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Review Article

Plant Flavonoids as Potential Source of Future Antimalarial leads

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ABSTRACT
In this article, a comprehensive review on bioactive flavonoids that are abundant in medicinal and functional food (dietary) plants has been made, with special reference to antimalarial flavonoid molecules. Flavonoids have been found to exist in plants/plant medicines comprising numerous polyphenolic compounds with a wide structural diversity having pharmacological potential in diverse range of therapeutic areas. Flavonoids derived from certain dietary plants described herein have been investigated for their antimalarial effectiveness against malaria parasites, particularly *Plasmodium falciparum*. The biological target specificity of their antimalarial action is so interesting that they act at protein targets at molecular level other than the conventional antimalarial targets. This approach may be a basis of establishing plant flavonoids as future antimalarial leads for the development of new and potent antimalarial drug molecules.
Key words: Malaria, *P. falciparum*, Drug resistance, Flavonoids, Leads, Antimalarial.

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INTRODUCTION

Malaria is a serious infectious illness which affects people of all ages around the world. According to the World Health Organization (WHO), approximately 40% of the world population lives in malaria endemic areas, with around 300-500 million clinical cases and about 1.5-2.7 million deaths per year globally.[1] In the South East Asian region, out of about 1.4 billion people living in 11 countries, 1.2 billion (85.7%) are exposed to the risk of malaria, most of whom live in India. Of the 2.5 million reported cases in the South East Asia, India alone contributes about 70% of the total cases.[2,3] Human malaria is caused by five protozoan species of the genus *Plasmodium*, namely, *P. falciparum*, *P. vivax*, *P. ovale*, *P. malariae* and *P. Knowlesi*. *Plasmodium falciparum* is the most widespread and deadly species which causes potentially fatal malaria such as cerebral malaria, and most of the malaria-related deaths worldwide.[4,5] In patients with severe and complicated malaria, the mortality rate is accounted for 20-50% due to *P. falciparum*.[6] *P. falciparum* strains also produces varying degree of resistance against currently available antimalarial drugs in a very short duration of treatment. In recent days, the emergence and spread of multi-drug resistant strains of *P. falciparum* has become an increasingly important clinical issue in malaria chemotherapyworldwide.[7,8]

Plant-based medicines have been playing an important role in the treatment of malaria since ancient times. Malaria treatment in modern chemotherapeutic form started with the discovery of quinine (QN) from cinchona bark. The quinoline-based synthetic anti-malarial drugs (Figure 1) such as chloroquine (CQ), mefloquine (MQ) etc. Have been used in the treatment of malaria for a long time.[6,9] However, with the pace of time their clinical uses have been limited because of the development of resistant strains of malarial parasites, especially *P. falciparum*.

Artemisinin (ART), isolated from the leaves of *Artemisia annua* (*qinghaosu*), was later introduced to treat CQ-resistant *P. falciparum* malaria. Its several semi-synthetic derivatives (Figure 2) which are nothing but the structural analogues of dihydro artemisinin (DHT), the reduced form of ART, were then successfully incorporated as potent anti-malaria drugs for the treatment of multi-drug malaria, particularly *P. falciparum* malaria.[9-11]

Currently, artemisinin-based combination therapies (ACTs) are being recommended by WHO for the treatment of multidrug-resistant *P. falciparum* malaria. Some examples of ACTs include artemether plus lumefantrine, artesunate plus mefloquine, and artesunate plus pyronaridine. But, resistance to ACTs (for example, MQ-ART) against *P. falciparum* has begun to emerge in Southeast Asia. Besides, high treatment cost (relative to CQ or QN), unsatisfactory physicochemical/pharmacokinetic properties (poor lipid/water partitioning behaviour, inadequate bioavailability, short plasma half life etc.), toxicities and lower abundance (limited availability from natural sources) are some other notable problems associated with ART- based anti-malaria. Therefore, the treatment of multi-drug resistant malaria has increasingly become a challenging task in most malaria endemic regions of the world, which necessitates the urgent development of newer and effective antimalarial drugs that would fight against resistant malaria.[11-14]

