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Phyto-Molecules Utilised in Malaria Therapy: A Review

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ABSTRACT- Malaria is one of the most lethal tropical illnesses known to man, and it's becoming worse because to an increase in drug resistance in the malaria-causing protozoan to conventional treatments. There are many species of the protozoan falciparum which causes various types of malaria. Several, synthetic, semisynthetic & 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

I. INTRODUCTION

Malaria causes increased mortality & morbidity in the tropics. Plasmodium ovale, Plasmodium vivax, Plasmodium falciparum, and Plasmodium malariae are some of the Plasmodium species that cause malaria. 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 & 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 & forms trophozoites & 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][3].

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[4] [5].

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

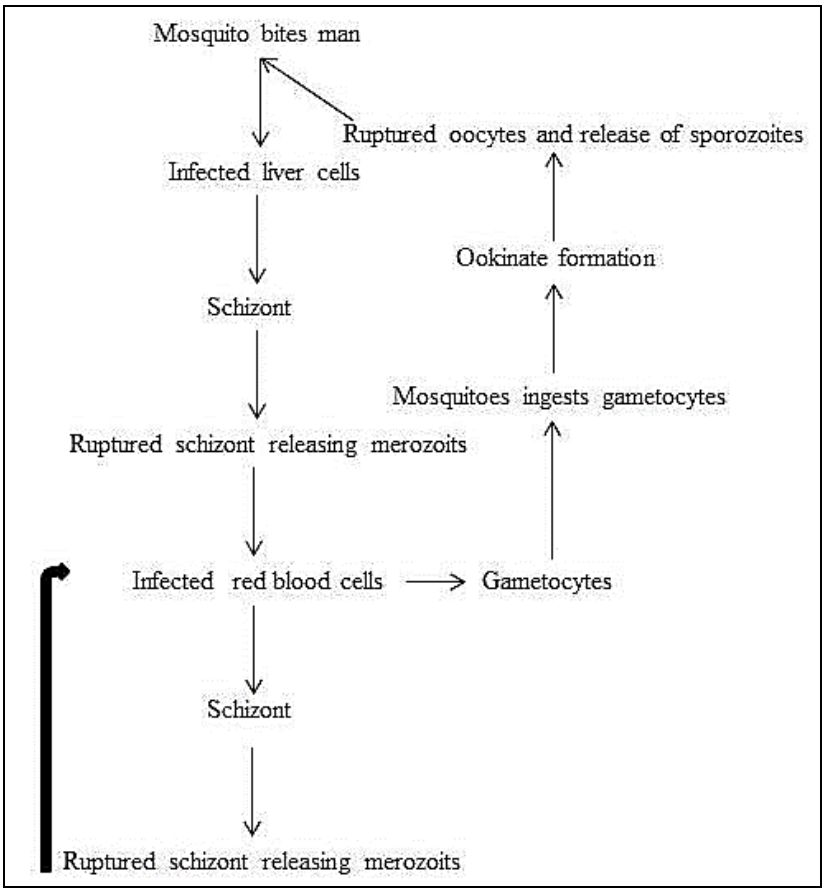

Figure 1: Illustrating the Malarial Life Cycle

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[6][7].

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 & 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 are the synthetic derivatives of pyrimidine, are also used alongside artemisinin or its derivatives. In comparison to chloroquine, artemisinin derivatives such as artesunate, artemether, and dihydroartemisinin, as well as 2° medications like as piperaquine, have been shown to lower parasite burden. In comparison to artemisinin derivatives, chloroquine, which has a half-life of 1–2 months, minimizes the risk of malaria return. However, ACT is the only mode of treatment in the malaria resistant to chloroquine (Table 2 and 3)[8][9].

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[10].

Medicines	Patient sample	Response
Combination therapy based on Artimesinin (ACT) Clindamycin, Quinine	Uncomplicated malaria; Plasmodium falciparum	Children & Adults Pregancy: First trimester
Chloroquinine, ACT	Uncomplicated Plasmodium malariae, Plasmodium vivax	Chloroquinine susceptible & resistant areas
Primaquinine, Chloroquinine then by Primaquinine	Prevention of relapse of Plasmodium vivax and Plasmodium ovalae	Children & 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[6].

