Role of plant secondary metabolites as potential antimalarial drugs

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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 novel natural products as potential therapeutic agents. There are seven major classes of antiplasmodium agents which 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 Plasmodium, whose transmission 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 fatality 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 efficiency, there is an urgent requirement to discover new drugs to fight this disease. That’s why scientists 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 derivatives 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,
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 that act 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 extracted from red algae *Callophycus serratus* diterpene-benzoate macrolides had shown some significant antimalarial activity. Polyphenols are isolates of *Septoria pistisciariaum* (14-O-acetylcercosporin, and di-O-acetylcercosporin) and the extracted phytotoxins have the capability of inhibition of *P. falciparum* Dd and W2 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, (peroxido 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 | Bisanthraquione, schrylandicin and 10-(chrysophanol-7-yl)-10-hydroxy-chrysophanol anthrone, and the phenylanthraquinone, knipholone, Aloe-emodin | Kniphofia ensifolia | Active against Dd2 *P. falciparum*. | [16] |
|         |                | Pentalongin and Psychorubrin. | Pentas longiflora | Active against *P. falciparum*. | [9, 17-20] |
|         |                | Ethyl acetate | Markhamia tomentosa | Active against W2 and K1 strains | [21] |
|         |                | Plumbagin | Plumbaginaceae | Inhibits 3D7 and K1 *P. falciparum strains* | [22] |
|         |                | Perylenequinones cercosporin, 14-O-acetylcercosporin, and di-O-acetylcercosporin | Septoria pistisciariaum | Inhibits *P. falciparum* D6 and W2 strain. | [23] |
|         |                | Polylektide 3-ketoadociaquinone A | Xestospongia testudinaria | Inhibits FcB1 and 3D7 strains | [24] |
|         |                | Geldanamycin and 17-demethoxyreblastatin | | Significant antiplasmodial activity against the K1 strain | |
|         |                | Longirostrone A and C | Chaetomium longirostre | Inhibits K1 *P. falciparum* strain. | |
|         |                | Poupartines A–C | Poupartia borbonica | Inhibits 3D7 strain of *P. falciparum* | |
| b)      | Cyclic phosphoptriesters | Diterpene-benzoate | *Callophycus serratus* | Antiplasmodial activity | [26] |
|         |                | Bromophycolides R, S, and U | *Callophycus serratus* | Significant antiplasmodial activity | |
|         |                | Bastimolide A | *Cyanobacterium* (Okraenia hirsuta) | Significant activity against strains TM00-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] |
|         |                | Octanimomycins A and B | Streptomyces sp (RK85-270) | Active against 3D7, Dd2, and K1 strains | [32] |
| c)      | Macrocyces | Cercosporin, 14-O-acetylcercosporin, and di-O-acetylcercosporin | Septoria pistisciariaum | 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] |
|         |                | Longirostrone A and C | Chaetomium longirostre | These inhibits K1 strain of *P. falciparum* | [23] |
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 arteisinin. The main alkaloid drug is quinine (its derivative Chloroquine, a 4-aminoquinoline) which is an extract of Cinchona bark and still 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]. Arteisinin extract of *Artemisia annua*, the same along with its analog sartemether, artether, and artesunate are the best possible antimalarial agents [36, 57]. WHO has recommended arteisinin 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 and indolo terpene extraction of *Caesalpinia minax*, *Polyalthia longioides*, and *Strychnos nux vomica*, shows a better antimalarial activity [58]. Caesalminines A and B with γ-lactam ringextracted from the seeds of *Caesalpinia minax*, which show antimalarial activity with IC50 values of 0.42 and 0.79 μM [39]. In another study some other alkaloids such as 8α-polyveoline, N-acetyl-polyveoline and N-acetyl-8α-polyveolineone are the isolation of *Polyalthia longioides*, out of these both N-acetyl-polyveoline and N-acetyl-8α-polyveolineone shows moderate antimalarial activity against *P. falciparum* [40].

