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Phyto-Molecules used for the Treatment of Malaria: A Review

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ABSTRACT

Malaria is one of the most fatal of the tropical diseases known to man which has now become worse due to rising incidence of drug resistance in the malarial causing protozoan towards conventional medications. There are many species of the protozoan falciparum which causes various types of malaria. Several, synthetic, semisynthetic and natural origin compounds having anti-malarial property has been commercialized. Some of them are as follows: chloroquine is a quinine derivative whereas artesunate having sesquiterpene lactone core is derived from artemisinin that is isolated from Artemisia annua L. Though the Artemesinin-Based Combination Therapy (ACT) has showed excellent results however, the rising cases of drug resistance is now making the researchers to search for more novel therapies. In this review paper, the life cycle of a malarial protozoan, the current artemesinin combination therapy and the other phyto-molecules having anti-malarial activity has been briefed upon. One can believe that the discovery of novel phyto-molecules having would lead to a much safer, effective and cheaper mode of treatment of malaria.

Keywords: Anopheles Mosquitos, Artemesinin, Artemesinin-based Combination Therapy (ACT), Malaria, Falciparum, Phyto-Molecules

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INTRODUCTION

Malaria causes increased mortality and morbidity in the tropics. Malaria is caused by many species of the protozoan *plasmodium* such as *Plasmodium ovale*, *Plasmodium vivax*, *Plasmodium falciparum* and *Plasmodium malariae*. As per the recommendations by the World Health Organization (WHO), observation of blood smear which denotes the shapes of the infected Red Blood Cells (RBCs) under a light microscope is most accurate and cheap method to diagnose the type of malaria (Table 1). The progression of the malarial disease depends upon the life cycle of the protozoan; following the blood meal by an infected Anopheles female mosquito, sporozoites reach the hepatocytes *via* the bloodstream where they are converted to the schizont form which ruptures the hepatocytes to release as merozoites in the bloodstream. This is called as the exo-erythrocytic cycle. Merozoites then enter the RBC and forms trophozoites and schizonts by asexual reproduction and subsequently rupture the RBCs to release as merozoites. Some of the merozoites converts to gametocytes which when ingested by the mosquitos during a blood meal fuses to form ookinete and forms sporozoites in the salivary glands of the mosquitos (Figure 1) [1,2].

Table 1. Characteristics of infected RBCs. Upon taking a blood smear such RBC characteristics are used for the primary diagnosis of the various types of malaria.

Parasite	Schuffner's dots	Infected RBC's shape	Size of infected RBC
Plasmodium falciparum	No	Crescent	Normal
Plasmodium vivax	Yes	Amoeboid	>>Normal
Plasmodium ovale	Yes	Elongated	>Normal
Plasmodium malariae	No	-	<Normal, Normal

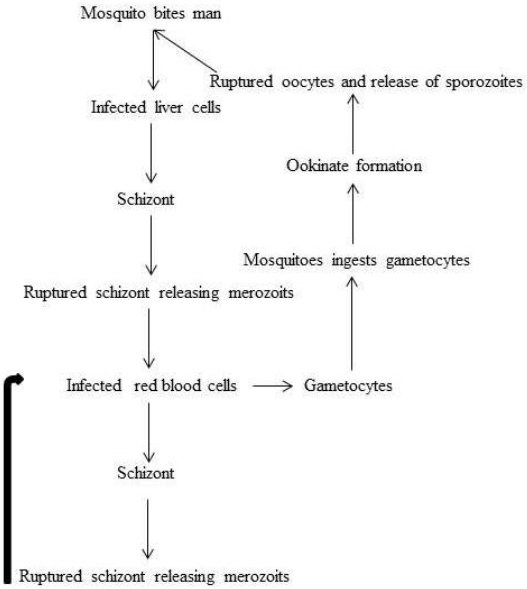

Figure 1. Malarial life cycle: Mosquito transfers sporozoits to human liver cells to form the Schizont stage. The Schizont then ruptures to release merozoits which in turn infects the red blood cells. The released merozoits then formed into gametocytes which forms into Ookinate inside a mosquito's gut following a blood meal. The ookinates are converted into oocytes which rupture to release sporozytes which then migrates to the salivary glands of the mosquitos.

