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Flavonoids: Biosynthesis, Metabolism, Mechanism of Antioxidation and Clinical Implications: A Review

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ABSTRACT

Flavonoids are the molecules derived from a core molecule flavan which are synthesized in plants and microbes by a complex process catalyzed by enzymes located in endoplasmic reticulum. These exist in human body in association with glycosides which can be absorbed in small intestine and are metabolized further in liver. This review consolidates the Biosynthesis of flavonoids in plant systems, its metabolism in human body, the role of different rings and groups on the antioxidant potential of flavonoids, the chemical mechanisms of its actions and finally clinical implications of these molecules against Alzheimer's disease, Parkinson's disease, cardiovascular diseases, diabetes, Osteoarthritis and Rheumatoid Arthritis and cancers.

Key words: Alzheimer's disease, Antioxidant, Arthritis, Cardiovascular diseases, Diabetes, Flavonoids, Parkinson's disease.

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Flavonoids are small, plant derived, polyphenolic compounds based on the flavan core (Fig 1). Basic structure of flavan molecule is a C6-C3-C6 frame consisting of benzopyran group attached to a phenyl ring. The three rings in the molecule are regarded to as the A, B and C rings. Flavonoids are differentiated by the arrangement of functional groups (hydroxyl, methoxy and glycosidic side group) and in the relative position of the C and B rings which gives rise to a large number of compounds which are classified according to the groups present.

Based on the position of the attachment of the carbon atom of the C ring through which B ring is attached these phytochemicals are classified as Flavonoids (2 phenyl benzopyran), Isoflavonoids (3 benzopyran) and Neoflavonoids (4 benzopyran). Additionally, aromatic and aliphatic acids, sulphate, prenyl or methylenedioxyl groups also attach to flavonoid nucleus and their glycosides. Flavonoids are present in conjugation with sugar residues and polymers as 3-O-glycosides. Physiochemical and functional properties of the flavonoids and its derivatives are significantly affected by the relative position of different functional groups around the core nucleus.

The biochemical activities of the flavonoids in the cells in which they are produced in plants and in the cells of human beings are varied. In plants they play a central role in the protection against ultraviolet radiation, exhibit antimicrobial activity and are proven deterrent to the animals ingesting it by inhibiting digestive enzymes and preventing absorption of proteins. Many of the flavonoids act as colored pigments (anthocyanin) and attractants for pollination, as well as oviposition stimulants (e.g. naringenin and hesperetin-7-O-rutinoside) which help in attracting and stimulating insects to lay egg over them while some act as feeding attractant (e.g. isoquercitrin and morin) others are used by plants as feeding deterrents against harmful insects (e.g. genistein and luteone) (Iwashina 2003). Flavonoids are also found in flour as a functional compound (Verma *et al.* 2018). One of the exciting features of flavonoids is found in form of allelopathy which is described as 'biochemical interactions between all types of plants and include both deleterious and advantageous interactions'. Some of the flavanone, flavonol and dihydroflavonols have been reported by some authors, which act as allelopathic. Plants produce certain chemicals at the time of infection by microorganisms which ward off the disease causing organism from the plants called as "Phytolexin". Flavonoid compounds reported to act as phytolexin (Iwashina 2003). Although a lot of these compounds have been identified and characterized in plants but the biological roles they play are still not elucidated for all. Dietary flavonoids are found to display a wide range of effects on the biochemical pathways of human body. They are found to have antioxidant, antihypertensive, anticarcinogenic, anti-inflammatory effects and play therapeutic roles against pathological, metabolic, life style diseases like diabetes, ageing and dermatological problems.

The antioxidative and proven anticarcinogenic properties of dietary polyphenols have attracted interest of several researchers. The anticarcinogenic properties are hypothesized to be arising mainly due to its antioxidative properties. These polyphenolic compounds inhibit events of cancer development at various stages of initiation,

promotion and progression. It is also found that isoflavones and lignans affects the estrogen related activities that influences tumor formation (Yang *et al*. 2001).

Galati *et al.*(2004) suggested that the chemopreventive activity exhibited by these compounds *in vivo* experiments can be attributed to its property of checking the initialization of carcinogenesis by inhibiting phase I and phase II carcinogen metabolizing enzymes. The promotion of carcinogenesis may also be reduced by several mechanisms like inhibiting enzymes responsible for oxygen radical formation or DNA synthesis. These compounds may also induce tumor cell apoptosis by inhibition of DNA topoisomerase II and downregulation of p53 or mitochondrial toxicity (Galati and O'Brien 2004). Ross *et al.* (2002) have comprehended the roles of flavonoids and related compounds on cardiovascular disesases and found a positive effect of flavonoids on these diseases. Ren *et al.* 2003 also reported a positive effect of flavoniods on chemoprevention. They reported several mechanisms and their combination may be responsible for the observed chemopreventive activity (Ren *et al*. 2003).

Kanadaswami *et al.* (2005) reviewed the reports on *in vivo* activity of flavonoids and has found that inhibition of kinase activity and suppression of secretion of matrix metalloproteinases are the most common mechanisms of chemopreventive action (Kanadaswami *et al*. 2005). It shall be emphasized here that these are not the only mechanisms which may be responsible for anticancerous activity and new mechanisms may be elucidated with time.

