International Journal of Mosquito Research

ISSN: **2348-5906**
CODEN: **IJMRK2**
IJMR 2022; 9(3): 13-22

www.dipterajournal.com
Received: 05-03-2022
Accepted: 09-04-2022

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Role of plant secondary metabolites as potential antimalarial drugs

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DOI: https://doi.org/10.22271/23487941.2022.v9.i3a.609

Abstract
Malaria is a global problem affecting a large population without any demarcation between developed and developing world communities. The already approved compounds for the treatment of the disease hold significant efficacy but the emergence of resistant strains and reduced efficacy of drugs against the disease leave the scope for the identification of noval natural products as potential therapeutic agents. There are seven major classes of antiplasmodium agents which are plant secondary metabolites and can be used as a potential antimalarial drugs. In the present review, the focus is on the antimalarial compounds which have been isolated from plants which could be potentially used as antimalarial drugs.

Keywords: Antimalarial compounds, secondary metabolites, alkaloids, endoperoxides, terpenes

1. Introduction
Malaria is a highly threatening parasitic disease with highest mortality and morbidity rate affecting almost equally the developed and developing countries of the world. According to whose report on malaria data worldwide, there has been increased incidence of malaria cases in 2020 in comparison with 2019 by about 14 million with reported deaths increased by about 69,000. In totality, about 627,000 malaria deaths and 241 million cases were observed in the year 2020 [1, 2]. It is the most common disease in Africa and some countries of Asia with the highest number of cases. In some countries of the world malaria mortality rate among children less than five years of age fell by an estimated 11-30% and the mortality rate globally nearly about 0.3 to 2.2% [3]. Scientists are focused more research aimed to improve the prevention, diagnosis, and treatment of malaria. The causative agent of malaria is a parasite of the genus belonging to the group of *Plasmodium* species, which is transmitted to humans by a biting of an infected female mosquito of the species *Anopheles*. They consist of 172 species and out of them, five protozoan species cause malaria in humans [4]. *P. falciparum, P. vivax, P. ovale, P. malariae* and *P. knowlesi* are the main species of malaria [5]. However, the severity and fatal rate of the infection is mostly by *P. falciparum* followed by *P. vivax.* Historically *P. falciparum* has high selective pressure on humans than any other pathogen of malaria because of the severity of the cases with the large majority of the world has been infected in Asia and South Asia with 90% of death occurring in Africa mostly in children's. Malaria has been treated with natural products and their synthetic derivatives that show antiplasmodial properties and one of the most effective and popular drug is Chloroquine, which is used worldwide against malaria. However due to continuous emergence of resistant strains and low effectiency, there is an urgent requirement to discover new drugs to fight this disease. That's why scientist are focusing on identification of noval secondary plant derivatives such as alkaloid, polyphenols, terpenoids and endoperoxides to treat the already resistant strains of malaria. In the review, we focus on noval plant derivates which can be very effective against the malaria.

2. Anti-plasmodial natural products
The antiplasmodial natural products are organized in various classes, approximately these are divided in seven classes (Table. 1): (a) Quinones and Polyketides, (b) cyclic phosphodiester,

(c) Macrocycles, (d) Polyphenols, (e) Endoperoxides, (f) Terpenes, and (g) Alkaloids. These natural products have a probable potential for transmission-blocking in *Plasmodium* [6].

Quinones and Polyketides are the natural pigments thatact as the arbitrators among cellular respiration and photosynthesis. Some of the quinone compounds play a vital role in energy production. Quinones are further classified into various classes and are based on the number of aromatic rings present as monocyclic, bicyclic, or tricyclic such as benzoquinone, naphthoquinone, and anthraquinone [7, 8]. Macrocycles extracted from red algae *Callophycus serratus* diterpene-benzoate macrolides had shown some significant antiplasmodial activity. Polyphenols are isolates of *Septoria pistaciarum* (14-O-acetylcercosporin, and di-O-acetylcercosporin) and the extracted phytotoxins have the capability of inhibition of *P. falciparum* D_6 and W_2 strains, along with some of the cytotoxic effects against a particular type of cells (MCF-7 and Vero cells) [9, 10]. Endoperoxide polyketides which are the isolates of marine sponges, have shown well-proven antimalarial activities (antiplasmodial activities). Plakortin, an isolate of marine sponge *Plakortis simplex*, is considered to be the best probable with the antiplasmodial activity against chloroquine-sensitive and resistant parasites [11]. Artemisinin involves a reaction among various compounds/groups. (peroxidic bond reacts with Fe(II) heme groupand forms an O-centred radical, by the reaction step the intramolecular rearrangements take place which forms a converted C-centred radical from O-centered radical) such rearrangement represents toxic species that kill the parasites [12]. Many plant species are used as traditional medicines for the treatment of malaria or are responsible for antiplasmodial activity [13]. Alkaloids, sesquiterpene lactones, and quassinoids are considered the most important compounds for the treatment of malaria [14]. These are composed of naphthalene and isoquinoline, and are biosynthetic derivatives of acetate-polymalonate pathway. Several compounds associated with these derivatives have displayed nanomolar selective inhibition of the *Plasmodium* parasite viability [15].