In order to resolve the above challenging issue, plants and/or plant-based traditional medicines is believed to be the most reliable and alternative means for the discovery of new antimalarial molecules as nature always serves as the richest source of chemicals of pharmacological importance. Such nature derived chemical compounds are basically secondary metabolites of plant or other natural origin belonging to several important natural products classes such as terpenoids, alkaloids, flavonoids, coumarins, steroids etc., which possess a wide array of biological functions and health benefits. Among several natural products or phytochemical classes cited above, flavonoids have recently gained significant interest among medicinal chemists because of their promising chemopreventive/chemo-protective potentials in inflammatory disorders, cardiovascular diseases, diabetic complications, neurodegenerative disorders, cancerous illness, malaria and microbial infectious diseases.15,16

In tune with the above facts, researchers have investigated many plant species in search of their antimalarial potential, and also reported plant flavonoids as anti-malarial bioactive principles. A number of polyphenolic flavonoids that are abundant in dietary or medicinal plants have been identified to possess good *in vitro* and *in vivo* antimalarial activities.[17,18] In this review, plant derived flavonoids, their chemistry and structural diversity, and basis of their bio-effectiveness are described with special reference to flavonoids having antimalarial potential.

Bio flavonoids

Flavonoids comprise a large group of aromatic organic compounds of around 10,000 structures that are ubiquitously distributed in the plant kingdom. These compounds are secondary metabolites biosynthesized in plants as metabolic hybrids through a combination of

the shikimate-derived phenylpropanoid (-->C_6-C_3) pathway and the acetate/mevalonatepolyketide (-->C_6) pathway. Therefore, they possess the carbon skeleton of phenylpropanoid (C_6-C_3 unit), and constitute an important class of natural products, so called phenylpropanoids. More precisely, the molecular framework of flavonoids consists of a C_6-C_3-C_6 unit i.e., flavonoid (phenyl-benzopyrone) skeleton in which the parent C_6-C_3 unit is present as chromone (benzo-γ-pyrone) nucleus (Figure 3). The term flavonoid was derived from the Latin word *flavus* meaning yellow, and the prefix 'bio' denotes their biological origin as well as their manifested biological significances (including pharmacological effects) on other organisms.[19-21]

Chemistry

The chemical structure of flavonoids are based on the flavonoid molecular framework (C_6-C_3-C_6) which is a fifteen-carbonskeleton consisting of two benzene rings (A ring and B ring) interconnected by a three carbon heterocyclic pyran ring (C ring). The chroman ring (C ring) is connected to the second aromatic ring (ring B, benzenoid substituent) at the C-2 (flavone), C-3 (e.g., iso-flavone) or C-4 (neoflavone) positions. Sometimes, in place of six-membered heterocyclic pyran ring (ring C) an acyclic moiety (chalcone) or a five membered heterocyclic furan ring (aurone) is found. Six-membered ring condensed with the benzene ring is either a γ-pyrone (flavones, flavonols and isoflavones) or its dihydroderivatives (flavanones and flavanols). Flavonoids are generally hydroxylated phenolic substances and therefore referred as plant polyphenols. They are often hydroxylated in positions 3, 5, 6, 7, 3', 4', and 5'. The structural skeletons of various types of flavonoids are represented in the Figure 4.[21-23]

According to the oxidation state of the central pyran ring, they can be broadly classified into:

Flavonoids: These are all ketone containing compounds that include anthoxanthins (flavones and flavonols), iso-flavones and neo-flavones. The skeletal structures of this class of compounds are based upon flavone backbone, and

Flavanoids: These are non ketone compounds having flavan backbone that include flavanones, flavanols, and flavanonols.

Flavonoids differ from flavanoids mainly by a C2-C3 double bond. Individual bioactive compounds within a class differ primarily in the pattern of hydroxyl substitution of the A and B rings.[21,22] In a much broader sense, the term bioflavonoids refer to all compounds of natural origin that collectively includes both flavonoids and flavanoids.