So, to showcase the importance of flavonoids, this article comprehends the role of active groups and its mechanism of action that imparts important functions to a particular flavonoid. This article also includes the clinical implications of these active groups in alleviating several diseases.

Biosynthesis of flavonoids

Biosynthesis of flavonoids is a complex process as given in the schematic in Fig 2. Earlier work for elucidation of flavonoid biosynthetic pathway was done using the mutants having alteration in genes affecting flavonoid biosynthesis. Maize, Snapdragon, Petunia were first developed as model systems for the study and most recently Arabidopsis is being used because of the feature that all the enzymes except one of the central flavonoid metabolism are coded by single copy genes. These genes are scattered all over the genome of Arabidopsis. The alteration in pigment pattern in the seed coat is studied for the identification of these genes.

Biosynthetic metabolism of flavonoid molecules is catalyzed by an endoplasmic reticulum localized enzyme complex. This has been validated by experimental studies (Hrazdina and Wagner 1985, Burbulis and Winkel-Shirley 1999).

Metabolism

Flavonoids exist as O-glycosides in the human body with glucose being the most common residue joined by β-linkage. Glycosides are those molecules which are metabolized to their respective aglycones by bacterial activity in lower intestine but some of this may be metabolized in oral cavity as well (Walle 2004, Walle *et al*. 2003). It is generally accepted that flavonoid glycosides are absorbed in small intestine with the help of a sodium dependent glucose transporter, which are cleaved by a broad-specific β-glucosidase enzyme or by lactase phloridzin hydrolase (LPH). After absorption of the flavonoids they are transported to liver for further metabolism which includes conjugation by *O*-methylation, sulfation and glucuronidation. The flavonoids may also undergo oxidative metabolism as shown with the study using microsomes which is mediated by cytochrome P450 (CYP) enzymes. Metabolism of flavonoids is also known to be carried out by bacteria in the colon that

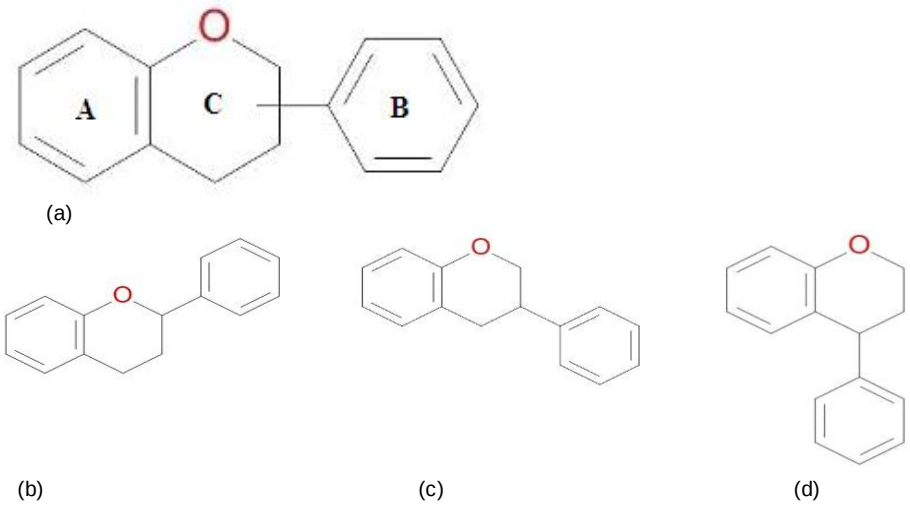

Fig 1: Structure of major flavonoid classes (a) Core structure (b) Flavonoids (c) Isoflavonoids (d) Neoflavonoids.

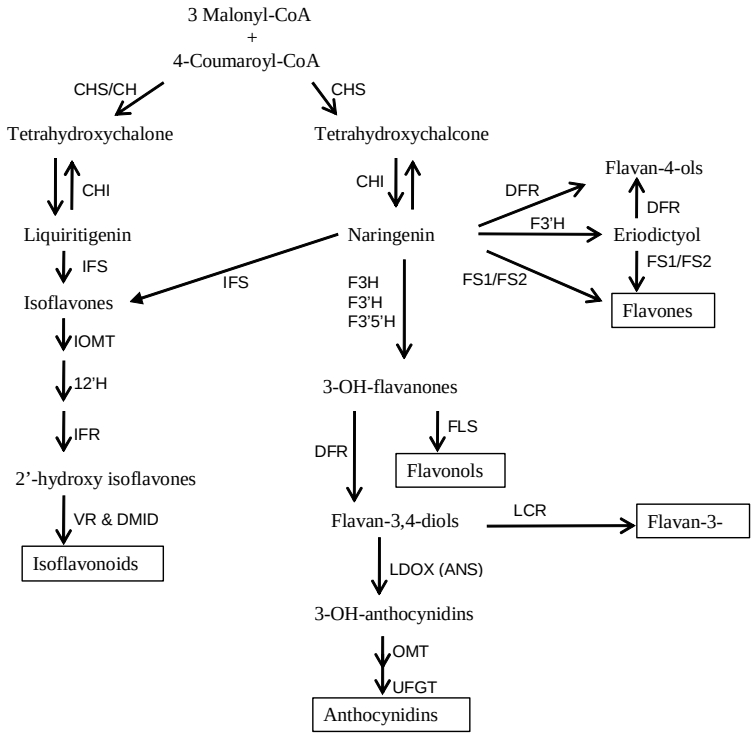

Fig 2: Biosynthetic pathway of flavonoids.