Table 1: Natural products and the derived compounds having bioactivity against malarial parasites

Sr. No.	Natural Product	Class of derived compound	Source	Activity (Parasite strain)	Ref. No
a)	Quinones and Polyketides	Bisanthraquinone schryslandicin and 10-(chrysophanol-7-yl)-10-hydroxy-chrysophanol anthrone, and the phenylanthraquinone, knipholone, Aloe-emodin	*Kniphofia ensifolia*	Active against Dd2 *P. falciparum.*	[16] [9, 17-20] [21] [22] [23] [24]
		Pentalongin and Psychorubrin.	*Pentas longiflora*	Active against *P. falciparum*	
		Ethyl acetate	*Markhamia tomentosa*	Active against W2 and K1 strains	
		Plumbagin	*Plumbaginaceae*	Inhibits 3D7 and K1 *P. falciparum* strains	
		Perylenequinones cercosporin, 14-O-acetylcercosporin, and di-O-acetylcercosporin	*Septoria pistaciarum*	Inhibits *P. falciparum* D6 and W2 strain.	
		Polyketide 3-ketoadociaquinone A	*Xestospongia testudinaria*	Inhibits FcB1 and 3D7 strains	
		Geldanamycin and 17-demethoxyreblastatin		Significant antiplasmodial activity against the K1 strain	
		longirostrerone A and C	*Chaetomium longirostre*	Inhibits K1 *P. falciparum* strain.	
		Poupartones A–C	*Poupartia borbonica*	Inhibits 3D7 strain of *P. falciparum*	
b)	Cyclic phosphotriesters	Salinipostins A-D, F-G, and I	*Salinispora*	Probable inhibition activity against W2 *P. falciparum*	[25]
c)	Macrocycles	Diterpene-benzoate	*Callophycus serratus*	Antiplasmodial activity	[26]
		Bromophycolides R, S, and U	*Callophycus serratus*	Significant antiplasmodial activity.	
		Bastimolide A	*Cyanobacterium* (*Okeania hirsuta*)	Significant activity against strains TM90-C2A, TM90-C2A, TM91-C235 strains.	[27, 28]
		paecilomycins A, E, F, aigilomycin B and aigialomycin F.	*Paecilomyces* sp.	Potent antiplasmodial activity against 3D7 strain.	[29]
		lagunamides A–C	*Lyngbya majuscula*	Shows antiplasmodial activity against NF54 *P. falciparum* strain	[30]
		Mollemycin A	*Streptomyces* sp	Antiplasmodial activity	[31]
		Octaminomycins A and B	*Streptomyces* sp (RK85-270)	Active against 3D7, Dd2, and K1 strains	[32]
d)	Polyphenols	Cercosporin, 14-O-acetylcercosporin, and di-O-acetylcercosporin	*Septoria pistaciarum*	Inhibits inhibited *P. falciparum* D6 and W2 strain	[9]
		3-ketoadociaquinone A	*Xestospongia testudinaria*	Inhibits the FcB1 and 3D7 strains	[21]
		geldanamycin and 17-demethoxyreblastatin	*Streptomyces* sp.	Actively shows antiplasmodial activity against the K1 strain.	[22]
		longirostrerone A and C	*Chaetomium longirostre*	These inhibits K1 strain of*P. falciparum*	[23]

