Review Article

Chemistry and Pharmacology of Flavonoids- A Review

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ABSTRACT

Several modern and most of the traditional drugs have been developed from natural sources. Flavonoids or bioflavonoids, most ubiquitous polyphenolic compounds, are secondary metabolites of plants and fungal origin. Apart from their biological functions in plants (protection against herbivores, ultraviolet radiation and pathogens), they perform myriads of pharmacological activities in humans as well. Though flavonoids are not acknowledged as nutrients still their intake on regular basis is considered fruitful for human health. Flavonoids are biosynthesized through phenylpropanoid pathway and contain a C6-C3-C6 carbon framework. The present review has reviewed the chemistry, structure and classification of flavonoids. Additionally, their occurrence and chemical properties have also been explored. Moreover, we discuss about the different mechanisms through which flavonoids act like direct radical scavenging, leukocyte immobilization and interaction with different enzymes. Flavonoids own a number of pharmacological activities such as anti-parkinson, anti-ulcer, spasmolytic, anti-depressant, anti-bacterial, anti-hypertensive, anti-diabetic, anti-inflammatory and anti-cancer. This review intent to give healthy information for formation of new flavonoid based pharmaceutical formulation to act against various diseases.

Key words: Flavonoids, Polyphenolic compound, Pharmacological activity, Mechanism, Biosynthesis.

INTRODUCTION

'Flavonoid' word was initially derived from 'flavous', a latin word which means yellow, resembling flavonoid's colour in nature.[1-3] Despite of its meaning, plentiful of other flavonoids are white and the chief flavonoid-related anthocyanins are purple, red or blue in colour as well.[3] Flavonoids or bioflavonoids, are a category of secondary metabolites of plants and fungal origin.[4-9] They are a class of natural compounds having variable phenolic structures.[6] A new substance was screened out from oranges in 1930 which was thought to be a member of a new class of vitamins and was designated as vitamin P.[7,10,11] Later on, that substance was confirmed to be a flavonoid, called rutin.[11] The term "flavonoid" is basically used to describe a broad assemblage of natural compounds that contain a C6-C3-C6 carbon framework or more accurately a phenylbenzopyran functionality.[12] The position at which the aromatic ring links with the benzopyrano functionality helps to determine the three classes into which this group of natural compounds can be divided: the flavonoids (2-phenylbenzopyrans) Figure 1, isoflavonoids (3-phenylbenzopyrans) Figure 2 and the neoflavonoids (4-phenylbenzopyrans) Figure 3 and (Chalcone) Figure 4. These groups generally share a common precursor (chalcone) and are therefore structurally and biogenetically related.[13-17] Flavonoids possess different pharmacological activities and act through several mechanisms. All the healthy information regarding flavonoids will be discussed in this paper.

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Chemistry and Structure

Flavonoids are naturally occurring compounds present in plants. They have variable phenolic structures. Stereochemically flavonoids are composed of a 15-Carbon skeleton comprising of two benzene rings (A and B as shown in Figure 1) which are linked through a heterocyclic pyrane ring (C). Flavonoids have been classified into a number of classes. Biosynthesis of flavonoids occurs via phenylpropanoid pathway. In this pathway phenylalanine which is an amino acid, gets transformed into 4-coumaroyl-CoA and this 4-coumaroyl-CoA conjugates with malonyl-CoA to give chalcones consisting of two phenyl rings. Conjugate ring-closure of chalcones produces a three-ringed similar form of flavonoids called as flavone. This pathway continues via a sequence of various enzymatic modifications to form flavanones, dihydroflavonols and anthocyanins. Along with these compounds flavan-3-ols, proanthocyanidins (tannins), flavonols and several other poly-phenolics can also be formed.[19] Flavonoid's basic structure is aglycone (Figure 1).[20] In the structure of flavonoids, a six-member ring that is condensed with the benzene ring can either be a α-pyrone (flavanones and flavonols) or its dihydroderivative (flavanones and flavonols).[20,22-26] Flavanones differ from flavonols by lacking a hydroxyl group (OH) at the 3- position and a C2-C3 double bond.[27,28] Different class of Flavonoids are frequently hydroxylated at different positions (2,3,3',4',5,5' and 7). The carbohydrates (D-glucose, L-rhamnose, glucorhamnose, galactose or arabinose) are formed via glycosidic linkage generally positioned at positions 3 or 7.[6,29]