Structural diversity

Flavonoids are widely distributed in plants and occur virtually in all plant parts, which impart a variety of colours such as yellow, orange, purple, blue etc. to flower petals, fruit peels, vegetables and certain grains. Because of their widespread distribution in dietary plants such as fruits and vegetables, flavonoids form an integral part of human diet. Flavonoids consumed (in considerable amounts) through diet (raw forms, processed products or cooked preparations) contributes beneficial effects to human health. Owing to their desirable bio-physicochemical properties such as water solubility, lipophilicity and thermostability flavonoids possess favourable absorption and distribution characteristics in human body, which in turn responsible for their better bioavailability and eventual therapeutic outcomes. Flavonoids are also abundantly found in many medicinal and aromatic plants, (Table 1) and certain herbal remedies. For instance, the traditional use of liquorice extract (rich in flavonoids content) in the treatment of peptic ulcer disease is well documented.[17,20-23]

Flavonoids rich in human diet constitute a large group of polyphenolic compounds (also known as poplyhydroxyphenols), which are usually considered as non-nutritive bioactive components that play a significant

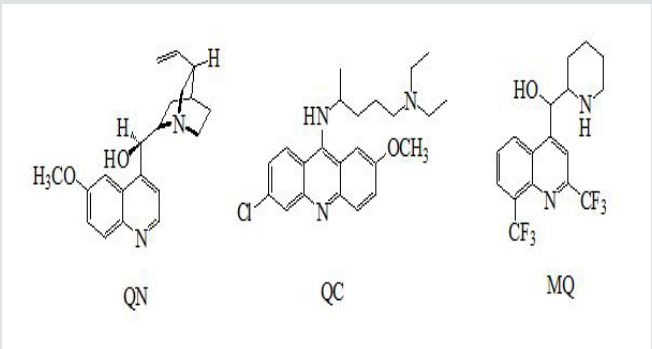

Figure 1: Quinoline-based antimalarial drugs.

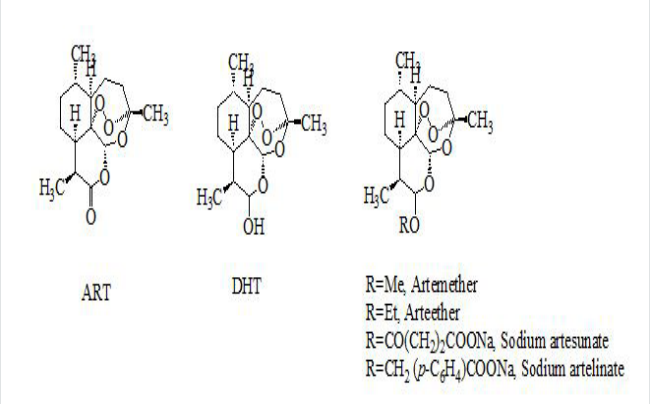

Figure 2: Artemisinin (ART) and its semi-synthetic derivatives..

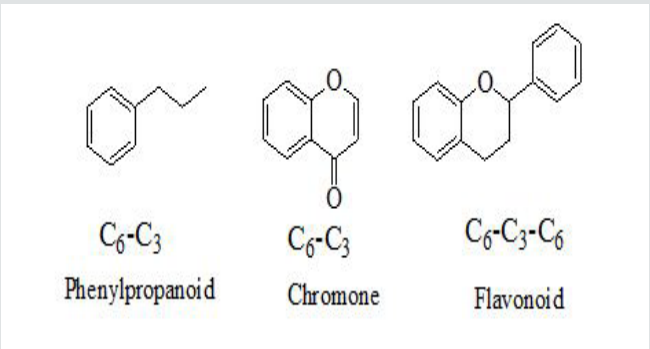

Figure 3: Parent structures of flavonoids.