e)	Endoperoxides	1,2-dioxane and 1,2-dioxolane (Endoperoxide polyketides)	Marine sponges	Antiplasmodial	[33]
f)	Terpenes	Ethyl acetate	*Kigelia africana*	Significantly active against the *P. falciparum* W2, CAM10 and SHF4 strains	[34] [35] [36] [6] [6, 37] [38] [39] [40] [41] [42] [43] [13, 44, 45]
		1β-(p-coumaroyloxy)polygodial	*Drimys brasiliensis*	*P. falciparum*(antiplasmodial)	
		Sanandajin	*Ferula pseudalliacea*	Antiplasmodial	
		Aesquiterpenoid sporogen-AO1	*Penicillium copticola* PSURSPG138	Have inhibiting characters against K1 parasites	
		Isonitrile sesquiterpenes, 2-isocyanoclovene, 2-isocyanoclovane and 4,5-epi-10-isocyanoisodauc-6-ene	*Phyllidia ocellata*	Antiplasmodial activity against the 3D7 and Dd2 strains	
		Germacranolide sesquiterpene lactone, urospermal A 15-O-acetate	*Dicoma tomentosa*	Antiplasmodial	
		Germacranolide trichospirolide A	*Trichospira verticillata*	Antiplasmodial activity against Dd2 *P. falciparum*	
		Chloroform, caesalsappanins G–I	*Caesalpinia sappan*	Inhibiting property; K1 strain of*P. falciparum*	
		Norcaesalpin D	*Caesalpinia bonducella*(Root extraction)	Acted as antiplasmodial component	
		lactones amphadilactones A–F and H–I	*Aphanamixis grandifolia*	Shown inhibiting properties of Dd2 strain	
		Δ_9-ferruginol, and 7α-acetoxyroyleanone	*Salvia sahendica*	Inhibiting property against K1 parasites	
		Betulin coumaroyl esters	*Buxus cochinchinensis*		
g)	Alkaloids	Ancistectorines A1, N-methyl A_1, A_2, 5-epi-A_2, A_3, and C_1	*Ancistrocladus tectorius*	Having properties of inhibition to the K_1 strain of *P. falciparum*	[46]
		Dioncophyllines C_2, F, and ancistrocladisine A, and 5′-O-methyldioncophylline D, Jozilebomines A and B	*Ancistrocladus ileboensis*	These compounds have an activity against NF_{54} strain (selective antiplasmodial activity)	[47] [48]
		cassiarin J, cassiarin K	*Cassia siamea*	Shown inhibition property of $3D_7$ strain of *P. falciparum*	[49] [50]
		Boldine and (−)-O,O-dimethylgrisabine	*Dehaasia longipedicellata*	Both areactive against the K1 strain of *P. falciparum*	[51]
		Preocoteine, Pseudoberberin, Berberin, Bisbenzylisoquinoline thaligosidine	*Thalictrum flavum*	These have shown antiplasmodial activity against the FcB_1 strain	[6] [52]

2.1 Alkaloids

Alkaloids are considered to be the most significant group with antimalarial activity along with various biological activities (Table 2). This class of compounds have a nitrogen atom in the heterocyclic ring and termed as terpenoid ring [53]. Most commonly used alkaloids and their derivatives are chloroquine, amodiaquine, mefloquine, and artemisinin. The main alkaloid drug is quinine (its derivative Chloroquine, a 4-aminoquinoline) which is an extract of Cinchona bark andstill quite useful for the treatment of multidrug-resistant malaria due to its goof efficacy with lesser toxic effects. But in modern malarial therapies, its use has been restricted due to the reason of parasite resistance to the drug [54] and neuropsychiatric side effects caused by Mefloquine when used for the treatment of chloroquine-resistant malaria [55]. Artemisinin extract of *Artemisia annua*, the same along with its analog sartemether, artether, and artesunate are the best possible antimalarial agents [56, 57]. WHO has recommended artemisinin use along with its analogs in combination with other drugs (ACT) for malarial treatment [58].