ANS: Anthocynidin synthase; AS, Aureusidin synthase; C4H, cinnamate-4-hydroxylase; CHR, chalcone reductase; DFR, dihydroflavonol 4-reductase; DMID, 7,2'-dihydroxy 4'-methoxyisoflavanol dehydratase; F3H, flavanone 3-hydroxylase; F3'H, flavonoid 3' hydroxylase; F3'5'H, flavonoid 3'5' hydroxylase; FS1/FS2, flavone synthase; I2'H, isoflavone 2'-hydroxylase; IFR, isoflavone reductase; IFS, isoflavone synthase; IOMT, isoflavone O-methyltransferase; LCR, leucoanthocynidin reductase; L DOX, leucoanthocyanidin dioxygenase; OMT, O-methyltransferase; VR, vestitone reductase.

that hydrolyses flavonoid glycosides and flavonoid glucuronides and sulfates (Griffiths and Barrow 1972). The further hydrolysis may go on and lead to catabolism of flavonoid backbone to its constituent phenolic and carboxylic acid products and finally to carbon dioxide (Rechner *et al*. 2002). Nevertheless the metabolism due to oxidation by ROS is one of the major pathways leading to formation of different metabolites.

Antioxident action

Antioxidants are chemical species which reacts with free radicals and terminate the chain reaction before the radicals damages the other functional molecules like proteins, DNA and lipid in membranes. There are several enzyme systems like catalase, superoxide-dismutase etc. and molecules that scavenge free radicals *e.g*. glutathion. Cells can also obtain antioxidants through the circulation after consumption of antioxidant rich beverages and food in diet. However, several chemicals, which normally cannot be obtained from food, have also been found to possess antioxidant property (Kasote *et al*. 2005).

The dietary components of vegetables, fruit and nuts and seeds are rich source of antioxidants which are able to reverse the effects of oxidative stress towards cells e.g. water soluble antioxidant Vitamin C possesses a good antioxidant and is able to quench a variety of ROS. Vitamin E displays a high biological activity related to its antioxidant power. It is a lipid soluble antioxidant in human. Polyphenols include the flavonoids, lignans, glucosinolates, trihydroxystilbenes (resveratol and polydatin) and phenolic acids. Over 9000 different flavonoids have been isolated from plants. These directly modify the redox status of cells and also interfere with cellular functions like cell cycle and apoptosis (Cipak *et al*. 2003).

ROS or RNS are regularly produced as an activity of normal human metabolism and has both beneficial and deleterious effects in various diseases. ROS and RNS play a bimodal role in cellular functions by functioning beneficial as cytotoxic agents against bacteria and parasites while on other hand they are able to induce damage to normal tissue. The balance between prooxidant (chemicals that induce oxidative stress) and antioxidant is found to be crucial for normal functioning of biological systems and an imbalance generally leads to damage that's defined as oxidative stress (Di Meo *et al*. 2016). Oxidative stress is special feature of these agents (ROS and RNS) causing significant loss of redox sensitive cellular components like proteins, lipids and nucleic acids. ROS and RNS were recognized as key players for host defense mechanism

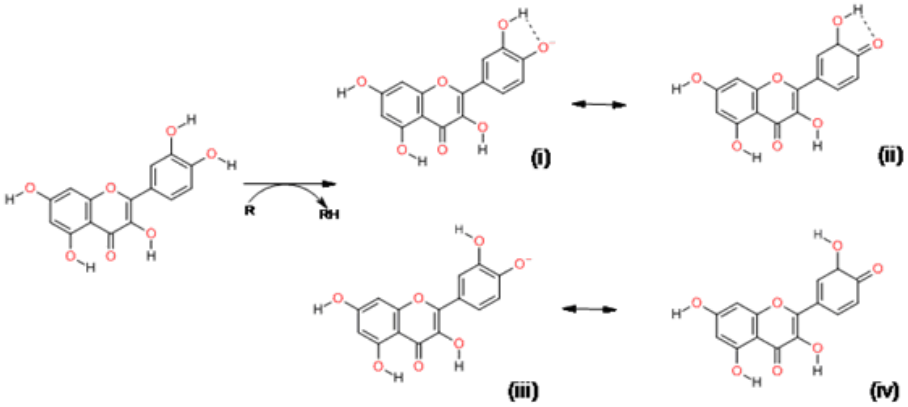

Fig 3: Mechanism of direct hydrogen transfer.

