heining* (Man), *Tammu* (Rongmei	Fruit	
Carica papaya L.	Caricaceae	*Papeya* (Beng)	Leaf	
Cinchona officinalis Linn f.	Rubiaceae		Bark	The bark of the tree is grounded into powder and then it is boiled in water and fed to the patient
Cinnamonum bejolghota (Buch.-Ham)	Lauraceae	*Tezpta* (Mi)	Bark and leaf	The bark and leaves are boiled with the leaves of Anacolosa crassipes. The water is used for bathing, the steam inhaled and the water taken internally
Cissampelos pareira L.	Menispermaceae	*Tubuki lot* (As), *Papurilota*	Root	Juice is used
Citrus medica L.	Rutaceae	*Baranimbu* (Beng)	Fruit	Juice is used
Citrus sinensis (L.) Osbeck	Rutaceae	*Musambi* (M, H and B) Sweet orange *Serthlum* (M), *Kamala-nimbu* (H)	Leaf	Decoction is taken
Clausena excavata Burm. f.	Rutaceae	*Bhant* (H)	Leaf	Juice rubbed to alleviate muscular pain
Clerodendron infortunatum Gaertn.	Verbenaceae	Assam	Root and leaf	
Clerodendrum colebrookoianum Walp.	Verbenaceae	*Nephaphu* (Ass), Ar	Leaf	Decoction is given to cure
Clerodendrum serratum (L.) Moon	Verbenaceae	*Barangi* (H)	Root	
Coptis teeta Wall	Rananculaceae	*Mishmi teeta*	Root, rhizome	It is administered orally at a dose of 150 g thrice a day
Crotolaria occulta Grab	Fabaceae		Plant	Plant juice taken with warm water

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Antimalarial Plants and their Properties

There are following antimalarial plants in India by which antimalarial compounds are obtained –

1) Cinchona
2) Ocimum sanctum
3) Crotoloria occulta
4) Vitex peduncularis
5) Coptisteeta
6) Artimisia maritima
7) Polyglapersicariaefolia
8) Accacia claviger
9) Azadirachta indica
10) Carica papaya
11) Citrus medica L
12) Cinnamonumbejolghota
13) Croton tiglium L

CINCHONA

Bark from Cinchona trees (Cinchona L., Rubiaceae) of the Andean mountain forests produce quinine alkaloids, which were the only effective treatment of malaria for more than four centuries [4]. The medicinal value of Cinchona bark was first discovered in Loxa (now Loja, Ecuador) in the seventeenth century by Jesuit monks, and soon exports of different varieties of Cinchona pubescensVahl (red bark) from South America to Europe were reaching half a million kilograms bark per year [5]. Import could not meet demand, and a quest began for the most productive source of Cinchona trees to establish plantations by the British, Dutch, and French empires. The Bolivian Cinchona calisaya Wedd. Proved to be the most productive species known to date [6].

C. calisaya is one of 23 species of trees in the genus Cinchona described to date, which produce varying amounts of alkaloids. The four major Cinchona alkaloids (quinine, quinidine, cinchonine, and cinchonidine) all possess antimalarial activity but have different pharmacological profiles.

Chemical constituents

All four major alkaloids found within C. calisaya showed substantial variability among samples. A significant phylogenetic signal was found for quinine, cinchonidine, and total major alkaloid content, whilst there was no correlation between phylogeny and quinidine or cinchonine. Given the contrast in alkaloid content visually identified between the highly supported clade A compared to the rest of the tree, t-tests were performed to test for significance between the two clades[7].