Several alkaloid compounds have a varying terpenoidal backbone and are extracted from various medicinal plants. For example, cassane-type diterpenes andindolo terpene extraction of *Caesalpinia minax*, *Polyalthia oliveri*, and *Strychnos nux vomica*, shows a better antiplasmodial activity [58]. Caesalminines A and Bwith γ-lactam ringextracted from the seeds of *Caesalpinia minax*, which show santiplasmodial activity with IC50 values of 0.42 and 0.79 μM [59]. In another study some other alkaloids such as 8α-polyveolinone, N-acetyl-polyveoline and N-acetyl-8α-polyveolinone are the isolation of *Polyalthia oliveri*, out of these both N-acetyl-polyveoline and N-acetyl-8α-polyveolinone shows moderate antiplasmodial activity against *P. falciparum*, NF54 strainwith low cytotoxicity on l myoblast (L6) cell line. Polyalthenol and N-acetyl-polyveolineare indolo sesquiterpene alkaloids extraction of *Greenwayodendron suaveolens* tree which are observed to be effective against *P. falciparum* [60].

Table 2: Some of the main antimalarial alkaloids derived from plants (source) followed by the structures of the compounds

S. No	Name of the Compound/s	Source
1	Caesalminines A	*Caesalpinia minax*
	Caesalminines B	
2	Polyveolinone	*Polyalthia oliveri*
	N-acetyl-8*α*-Polyveolinone	
	N-acetylpolyveoline	
3	Strychnochrysine	*Strychnosnux vomica*
4	Polyalthenol	*Greenwayodendron suaveolens*
	N-Acetyl-Polyveoline	
5	Conesine	*Holarrhena antidysenterica*
6	Mokluangin D	*Holarrhena pubescens*
	MokluanginA	
7	N-3-Benzoyldi-hydroCycloMicrophylline F	*Buxus cochinchinensis*
8	Alstoniaphyllines A	*Alstonia macrophylla*
	Alstoniaphyllines B	
	Alstoniaphylline C	
9	12-hydroxy-Nacetyl-21(N)-Dehydroplumeran-18-oicacid	*Aspidosperma ulei*
10	Strychnobaillonine	*Strychnos icaja*
11	4a,b-secodehydroantofine	*Ficus septica*
	Dehydrotylophorine	
	Dehydroantofine	
	Tylophoridicine D	
12	Cycleanine	*Actinodaphne macrophylla*
	10-demethylxylopinine	
	Reticuline	
	Laurotetanine	
	Bicuculine	
	α-hydrastine	
	Anolobine	
13	(+)-Nmethylisococlaurine	*Cryptocarya nigra*
	Atherosperminine	
	Hydroxyathersperminine	
	Noratherosperminine	
14	Palmatine	*Annikkum meriye*
15	Dihydronitidine	*Zanthoxylum heitzii*
	Pellitorine	
	Heitziquinone	
16	(-)-Pseudocurine	*Stephania abyssinica*
	(-)-Pseudoisocurine	
	(-)-10-oxoaknadinine	
17	(+)-Laurotetanine	*Alseodaphne corneri*
	(+)-Norstephasubine	
18	Dioncophylline F	*Ancistrocladus ileboensis*
19	Mbandakamines A and B	*Congolese ancistrocladus*
	Jozimine A2	
20	Vireakine	*Stephania rotunda*
	Stephanine	
	Pseudopalmatine	
21	Obtusipetadione	*Dasymaschalon obtusipetalum*
22	(-)-O-O-Dimethylgrisabine	*Dehaasia longipedicellata*
	(-)-Milonine	
23	Anonaine	*Xylopia sericea*
24	Tavoyanine A	*Phoebe tavoyana*
	Roemerine	
	Laurolitsine	
	Boldine	
	Sebiferine	
25	Simplicifolianine	*Meconopsis simplicifolia*
26	Coptisine	*Coptidi srhizoma*
27	Miliusacunines A-E	*Miliusa cuneata*
28	(+)-5,6-Dehydrolycorine,	*Lycoris radiata*
	(+)-8,9-Methylene Dioxylhomolycorine-Noxide	
	(+)-3α,6β-Diacetyl-bulbispermine	
	5,6-Dihydro-5-methyl-2-Hydroxyphenanthridine	
	(+)-3α-Hydroxy-6β-Acetyl-Bulbispermine	

29	Cripowellin A	*Crinum erubescens*
	Cripowellin B	
	Hippadine	
	Cripowellin C and D	
30	1,4-dihydroxy-3-methoxy powellan	*Amaryllis belladonna*
	Distichamine	
	O-acetylambelline	
	Ambelline	
	Acetylcaranine	
	Hippadine	
31	Lycorine	*Worsleya procera*
32	Hymenocardinol	*Hymenocardia acida*
	Hymenocardine N-oxide	
	Hymenocardine-H	
33	O-desmethylnummularine-R	*Ziziphus oxyphylla*