| e) | Endoperoxides | 1,2-dioxane and 1,2-dioxolane (Endoperoxide polyketides) | Marine sponges | Antiplasmodial |
|---|---|---|---|---|
| Ethyl acetate | *Kigelia africana* | Significantly active against the *P. falciparum* W2, CAM10 and SHF4 strains |
| 1β-(p-coumaroyloxy)polygoidal | *Drimys brasiliensis* | Antiplasmodial activity against the 3D7 and Dd2 strains |
| Sanandajin | *Ferula pseudwalliacea* | Antiplasmodial |
| Aesquerpenoid sporogen-AO1 | *Penicillium copticola* | Have inhibiting characters against K1 parasites |
| Isonitrile sesquiterpenes, 2-isocyanoclovene, 2-isocyanoclovene and 4,5-epi-10-isocyanosodacene-6-ene | *Phyllidia ocellata* | Antiplasmodial activity against the 3D7 and Dd2 strains |
| Germacranolide sesquiterpene lactone, 15-O-acetate | *Dicoma tomentosa* | Antiplasmodial |
| Germacranolide trichospiroli A | *Trichospira verticillata* | Antiplasmodial activity against Dd2 *P. falciparum* |
| Chloroform, caesalspanin G-I | *Caesalpinia sappan* | Inhibiting property; K1 strain of *P. falciparum* |
| Norcaesalpin D | *Caesalpinia bondocella* (Root extraction) | Acted as antiplasmodial component |
| lactones amphadiactones A–F and H–I | *Aphanamixis grandifolia* | Shown inhibiting properties of Dd2 strain |
| Δ8-ferruginol, and 7α-acetoxyroleanone | *Salvia sahendica* | Inhibiting property against K1 parasites |
| Betulin coumaroyl esters | *Buxus cochinichinesis* | |
| f) | Terpenes | | |
| Ancistectorines A1, N-methyl A1, A2, 5-epi-A3, A1, and C1 | *Ancistrocladus teotitlanus* | Having properties of inhibition to the K1 strain of *P. falciparum* |
| Dioncophyllines C1, F, and ancistrocladisine A, and 5′-O-methylidioncophylline D, Jozilebomines A and B | *Ancistrocladus ileboensis* | These compounds have an activity against NF54 strain (selective antimalarial activity) |
| cassiarin J, cassiarin K | *Cassia siamea* | Shown inhibition property of 3D7 strain of *P. falciparum* |
| Boldine and (−)-O, O-dimethylgrisabine | *Dehaasia longipedicellata* | Both are active against the K1 strain of *P. falciparum* |
| precocetine, Pseudoberberin, Berberin, Bisbenzylisoquinoline thaligosidine | *Thalictrum flavum* | These have shown antimalarial activity against the FcB1 strain |

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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     | N-acetyl-8a-Polyveolinone                                  | Polyalthia oliveri                         |
|       | N-acetyl-polyveoline                                      |                                             |
| 3     | Styrchnochrysin                                           | Styrchnosus vonica                         |
|       | Polyalthenol                                              |                                             |
| 4     | N- Acetyl-Polyveoline                                      | Greenwayodendron suaveolens                |
|       | Conesine                                                  | Holarrhena antidyssenterica                |
| 5     | Mokluangin D                                              | Holarrhena pubescens                       |
|       | Mokluangin A                                              |                                             |
| 6     | N-3-Benzoyldi-hydroCycloMicrophylline F                   | Buxus cochinchinensis                      |
|       | Alstoniaphyllines A                                       | Alstonia macrophylla                       |
|       | Alstoniahyphillines B                                     |                                             |
|       | Alstoniahyphilline C                                      |                                             |
| 7     | 12-hydroxy-Nacetyl-21(N)-Dehydroplumeran-18-oicacid       | Aspidosperma ulei                          |
| 8     | Strychnoballonine                                         | Strychnos icaja                            |
|       | 4a,b-secoedehydroantofoil                                 | Ficus septica                              |
|       | Dehydrotylophorine                                        |                                             |
|       | Tylophoridine D                                           |                                             |
|       | Cyclaneanine                                              |                                             |
|       | 10-demethylxylopinine                                      |                                             |
| 9     | Reticuline                                                | Actinodaphne macrophylla                   |
|       | Laurotetanine                                             |                                             |
|       | Bucuculine                                                |                                             |
|       | α-hydastine                                               |                                             |
|       | Anolobine                                                 |                                             |
| 10    | (+)-Nmethylisococlaraine                                  | Cryptocarya nigra                          |
|       | Atherosperminine                                          |                                             |
|       | Hydroxyathersperminine                                    |                                             |
|       | Norathersperminine                                        |                                             |
| 11    | Palmatine                                                 | Annikkum meriye                            |
|       | Dihydrorotidine                                           | Zanthoxyllum heitzii                       |
|       | Pellitorine                                               |                                             |
|       | Heitzifquinone                                            |                                             |
| 12    | (-)-Pseudocurine                                          | Stephania abyssinica                       |
|       | (-)-Pseudoisocurine                                       |                                             |
|       | (-)-10-oxoacondinline                                     |                                             |
|       | (+)-Lauroetanine                                          | Alseodaphne corneri                        |
|       | (+)-Norstephasubine                                       |                                             |
| 13    | Dioncophylline F                                          | Ancistrocladus ileboensis                  |
|       | Mbandakamines A and B                                     | Congolese ancistrocladus                   |
|       | Jozimine A2                                               |                                             |
|       | Vireakine                                                 | Stephanie rotunda                          |
|       | Stephanean                                                |                                             |
|       | Pseudopalmatine                                           |                                             |
| 14    | Obtusipetadione                                           | Dasymaschalon obtusipetalum                |
|       | (-)-O-O-Dimethylgrisabine                                 | Dehaasia longipedicellata                  |
|       | (-)-Miltonine                                             | Xylophia sericea                           |
| 15    | Anonaine                                                  |                                             |
|       | Tavoyanine A                                              | Phoebe tavoyana                            |
|       | Roemerine                                                 |                                             |
|       | Laurolithine                                              |                                             |
|       | Boldine                                                   |                                             |
|       | Sebiferine                                                |                                             |
| 16    | Simplicifolianine                                          | Meconopsis simplicifolia                   |
|       | Coptisine                                                 | Coptidi srhizoma                           |
|       | Milusacunines A-E                                         | Milusia cuneata                            |
| 17    | Lycoris radiata                                           |                                             |
|       | (+)-5,6-Dehydrolycorine                                   |                                             |
| 18    | (+)-8,9-Methylene Dioxyethylomalocorine-Noxide             |                                             |
|       | (+)-3α,6β-Diacetyl-bulbispermine                           |                                             |
|       | 5,6-Dihydro-5-methyl-2-Hydroxyphenanthridine              |                                             |
|       | (+)-3n-Hydroxy-6β-Acetyl-Bulbispermine                    |                                             |
2.2 Endoperoxides