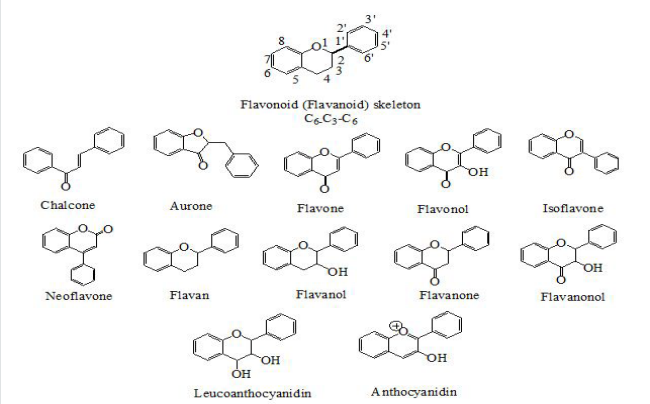

Figure 4: Structural skeletons/backbone structures of flavonoids.

role in human health and nutrition. The dietary sources of various types of flavonoids are enumerated in Table 2. Their nutritional and medicinal benefits are mainly attributed due tothe free radical scavenging activity (redox property), which mitigates oxidative stress-induced tissue damage associated with some chronic non-communicative disordersand certain infectious diseases.[20,22]

Foods rich in flavonoids (polyphenols) include fruits, grains, legumes, vegetables and beverages such as fruit juice, tea, coffee, red wine, beer, dark chocolates and other cocoa-rich products. The skins of the fruits(apple skin, orange peel) or the outer edge of the vegetables (tomato skin) and leaves of certain vegetables (alfalfa, broccoli) relatively contain more amount of phenolics than the edible portions because of their accumulation in the outer surface of plant tissues for their functional roles in producing organisms. Flavonoids found in the highest amounts in human diet are flavonols, flavones and soy iso-flavones. Flavonols are the most abundant flavonoids in human foods. The major flavonol of our diet is quercetin that is present either as free state or in the form of its 3-*O*-glycoside, calledrutin. Flavanols like catechins (monomeric forms) are also commonly encountered in high amount in functional food plants like tea, coffee etc. Flavonoids are most commonly found in plants either as free polyhydroxylated compounds (polyphenols) or in the form of their derivatives like methyl ethers and acetyl esters (Figure 5). It is clearnow that a wide structural diversity and a little molecular complexity in terms of the fundamental carbon skeletons with functionalized structural substitutions exist in flavonoid group of compounds, which therefore remains to bea rich source of flavonoid structural scaffolds or active compounds that are having potential role in several human ailments. It is believed that such structural scaffolds are the fundamental pharmacophoric features (nucleus/skeletal component) of these bioactive flavonoids, which is considered as an essential requirement for their pharmacological actions and/or medicinal benefits.

Clinical evidences also support the chemopreventive roles of polyphenolic flavonoids on cardiovascular diseases such as coronary heart disease, stroke, atherosclerosis and hypertension; inflammatory disorders like osteoprosis, osteoarthritis; aging and neurologic disorders such as Alzheimer's disease (AD), Parkinson's disease (PD), multiple sclerosis (MS); cancer (skin, lung and breast); diabetic complications, and bacterial infections. The pharmaco dynamic property of their disease preventing actions is mainly attributed due to the strong antioxidant effect in moderate to severe cellular oxidative stress (OS). Literature suggest

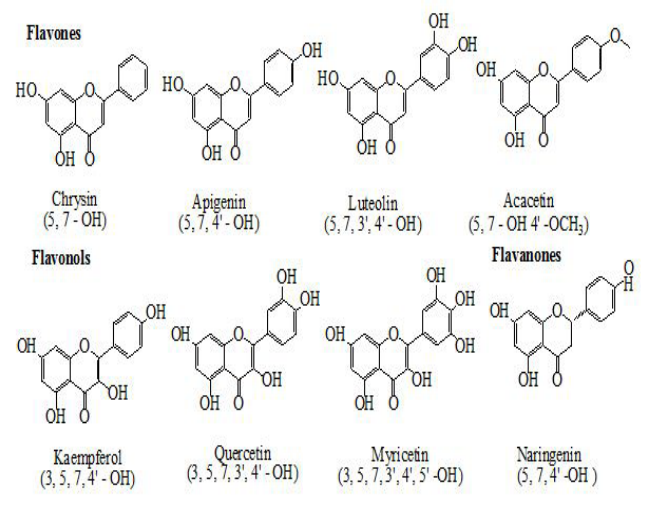

Figure 5: Illustrative structures of flavonoid polyphenols and their methylated derivatives.

