STRUCTURALLY DIVERSE BIOFLAVONOIDS AS POTENTIAL SOURCE OF ANTIMALARIAL LEAD MOLECULES

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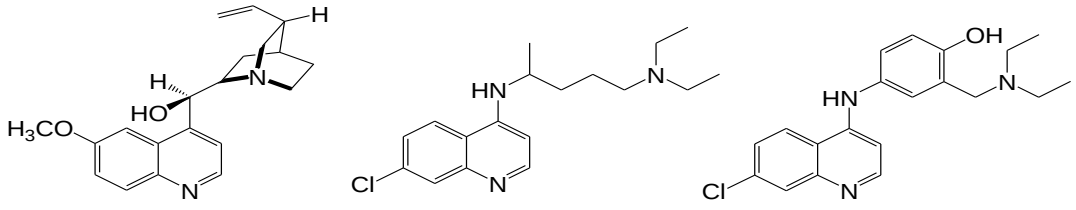
Abstract: In this article, a review on bioactive flavonoids that are abundant in medicinal and functional food (dietary) plants has been made, with special reference to antimalarial flavonoid molecules. Flavonoids have been found to exist in plants/plant medicines with a wide structural diversity consisting of numerous polyphenolic compounds and having well defined molecular target specificity. These phytoconstituents may serve as important natural lead molecules for their development as potent antimalarial therapeutic agents.

Keywords: Malaria, drug resistance, bioflavonoids, pharmacophoric scaffolds, antimalarial drugs

1. INTRODUCTION

Malaria is a serious infectious disease that affects people of all ages, particularly in tropical and subtropical regions of the world. According to the World Health Organization (WHO), approximately 40% of the world population live in malaria endemic areas, with 300-500 million clinical cases and 1.5-2.7 million deaths per year globally. 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. Of the 2.5 million reported cases in the South East Asia, India alone contributes about 70% of the total cases. Human malaria is caused by five species of *Plasmodium*, namely, *P. falciparum*, *P. vivax*, *P. Ovale*, *P. malariae* and *P. knowlesi*. *Plasmodium falciparum* is the most widespread and extremely dangerous species, which causes potentially fatal malaria such as cerebral malaria, and most of the malaria-related deaths worldwide. Moreover, *P. falciparum* strains produce rapid as well as varying degree of resistance against currently available antimalarial drugs, which has become a major clinical issue in the malaria chemotherapy [1-6].

Plant-based medicines have been playing an important role in the treatment of malaria since ancient times. Malaria treatment in the modern therapeutic form started with the discovery of quinine (QN) from cinchona bark. The quinoline-based synthetic antimalarial drugs (Figure I) such as chloroquine (CQ) were successfully used in the treatment of malaria for a long time [2, 3, 7]. However, with the pace of time their clinical uses have become limited because of the development of resistant strains of malarial parasites, especially of *P. falciparum*.



Quinine (QN) Chloroquine (CQ) Amodiaquine (AQ)

Fig. I: Quinoline-based antimalarial drugs

Artemisinin (ART), isolated from the plant, *Artemisia annua* was later introduced, and its several semi-synthetic derivatives (Figure II) were then successfully incorporated as potent drugs in the treatment of malaria in resistant cases [7, 8].