Endoperoxides are Dioxgen 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 (Fe(21)) 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 extracts. 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 cell by 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 (artether, arteether, artelinate, and artesunate) are the esters or ethers of the lactol [66]. Other example of endoperoxide is Plakortide C, a unique structure to kill the malarial parasite. As the 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

Terpenes 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                   | (C₅H₈)₁         |
| Monoterpenoid| 2                     | 10                  | (C₅H₈)₂         |
| Sesquiterpenoids| 3                 | 15                  | (C₅H₈)₃         |
| Diterpenoids | 4                     | 20                  | (C₅H₈)₄         |
| Sesterpenoid | 5                     | 25                  | (C₅H₈)₅         |
| Triterpenoid | 6                     | 30                  | (C₅H₈)₆         |
| Tetraeterpenoid| 7                  | 40                  | (C₅H₈)₇         |
| Polyterpenoid| 8                     | 40 or >40           | (C₅H₈)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 specioside, 2β 3β, 19α-trihydroxy-urs-12-en-28-oic acid, atranorin and p-hydroxy-cinnamic acid. Drimys angustifolia is a sesquiterpene having polyagodial 1-β-(p-methoxycinnamoyl)-polyagodial and drimanal isolated from the chloroform stem bark of Drimys angustifolia. These compounds exhibit antimalarial, antifungal and anti-inflammatory activities. The roots of Ferula pseuddaliezca contains a rich source of biologically active compound sesquiterpenoids coumarins in which sanadajin and methyl galbanate show resistance to the K1 strain of malaria. Balsamisinside A and karavilagenin E were isolated from the methanol extract of aerial parts of Monordica 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). 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 odoror (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. 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. 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. The availability of both azadirachtin and limonoids in neem extracts is active on malaria vectors.

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 Plasmodium falciparum. 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,14′Z-heptadecatrienyl)-salicylic acid reported antiplasmodial activity with IC50 = 10.1 ± 3.2 μM of 1° compound and IC50 = 13.3 ± 6.7 μM of other compound reported that antiplasmodial activity might not be due to general toxicity. Pyknanthus 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.