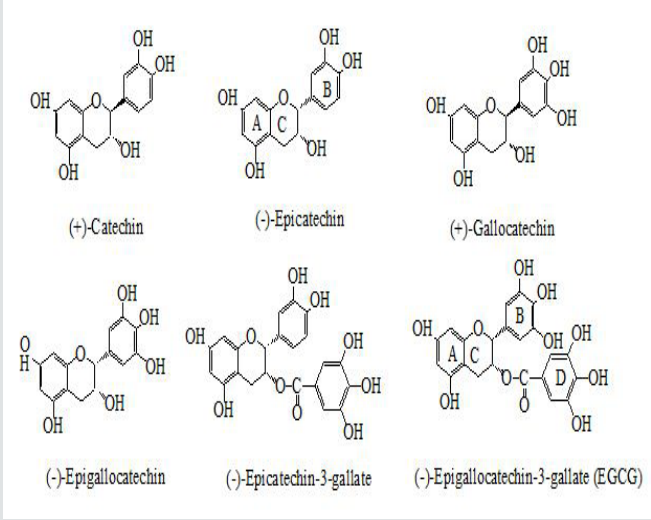

Figure 7: Polyphenolic flavonols and their gallate esters.

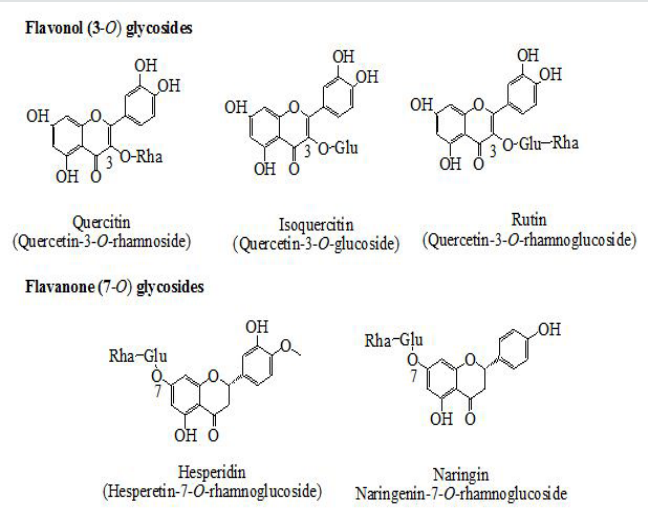

Figure 6: Structures of some flavonoid glycosides..

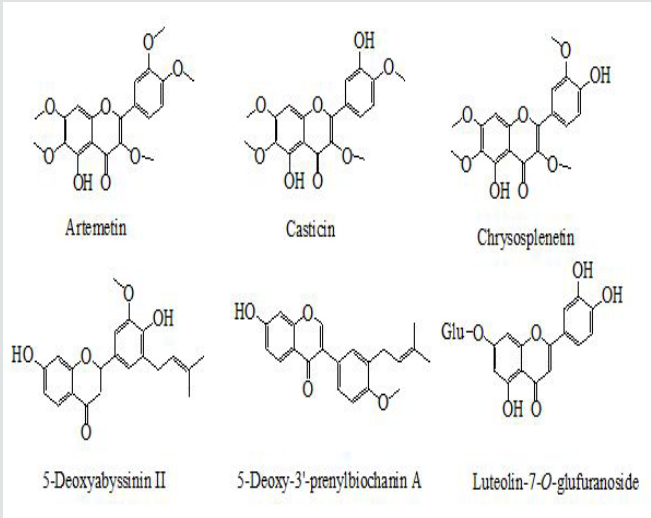

Figure 8: Structures of some antimalarial flavonoids.