2.2 Endoperoxides

Endoperoxides are Dixygen Bridge containing compounds that contribute to their antimalarial activities. Their mechanism of action of antimalarial activities are in two-phases: (1) Activation phase: It comprises the iron-mediated (Fe21) cleavage of endoperoxide that generates an unstable organic free radical or electrophilic species and, (2). Alkylation phase: It leads to the formation of the covalent bond between the drug and malarial protein [61, 62]. As the malaria parasite is rich in heme iron which is derived from the breakdown of the host cell hemoglobin and it is to be thought that Fe21-haem is responsible for the activation of artemisinin inside the parasite [63, 64], soendoperoxide are used as dual-purpose drugs against drug-resistant parasites and rapid cure for malarial illness. Endoperoxides are classified into two generations, first-generation and second generation based on their origin of extarcts. The first-generation endoperoxides include artemisinin isolated from *Artemisia annua* Linn and its analog such as arteether, artemether, and artesunate that are synthesized by the modification of the chemical structure of artemisinin [65]. These drugs can effectively kill the plasmodium in the red blood cellby forming an endoperoxide bridge (C-O-O-C), a unique structure to kill the malaria parasite. The second generation endoperoxides dihydroartemisinin is a reduced lactol derivative of artemisinin and their structural analogue (arteether, artemether, artelinate, and artesunate) are the esters or ethers of the lactol [66]. Other example of endoperoxide is Plakortide fatty acid belonging to a cyclic peroxide metabolite produced by a genus *Plakortis* of marine sponge related to *Plakinidae* family. The Sponge is rich in Caribbean and Indo-Pacific coral reef which is recognized in rich bioactive secondary metabolite such as cyclic peroxide and show antimalarial activity.

Endoperoxides have several advantages over existing antimalarial drugs because there is no cross resistance with other antimalarial drugs and they clear the peripheral blood of parasites more rapidly than any other antimalarial drug. However, there is some disadvantage because of short half-life and effective levels in plasma for brief periods, which are sustained for only a short period and is responsible for the rapid arrival of recrudescent infection.

2.3 Terpenes

Terpenoids are the most abundant and structurally diverse group of plant secondary metabolites containing carbon backbone made of minimum five carbon containing isoprene (2-methylbuta-1, 3-diene) unit (Table 2). The nomenclature of terpenoids is based on presence of isoprene units such as terpenoids containing one isoprene unit termed as hemiterpenoid, two isoprene units as monoterpenoid, three isoprene units as sesquiterpenoid and four isoprene units known as diterpenoids (Table 3). More than 35000 terpenoids are identified, making terpenoids the largest class of plant secondary metabolites. Terpenoids have prime role in ecological roles such as in plant-insect, plant pathogens and act as an attractant for animals that disperse pollen or seed or as an inhibitor of germination and growth of the neighboring plant. Apart from this terpenoids shows pharmacological activities, such as antimalarial activity, antiviral activity, anti-inflammatory, anti-cancer, and inhibition of cholesterol synthesis [67-69].

Table 3: Classification of terpenoids based on the number of isoprene units and number of carbon atoms

Terpenoids	No of isoprene unit 3	No. of carbon atoms	General formula
Hemiterpenoid	1	5	$(C_5H_8)_1$
Monoterpenoid	2	10	$(C_5H_8)_2$
Sesquiterpenoids	3	15	$(C_5H_8)_3$
Diterpenoids	4	20	$(C_5H_8)_4$
Sesterpenoid	5	25	$(C_5H_8)_5$
Triterpenoid	6	30	$(C_5H_8)_6$
Tetraterpenoid	7	40	$(C_5H_8)_7$
Polyterpenoid	8	40 or >40	$(C_5H_8)_8$

Artemisinin isolated from *Artemisia annua* Linn in 1970 containing sesquiterpene lactone compound. It is the most effective antimalarial drug after chloroquine, pyrimethamine, primaquine and has high efficacy and low toxicity [70]. Antimalarial drugs such as arteether, artemether, artesunate are synthesized by modification of the chemical structure of artemisinin. These drugs can effectively kill the plasmodium in the red blood cells [69, 71].