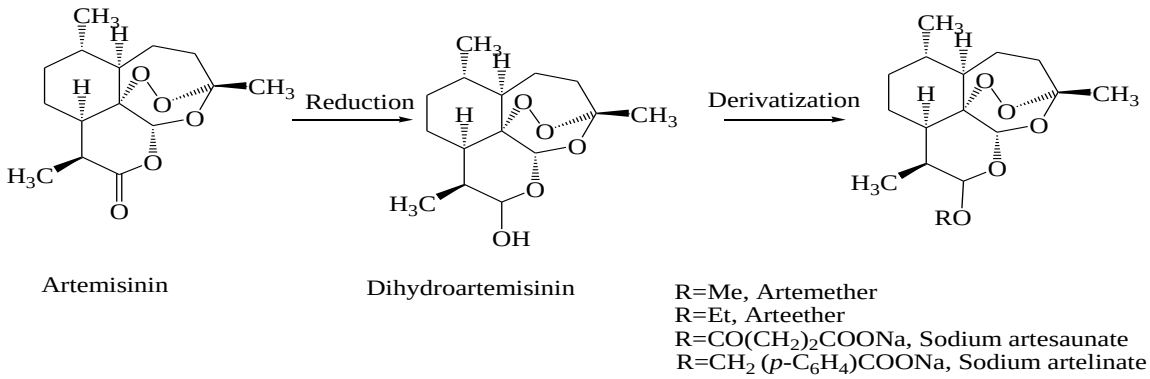


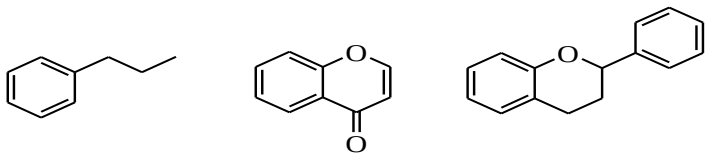
Fig. II: Artemisinin (ART) and its semi-synthetic derivatives

Currently, artemisinin-based combination therapies (ACTs) are recommended by the WHO for the treatment of multidrug-resistant *P. falciparum* malaria. Some examples of ACTs are artemether plus lumefantrine, artesunate plus mefloquine (MQ), and artesunate plus pyronaridine. But, the ACTs are costlier relative to CQ and QN, and also, resistance to ART and MQ-ART against *P. falciparum* has begun to emerge in Southeast Asia. Therefore, the treatment of malaria has increasingly become a challenging task because of the emergence of the resistant strains of malaria parasites, which has created an urgent need to develop new and therapeutically efficacious antimalarial agents [8-10].

However, in order to resolve the above challenging issue, the discovery of newer antimalarial drugs from plants and/or plant-based traditional medicines is considered to be the most reliable alternative approach as nature always serves as the richest source of chemicals with a wide range of structural- and bio- diversity. These chemical compounds are basically secondary metabolites of plant origin belonging to several important phytochemical classes such as terpenoids, alkaloids, flavonoids, coumarins, xanthones, limonoids, steroids etc. and they possess a diverse range of activity profile in terms of health implications. Among all these, flavonoids have recently gained significant interest among medicinal chemists because of their promising chemopreventive /chemoprotective potentials in inflammatory disorders, cardiovascular diseases, diabetes, neurodegenerative disorders, cancer, bacterial infections and malaria [11, 12]. In tune with the above facts, researchers have investigated many plant species for their antimalarial activities and have reported the bioactive principles including flavonoids responsible for antimalarial effectiveness. A number of polyphenolic flavonoids that are abundant in dietary and medicinal plants have been identified to have good antimalarial effectiveness both *in-vitro* and *in-vivo* [13]. In this review, plant derived flavonoids which have been identified to possess antimalarial potential, their chemistry and structural diversity, and basis of their bioactivity are described. Flavonoid compounds with their pharmacophoric structural scaffolds may therefore be potential lead molecules for the development of flavonoid-based antimalarial drugs against the resistant strains of the malaria parasites.

2. BIOFLAVONOIDS

Flavonoids comprise of a large groups of aromatic organic compounds of around 10,000 structures that are ubiquitously distributed in the plant kingdom. In fact, these compounds are secondary plant metabolites biosynthesized in plants as metabolic hybrids through a combination of the shikimate-derived phenylpropanoid (-->C_6-C_3) pathway and the acetate/mevalonate polyketide (-->C_6) pathway. They therefore possess a carbon skeleton of phenylpropanoid (C_6-C_3 unit), and hence 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 (phenylbenzopyrone) skeleton in which the parent C_6-C_3 unit is present as chromone (benzo-γ-pyrone) nucleus (Figure III). 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 [14-16].