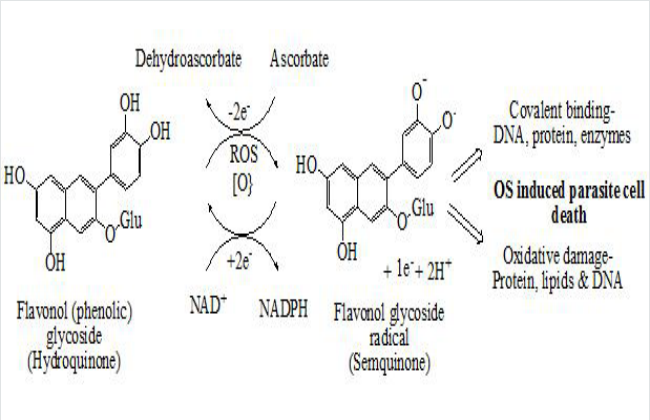

Figure 9: Radical scavenging action of flavonoids.

Table 1: Some medicinal plants rich in flavonoids[17, 20]

Plant (Family)	Representative flavonoid(s)
Aloe vera (Asphodelaceae)	Luteolin
Acalypha indica (Euphorbiaceae)	Kaempferol
Azadirachta indica (Meliaceae)	Quercetin
Betulapendula (Betulaceae)	Quercetin
Butea monospermea (Fabaceae)	Genistein
Cannabis sativa (Compositae)	Quercetin
Citrus medica (Rutaceae)	Hesperetin
Glycyrrhiza glabra (Leguminosae)	Liquitrin
Mentha longifolia (Lamiaceae)	Luteolin
Mimosa pudica (Mimosoideae)	Isoquercetin (a glycoside)
Oroxylum indicum (Bignoniaceaea)	Chrysin

that the redox active pharmacophoric moiety such as phenolic hydroxy groups (particularly of B ring) is responsible for such antioxidant action which fight against harmful reactive oxygen species (ROS) in OS conditions at biological targets (proteins, enzymes, nucleic acids etc.) by the virtue of their free radical trapping mechanism. However, the high degree of functional specificity for biomolecular targets which is an intrinsic molecular property of the pharmacophoric structural scaffold is required for the overall biological effectiveness of drug substances.[17, 20-24]

Flavonoids also occurabundantly in plants as glycosides in which one or more phenolic hydroxyl groups are combined with sugar residues. The basic flavonoid structure of glycosides is known as aglycone. They are water soluble and thermostable compounds possessing acidic property of aromatic phenols. In plants, glycosides of flavonoid aglycones are formed with sugars (glycone moiety) such as L-rhamnose (rhamnoside), D-glucose (glucoside), glucorhamnose/rutinose (rhamnoglucoside/rutinoside), sometimes with galactose and arabinose by a condensation reaction with the elimination of water molecules. The resulting condensed products having C-O-C glycosidic linkage is called acetals (glycosides). Depending on the location of glycosidic linkage, flavonoid glycosides are normally grouped into 3-O-glycosides of flavonolaglycones(e.g., quercitin, quercetin-3-O-α-L-rhamnopyranoside; isoquercitin/isoquercetin, quercetin-3-O-β-D-glucopyranoside; rutin, quercetin-3-O-(α-L-rhamnopyranosyll-(1-->6)-β-D-glucopyranoside)/rutinoside) and flavanoneaglycone based 7-O-glycosides (e.g., hesperidin, hesperetin--O-α-L-rhamnopyranosyl-(1-->6)-β-D-glucopyranoside; naringin, naringenin-7-O-α-L-rhamnopyranosyl-(1-->6)-β-D-glucopyranoside). The structures of some flavonoid glycosides are given in the Figure 6.[19,21,25]