As per the WHO guidelines on malaria which is chloroquine-resistant, the 1st line of treatment is the Artemisinin-Based Combination Therapies (ACTs). As Artemisinin possesses less half-life; in order to inhibit drug resistance and also to preserve the proper blood amount of the antimalarial drugs, a secondary (2°) medicine like lumefantrin was involved to the ACT. Similarly sulfadoxine/pyrimethamine, which is the synthetic derivatives of pyrimidine, is also used alongside artemisinin or its derivatives.

It has been observed that Artemisinin derivatives like artesunate, artemether and dihydroartemisinin along with 2° medicines like piperaquine reduces parasite load with respect to chloroquine.

However chloroquine which has a half-life of 1–2 months reduces the possibility of malaria relapses with respect to the artemisinin derivatives.

However, ACT is the only mode of treatment in the malaria resistant to chloroquine (Table 2 & Table 3) [1,3].

Table 2. Medications recommended under the World Health Organization (WHO) guidelines. These medications are dependent on the area of malaria incidence and type of patients and pathogen.

Medicines	Patient sample	Response
Combination therapy based on Artimesinin (ACT) Clindamycin, Quinine	Uncomplicated malaria; Plasmodium falciparum	Children and Adults Pregancy: First trimester
Chloroquinine, ACT	Uncomplicated Plasmodium malariae, Plasmodium vivax	Chloroquinine susceptible and resistant areas
Primaquinine, Chloroquinine then by Primaquinine	Prevention of relapse of Plasmodium vivax and Plasmodium ovalae	Children and Adults Pregnant and breastfeeding
Artesunate, Artemether	Severe malaria	Children and Adults Pregnant and breastfeeding
Artesunate, Artemether	Severe malaria	Children and Adults

Table 3. Examples of artemisinin's commercial derivatives. These derivatives have been reported to more effective than the parent compound.

Name of brand	Derivatives of Artemisinin
Artenam, Artem, Larither	Artemether
Coartem, Lifart-L	Artemether with lumefantrine
Artesun, Falcigo	Artesunate with amodiaquine

Co-Artesum	Artesunate with amodiaquine
Artequin, Falcigo plus	Artesunate with mefloquine
Dihydroartemisinin	Alaxin

Chemically, artemisinin has a structure of sesquiterpene lactone along with peroxide bridge whose reduction with Fe2+ produces radical substances which fatally alkylates the proteins of the parasite in the blood itself. Some of the derivatives of the artemisinin like the water soluble dihydroartemisinin were synthesized upon reduction of the carbonyl functional group of artemisinin. Upon adding a methyl group to the carbonyl group of artemisinin, artemether is synthesized whereas dihydroartemisinin's steric form is Artesunate. The core structure for many antimalarial agents like quinine, amodiaquine, chloroquine, piperaquine and mefloquine is Quinoline. Chloroquine and primaquine are derivatives of quinine having 4- and 8-aminoquinoline backbone, respectively. As an anti-malarial drug, Quinacrine with a synthetic 9-aminoacridine shows an unsatisfactory therapeutic profile whereas as compared with other quinine derivatives, Piperaquine with a heavy bisquinoline structure inhibits drug efflux which is the main cause for the chloroquine resistance. Thereby, piperaquine is administered in drug resistant incidences (Figure 2) [1,4].

Owing to the large scale production of anti-malarial compounds, a comparison has become warranted so as to distinguish between the natural and the synthetic origin compounds. There is a growing belief that herbal origin medicines are safe and are also cheaper to use. In Table 4, a comparison has been provided between the herbal compounds and the synthetic ones. Also due to increase in the cases of drug resistant malaria, several other phytochemicals have been isolated which have the potential to be used as anti-malarial agents (Table 5). Many of the chemical structures of the anti-malarial compounds have been elucidated which will help in development of various lead agents.