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

II. LITERATURE REVIEW

Samin Mohammadi in his study discloses drug development based on natural products and Secondary metabolites are being considered as antimalarial therapy alternatives. Herbal pharmaceuticals have many advantages over conventional therapies, including less side effects, cost-effectiveness, and affordability, all of which encourage the creation of herbal-based drugs. Antimalarial drugs are available in a variety of natural, semi-synthetic, and synthetic forms. Chloroquine, for example, is a synthetic antimalarial medication developed from quinine. Furthermore, artemisinin and its derivative, artesunate with sesquiterpene lactone backbone, are antimalarial drugs produced from Artemisia annua L. Artemisia annua L. has traditionally been used in China to cleanse blood and relieve fever. Although the artemisinin-based combination therapy for malaria has shown promising results, the limited pharmacological options need the development of novel medicines. Furthermore, in the majority of cases, medication resistance is the cause, and new drugs are recommended to overcome the resistance. This research comprises many important genera in this area, including Artemisia, Cinchona, Cryptolepis, and Tabebuia, all of which have antimalarial activities that have been finely verified[11][12].

Another research by Elizabeth A. Ashley found that Plasmodium falciparum is resistant to artemisinin derivatives, piperaquine, and mefloquine in Southeast Asia, suggesting that novel antimalarials are urgently needed. At least 13 drugs are now in clinical trials. The majority of these are plasma schizonticides for the treatment of uncomplicated falciparum malaria, which are being studied separately or in combination with other drugs. Artefenomel–ferroquine and lumefantrine–KAF156, both in Phase 2b, are two of the most promising prospects in the pipeline. Severe malaria is still treated with two parenteral drugs that have been around for a long time: artesunate and quinine, with sevuparin being studied as an adjuvant therapy. Tafenoquine is being evaluated for licensure as a single-dose treatment for Plasmodium vivax relapse prevention by strict regulatory bodies[13][14][15].

Wen-Hui Pan's research reveals natural products that are still recognized as a key source for medical drug discovery and development, and the authors of this study tested over 2000 plant extracts against Plasmodium falciparum. As a result, they discovered hundreds of plant leads with antimalarial properties. Numerous potent antimalarial compounds were discovered after phytochemical study of some of these plant extracts. Schwikkard and Van Heerden (2002) published a comprehensive review study titled “Antimalarial activity of plant metabolites” that disclosed the structures of plant-derived substances with antiplasmodial activity and covered literature up to the year 2000. The present analysis contains antimalarial compounds found from plants, including marine plants, that have been reported in the literature between 2001 and the end of 2017. In the last 17 years, 175 antiplasmodial compounds have been discovered in plants[16][17].

III. DISCUSSION

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 & mefloquine is Quinoline. Chloroquine & primaquine are derivatives of quinine having 4- and 8-aminoquinoline backbone, respectively. As an anti-malarial drug, Quinacrine with a synthetic 9-aminoacridine has an unfavorable therapeutic profile, but Piperaquine with a hefty bisquinoline structure decreases drug efflux, which is the major cause of chloroquine resistance, when compared to other quinine derivatives. Thereby, piperaquine is administered in drug resistant incidences (Figure 2)[18][19].

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[20][21][22].

Table 4: Comparison between medicinal plants having anti-malarial properties with synthetic drugs. Many drugs are nowadays derived from natural lead agents[4][23].

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[8][24].