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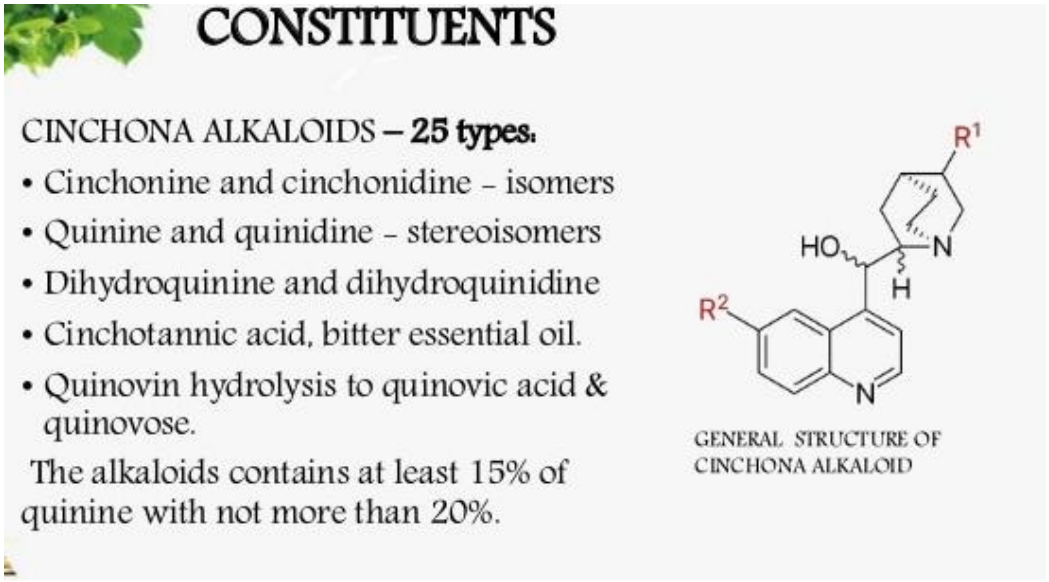

Uses

- Cinchona is used for increasing appetite;
- promoting the release of digestive juices; and treating bloating, fullness, and other stomach problems.
- It is also used for blood vessel disorders including haemorrhoids, varicose veins, and leg cramps.
- Antimalarial.

Ocimum sanctum

The plant Tulsi or Holy Basil (Botanical name Ocimum Sanctum Linn.) belongs to family Lamiaceae. It is a tropical plant which grows as weed and also cultivated. Tulsi is worshipped by Hindus and is an important symbol of Hindu religion. The beneficial medicinal effects of plant materials typically result from the combinations of secondary products present in the plant.[8]

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Chemical constituents-

Different part of plant containing various amounts of constituents.

Leaves contain 0.7% volatile oil comprising about 71% eugenol and 20% methyaleugenol. In oil carvaxrol and sequiterpine hydrocarbon caryophyllene [9]Ursolicaxid has been isolated from the leaves. So main constituents can be counted as oleanolic acid, ursolic acid, rosmarinic acid, eugenol, carvacrol, Linalool and βcaryophyllene [10]

Used as-

- Antimalarial
- Antidiabetic
- Anticancer
- Antiarrhythmic

Crotoloria occulta

Crtolaria is a genous of flowering plants in the legume family Fabaceae commonly known as rattlepods.[11] Some species of Crotalaria are grown as ornamentals. The common name rattlepod or **rattlebox** is derived from the fact that the seeds become loose in the pod as they mature, and rattle when the pod is shaken.[12]More than half of the diversity of the tribe belongs to the genus Crotalaria L., with 702 species [13],[14]. The genus Crotalaria is distributed in tropical and sub-tropical regions of the world. The species of Crotalaria exhibits great diversity of habit andecological preferences. The genus chiefly colonizes open grasslands and forest edges. There are both annual and perennial species, the habit including prostrate or erect herbs, under-shrubs, robust shrubs and rarely trees[15],[16].

Chemical constituents

Pyrrolizidine-derived alkaloids are frequently isolated as macrocyclic dilactones, using a combination of a pyrrolizidine (necine base) with necic acid to produce macrocyclic rings with a range of sizes. In addition to macrocyclic dilactones, mono and diesters of necine as open chains, such as lycopsamine and echimidine, were reported[17].

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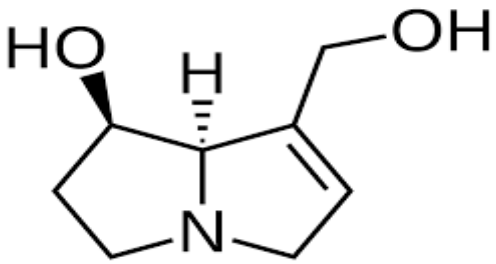

Necine base

Class of compounds	Result
Alkaloids	+++
Flavonoids	++
Phenols/Phenolic compounds	+
Glycosides	+
Tannins	+++
Carbohydrates	+
Phytosterol	-
Resins	+
Steroids	+
Saponins	-

Uses [17]

- Antimalarial agent
- food and refreshing drink for humans,
- cover crop or green manure,
- improvement of fallows,
- paper elaboration,
- medicinal plant and honey production

Vitex peduncularis

The increasing demand for herbal medicines, both in the developing and developed countries, has inevitably led for sustaining the quality and purity of herbal raw materials and finished products[18],[19].WHO, therefore, acknowledged that Pharmacognostical standards should be proposed as a protocol authentication, and quality assurance of herbal drugs[20]? It grows in moist deciduous forests along streams and rocky slopes at an altitude up to 1000m; distributed in Eastern Himalaya and tropical region of India [21]. Young stem bark and leaves of this plant are used traditionally as folk remedies to treat Black Water fever, Diabetes, Malaria, and Jaundice; roots used to treat excessive menstrual bleeding [22].Both leaves and stem bark possess antibacterial and antifungal properties[23]. Leaves of the plant contain compounds like peduncularaside, iridoidanguside, vitexin, triterpenoids and flavonoids [24],[25].