Flavanols such as (+)-catechin (C), (-)-epicatechin (EC) , (+)-gallogatechin (GC) and (-) epigallocatechin (EGC) are found largely in green tea leaves in the form of their tannic acid esters (as gallates) like (+)-catechin-3-gallate (CG), (+)-gallocatechin-3-gallate (GCG), (-)-epicatechin-3-gallate (ECG), (-)-epigallocatechin-3-gallate (EGCG) (Figure 7). These are all collectively known as tea polyphenols or polyphenolic antioxidants. Black tea contain theaflavin (a complex dimer of polyphenol) as theaflavin-3-gallate, theaflavin-3'-gallate, theaflavin-3,3'-digallate.[20,24]

Flavonoids as antimalarial drug molecules

Plant flavonoids having antimalarial potential could be identified by investigating the plant species (extracts) found in traditional herbal remedies used in the treatment malariafollowed by a bioactivity-guided isolation of active compounds. Random screening of dietary components (phytochemicals as biomarkers) provides an alternative means of investigating antimalarial compounds abundantly presentin our foods or food products. Several bioflavonoids from dietary sources as well as from medicinal plants have been found to possess *in vitro* and *in vivo* antiplasmodial effectiveness in both sensitive- and resistant- strains of *P. falciparum*. Table 3 depicts some antimalarial flavonoids along with their plant sources. Dietary flavonoids having antimalarial activity are acacetin, baicaclein, chrysin, genistein, hesperetin, isoquercetin, kaempferol, luteolin, myricetin, naringenin and quercetin, just to name some of the important compounds. The structures of some potent antimalarial flavonoids apart from conventional flavonoids are represented in Figure 8. The *in vitro* antiplasmodial activities of these compounds are well reported in literature. Though the molecularmechanism of antimalarial action of flavonoids is not fully elucidated, it is believed that flavonoids act by inhibiting the fatty acid biosynthesis in the parasite biochemistry. They also act probably by inhibiting the influx of L-glutamine and myoinositol into infected erythrocytes during intraerytrhocytic phase of *Plasmodium* life cycle.[26-28]

Unlike quinoline-based antimalarials which are basic in nature, flavonoids possess acidic character (due to the phenolic –OH groups) which impedes their entry into the acidic food vacuole (FV) of parasites, and hence they do not directly interfere with the action of enzymes involved in the haemoglobin degradation process, the site of action of all major group of antimalarial drugs.[17, 26-28] They might act at the same site within the parasite but with a different mechanism of action. It is attributed that flavonoids exert their antimalarial action by targeting certain functional biomolecules (protein, enzymes, DNA etc.) that are essential for parasite survival. The phenolic –OH groups of such polyphenolicflavonoids(hydroquinones) is readily converted to a stable phenoxy radical anion (semiquinones) under cellular oxidative stress (*in vivo*) which in turn exerts either oxidative damage to cellular components of parasites or direct tissue damage by irreversible covalent interaction with parasitic structural proteins or DNA. In such circumstances, the antioxidant property of flavonoids could be the basis of their antimalarial action (Figure 9).[29,30]

CONCLUSION

Plant flavonoids comprise a hugenumber of bioactive substances with wide structural diversity that plays a vital role in human ailments. They are the valuable natural resources abundantly found in functional food plants. They serve as a good and reliable source of pharmacologically active compounds having potential in diverse therapeutic areas. Further scientific investigation is required on this important class of bioactive substances for more exploration of their potential lin health implications. The antimalarial potential of flavonoids derived from certain dietary plants has been investigated, but information about their effectiveness against malaria parasites and biological target specificity is not up to the mark. So, the pharmacodynamics offlavonoids as antimalarial

Table 2: Subclasses of plant flavonoids and their common dietary sources[17-22]