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

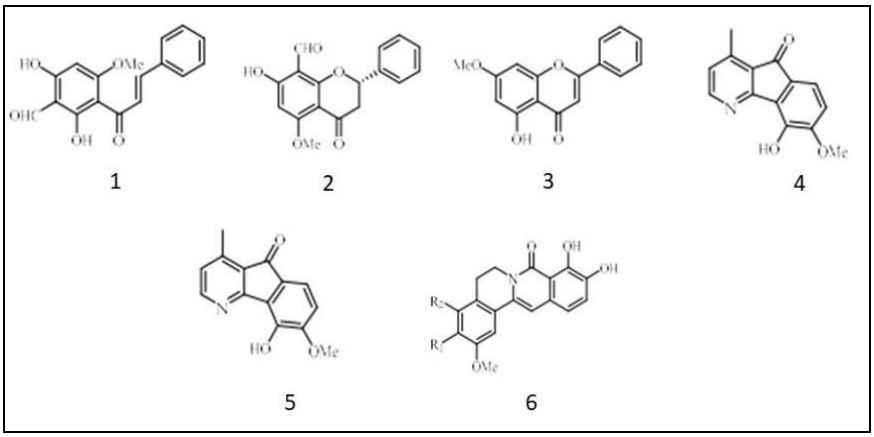

Figure 2: Chemical structures of chemicals isolated from the Annonaceae plants. (1) 3'-formyl-2', 4' -dihydroxy-6' – methoxychalcone, (2) 8-formyl-7-hydroxy-5-methoxyflava-none (3) tectochrysin (4) 5-hydroxy-6-methoxyonychine (5) an alkaloid (6) Miliusacunines [11].

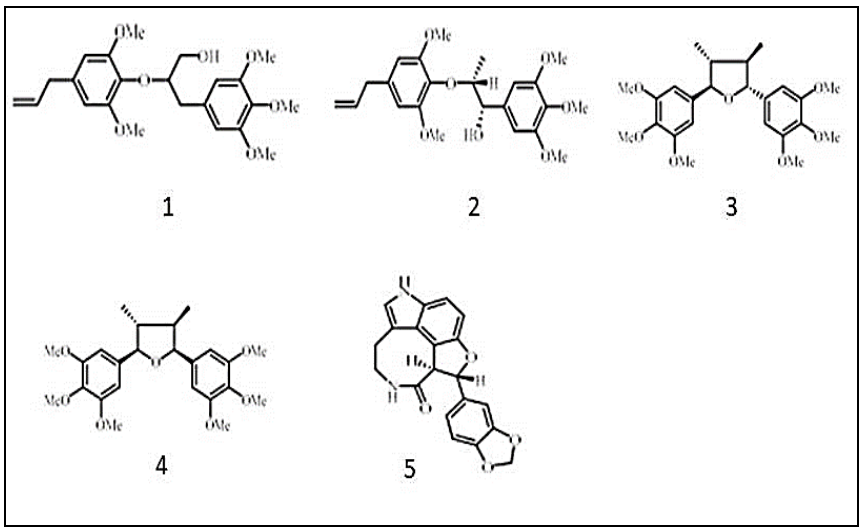

Figure 3: Chemical structure of compounds isolated from Araceae plants. (1) Raphidecursinols A (2) Raphidecursinols B (3) grandisin (4) epigrandisin (5) decursivine [13].

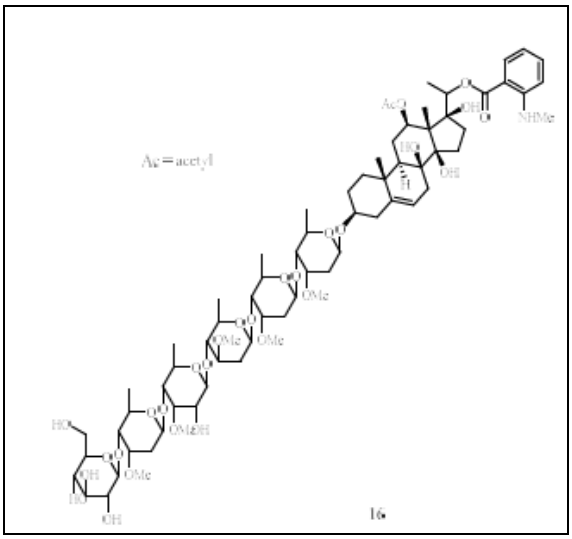

Figure 4: Chemical structure of compound isolated from Asclepiadaceae plants; Gongroneside A [20].