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. Cyperaceaea local spice, an extract of this plant (CH3CO2-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. 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. 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 arteether, arteether (artemocin), artemesinate and artemimol 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 monosperma  | 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 Dα/Wα 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  | Liquiritin            | Licochalcone A (chalcone) in liquorice has reported to possess very good antimalarial activity.                     | [93]       |
| 9     | Mentha longifolia | Lamiaceae    | Luteolin-7-O-glycoside| Bioactive in nature with wide structural diversity that plays a vital role in human ailments.                        | [75, 94]   |
| 10    | Mimosoideae       | Mimosoideae  | Isoquercetin (a glycoside)| Potent antimalarial flavonoid                                                                                       | [75]       |

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

6. References
1. WHO. World malaria report 2020: 20 years of global progress and challenges, World Health Organization Geneva, 2020, 1-151.
2. Talapko J, Skrlec I, Alebić T, Jukić M, Vžeć A. Malaria: The past and the present. Microorganisms. 2019;7(6):179-185.
3. Schlagenhauf P, Petersen E. Standby emergency treatment of malaria in travelers: experience to date and new developments. Expert Review of Anti-infective Therapy. 2012;10(5):537-546.
4. Walker JB. On malaria, Medical College of the State of South Carolina, 1843.
5. Singh B, Daneshvar C. Human infections and detection of Plasmodium knowlesi. Clinical Microbiology Reviews. 2013;26(2):165-184.
6. Tajuddeen N, Van-Heerden FR. Antiplasmodial natural products: An update. Malaria Journal. 2019;18(1):404.
7. Daniel M. Medicinal plants: Chemistry and properties. Science Publishers. 2006.
8. Osman CP, Ismail NH. Antiplasmodial anthraquinones from medicinal plants: The chemistry and possible mode of actions. Natural Product Communications. 2018;13(12):1934578X1801301207.
9. Kumarihany M, Khan SI, Jacob M, Tekwani BL, Duke SO, Ferreira D, et al. Antiprotozoal and antimicrobial compounds from the plant pathogen Septoria pisiacarum. Journal of Natural Products. 2012;75(5):883-889.
10. Moreno E, Varughese T, Spadafora C, Arnold AE, Coley PD, Kursar TA, et al. Chemical constituents of the new endophytic fungus Mycosphaerella sp. Nov. and their anti-parasitic activity. Natural Product Communications. 2011;6(6):1934578X1100600620.
11. Fattorusso C, Persico M, Calcina B, Cerrano C, Parapini S, Taramelli D, et al. Manadoperoxides A–D from the Indonesian sponge Plakortis cfr. simplex. Further insights on the structure activity relationships of simple 1, 2-dioxane antimalarials. Journal of Natural Products. 2010;73(6):1138-1145.
12. Tagliatela-Scafati O, Fattorusso E, Romano A, Scala F, Barone V, Cimino P, et al. Insight into the mechanism of action of plakortins, simple 1, 2-dioxane antimalarials. Organic and Biomolecular Chemistry. 2010;8(4):846-856.
13. Sharma V, Varshney A, Choudhary R, Sharma AK. Current paradigms to explore the gut microbiota linkage to neurological disorders. European Medical Journal of Neurology. 2020, 68-79.
14. Saxena S, Pant N, Jain D, Bhakuni R. Antimalarial agents from plant sources. Current Science, 2003, 1314-1329.
15. Bringmann G, Tasler S. Oxidative aryl coupling reactions: A biomimetic approach to configurationally unstable or axially chiral biaryl natural products and related bioactive compounds. Tetrahedron. 2001;57(2):331-343.
16. Dai Y, Harinantenaina L, Bowman JD, Da Fonseca IO, Brodie PJ, Goetz M, et al. Isolation of antiplasmodial anthraquinones from Kniphofia ensifolia, and synthesis and structure–activity relationships of related compounds. Bioorganic and Medicinal Chemistry. 2014;22(1):269-276.
17. Tantangmo F, Lenta B, Boyom F, Ngouela S, Kaiser M, Calcinai F, Cerrano C, Parapini S, Taramelli D, et al. Antiprotozoal activities of some constituents of Markhamia tomentosa (Bignoniaceae). Annals of Tropical Medicine and Parasitology. 2010;104(5):391-398.