Kigelia Africana is widely distributed in South, Central and West Africa and extracted from the stem bark yielding four

compounds with effective antiplasmodium activity against three malaria parasite strains. These compounds include specicoside, 2β 3β, 19α-trihydroxy-urs-12-en-28-oic acid, atranorin and p-hydroxy-cinnamic acid. *Drimys angustifolia* is a sesquiterpene having polygodial 1-β-(p-methoxycinnamoyl)-polygodial and drimanial isolated from the chloroform stem bark of *Drimys angustifolia.* These compounds exhibit antimalarial, antifungal and anti-inflammatory activities [72]. The roots of *Ferula pseudalliacea* contains a rich source of biologically active compound sesquiterpenoids coumarins in which sanandajin and methyl galbanate show resistance to the K1 strain of malaria [73]. Balsaminoside A and karavilagenin E were isolated from the methanol extract of aerial parts of *Momordica balsamina* L. (Cucurbitaceae) and had antiplasmodial activity against two *Plasmodium* strains (IC50 values for balsaminaceae A = 4.6 and 4.0 µM, and karavilagenin E = 7.4 and 8.2 µM, respectively, on 3D7 and Dd2) [74]. *Dicoma tomentosa* is a plant of the Asteraceae family growing in Asia and tropical Africa One reasonably active ursane triterpene, brein (75), was isolated from 70% ethanolic extract of aerial parts of *Kleinia odora* (Forssk) DC (Asteraceae) with IC50 on K1 strain of 9.7 µM.

2.4 Polyphenols

These are the micronutrients that are mainly found in certain plant-based foods such as tea, coffee, red wine, dark chocolates and other cocoa rich products; fruits, legumes, grains, vegetables. Polyphenols along with antioxidants is provided in the form to be used for humans. In its medicinal aspects, it provides great support for the treatment of diabetes, digestive issues, cardiovascular levels, neurodegenerative disorders, etc. [75]. The composition of polyphenol varies in acai pulp, which upon investigation demonstrated that anthocyanins cyanidin-3-rutinoside and cyanidin-3-glucoside were characterized in phenolics and anthocyanins. In composition, it has been shown that in nonanthocyanin polyphenols the abundance of protocatechuic acid, orientin, and isoorientin, considered flavonol-C-glucosides was observed [76]. Screening of phytochemicals as biomarkers provides means of identifying antimalarial compounds from different sources, the medicinal plants possess both *in vitro* and *in vivo* antiplasmodial efficacy in *P. falciparum* in its both sensitive/resistant strains.

In a study, it has been proven that the extract of neem bark (NBE) has promisingly blocked HSV-1 entry into cells. The same activity has been shown at variable concentrations with a range from 50 to 100 µg/mL [77]. The availability of both azadirachtin and limonoids in neem extracts is active on malaria vectors [78].

Quinine one of the oldest antimalarial drugs which is an aminoquinoline alkaloid, which is an extract of bark of *Cinchona species,* for about a longtime the same was active and effective against *Plamodium falciparum* [14]. The petroleum ether extracts of *Viola websteri* showed a significant inhibition with a value of 31.7 as a percentage of parasite inhibition at 25 µg/mL, the investigations were performed for the extract for its activity against chloroquine-sensitive D10 strain of *P. falciparum,* the observed activity of the extract reported that 6-(8'Z-pentadecenyl)-salicylic acid and 6-(8'Z, 11'Z, 14'Zheptadecatrienyl)-salicylic acid reported antiplasmodial activity with IC50 = 10.1 ± 3.2 µM of 1st compound and IC50 = 13.3 ± 6.7 µM of other compound reported that antiplasmodial activity might not be due togeneral toxicity [79]. *Pycnanthus angolensis* another plant whose stem bark extract containing methanol, dichloromethane, and aqueous ethanol were exposed for the activity (*in vitro*) against a particular strain (3D7) *P. falciparum.* The same has shown IC50 = 1.6 µg/mL values of activity. These have shown the synergistic effects among various constraints and provided a rationale to use this traditional antimalarial plant against *P. falciparum* strain [80, 81]. Artemisinin and its derivatives were also have been involved in the treatment of *P. falciparum,* it has a short span in the vertebrates. In the treatment of malaria where the disease is transmitted by *P. vivax* certain changes were suggested by WHO, in which artemisinin-based combined therapy (ACT) was given to the malarial patients [82]. Cyperaceaea local spice, an extract of this plant (CH_2C_{l2}-MeOH) exhibited reduced activity levels against two sensitive strains (one is D6 sensitive to chloroquine with IC50 = 80.4 µg/mL values and W2 resistant another stain with IC50 = 89.4 µg/mL values) of *P. falciparum* [83]. *Ekebergia capensis* another plant, the bark of which provides new triterpenoid compounds upon screening against chloroquine-sensitive (FCR-3) and -resistant (K-1) *P. falciparum* isolates reveals better antiplasmodial activity with IC50 values of 6 and 7 µM, respectively [81, 84]. Some of the common plants have been reported for the treatment of malaria are leaves of *M. oleifera* which has various properties for the treatment of various diseases and also shows antimalarial effects (Table 4). *M. peregrine* is another plant whose roots and leaves have traditionally been used against malaria.