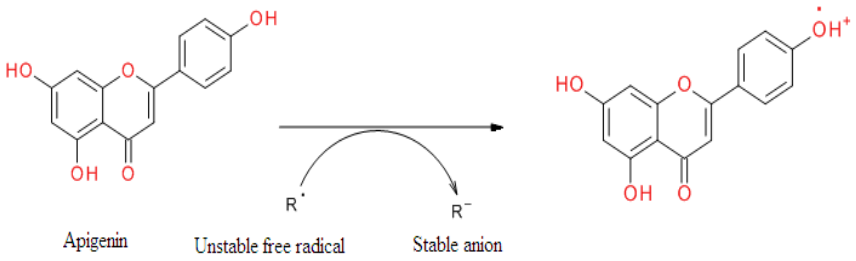

Fig 4: Mechanism of direct electron transfer.

including the respiratory burst of neutrophils and of the NADP oxidase complex.

Mechanism of antioxident action

Flavonoids exert their antioxidative actions by a number of mechanisms like (i) direct radical scavenging; (ii) scavenging of peroxynitrile (iii) inhibition of pro-oxidant enzymes, (iv) regulation of genes, (v) metal chelation.

Direct radical scavenging

Flavonoids stabilizes the free radical species and terminates the further formation of free radicals by the following ways, (i) by transfer of a hydrogen atom to the radical (Fig 3) by which radical becomes stabilized and (ii) electron transfer (Fig 4) in which an electron is transferred to radical so that its reactivity due to single electron is reduced. Fig 5 shows the structural mechanism of radical scavenging of quercetin.

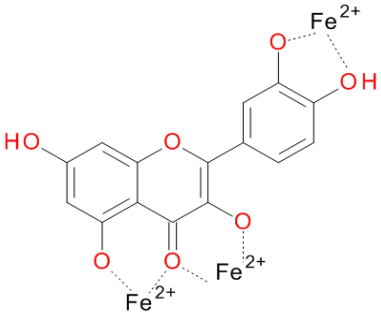

Fig 5: Three possible metal chelating positions present in quercetin molecule.

The hydroxyl groups on the B ring are able to form intramolecular hydrogen bond which can be stabilized in different ways (Zhang 1999).

Scavenging of peroxynitrite ion and nitric oxide

Peroxynitrite (sometimes called peroxonitrite) is the anion with the formula $ONOO^-$. It is an oxidant and due to its property it can cause lot of damage to the biomolecules. It is produced by the chemical reaction between unstable radical superoxide and nitric oxide. Nitric oxide and superoxide are produced during the inflammation process by nitric oxide synthase. It has been shown that not only peroxynitrite but nitric oxide as well can cause a lot of tissue injury as it is also a potent oxidizing radical.

Flavonoids can scavenge free radical like superoxide and hence can stop the formation of peroxynitrite ion which leads to reduction in oxidative damage. Also it has been established that flavonoid can directly lead to scavenging of nitric oxide which blocks the further formation of peroxynitrite. Quercetin was found to be most active is scavenging of peroxynitrite ion with 0.93 µM as the concentration for producing 50% inhibition of reaction producing the ion (Zhang 1999).

Inhibition of enzymes

Several enzymes are responsible for generation of intermediates which are implicated in oxidative loss of tissue. Xanthine oxidoreductase is an enzyme complex which helps in oxidation of hypoxanthine to xanthine and can further oxidize xanthine to uric acid. This enzyme complex, which

exists as different moiety which can exist in interconvertible forms xanthine dehydrogenase and xanthine oxidase, is responsible for generating reactive oxygen species (ROS), which is known to involved in development of ischemic injury and also in some other diseases (van Acker *et al*. 1996a). Inhibition of the enzyme XO is used to treat various diseases of the system. Flavonoids are found to inhibit the XO and thereby reduction in production of ROS (Van Acker *et al*. 1996b).

Cyclooxygenase (COX) is an enzyme which is involved in synthesis of important biological mediators including prostacyclin, prostaglandins and thromboxane. Lipoxygenases (LOX) are a family of iron containing enzymes containing which catalyze the deoxygenating of polyunsaturated fatty acids (PUFA) in lipids. It has been shown that free radicals are generated during the biochemical activity of COX and LOX. Green tea flavonoids were found to inhibit the COX and LOX based metabolic activities. EGCG and ECG displayed noncompetitive inhibition against COX-1 (Russo *et al*. 2000).

Regulation of genes

As already stated above, the role of Nitric oxide (NO) is crucial in production of oxidative stress. NO is produced by induction of inducible nitric oxide synthase (iNOS) and black tea flavonoids EGCG are found to reduce the induction of iNOS expression in macrophages by down-regulating NF-kB (Burda and Oleszek 2001).

Metal chelation

Metal ions (mainly copper and iron) are found to act as catalyst in the reaction producing free radicals. Hydrogen peroxide is found to produce hydroxyl radical in presence of metal at low oxidation state. Metal chelating compounds can bond with the free metal ions and render them stable in terms of their redox potential and thus preventing them to participate in the reaction generating free radicals. Flavonoids are found to be effective metal ion chelators that attribute to their antioxidant mechanisms (Pasha *et al*. 2007). Metal binding efficacy of Quercetin and its potential to inhibit the radical formation of studied and it is found that it can chelate iron(ii) in different hydration states (Tripoli *et al*. 2007). Electrospray mass spectroscopy study of flavonoid-metal complexes has revealed that for the flavonoid naringenin and few flavones, the chelating site is preferentially located at the 5-OH and 4-oxo groups (Wolfe and Liu 2008).