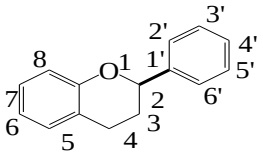
C_6-C_3 Phenylpropanoid | C_6-C_3 Chromone | C_6-C_3-C_6 Flavonoid

Fig. III: Parent structures of flavonoids

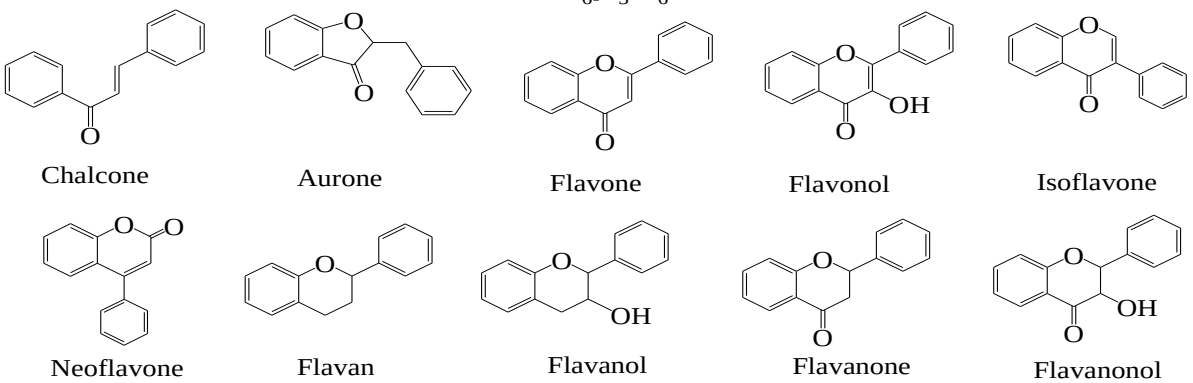
2.1 Chemistry

The chemical structure of flavonoids are based on the flavonoid (C_6-C_3-C_6) molecular framework which is a fifteen-carbon skeleton 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., isoflavone) 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 to 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 IV [14-18].

According to the oxidation state of the central pyran ring, they can be broadly classified into: (i) Flavonoids: These are ketone compounds that include anthoxanthins (flavones and flavonols), isoflavones and neoflavones. The skeletal structures of this class of compounds are based upon flavone backbone. (ii) Flavanoids: These are mostly non ketone compounds (except flavanols) 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 [16, 17].



Flavonoid (Flavanoid) skeleton
C_6-C_3-C_6



Chalcone | Aurone | Flavone | Flavonol | Isoflavone

Neoflavone | Flavan | Flavanol | Flavanone | Flavanonol

Leucoanthocyanidin | Anthocyanidin

Fig. IV: Structural skeletons/backbone structures of flavonoids

In a much broader sense, the term bioflavonoids refers to all compounds of natural origin that collectively includes both flavonoids and flavanoids.

2.2 Bio- and Structural- diversity

Flavonoids are widely distributed in plants and occur virtually in all plant parts to 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, like 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 properties to human health. Owing to their desirable biophysicochemical 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 I), and certain herbal remedies. For instance, the traditional use of liquorice extract (rich in flavonoid content) in the treatment of peptic ulcer disease is well documented [13, 15, 17, 18].

Table I: Some medicinal plants rich in flavonoids

Plant (Family)	**Representative flavanoid(s)**
Aloe vera (Asphodelaceae)	Luteolin
Acalypha indica (Euphorbiaceae)	Kaempferol
Azadirachta indica (Meliaceae)	Quercetin
Betula pendula (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

Flavonoids rich in human diet constitute a common group of polyphenolic compounds (also known as poplyhydroxyphenols), which are usually considered as non-nutritive bioactive components that play a significant role in human health and nutrition. The dietary sources of various types of flavonoids are enumerated in Table II. Their nutritional and medicinal benefits are mainly attributed to be due to their free radical scavenging activity (redox property), which in turn mitigates oxidative stress-induced tissue damage associated with some chronic non communicative disorders and certain infectious diseases [15, 17].