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Chemical constituents

A review of the literature reveals that the presence of various chemical constituents in the different parts of the Vitex peduncularis are flavones, 4'-acetoxy-5-hydroxy-6, 7-dimethoxyflavone together with four known compounds, crisimartin, genkwanin, 3α-friedeliniol and 3β-friedeliniol have beeMOJBOC-02-00047n isolated from the leaves of Vitex peduncularis.[10] A new iridoid, peduncullariside, together with the known agnuside were isolated from the butanol extract of Vitex peduncularis stem bark[26]. Earlier studies on different parts of the plant reported the isolation of flavonoids-vitexin, pachypodol, peduncularism, ursolic acid and 2α-hydroxyursolic.[27]

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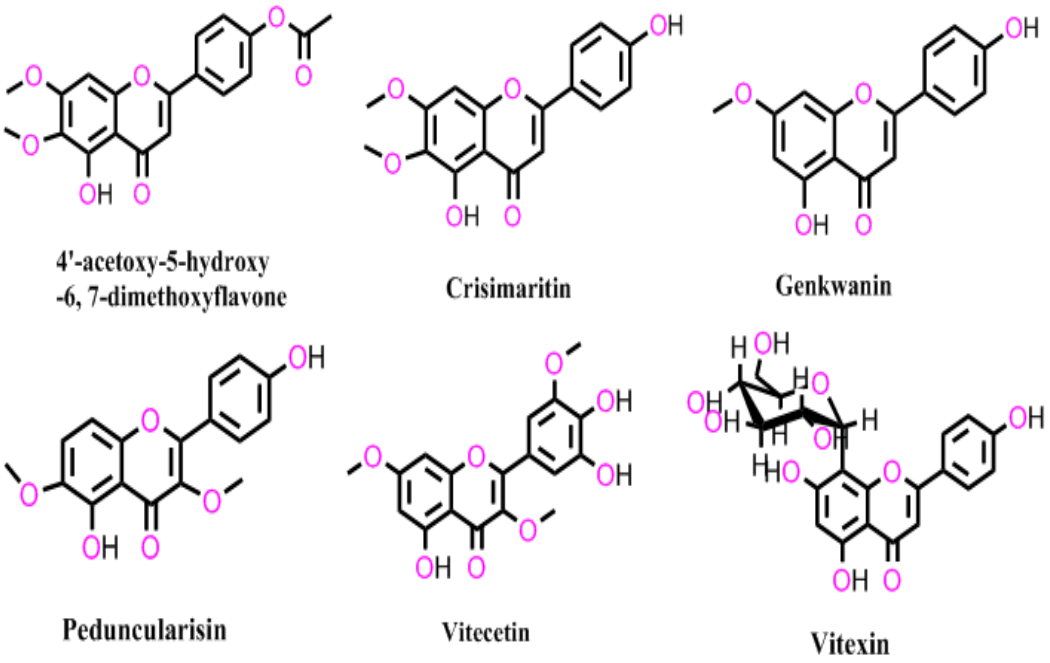

Uses [15]

Antimalarial activity
Antipyretic activity
Antifungal activity
Cytotoxic activity

Artemisia maritima

The genus Artemisia comprises some 350 species, of which only about 30 have been chemically examined. In most cases the investigation has been confined to the essential oil, but a few of the more important species such as wormwood, Artemisia maritima var. Stechmanniana Bess, which grows in Turkestan, are the sole source of the anthelmintic and santonin. They have been more thoroughly examined. In consequence of the difficulty of obtaining santonin since 1914, other sources of this indispensable drug have been sought and, in this connection, attention has been given to other species of Artemisia. A. brevifolia Wall. (This according to the Index Kewensis is a form of A. maritima Linn.) from India was found to contain santonin [28].