Occurrence and Properties of Flavonoids

Flavonoids are composed of a wide-range of polyphenolic entities having a benzo-γ-pyrone system and are pervasive in plants.[30-31] Because flavonoids are secondary metabolites (biosynthesized through shikimic acid pathway) of plants, they are consumed by man via food too.[30,32] Flavonoids are polyhydroxyphenols which are synthesized by plants to act against microbial infection.[22,33] The major dietary sources of flavonoids within the reach of human beings are vegetables and fruits including tea and wine.[20,34] Greater than 8000 compounds possessing basic flavonoid structure have been found, out of which several compounds are responsible for magnificent colors of various parts of plants (for e.g.-leaves, flowers and fruits). These secondary metabolites provide protection to plants against herbivores, ultraviolet radiation and pathogens (bacteria, virus and other microorganisms).[35,36] Various reports related to different substances of plant origin have stated the impact of flavonoids on metabolism of thyroid hormone, chemically distinct from ascorbic acid which has been assigned as vitamin P and has been considered useful in hemorrhage.[10] Flavonoids, in common, are hydrophilic substances having low values of log P and low molecular weights. It is considered that transport of flavonoids across cell membrane should take place through particular transmembrane transporters instead of simple diffusion through lipid part of the cell membrane.[37] Flavonoids act as functional foods by promoting health and preventing diseases.[35,38] Regardless of such useful properties of flavonoids, one major con is their low bioavailability which can differ between individual flavonoids in a specific class and between different classes as well.[38] Variability in bioavailability of different flavonoids can be detected from the data of comparative urinary excretion of daidzin and anthocyanins intake which was 43% and 0.3% respectively.[38,39] The bioavailability of flavonoids with complex higher structures and high molecular weights can even be lower.[38,40] Classification of flavonoids is presented in Table 1.

Working Mechanisms

Antioxidative Effects

The most illustrated property of almost every class of flavonoids is their ability to function as antioxidants. All the body cells and tissues are always vulnerable to

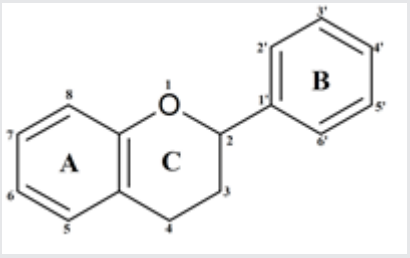


Figure 1: Basic structure of flavonoids.

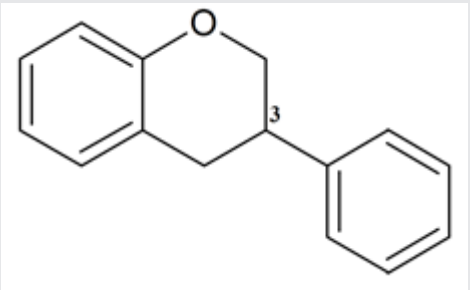


Figure 2: Basic structure of isoflavonoids.

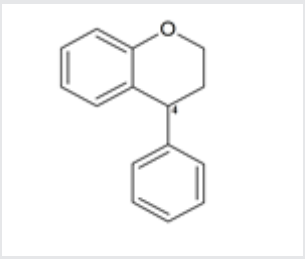


Figure 3: Basic structure of neoflavonoid.

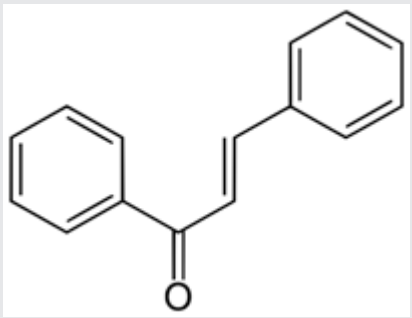


Figure 4: Basic structure of chalcone.

the devastating effect of reactive oxygen species and free radicals, which are formed during normal oxygen metabolism or are induced by damage due to exogenous factors.[41,42] The mechanisms and the procedure via which free radicals interrupt normal cellular functions are not entirely known. However lipid peroxidation has been assumed to be one of the most important mechanisms through which free radicals act. Lipid peroxidation generally causes damage to cell membranes. This damage results in shifting of the cell's net charge which causes a change in cell's osmotic pressure and this leads to swelling and ultimately cell death. Another way by which free radicals cause tissue damage is by causing general inflammatory response by attracting inflammatory mediators.[43,44] Human body's antioxidant defence mechanism include both enzymatic (glutathione peroxidase, superoxide dismutase and catalase) and non-enzymatic (ascorbic acid, α-tocopherol and glutathione) parts. A hike in the formation of ROS during damage or injury results in utilization and reduction of the cell's scavenging compounds. At single point of time, flavonoids can interrupt more than three different ROS generating systems that are explained below. Flavonoids may upregulate the effect of endogenous antioxidants as well.[41,44]