18. Wanyoike G, Chhabra S, Lang’at-Thoruwa C, Omar S. Brine shrimp toxicity and antiplasmodial activity of five Kenyan medicinal plants. Journal of Ethnopharmacology. 2004;90(1):129-133.
19. Thengsusuks A, Chaijaroenkul W, Na-Bangchang K. Antimalarial activities of medicinal plants and herbal
formulations used in Thai traditional medicine. Parasitology Research. 2013;112(4):1475-1481.
20. Sumsakul W, Plengsuriyakarn T, Chaijaroenkul W, Viyanant V, Karbwang J, Na-Bangchang K. Antimalarial activity of plumbagin in vitro and in animal models. BMC Complementary and Alternative Medicine. 2014;14(1):15.
21. Longeon A, Copp BR, Roué M, Dubois J, Valentín A, Petek S, et al. New bioactive halenaquinone derivatives from South Pacific marine sponges of the genus *Xestospongia*. Bioorganic and Medicinal Chemistry. 2010;18(16):6006-6011.
22. Supong K, Sripreechasak P, Tanasupawat S, Danwisetkanjana K, Ratchawee P, Pittayakhajonwut P. Investigation on antimicrobial agents of the terrestrial *Streptomyces* sp. BCC71188. Applied Microbiology and Biotechnology. 2017;101(2):533-543.
23. Panthama N, Kanokmedhakul S, Kanokmedhakul K, Soytong K. Cytotoxic and antimalarial azaphilones from *Chaetomium longisporum*. Journal of Natural Products. 2011;74(1):2395-2399.
24. Ledoux A, St-Gelais A, Cieckiewicz E, Jansen O, Bordignon A, Illien B, et al. Antimalarial activities of alkyl cyclohexenone derivatives isolated from the leaves of *Poupartia borbonica*. Journal of Natural Products. 2017;80(6):1750-1757.
25. Schulze C, Navarro G, Ebert D, DeRisi J, Lintongtong RG, Salinopostins AK. Long-chain bicyclic phosphotriesters as a potent and selective antimalarial chemotype. The Journal of Organic Chemistry. 2015;80(3):1312-1320.
26. Lin AS, Stout EP, Prudhomme J, Roch KL, Fairchild CR, Franzblau SG, et al. Bioactive bromophycolides R–U from the Fijian red alga *Callophycus serratus*. Journal of Natural Products. 2010;73(2):275-278.
27. Shao CL, Lintongtong RG, Balunas MJ, Centeno A, Boudreau P, Zhang C, et al. A potent antimalarial polyhydroxy macrolide from the marine cyanobacterium *Okeania hirsuta*. The Journal of Organic Chemistry. 2015;80(16):7849-7855.
28. Shao CL, Mou XF, Cao F, Spadafora C, Glukhov E, Gerwick L, et al. An antimalarial 24-membered marine macrolide possessing a tert-butyl group. Journal of Natural Products. 2018;81(1):211-215.
29. Xu L, He Z, Xue J, Chen X, Wei X. β-Resorcyclic acid lactones from a *Paeuclomycyes* fungus. Journal of Natural Products. 2010;73(5):885-889.
30. Tripathi A, Puddick J, Prinsep MR, Rottmann M, Chan KP, Chen DYK, et al. Lagunamide C, a cytotoxic cyclodepsipeptide from the marine cyanobacterium *Lyngbya majuscula*. Phytochemistry. 2011;72(18):2369-2375.
31. Raju R, Khalil ZG, Piggott AM, Blumenthal A, Gardiner DL, Skinner-Adams TS, et al. Mollemycin A: An antimalarial and antibacterial glyco-hexadepsipeptide-polyketide from an Australian marine-derived *Streptomyces* sp. (CMB-M0244). Organic Letters. 2014;16(6):1716-1719.
32. Son S, Ko SK, Kim JW, Lee JK, Jang M, Ryoo HJ, et al. Structures and biological activities of azaphilones produced by *Penicillium* sp. KCB11A109 from a ginseng field. Phytochemistry. 2016;122:154-164.
33. Chianese G, Persico M, Yang F, Lin HW, Guo YW, Basilico N, et al. Tagialatela-Scatali, Fattorusso C, Endoperoxide polyketides from a Chinese *Plakortis simplex*: Further evidence of the impact of stereochemistry on antimalarial activity of simple 1, 2-dioxanes. Bioorganic and Medicinal Chemistry. 2014;22(17):4572-4580.
34. Zofou D, Tene M, Tane P, Titanji VP. Antimalarial drug interactions of compounds isolated from *Kigelia africana* (Bignoniaceae) and their synergism with artemether, against the multidrug-resistant W2mef Plasmodium falciparum strain. Parasitology Research. 2012;110(2):539-544.
35. Claudino VD, Silva KCD, Cechinel Filho V, Yunes RA, Monache FD, Giménez A, et al. Drimanes from *Drimys brasiliensis* with leishmanicidal and antimalarial activity. Memórias do Instituto Oswaldo Cruz. 2013;108(2):140-144.