Role of particular groups on the activity

The antioxidant activity of flavonoid is particularly related to their structure. Among the various mechanisms, terminating the chain reaction leading to formation of stable molecule is the most important. In general many factors, such as positions of OH groups, properties of substituent group and hydrogen bond formation, influences the antioxidant activity The different rings of the flavonoid displays varied functional properties in relation to antioxidation.

A ring

The effect of substituent is very low for the antioxidant activity of flavonoids but can show considerable significance when the B and C ring are lacking the active groups. Catechol group is found to be effective when present on A ring (*e.g.* 7, 8-dihydroxyflavone and 8-hydroxyacacetin). The low contribution of A ring to the antioxidative nature is due to its low accessibility to the radical.

Glycosylation of the free hydroxyl reduces the activity of flavonoid towards radical scavenging and metal chelation. The steric tension developed due to addition of sugar residue reduces the ability to chelate ions. The importance of sugar residue on the activity of flavonoids can be seen with studies on luteolin and rutin, which has the same base structure (Van Acker *et al*. 1996b).

B ring

B ring of flavonoid is the more active in the antioxidant property as compared to A and C ring. Its hydroxyl groups are preferentially attacked to abstract hydrogen or electron transfer (Wolfe and Liu 2008) The B ring acts as a proton donor, which attributes significantly to its activity. It also enables the formation of a relatively stable radical through electron delocalization between the functional groups. The catechol (ortho dihyroxy) group of B ring is the found to be important antioxidant activity. It is involved in the abstraction of hydrogen and chelation of metal ions (Leopoldini *et al*. 2006). Substantial difference in the activities of Morin and Myricetin suggests the importance of ortho dihydroxyl group (Wolfe and Liu 2008). Flavonoids containing two hydroxyl groups at B ring are found to possess antioxidative potential as they are able to form intramolecular hydrogen bonding between the 3′ - and 4′ -hydroxyls and stabilized radical due to electron delocalization (Van Acker *et al*. 1996b). A very low activity is shown by flavanones (naringin and naringenin), which possess hydroxyl group at C4' in B ring and single bond at C2-C3 position in C ring. Methylated flavanone hesperetin (5, 7, 3'-trihydroxy-4'-methoxyflavanone) shown certain activity which suggests that methoxy substitution at certain position increases the antiradical activity (Burda and Oleszek 2001). When B ring is pyrogallol (o-m-p trihydroxy), as in Myricetin, the antioxidant activity is found to decrease which is attributed to the pro-oxidant activity of additional C5' hydroxyl group (Van Acker *et al*. 1996b). The position of B ring w.r.t. benzopyran is also a determinant factor for antioxidative activity as studies of isoflavones reveals their poor hydrogen donor capacity and higher antioxidant activity (Wolfe and Liu 2008). Genistein is found to be a poor antioxidant when used in liposomic and miceller systems, however, it was shown to be an effective antioxidant in assays involving hydrogen peroxide or iron, despite it is not a good metal chelator. It may be due to the absence of a 2, 3-double bond, which is a significant determinant of isoflavone antioxidant activity.

C ring

Presence of C2-C3 double bond, C4-oxo group and C3-

hydroxyl are the most important structural features for the activity of flavonoids. The flavonoids containing C3 hydroxyl groups e.g. kaempferol, fisetin, galangin, robinetin, quercetin, morin and kaempferide show comparable antioxidant activity with the synthetic antioxidant BHT (2, 6-bis (1, 1-dimethylethyl- 4-methylphenol) and D,L-R-tocopherol which have high antioxidant property and this property is lost when the C ring is devoid of C3 hydroxyl group (Burda and Oleszek 2001). Studied on flavonoids of *Chorizante diffusa* have shown that the flavonols with a free hydroxyl group at 3rd position possesses better antioxidant potential than its derivatives (Chung *et al*. 1999). Flavonol 3-O-glycosides do not possess free C-3 hydroxyl group which results in their inability to inhibit oxidation. Favonoids devoid of any hydroxyl group e.g. flavone, flavanone and 8-methoxyflavone, or having free hydroxyl groups only at C-5 or C-7 *e.g*. 5-hydroxyflavone, 7-hydroxyflavone and 5, 7-dihydroxyflavone, does not scavenge free radicals (Burda and Oleszek 2001). In flavonoids, such as quercetin, luteolin, taxifolin and catechin, loss of any of the functional groups from C-ring, 4-keto group, the 2, 3-double bond, or 3-hydroxyl group, is shown to cause reduction of antioxidant activity (van Acker *et al*. 1996a). Structurally, when a flavonoid loosed a 3-OH group, a change in bond angles of B ring relative to A and C ring takes place, which may be responsible for causing loss in electron delocalization efficiency and hence the antioxidant activity. Also, 4 keto-3/ 5hydroxyl bonds, which are responsible for flavonoid radical stabilization contributes to the importance of C ring in antioxidant activity(Guo *et al*. 2002).