Table II: Subclasses of bioflavonoids and their common dietary sources

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), grape fruits, 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

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 isoflavones. Flavonols are the most abundant flavonoids in human foods. The major flavonol of our diet is quercetin that is present either in free state or in the form of its 3-*O*-glycoside, rutin. 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 V). A wide structural diversity and a little molecular complexity in terms of the fundamental carbon skeletons and various structural substitutions (highly functionalized) exist in flavonoid group of compounds, which are the rich source of huge number of active compounds or flavonoid structural scaffolds which have potential role in several human ailments. It is believed that such structural scaffolds are the fundamental pharmacophoric features (nucleus/skeletal component) of those bioactive flavonoids and hence required to be essential for their desired pharmacological actions/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 osteoporosis, osteoarthritis; aging and neurologic disorders such as Alzheimer's disease (AD), Parkinson's disease (PD), multiple sclerosis (MS); cancer (of the skin, lung and breast); diabetes, and bacterial infections. The pharmacodynamic property of their disease preventing actions is mainly due to their strong antioxidant activities in moderate to severe oxidative stress induced pathologic conditions, which in turn is brought about by virtue of their free radical scavenging actions. The redox active pharmacophoric moiety such as phenolic hydroxy groups (particularly of B-ring) is attributed to be responsible in bringing out their antioxidant actions by sequencing the harmful reactive oxygen species (ROS) by a free radical trapping mechanism at the target site. The high degree of functional specificity for biomolecular targets is of paramount importance besides their intrinsic structural

properties (of pharmacophoric scaffolds) for their overall biological effectiveness [13, 15-19].

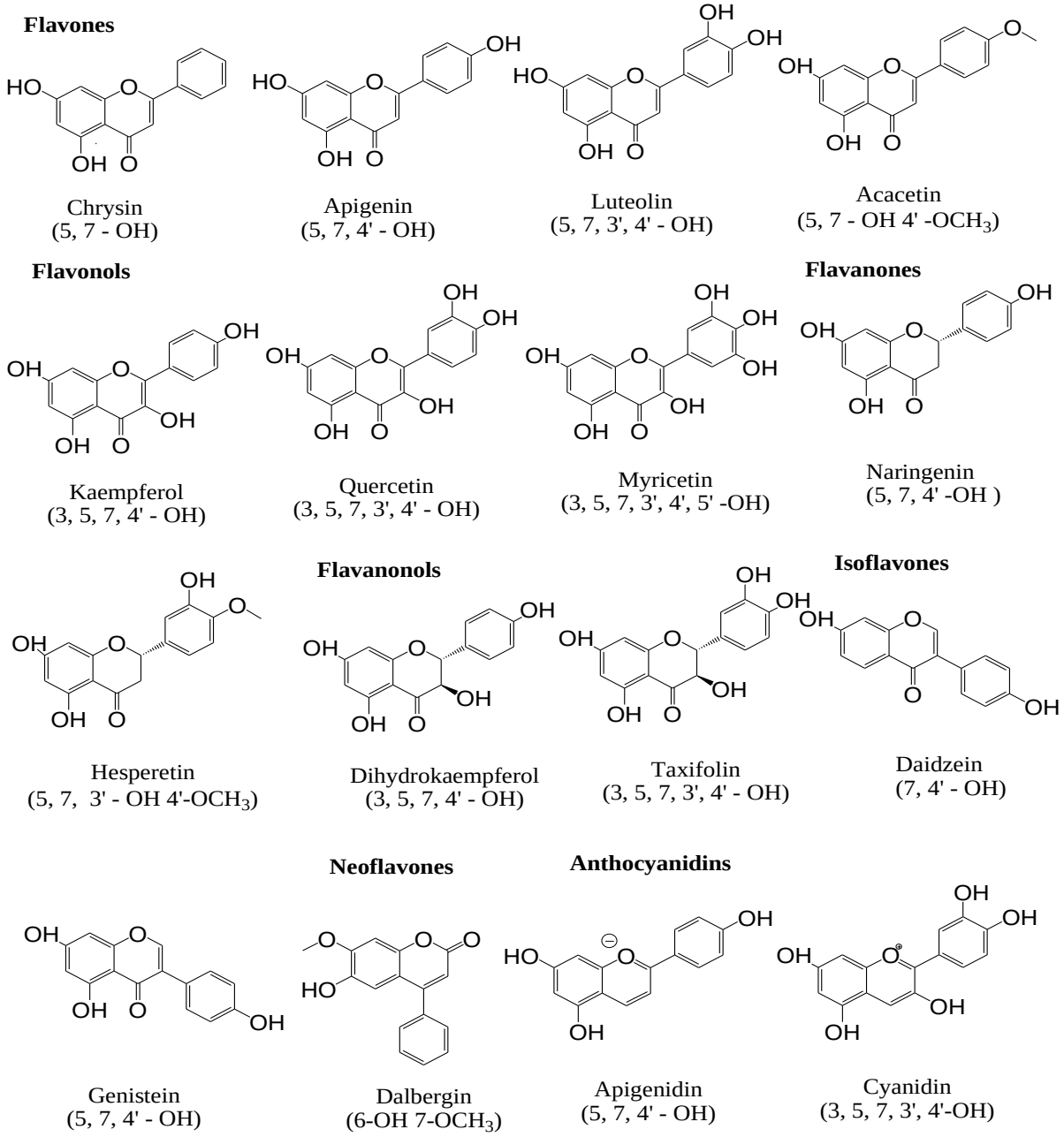
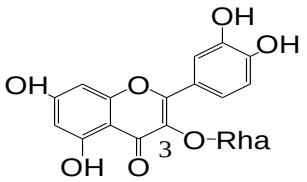