The anti-malarial compounds have been isolated from a wide family of plants, some of which has been nominated in this paper. Moreover, each plant family has particular classes of chemicals whose molecular structures have been illustrated in Figure 2, which has chemicals isolated from the *Annonaceae* plants. In Figure 3 Chemical structure of compounds isolated from *Araceae* plants. (1) Raphidecursinols A (2) Raphidecursinols B (3) grandisin (4) epigrandisin (5) decursivine have been illustrated. In Figure 4 the chemical structure of compound isolated from *Asclepiadaceae* plants; Gongroneside A has been illustrated. In Figure 5, the Chemical structure of compounds isolated from an Asteraceae plant has been illustrated: (1) Apigenin 7-O-glucoside, (2) luteoline 7-O-glucoside (3) Flavonoid glycoside (4) 2-Isopropenyl-6-acetyl-8-methoxy-1,3-benzodioxin-4-one (5) E-phytol. In Figure 6 the chemical structure of compounds isolated from *Cecropiaceae* plants has been illustrated: (1) ß-sitosterol (2) tormentic acid. In Figure 7 Chemical structure of compounds isolated from Cucurbitaceae plants has been illustrated: Cucurbitacins B (3) Cucurbitacins D (3) 20-epibryolonic acid [5-10].

Table 4. Comparison between medicinal plants having anti-malarial properties with synthetic drugs. Many drugs are nowadays derived from natural lead agents.

Advantages	Disadvantages
Herbal drugs can be used to treat resistant cases too	High cost of herbal drugs
Herbal drugs have less severe side effects	Herbal drugs may not be available every time
Higher compliance in patients	In herbal drugs more than one dosage is needed.
Novel drugs can be designed from herbal agents	Misuse can occur

Table 5. Some of the other anti-malarial phytochemicals hence isolated. These compounds have the potential to be developed into anti-malarial compounds.

Plant family	Species of plant	Phyto-molecule isolated
Annonaceae	*Friesodielcia discolor*	techtochrysin
Araceae	*Raphidophora decurciva*	Grandisin, epigrandisin
Asclepiadaceae	*Gongronema napalense*	Gongroneside A
Asteraceae	*Microglossa purifolia*	E-phytol
Buxaceae	*Buxus semperviren*	23-O-(trans)-feruloyl-23-hydroxybetulin
Cecropiaceae	*Cecropia pachystachya*	Tormentic acid

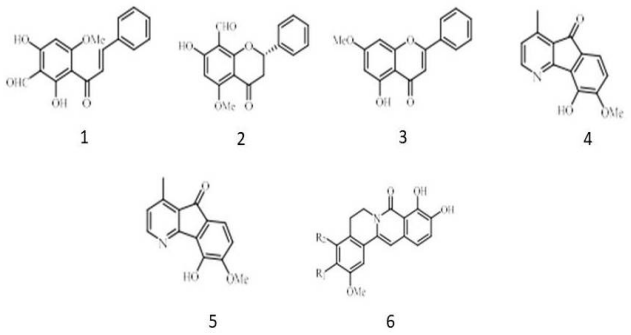

Figure 2. Chemical structures of chemicals isolated from the Annonaceae plants. (1) 3'-formyl-2', 4' -dihydroxy-6' –methoxychalcone, (2) 8-formyl-7-hydroxy-5-methoxyflava-none (3) tectochrysin (4) 5-hydroxy-6-methoxyonychine (5) an alkaloid (6) Miliusacunines Figure courtesy.

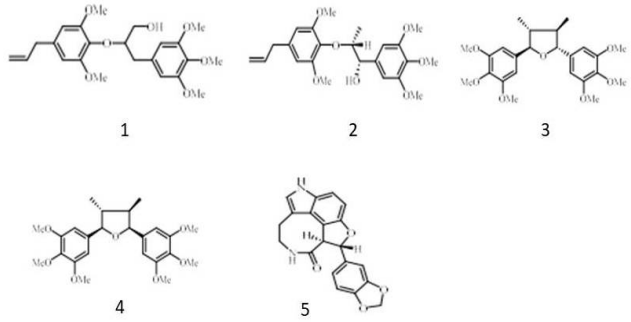

Figure 3. Chemical structure of compounds isolated from Araceae plants. (1) Raphidecursinols A (2) Raphidecursinols B (3) grandisin (4) epigrandisin (5) decursivine Figure courtesy.