Flavonoids/ Flavanoids subclass	Structural backbone	Representative flavonoid(s)/ flavanoid(s)	Dietary sources
Flavones	2-Phenylchromen-4-one (or 2-phenylchromone)	Acacetin, apigenin,baicaclein, chrysin, luteolin, tangeritin	Buckwheat, celery, parsley, red pepper, red wine, tomato
Flavonols	3-Hydroxy-2-phenylchrmone (or 3-Hydroxyflavone)	Kaempherol, myricetin, quercetin, tamarixetin	Apples, berries, broccoli, buck wheat, cherries, fennel, grapes, kale, olive oil, onions, red wine, tea, tomato
Isoflavones	3-Phenylchromone	Daidzein, genistein, formononetin	Alfalfa, chickpea, legumes, soyabeans
Neoflavones	4-phenylcoumarin	Dalbergin	Not found in food plants
Flavanones	2,3-Dihydro-2-phenylchrmone (or 2,3-Dihydroflavone)	Eriodictyol, hesperetin, naringenin	Citrus fruits (lemons, oranges), grapefruits, prunes
Flavanols	Flavan-3-ol (2-Phenyl-3,4-dihydro-2*H*-chromen-3-ol)	Catechins, theaflavin	Apples, tea
Leucoanthocyanidins	Flavan-3,4-diol	Leucopelargonidin	-
Flavanonols	3-Hydroxy-2,3-dihydro-2-phenylchromen-4-one (or 3-Hydroxyflavanone (or 2,3-Dihydroflavonol)	Dihydrokaempferol, Taxifolin (2,3-dihydroquercetin)	Aurantium, limon
Anthocyanidins	Flavylium(2-phenyl chromenylium) ion	Apigenidin, cyanidin	Cherry, grapes, strawberries

Table 3: Plant derived antimalarial flavonoids[26-28]

Medicinal plant species (Family)	Flavonoids and/or their glycosides	Flavonoid class
Andirainermis(Fabaceae)	Calycosin, genistein	Isoflavones
Artemisia afra (Asteraceae)	Acacetin	Flavones
Artemisia annua (Asteraceae)	Artemetin, casticin, chrysosplenetin, cirsilneoleupatorin and quercetin-3,3'-dimethylether rhamnoglucoside	Flavones (available as methyl ether derivatives)
Artemisia indica (Asteraceae)	*(-)-cis*-3-Acetoxy-4,5,7-trihydroxyflavanone	Flavanones
*Calycolpuswarszewiczianus (*Myrtaceae)	5-Galloylquercetin-3-*O*-arabinofuranoside	Flavonols
Camellia sinensis (Theaceae)	*(-)*-Epigallocatechin-3-gallate (EGCG) and other catechins	Flavanols (as esters of gallic acids)
Erythrinaabyssinica (Leguminosae)	5-Deoxyabyssinin II	Flavones
Erythrinasacleuxii (Leguminosae)	5-Deoxy-3'-prenylbiochanin A	Isoflavones
Garcinialivingstonei (Clusiaceae)	Methyl ether derivative of bis-naringenin	Flavanones
Phlomisbrun neogaleata (Lamiaceae)	Luteolin-7-*O*-glucofuranoside	Flavones
Polygonum senegalense (Polygonaceae)	9-Hydroxyhomoisoflavonoid, 2,3-dihydro-5-hydroxy-7-methoxy-2-phenylchromen-4-one	Flavanones

compounds is not clear. It is quite interesting to mention here that flavonoids have specificityfor biological targets other than the conventional antimalarial drug targets. This could be a basis of establishing plant flavonoids as future antimalarial leads for the development of new antimalarial drug molecules. Flavonoid-based antimalarial drugs are expected to have high therapeutic efficacy against resistant malaria with minimal toxicities.

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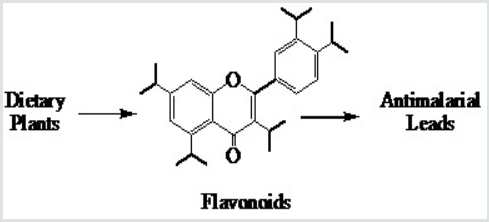
GRAPHICAL ABSTRACT



SUMMARY

Medicinal and functional food (dietary) plants are rich in biologically active polyphenolic compounds, known as flavonoids. They represent a huge number of structurally diverse compounds with a wide range of pharmacological activities. Certain dietary plants rich in flavonoids have proven antimalarial properties. Plant fla¬vonoids, therefore, may serve as potential sources of antimalarial lead molecules in the development of new and potent antimalarial drugs.

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