Fig. V: Illustrative structure of flavonoid polyphenols including their methylated derivatives

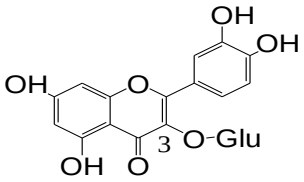
Flavonoids also occur abundantly in plants as glycosides in which one or more phenolic hydroxyl groups are combined with sugar residues. The basic flavonoid structure of glycosides is known as aglycone. They are water soluble and thermostable compounds possessing acidic property of aromatic phenols. 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 flavonol aglycones (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 flavanone

aglycone based 7-*O*-glycosides (e.g., hesperidin, hesperetin-7-*O*-*α*-L-rhamnopyranosyl-(1-->6)-*β*-D-glucopyranoside; naringin, naringenin-7-*O*-*α*-L-rhamnopyranosyl-(1-->6)-*β*-D-glucopyranoside). The structure of some flavonoid glycosides are given in the figure VI [14, 16].

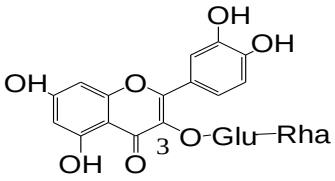
Flavonol (3-*O*) glycosides



Quercitin
(Quercetin-3-*O*-rhamnoside)

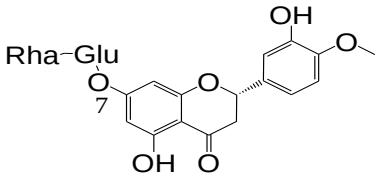


Isoquercitin
(Quercetin-3-*O*-glucoside)

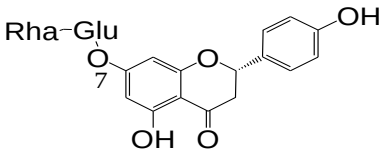


Rutin
(Quercetin-3-*O*-rhamnoglucoside)

Flavanone (7-*O*) glycosides



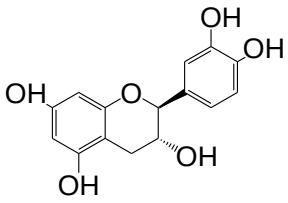
Hesperidin
(Hesperetin-7-*O*-rhamnoglucoside)