Clinical implicatons

The role of free radicals in development of diseases like Alzheimer's disease (AD), Wilson's disease, Parkinson's disease, joint diseases, chronic hepatitis C, dermatological diseases, cancers and diabetes have been reported by several authors. Action of free radicals is implicated in ageing and is also reported to be involved in development of epilepsy. Flavonoids have been shown to reduce ischemic-reperfusion injury in the rats as well (Zhang *et al*. 2017). Shahanas *et al*. 2019 have reviewed the health benefits of flavonoids obtained from cocoa plant.

Alzheimer's disease (AD)

It is found that some of the processes leading to free radical formation, e.g., brain trauma, ageing, are critical risk factors for AD (Benzi and Moretti 1995). Also Down's syndrome, where the accumulation of free radicals is observed to increase, has some symptom similarities with AD. The brains of AD patients show a marked increase in amyloid- β peptide (Aβ), the main constituent of senile plaques and cerebrovascular amyloid deposits, which can be associated with oxidative damage to brain cells (Boh 1996). Oligomeric Aβ induces the formation of fibrils of Aβ (fAβ) and exerts oxidative stress. fAβ increases accumulation of Aβ through induction of BACE-1 (β-site AβPP Cleaving Enzyme) expression and activation, which may contribute towards toxicity of fAβ. The significant amount of lipid peroxidation in brain of AD patients has been implicated with production of ROS and AD pathogenesis (Droge 2002). Multiple factors, such as amyloid-β peptide and tau protein aggregation, oxidative stress, excessive transition metals and reduced acetylcholine (ACh) level, also contribute towards development of AD (Ji and Zhang 2006). The drug designing strategy for combating the AD aims at targets like acetylcholinesterase (AChE), monoamine oxidase (MAO), β-secretase and ROS. Flavonoids which able to bind and sequester metal ions and scavenge ROS are therefore prospective start points for drug development strategies for AD. Flavonoids like quercetin, gossypetin, myricetin are found to block Aβ- or tau-aggregation and can also inhibit MAO (isoenzymes A and B) (Kim *et al*. 2005). Mie Hirohata has reported the molecular mechanisms underlying the anti-amyloidogenic effects of five flavonoids (myricetin, quercetin, morin, kaempferol, (+) - catechin and (-) -epicatechin). They found that Myricetin and other flavonoids, binds preferably and reversibly to the amyloid fibril (fAβ) and exerts its anti-amyloidogenic effects (Hirohata *et al*. 2007). Another study involved Epigallocatechin-3-Gallate (EGCG) establishes it as modulator of Amyloid Precursor Protein cleavage that reduces the formation of Aβ production and reduction of β-amyloid plaques in the brain (Rezai-Zadeh *et al*. 2005). Bakhtiari et. al. has recently reviewed the effect of flavonoids against AD and other related neural dysfunctions (Bakhtiari *et al*. 2017). They analyzed that, Phosphatidylinositol 3-kinase (PI3K)/AKT and mitogen activated protein kinase (MAPK) pathways, both are affected by flavonoids. Recently, Zaplatic and coworkers have have reviewed the molecular mechanisms involved in attenuation of AD by flavonoid quercetin (Zaplatic *et al*. 2019).

Parkinson's disease (PD)

PD is characterized by loss of neurons in the midbrain called as substantia nigra. The reduction in levels of nigral dopamine (neurotransmitter) results in a decrease in stratial dopamine that generates PD symptoms. The relationship between the oxidative stress and the dopamine cell degeneration and the process cascade in between has been well studied (Tretter *et al*. 2004).

The level of oxidative stress in the substantia nigra pars compacta (SNc) region of the PD patients is found to be higher as compared to normal people. The SN region of PD patients also shows markers for lipid oxidative damage, glutathione content reduction, increase level of iron which catalyzes the production of highly reactive OH radicals from hydrogen peroxide. These all factors are ultimately contributing to neural cell death in PD patients. In vivo study on mouse treated with the dopaminergic neurotoxin N-methyl,4-phenyl-1,2,3,6 tetrahydropyridine (MPTP), shows increased oxygen free radical production and antioxidant enzyme activities (Cassarino *et al*. 1997).

Among the various approaches for protection of nigrostriatal neurons against oxidative stresses, antioxidants have been suggested as an important and effective way. Studies conducted by Vitamin E supplementation as natural antioxidant revealed that the treatment significantly alleviates

PD symptoms (Fariss and Zhang 2003). Zhao *et al*. conducted experiments on rats with PD symptoms and have shown that green tea polyphenols protected dopaminergic neurons from a variety of factors *viz*. ROS and NO levels, nitrite/nitrate content, lipid peroxidation, inducible NO synthase, protein bound nitro tyrosine (Zhao 2009). Another animal model study by F. Mandel group demonstrated the significance of green tea extract and ECG in MPTP treated mice model of PD (Levites *et al*. 2001).