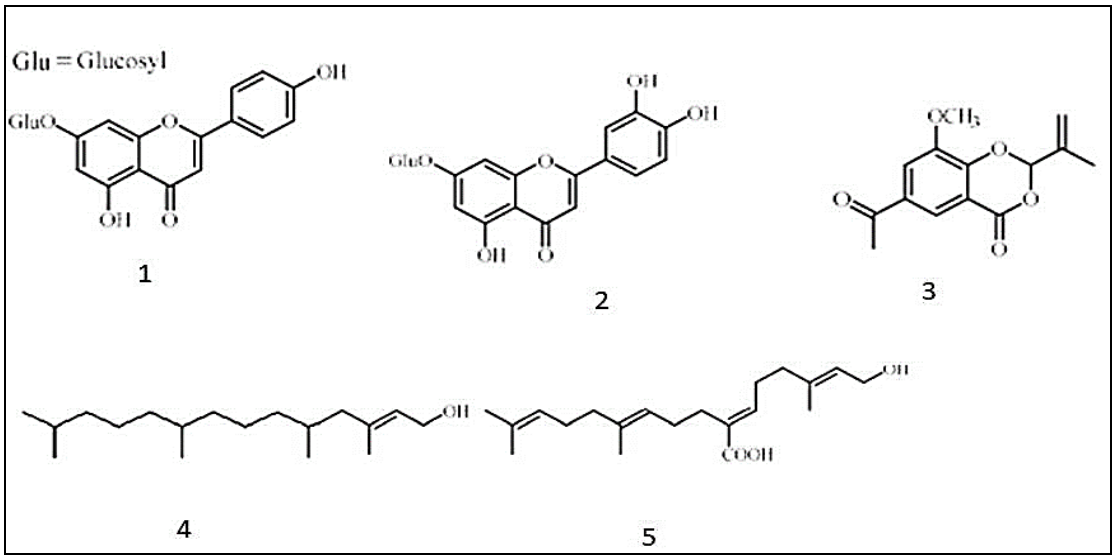

Figure 5: Chemical structure of compounds isolated from an Asteraceae plant: (1) Apigenin 7-O-glucoside, (2) luteoline 7-O-glucoside (3) Flavonoid glycoside (4) 2-Isopropenyl-6-acetyl-8-methoxy-1,3-benzodioxin-4-one (5) E-phytol [18].

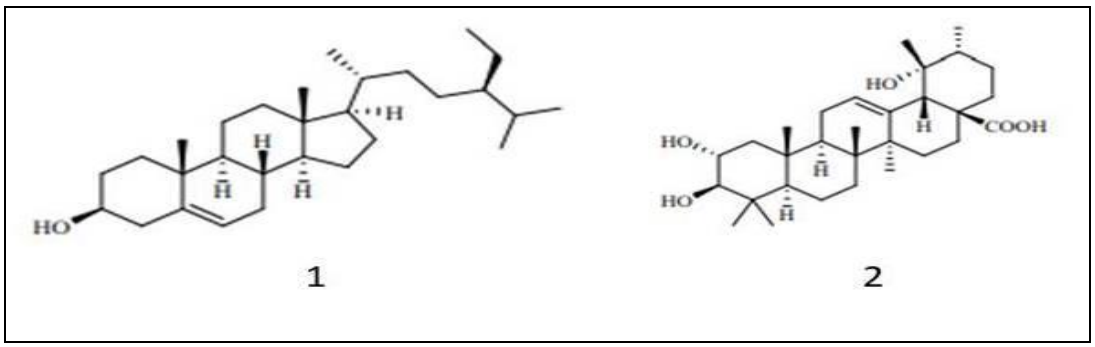

Figure 6: Chemical structure of compounds isolated from Cecropiaceae plants: (1) ß-sitosterol (2) tormentic acid [10].

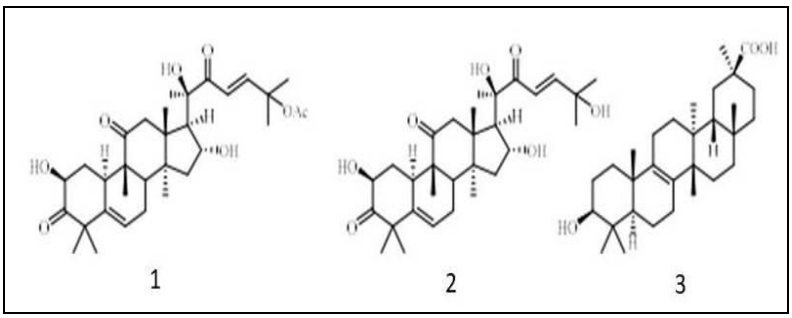

Figure 7: Chemical structure of compounds isolated from Cucurbitaceae plants: Cucurbitacins B (3) Cucurbitacins D (3) 20-epibryolonic acid [8][25].

III. 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 & 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 nove phyto-molecules would help in ushering agents which are effective, safe and cheap to use.

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