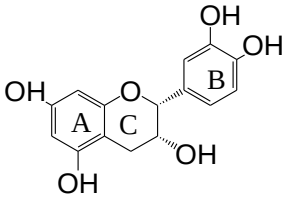
Naringin
Naringenin-7-*O*-rhamnoglucoside

Fig. VI: Structure of some flavonoid glycosides

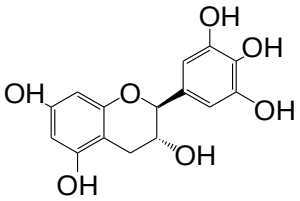
Flavanols such as (+)-catechin (C), (-)-epicatechin (EC) , (+)-gallogatechin (GC) and (-) epigallocatechin (EGC) are found largely in green tea leaves in the form of their tannic acid esters (as gallates) like (+)-catechin-3-gallate (CG), (+)-gallocatechin-3-gallate (GCG), (-)-epicatechin-3-gallate (ECG), (-)-epigallocatechin-3-gallate (EGCG) (Figure VII). 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 [15, 19].



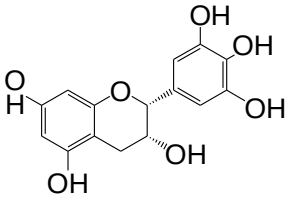
(+)-Catechin



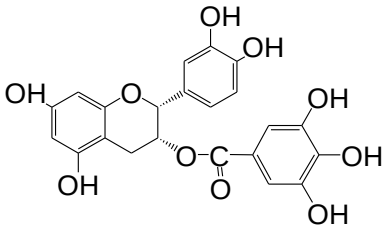
(-)-Epicatechin



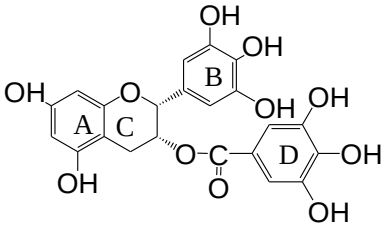
(+)-Gallocatechin



(-)-Epigallocatechin



(-)-Epicatechin-3-gallate



(-)-Epigallocatechin-3-gallate (EGCG)

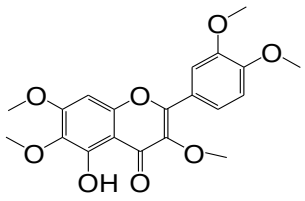
Fig. VII: Polyphenolic flavanols and their gallate esters

2.3 Flavonoids as antimalarial drug molecules

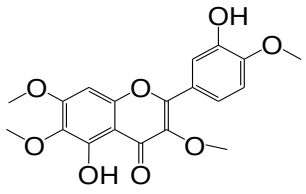
Plant flavonoids having antimalarial potential could be identified by investigating the plant species (extracts) or herbal medicines found in the traditional treatment of malaria, which is followed by a bioactivity-guided isolation of active compounds. Random screening of dietary components (phytochemicals as biomarkers) provides an alternative means of investigating antimalarial compounds widespread in 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 III depicts some antimalarial flavonoids (Figure VI) along with their sources (particularly medicinal plants). 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 *in vitro* antiplasmodial activities of these compounds are well reported in literature. Though the molecular mechanism 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 cyle. Unlike basic quinoline-based antimalarials, flavonoids possess acidic character (due to phenolic –OH groups) which impedes their entry into the acidic food vacuole of parasites and hence flavonoid based compounds does not interfere with the haemoglobin degradation process, the only site of actions for most of the existing drugs against which malaria parasites have developed resistance [13, 20-22].