Cardiovascular diseases

Several studies have shown that ROS is involved in development of various cardiovascular diseases (Kukreja and Hess 1992). Atherosclerosis is marked by elevated plasma LDL cholesterol concentrations and oxidized LDL is found to be associated with elevated levels of cholesterol in macrophages and atherogenesis. LDL is oxidized by free radicals which cause physical and chemical changes which are supposed to initiate and promote atherogenesis in several ways. Experimental reports have suggested a positive effect of intakes of phenolic antioxidants on LDL oxidation (Gaziano and Hennekens 1993) and a several dietary factors, including flavonoids, acts as effective antioxidants and helps in the prevention of Coronary Heart Disease (CHD). Study by Hertog *et al*. (Hertog *et al*. 1993) examined the relative occurrence of CHD and intake of flavonoids and they concluded a significant association between flavonoid intake and CHD development.

Flavonoids are shown to inhibit oxidative modification of LDL *in vitro* caused by activity of macrophages or copper ions. The *in vivo* capacity of the antioxidation depends upon their absorption and bioavailability and in particular the association of flavonoids with lipoproteins. There have been a number of mechanisms proposed by which the flavonoids act as inhibitors of LDL oxidation. Flavonoids inhibit the generation of free radicals or by preferentially being oxidized than α-tocopherol hence delaying the start of peroxidation (de Whalley *et al*. 1990). They regenerate α-tocopherol by donating hydrogen atom to α-tocopherol and inhibit the formation of free radicals by chelating metal ions. Flavonoids such as catechin, rutin and quercetin strongly inhibits oxidation of LDL, inhibits lactose peroxidase (LPO) and the associated toxicity of oxidized LDL towards the cells. Also, cells treated, in prior, with these flavonoids shows resistant towards the cytotoxic effects of previously oxidized LDL (Afanas' ev *et al*. 1989, Cholbi *et al*. 1991).

Plant flavonoids are also found to inhibit platelet aggregation and adhesion which are implicated in thrombosis and atherosclerosis (Duarte *et al*. 1993, Tzeng *et al*. 1991). There is more than one pathway involved in this property of flavonoids. Several reports have suggested the role of flavonoids in inhibiting platlet aggregation by stimulating adenylate cyclase or by inhibiting cAMP phosphodiesterase (PDE) activity (Duarte *et al*. 1993, Kuppusamy and Das 1992). Also Flavonoids may inhibit platelet aggregation by estranging the formation of thromboxane and thromboxane receptor function (Yazdanparast *et al*. 2007).

Antioxidant property of flavonoids is also found to attribute for their antithrombotic activity. These molecules can restore the synthesis and functions of endothelial prostacyclin and prostacyclin and endothelial derived relaxing factor (EDRF) when inhibited by free radicals Some may also act interacting with particular enzyme rather than acting as antioxidant (Beretz and Cazenave 1988).

The role of flavonoids is also found in vasodilation where they induce relaxationin smooth muscles of blood vessels. This is determined to be mediated through protein kinase C inhibition, phosphodiesterase inhibition, or reduction in calcium uptake (Duarte *et al*. 1993).

Diabetes

Diabetes is a metabolic disorder characterized by hyperglycemia, an increase in blood glucose level and elevated levels of ROS have been implicated in diabetes mellitus. There are several mechanisms which are proposed for the association of diabetes with high levels of ROS examined in biological systems.

Generation of superoxide radicals due to glucose auto-oxidation and the interaction of glycated proteins with cell surface receptors stimulate ROS production and intracellular glutathione level reduction (Van Dam *et al*. 1995). The elevated levels of ROS have been a major factor contributing towards the development of other complications like atherosclerosis etc. (Aragno *et al*. 2000, Baynes 1991). Hyperglycemia also induces peroxidation of LDL in endothelial cells which may be associated with increased ROS levels (Maziere *et al*. 1995).

Insulin is produced by β-cells in pancreas and ROS is found to destroy these cells and that is one of the main reasons which cause type1 diabetes. The activity of enzymes, like SOD, catalase, GPX, which are responsible for alleviating oxidative stress, are found to be low in islets β-cells than in other tissues that may lead to cell death by oxidative stresses (Yazdanparast *et al*. 2007, Matsuda *et al*. 2005). In a study involving *in vivo* expression of the antioxidant enzymes protected the β-cells from streptozotocin (STZ)-induced diabetes in animal model (Yazdanparast *et al*. 2007). Another work also revealed that Quercetin and Epicatechin, widely distributed plant flavonoids, are capable of inhibiting the negative effects of STZ on the pancreatic β-cells (Coskun *et al*. 2005, Kim *et al*. 2003). Another flavonoid, silymarin, has been found to suppress the production of inflammatory cytokines, such as IL-1β, IFN-γ and TNF-α which are supposed initiate the destruction of β-cells (Matsuda *et al*. 2005). Complexes for certain elements like Vanadium (IV) with naturally occurring glycosylated flavonoids, kaempferol-3-neohesperidoside and kaempferitrin are capable to mimic activity of insulin (Cazarolli *et al*. 2006). Kaempferitrin was found to decrease blood glucose levels in normal and diabetic rats effectively and interestingly this effect was not related to reduced intestinal absorption of glucose (de Sousa *et al*. 2004). Rezabaksh *et al*. have proved that quercetin plays a positive role in high glucose induced damage of endolithial cells thus saving them from effects of hyperglycemia (Rezabakhsh *et al*. 2019).