36. Dastan D, Salehi P, Ghanati F, Gohari AR, Maroofi A, Alnajar N. Phytotoxicity and cytotoxicity of disesquiterpenes and sesquiterpenes coumarins from *Ferula pseudalliacea*. Industrial Crops and Products. 2014;55:43-48.
37. Fisch KM, Hertzer C, Böhringer N, Wuisan ZG, Schillo D, Bara R, et al. The potential of Indonesian heterobenzone found around Bunaken Island for the production of bioactive compounds. Marine Drugs. 2017;15(12):384.
38. Jansen O, Tits M, Angenot L, Nicolas JP, De Mol P, Nikkiem JB, et al. Anti-plasmodial activity of *Dicoma tomentosa* (Asteraceae) and identification of urospermal A-15-O-acetate as the main active compound. Malaria Journal. 2012;11(1):289.
39. Du Y, Pearce KC, Dai Y, Krai P, Dalal S, Cassera MB, et al. Antiplasmodial sesquiterpenoid lactones from *Trichospora verticillata*: Structure elucidation by spectroscopic methods and comparison of experimental and calculated ECD data. Journal of Natural Products. 2017;80(5):1639-1647.
40. Ma G, Wu H, Chen D, Zhu N, Zhu Y, Sun Z, et al. Antimalarial and antiproliferative cassane diterpenes of *Caesalpinia sappan*. Journal of Advanced Pharmaceutical Technology. 2015;5:1133.
41. Petek S, Longeon A, Copp BR, Roué M, Dollfus J, Anderson TJ, et al. New bioactive compounds. Marine Drugs. 2014;12(16):6011.
42. Ebrahimi SN, Zimmermann S, Zaugj J, Smiesko M, Brun R, Hamburger M. Abietane diterpenoids from *Salvia sahendica*–antiprotozoal activity and determination of their absolute configurations. Planta Medica. 2013;29(02):150-156.
43. Pan L, Acula UM, Chai H, Park HY, Ninh TN, Van Thanh B, et al. New bioactive lupane triterpene coumaroyl esters isolated from *Buxus cochinichensis*. Planta Medica. 2015;81:1133.
44. Cai S, Risinger AL, Nair S, Peng J, Anderson TJ, Du L, et al. Identification of compounds with efficacy against malaria parasites from common North American plants. Journal of Natural Products. 2016;79(3):490-498.
45. Brüning J, Zhang G, Ölschläger T, Stich A, Wu J, et al. Antimalarial activity of extracts of extracts of *Ocimum basilicum* and *Citrus x paradisi* in vivo. Journal of Antimicrobial Chemotherapy. 2014;69(5):997-1001.
Chatterjee M, et al. Highly selective antimalarial naphthylisoquinoline alkaloids from Ancistrocladus tectorius. Phytochemistry. 2013;91:220-228.
47. Li J, Seipel R, Feineis D, Mudogo V, Kaiser M, Brun R, et al. Effertih EJ. Diconophyllines C2, D2, and F and related naphthylisoquinoline alkaloids from the Congolese liana, Ancistrocladus ileboensis with potent activities against Plasmodium falciparum and against multiple myeloma and leukemia cell lines. Journal of Natural Products. 2017;80(2):443-458.
48. Li J, Seipel R, Bruhn T, Feineis D, Kaiser M, Brun R, et al. Jozilebinones A and B, naphthylisoquinoline dimers from the Congolese liana Ancistrocladus ileboensis, with antiastucreity activities against the PANC-1 human pancreatic cancer cell line. Journal of Natural Products. 2017;80(10):2807-2817.
49. Deguchi J, Hirahara T, Hirasawa Y, Ekasari W, Widyawaryanti A, Shirotia O, et al. New tricyclic alkaloids, cassiariins G, H, J, and K from leaves of Cassia siamea. Chemical and Pharmaceutical Bulletin. 2012;60(2):219-222.
50. Matsumoto T, Kobayashi T, Ishida K, Hirasawa Y, Morita H, Honda T, et al. Vasodilator effect of Cassiariin A, a novel antiplasmodial alkaloid from Cassia siamea, in rat isolated mesenteric artery. Biological and Pharmaceutical Bulletin. 2010;33(5):844-848.
51. Leong KH. Antiplasmodial and antioxidant isouquinoline alkaloids from Dehaasia longipedicellata. Planta Medica. 2014;80(7):599-603.
52. Ropivia J, Derbré S, Rouger C, Pagniez F, Le Pape P, Richomme P. Isoquinolines from the roots of Thalictrum flavum L. and their evaluation as antiparasitic compounds. Molecules. 2010;15(9):6476-6484.
53. Angerhofer CK, Guinaudeau H, Wongpanich V, Pezzuto JM, Cordell GA. Antiplasmodial and cytotoxic activity of natural bisbenzylisoquinoline alkaloids. Journal of Natural Products. 1999;62(1):59-66.
54. Uzor PF. Alkaloids from plants with antimalarial activity: A review of recent studies. Evidence-Based Complementary and Alternative Medicine. 2020;2020:8749083.