Table III: Plant derived antimalarial flavonoids

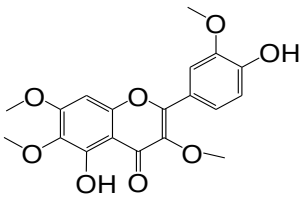
Medicinal plant species (Family)	**Flavonoids and/or their glycosides**	**Flavonoid class**
Andira inermis (Fabaceae)	Calycosin, genistein	Isoflavones
Artemisia afra (Asteraceae)	Acacetin	Flavones
Artemisia annua (Asteraceae)	Artemetin, casticin, chrysosplenetin, cirsilneol eupatorin and quercetin-3,3'-dimethylether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



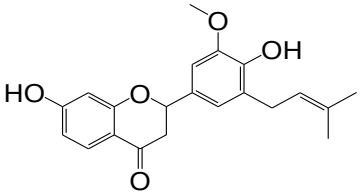
Artemetin



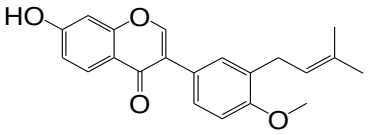
Casticin



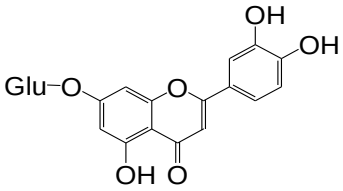
Chrysosplenetin



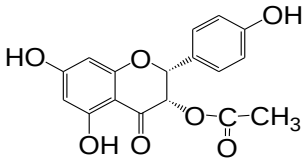
5-Deoxyabyssinin II



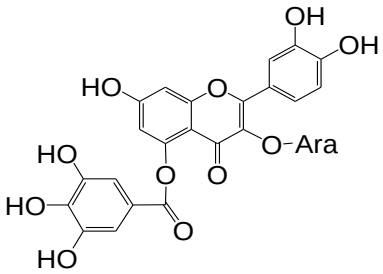
5-Deoxy-3'-prenylbiochanin A



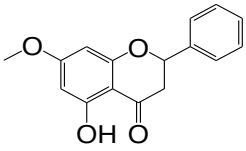
Luteolin-7-*O*-glufuranoside



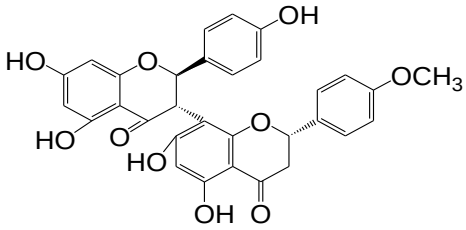
(-)-cis-3-Acetoxy-4,5,7-trihydroxy flavanone



5-Galloylquercetin-3-*O*-arabinofuranoside



2,3-Dihydro-5-hydroxy-7-methoxy-2-phenylchromen-4-one



Methyl ether derivative of bis-naringenin

Fig. VIII: Structure of some antimalarial flavonoids

3. CONCLUSION

Plant flavonoids comprise of a vast class of biologically active molecules that play a vital role in human ailments. Such structurally diverse bioactive compounds are the valuable natural resources of medicinal agents and may therefore provide useful lead molecules in the development of novel class of therapeutics. But, it needs scientific attention in order to explore these bioactive substances for their wide applicability in health implications. Though the antimalarial potential of some medicinal and dietary plants containing flavonoids is reported, but information regarding flavonoid molecules that are responsible for antimalarial activity is not adequate or poorly explored. The molecular basis of their antimalarial action is also unclear. Further study is required to give a complete insight into flavonoid molecules and their antimalarial action. It is quite interesting to note that flavonoids act on specific biological targets which are different from that of the common antimalarial drug targets. This would probably be the basis of further scientific investigation towards finding new flavonoid-based antimalarial drugs by rational design of flavonoid libraries (based on natural leads) through virtual screening techniques. In this aspect, the optimization of their molecular

as well as biopharmaceutical properties is highly desired in the transformation of such lead molecules into more effective flavonoid-based synthetic drugs or their semi-synthetic flavonoid congeners as a novel class of antimalarial agents. The specificity for molecular targets and host toxicity issues are however some integral properties that a flavonoid drug molecule must possess for its optimal therapeutic outcome.

4. REFERENCES

[1] K. I. Barnes, *Antimalarial Drugs and the Control and Elimination of Malaria*, in *Treatment and Prevention of Malaria-Antimalarial Drug Chemistry, Action and Use*. (Ed. H. M. Staines, S. Krishna), Springer Basel AG, Basel 2012, pp. 1-13.