3. Conclusions and Future Perspectives

Artemisinin, undoubtedly has been the drug of choice against malaria even quite effective against chloroquine-resistant malaria strains. More recently number of artemisinin analogs have also been synthesized such as artemether, arteether (artemotil), artesunate and artenimol showing superior efficacy. However using this therapy alone could develop drug resistance. Therefore, artemisinin-based combination therapy (ACT), has been employed as an effective therapy against malaria. However, the challenge still persists as far as developing drug resistance is concerned against artemisinin, ACTs, as well as the non-artemisinin-based combinations. This has further impeded the search for newer antimalarial compounds to counter the challenge posed by the antimalarial drug resistance. Towards that goal, a number of antimalarial compounds have been isolated from plants during the past few decades displaying significant efficacy against malaria, further leading the plant biotechnologists to explore novel lead compounds for the antimalarial drug discovery. It is equally important to unabatedly investigate plants for the presence of various phytochemicals and validate the ethnomedicines through biological parameters which may eventually form the strong platform for the antimalarial drug discovery and drug development.

Table 4: Functional aspects of flavonoids derived from various sources exhibiting antimalarial activity

S. No	Plant	Family	Flavonoid	The functional aspect of its antimalarial activity	References
1	*Aloe vera*	Asphodelaceae	Luteolin	Found in all *Artemisia* species (Presents antimalarial activity). The *Aloe vera* extract collected from colder climatic regions showed antiplasmodial activity	[85]
2	*Acalypha indica*	Euphorbiaceae	Kaempferol	The parts of the plant (stem and leaf). *Acalypha indica* have remarkable antibacterial activities against human pathogens.	[86]
3	*Azadirachta indica*	Meliaceae	Quercetin	Neem bark (NBE) has best probable antiviral activity	[87]
4	*Betula pendula*	Betulaceae	Quercetin	Its bark contains triterpenes, used in medicines.	[88]
5	*Butea monospermea*	Fabaceae	Genistein	Widely used in Ayurveda and has become a treasure of modern medicine, responsible for biological and pharmacological activities.	[89, 90]
6	*Cannabis sativa*	Compositae	Quercetin	Used in folk medicine, it is having potent bioactivities on human health, it is active on the D_6/W_2 parasitic strains.	[91]
7	*Citrus medica*	Rutaceae	Hesperetin	Present in the citrus fruits and having antioxidant and anti-inflammatory properties, and exhibits antimalarial activity.	[92]
8	*Glycyrrhiza glabra*	Leguminosae	Liquitrin	Licochalcone A (chalcone) in liquorice has reportedto possess very good antimalarial inactivity.	[93]
9	*Mentha longifolia*	Lamiaceae	Luteolin-7-O-glycoside	Bioactive in nature withwide structural diversity that plays a vital role in human ailments	[75, 94]
10	*Mimosa pudica*	Mimosoideae	Isoquercetin (a glycoside)	Potent antimalarial flavonoid	[75]

4. Acknowledgements
We greatly acknowledge Maharishi Markandeshwar (Deemed to be University) Mullana (Ambala) Haryana, India for providing the requisite platform to write this article.

5. Conflict of Interest
Certified that there is no conflict of interest pertaining to publication of this manuscript in your esteemed Journal.

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