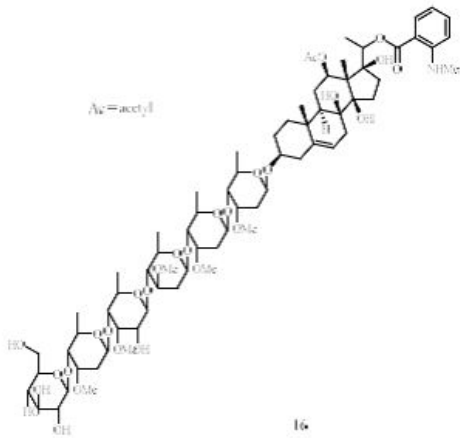

Figure 4. Chemical structure of compound isolated from Asclepiadaceae plants; Gongroneside A Figure courtesy.

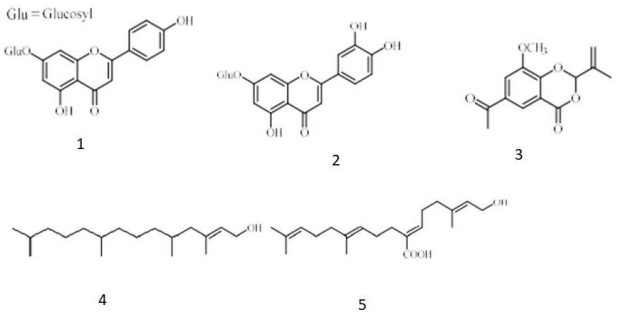

Figure 5. Chemical structure of compounds isolated from an Asteraceae plant: (1) Apigenin 7-O-glucoside, (2) luteoline 7-O-glucoside (3) Flavonoid glycoside (4) 2-Isopropenyl-6-acetyl-8-methoxy-1,3-benzodioxin-4-one (5) E-phytol Figure courtesy.

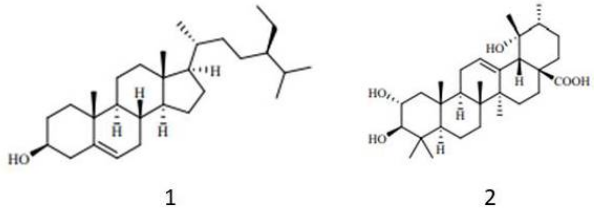

Figure 6. Chemical structure of compounds isolated from Cecropiaceae plants: (1) ß-sitosterol (2) tormentic acid Figure courtesy.

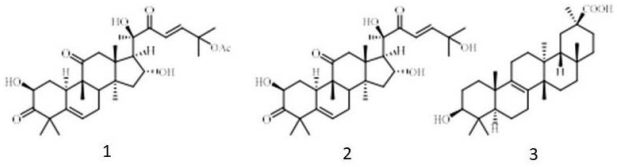

Figure 7. Chemical structure of compounds isolated from Cucurbitaceae plants: Cucurbitacins B (3) Cucurbitacins D (3) 20-epibryolonic acid Figure courtesy.

CONCLUSION

As per the World Health Organization (WHO), drug resistant malaria has emerged as one of the main killer of humans in the tropics. There are many species of the protozoan falciparum which are the causative pathogens for various types of malaria. In this regard, several, synthetic, semisynthetic and natural origin compounds having been anti-malarial property has been commercialized. For example, chloroquine is a quinine derivative whereas artesunate having sesquiterpene lactone core is derived from artemisinin which is isolated from Artemisia annua L.

Though the WHO recommended Artemesinin-Based Combination Therapy (ACT) has shown excellent results yet there are cases where drug resistance have been observed too. In this review, the life cycle of the malarial protozoan, ACT and the various other phyto-molecules having anti-malarial activity has been briefed upon with the belief that research on novel phyto-molecules would help in ushering agents which are effective, safe and cheap to use.

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