[2] M. A. Biamonte, J. Wanner, K. G. L. Roach, *Recent advances in malaria drug discovery*. Bioorg Med Chem Lett. 2013; 23, 2829–2843.

[3] R. J. Ridley, *Medical need, scientific opportunity and the drive for antimalarial drugs*. Nature. 2002; 415, 686−693.

[4] World Malaria Report 2013. http://www.who.int/malaria/publications/world_malaria_report_2013/en//index.html

[5] (accessed on 28 June 2013).

[6] A. P. Dash, N. Valecha, A. R. Anvikar *et al.*, *Malaria in India: Challenges and opportunities*. J Biosci. 2008; 33(4), 583–592.

[7] U. Farooq and R. C. Mahajan, *Drug Resistance in Malaria*. J Vect Borne Dis. 2004; 41, 45.

[8] P. G. Bray, S. A. Ward, P. M. O'Neil, *Quinolines and Artemisinin: Chemistry, Biology and History*. Curr Top Microbiol Immunol. 2005; 295, 3-38.

[9] X. D. Luo and C. C. Shen, *The Chemistry, Pharmacology, and Clinical Applications of Qinghaosu (Artemisinin) and its Derivatives*. Med Res Rev. 1987; 7, 29-52.

[10] P. Garner and P. M. Graves, *The benefits of artemisinin combination therapy for malaria extend beyond the individual patient*. PLoS Med. 2005; 2(4), e105.

[11] A. C. Aguiar, E. M. Rocha, N. B. Souza *et al.*, *New approaches in antimalarial drug discovery and development - A Review*. Mem Inst Oswaldo Cruz. 2012; 107(7), 831-845.

[12] G. Agati, E. Azzarello, S. Pollastri *et al.*, *Flavonoids as antioxidants in plants: Location and functional significance*. Plant Sci. 2012; 196, 67-76.

[13] K. Kaur, M. Jain, T. Kaur *et al.*, *Antimalarials from nature*. Bioorg Med Chem. 2009; 9(1), 3229-3256.

[14] A. M. Lehane and K. J. Saliba, *Common dietary flavonoids inhibit the growth of the intraerythrocytic malaria parasite*. BMC Res Notes. 2008. doi:10.1186/1756-0500-1-26.

[15] R. Ikan, *Natural Products - A Laboratory Guide*, Israel Universities Press, Jerusalem 1969, pp. 1-8.

[16] Crozier, I. B. Jaganath, M. N. Cliffordc, *Dietary phenolics: chemistry, bioavailability and effects on health.* Nat Prod Rep. 2009; 26, 1001–1043.

[17] S. Kumar and A. K. Pandey, *Chemistry and Biological Activities of Flavonoids: An Overview*. The World Scientific J. 2013. http://dx.doi.org/10.1155/2013/162750.

[18] A. J. A. Petrus, *Biophenols: The abundant Redox-Active Dietary Molecules of Life*. Asian J Chem. 2014; 26(16), 4929-4939.

[19] R. Tsao, *Chemistry and Biochemistry of Dietary Polyphenols*. Nutrients. 2010; 2, 1231-1246.

[20] N. T. Zaveri, *Green tea and its polyphenolic catechins*. Life Sci. 2006; 78, 2073-2083.

[21] S.S. Lim, H.S. Kim, D.U. Lee, *In vitro Antimalarial Activity of Flavonoids and Chalcones*. Bull Korean Chem Soc. 2007; 28(12), 2495.

[22] P. Rasoanaivo, C. W. Wright, M.L. Willcox *et al.*, *Whole plant extracts versus single compounds for the treatment of malaria: synergy and positive interactions*. Malaria J. 2011; 10 (Suppl 1), S4.

[23] F. Ntie-Kang, P. A. Onguéné3, L. L. Lifongo *et al.*, *The potential of anti-malarial compounds derived from African medicinal plants, part II: a pharmacological evaluation of non-alkaloids and non-terpenoids*. Malaria J. 2014; 13, 81.