Osteoarthritis and Rheumatoid Arthritis

Osteoarthritis (OA) is condition which is characterized by loss of the extracellular matrix (ECM) of articular cartilage (also called hyaline cartilage) in the affected joints. Investigations have shown that role of free radicals in the pathogenesis of articular cartilage degradation. This pathogenesis involves complex mechanism with multiple pathways. They act as integral factors for intracellular signaling mechanism and modulate the gene expression which is required for cartilage tissue homeostasis. Any imbalance in the free radicals metabolism can lead to deleterious effects to these tissues. In RA the process of angiogenesis is affected and newly formed blood capillaries aid in destruction of articular cartilage.

Several studies involving intake of flavonoids and their correlation with reduced inflammation in OA and RA have given an insight of the possible role of the antioxidant activity of the compounds and its effect disease. Hesperidin has shown to suppress the collagen induced arthritis in rats (Kawaguchi *et al*. 2006). Apigenin, which is found to act as inhibitor for COX-2 and NF-κB can be valuable in disease like RA (Kang *et al*. 2009). Activation of these factors (COX-2 and NF-κB) has been associated in pathogenesis of arthritis.

Cancer

The epidemiological studies regarding the flavonoid intake and cancer prevention has been documented in a review by Block (Block *et al*. 1992) which suggested that by increasing the flavonoid components in food a significant effect in health can be achieved. Flavonoids have anticarcinogenic, antimutagenic, antiprolifeartive effects. These compounds also induce apoptosis in cancerous cells. Dysregulation of apoptosis plays a critical role in oncogenesis. In recent, flavanone Naringenin found in tomato and citrus food is found to exert inhibitory effects on cancer cells growth and migration (Guerreiro *et al*. 2007). Protoapigenone, a novel flavonoid, showed a significant anti-ovarian cancer activity with low toxicity both *in vitro* and *in vivo* (Chang *et al*. 2008). Patil *et al*. (2009)with their studies on lime flaovonoids proposed that the antiproliferative activity is proportional to flavonoid content of the sample (Patil *et al*. 2009). Pittella *et al*. established that the level of flavonoids, antioxidant and antitumor activities are positively correlated in the aqueous extract of *Centella asiatica* (Pittella *et al*. 2009). Wogonin is found effective in inhibiting cell growth and induction of apoptosis in both *in vitro* and *in vivo* models (Chung *et al*. 2008). Aqueous chamomile extract (a traditional medicinal plant) containing apigenin 7-O-glucoside, luteolin, patuletin, quercetin, myricetin and rutin is found to inhibit COX-2 enzyme activity and inhibited the release of LPS-induced prostaglandin E(2) (Srivastava *et al*. 2009). Das *et al*. showed that apigenin, (-)-epigallocatechin, EGCG and genistein induce apoptosis in human glioblastoma cells but not in normal normal astrocytes. The apoptosis is found to be induced by increase in ROS (Das *et al*. 2010). Anthocyanins induced apoptosis in human colon cancer cells in part through activating p38 MAPK and suppressing Akt (Shin *et al*. 2009). The most comprehensive work for the effect of flavonoids on mammalian cells and its implication in various diseases is done by (Middleton *et al*. 2000). Sun *et al*. 2019 have used a modified quercetin and have shown that it has better bioavailability which can be used as a potential drug against breast cancer.

Others diseases

Apart from the above discussed diseases flavonoids can exert their effect on other ROS mediated diseases like skin diseases. UV radiations (UVR) generate ROS which causes cutaneous damage. Acute exposure of UVR results in a range of developments in the biological systems including edema and pruritus, followed by tanning and thickening of epidermis and further exposure may lead to aging and carcinogenesis which are found to be partly mediated by ROS (Boh 1996). Aging is also found to be related to deleterious side effects of free radicals (Harman 2002). Free radicals have been associated with disease damage in chronic hepatitis C (De Maria *et al*. 1996). Flavonoids are also found to have antimicrobial activity (Chacha *et al*. 2005, Kosalec *et al*. 2005). They possess antifungal activity as well (Kuster *et al*. 2009, Afifi *et al*. 1991).

Significant statement

Natural compounds have been found beneficial in alleviation complex disorders like AD, PD, CHD, Diabetes, OA, RA and cancers. Role of structural moieties of flavonoids have been correlated with the mechanisms through which these compounds exerts their effects in physiological complications. It is implicated through structural comparison that presence of certain structural features at a position may be responsible for the activity of that compound. E.g. presence of hydroxyl group in flavonoid 3' or 4' "B" ring is associated with anti amyloidogenic activity which alleviates AD symptoms. Further confirmation and better insights can be made by SAR studies and wet lab experiments.

This work is helpful in extracting the information for performing SAR studies and validation experiments. The future scope lies in development of new drugs based on structures of natural compounds.

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Conflict of interest

The author declares that there is no conflict of interest.

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