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Chemical constituents

Artemisia maritima, contain alkaloids which include isocoumarin and Flavonoids [29]. Artemisia maritima is an aromatic species and santonin, a valuable drug, is extracted from its flower buds[30]. Sesquiterpene Lactones: The phytochemical investigation of the methylene chloride/methanol extract of the aerial parts of Artemisia herba-alba afforded two new natural sesquiterpene lactones 1β,9βdiacetoxyeudesm-3-en-5α, 6β, 11β H-12,6-olide and 1 β, 9 β -diacetoxyeudesm-4-en-6 β,11 β H-12, 6-olide [31]. The drug also contain Artemin,Gallicin , lβhydroxy-6β,7α,11β-H-selin-4-en-6,12-olide, 1-keto-6β,7α,11β-H-selin-4-en-6,12-olide, Vulgarin, Maritimin[32].

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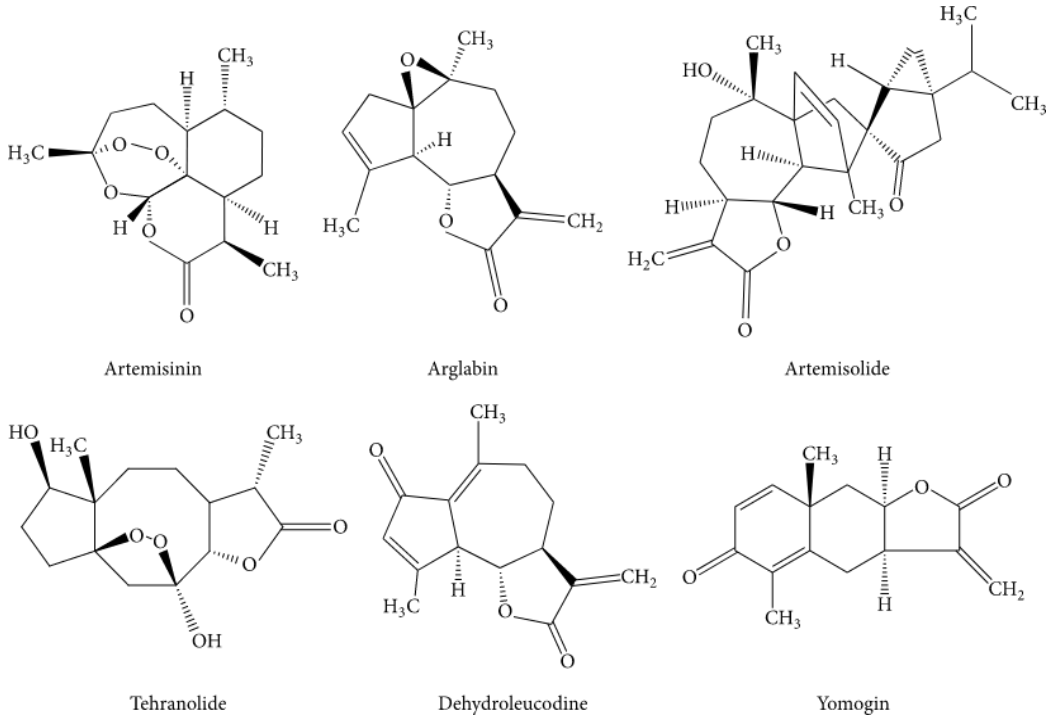

Uses[33],[34]

Antimalarial
Antialgal Activity
Antimicrobial Activity
Hepatoprotective Activity
Anthelmintic activity
Antifertility activity

II. CONCLUSION

The present survey has provided information about the range of species of plants used in the treatment of malaria in India. It develops good scope for Pharmaceutics to develop new drug for malaria after combining drugs having action against Plasmodium, anti-inflammatory drugs as well as hepatic protector by using this traditional information and furnishing chemical analysis, pharmacological action, and in vitro studies. Some antimalarial plants are used for preparing baths or for inhalations (aromatic plants).

This work also intends to stimulate and bring together new and intensive efforts from all research communities of the world to the quest of efficient phytomedicines and novel potential drug candidates both for malaria and other neglected diseases. It would be advantageous to standardize methods of extraction and in vitro testing so that the search could be more systematic and interpretation of results would be facilitated. Also, alternative mechanisms of infection prevention and treatment should be included in initial activity screenings. Disruption of adhesion is one example of an anti-infection activity not commonly screened for currently. Attention to these issues could usher in a badly needed new era of chemotherapeutic treatment of infection by using plant-derived principles.The symptomatic stage of malaria infection concurs with the development of the asexual cycle of the parasites in the red blood cells.

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