55. Hennequin C, Bourée P, Bazin N, Bisaro F, Feline A. Severe psychiatric side effects observed during prophylaxis and treatment with mefloquine. Archives of Internal Medicine. 1994;154(20):2360-2362.
56. Price RN. Artemisinin drugs: Novel antimalarial agents. Expert Opinion on Investigational Drugs. 2000;9(8):1815-1827.
57. Singh M, Kumar V, Sehrawat N, Yadav M, Chaudhary M, Upadhyay SK, et al. Current paradigms in epigenetic anticaner therapeutics and future challenges, Semin Cancer Biology, 2021;10.1016/j.semcancer.2021.03.013.
58. Upadhyay SK. Allelopathic activities of specific microbial metabolites in the inland prawn fisheries off eastern Uttar Pradesh, India. International Journal of Scientific Research. 2016;5(2):415-416.
59. Ma G, Sun Z, Sun Z, Yuan J, Wei H, Yang J, et al. Antimalarial diterpene alkaloids from the seeds of Caesalpinia minax. Fitoterapia. 2014;95:234-239.
60. Muganza DM, Fruth B, Nzunzu JL, Tuenter E, Foubert K, Cos P, et al. In vitro antiprotozoal activity and cytotoxicity of extracts and isolated constituents from Greenwayodendron suaveolens. Journal of Ethnopharmacology. 2016;193:510-516.
61. Meshnick SR, Taylor T, Kamchonwongpaisan S. Artemisinin and the antimalarial endoperoxides: from herbal remedy to targeted chemotherapy. Microbiological Reviews. 1996;60(2):301-315.
62. Posner GH, Wang D, Cumming JN, Oh CH, French AN, Bodley AL, et al. Further evidence supporting the importance of and the restrictions on a carbon-centered radical for high antimalarial activity of 1, 2, 4-trioxanes like artemisinin. Journal Of Medicinal Chemistry. 1995;38(13):2273-2275.
63. Ridley RG. To kill a parasite. Nature. 2003;424(6951):887-889.
64. Sharma VR, Sharma DK, Mishra N, Sharma AK, Batra N. New and potential therapies for the treatment of breast cancer: An update for oncologists. Breast Cancer. 2016;2:3.
65. Tuli HS, Mittal S, Aggarwal D, Parashar G, Parashar NC, Upadhyay SK, et al. Path of siliibinin from diet to medicine: A dietary polyphenolic flavonoid having potential anti-cancer therapeutic significance. Seminars in Cancer Biology. 2021;73:196-218.
66. M.O.H.a.F.U.o.C. https://pii.pib.gov.in/PressReleasePage.aspx?PRID=162869.
67. Sharma V, Gupta GK, Sharma AK, Batra N, Sharma DK, Joshi A, et al. PI3K/Akt/mTOR intracellular pathway and breast cancer: factors, mechanism and regulation. Current Pharmaceutical Design. 2017;23(11):1633-1638.
68. Sharma V, Sharma AK, Punj V, Priya P. Recent nanotechnological interventions targeting PI3K/Akt/mTOR pathway: A focus on breast cancer, Semin Cancer Biology, 2019, 133-146.
69. Sharma AK, Sharma VR, Gupta GK, Ashraf GM, Kamal MA. Advanced glycation end products (AGEs), glutathione and breast cancer: Factors, mechanism and therapeutic interventions. Current Drug Metabolism. 2019;20(1):65-71.
70. Sharma V, Sheikh I, Tuli HS, Aggarwal D, Sankhyan A, Vyas P, et al. Cancer chemoprevention by flavonoids, dietary polyphenols and terpenoids. Biointerface Research in Applied Chemistry. 2021;11(1):8502-8537.
71. Sharma VR, Singh M, Kumar V, Yadav M, Sehrawat N, Sharma DK, et al. Microbiome dysbiosis in cancer: exploring therapeutic strategies to counter the disease, Seminars in Cancer Biology, 2021, 61-70.
72. da Cunha FM, Fröde TS, Mendes GL, Malheiros A, Cechinel Filho V, Yunes RA, et al. Additional evidence for the anti-inflammatory and anti-allergic properties of the sesquiterpene polygalodial. Life Sciences. 2001;70(2):159-169.
73. Dastan D, Salehi P, Gohari AR, Zimmermann S, Kaiser M, Hamburger M, et al. Disesquiterpene and sesquiterpene coumarins from Ferula pseudalliacea, and determination of their absolute configurations. Phytochemistry. 2012;78:170-178.
74. Rasanoivo P, Wright CW, Willcox ML, Gilbert B. Whole plant extracts versus single compounds for the treatment of malaria: Synergy and positive interactions. Malaria Journal. 2011;10(1):1-12.
75. Rudrapal M, Chetia D. Plant flavonoids as potential source of future antimalarial leads. Systematic Reviews in Pharmacy. 2017;8(1):13.
76. Ferreira LT, Venancio VP, Kawano T, Abrão LC, Tavella
Chemical genomic profiling unveils the in vitro and in vivo antimalarial mechanism of açai (Euterpe oleracea mart.) polyphenols. ACS Omega. 2019;4(13):15628-15635.

77. Yerima M, Jodi S, Oyinbo K, Maishanu H, Farouq A, Junaidu A, et al. Effect of neem extracts (Azadirachta indica) on bacteria isolated from adult mouth. Nigerian Journal of Basic and Applied Sciences. 2012;20(1):64-67.

78. Su M, Mulla M. Activity and biological effects of neem products against arthropods of medical and veterinary importance. Journal of the American Mosquito Control Association. 1999;15:133-152.

79. Lee SJ, Park WH, Moon HI. Bioassay-guided isolation of antiparasitic and anacardic acids derivatives from the whole plants of Viola websteri Hemsl. Parasitology Research. 2009;104(2):463-466.

80. Abrantes M, Mil-Homens T, Duarte N, Lopes D, Cravo P, do Céu Madureira M, et al. Antiplasmodial activity of lignans and extracts from Pycnanthus angolensis. Planta Medica. 2008;74(11):1408-1412.

81. Batista R, De Jesus Silva Júnior A, De Oliveira AB. Plant-derived antimalarial agents: New leads and efficient pyrethroids. Part II. Non-alkaloidal natural products. Molecules. 2009;14(8):3037-3072.

82. Blasco B, Leroy D, Fidock DA. Antimalarial drug resistance: Linking Plasmodium falciparum parasite biology to the clinic. Nature Medicine. 2017;23(8):917.

83. Efange SM, Brun R, Wittlin S, Connolly JD, Hoye TR, McAkam T, et al. Okundoperoxide, a bicyclic cyclofarnesylsesquiterpene endoperoxide from Scleria striatinaux with antiparasitic activity. Journal of Natural Products. 2009;72(2):280-283.

84. Murata T, Miyase T, Muregi FW, Naoshima-Ishibashi Y, Umehara K, Warashina T, et al. Antiplasmodial triterpenoids from Ekebergia capensis. Journal of Natural Products. 2008;71(2):167-174.

85. Kumar S, Yadav M, Yadav A, Rohilla P, Yadav JP. Antiplasmodial potential and quantification of acohol and aloe-emodin in Aloe vera collected from different climatic regions of India. BMC Complementary and Alternative Medicine. 2017;17(1):369.

86. Nag A, Anoop M, Sharma K, Verma K. Acalypha indica L. an important medicinal plant with antimicrobial agents: A review. International Journal of Research and Analytical Reviews. 2018;5(4):304-309.

87. Alzohairy MA. Therapeutics role of Azadirachta indica (Neem) and their active constituents in diseases prevention and treatment. Evidence-Based Complementary and Alternative Medicine. 2016;2016:7382506.

88. Dallenbach-Tölke K, Nyiredy S, Gross G, Sticher O. Flavonoid glycosides from Betula pubescens and Betula pendula. Journal of Natural Products. 1986;49(6):1155-1156.

89. Karak P. Biological activities of flavonoids: An overview. International Journal of Pharmaceutical Sciences and Research. 2019;10(4):1567-1574.

90. Murlidhar A, Babu KS, Sankar TR, Redenna P, Reddy G, Latha J. Antiinflammatory activity of flavonoid fraction isolated from stem bark of Butea monosperma (Lam): A mechanism based study. International Journal of Phytopharmacology. 2010;1(2):124-132.

91. Soré H, Sanon S, Hilou A. Antiplasmodial properties of plants isolated flavonoids and their derivatives. International Journal of Herbal Medicine. 2018;6(5):43-56.