Direct Radical Scavenging Action

Damage due to free radicals can be prevented by flavonoids in various ways. Out of them one is the direct scavenging of radicals. As per the mechanism, radicals oxidize the flavonoids and themselves get reduced. The outcome of this is that the reduced radicals are now in a less-reactive and more stable form. Flavonoids react with reactive part of the free radical to stabilize it.[41] As hydroxyl group of flavonoids is highly reactive, the radicals are stabilized according to the mentioned equation:[45,46]

Flavonoid (OH) + R• -> flavonoid (O•) + RH

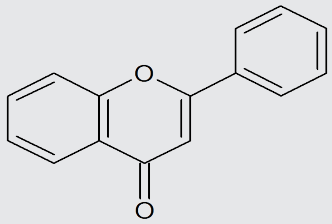
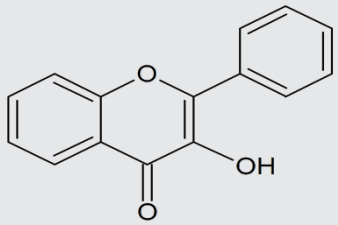
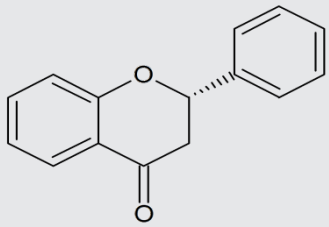
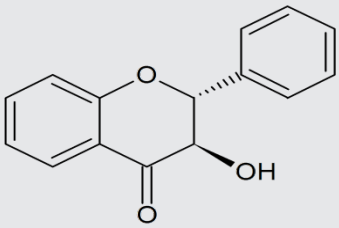
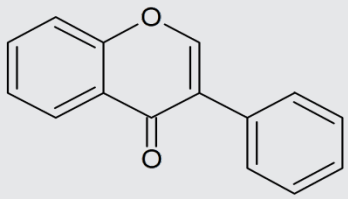
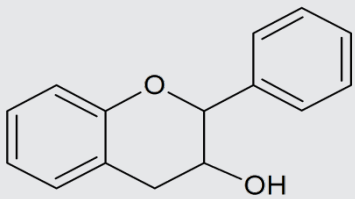
Where R• symbolizes a free radical and O• symbolizes an oxygen free radical. Some flavonoids inhibit superoxides while other flavonoids inhibit highly reactive peroxynitrite, which is an oxygen-derived radical. Rutin and epicatechin both are extremely strong radical scavengers.[47] Rutin inhibits xanthine oxidase enzyme and this ability of rutin helps it to act as a powerful scavenger. *Invitro* LDL oxidation can be inhibited by flavonoids via their radical scavenging property.[48] This effect of flavonoids on LDL oxidation helps to protect LDL particles and may be used as a preventive measure against atherosclerosis.[41,45]

Nitric Oxides

Occurrence of ischemia-reperfusion injury has been lowered by quercetin and various other flavonoids which act via interfering with the action of inducible nitric oxide synthase.[49,50] Nitric oxide is produced by various cell of the body including macrophages and endothelial cells. Dilation of blood vessels in the body is maintained by nitric oxide which is released by the action of nitric oxide synthase[51] but at the same time release of nitric oxide in higher amount in macrophages results in oxidative damage. Nitric oxide reacts with free radicals to form extremely devastating peroxynitrite which causes irreversible damage to the cell membrane by directly oxidizing the low-density lipoproteins.[52] Flavonoids act as antioxidants by scavenging the free radicals. Less damage to the body will be caused as free radicals will no more be available to react with nitric oxide.[53-55] Several studies have reported that flavonoids can scavenge nitric oxide molecules directly and this makes nitric oxide to be considered as a radical.[56-58] Thus it has been evaluated that scavenging of nitric oxide perform a crucial role in determining the therapeutic potential of different flavonoids.[58] According to a report nitric oxide has been dose dependently inhibited by a flavonoid named Silibin.[59]

Xanthine Oxidase Pathway

Table 1: Classification of Flavonoids6,18.

Class of flavonoid	Structural backbone	Examples
Flavones		Luteolin, Apigenin, Chrysin
Flavonols		Quercetin, Kaempferol, Galangin, Rutin, Myricetin
Flavanones		Hesperidin, Naringenin
Flavanonol		Aromadedrin, Taxifolin
Isoflavones		Genistein, Daidzein, Glycitein, Formononetin
Flavan-3-ols		Catechin, Gallocatechin, Epicatechin

After ischemic reperfusion, xanthine oxidase pathway has been considered as a vital route through which oxidative injury is caused to different cells and tissues.[60,61] Xanthine gets metabolise to uric acid via involvement of both enzymes xanthine oxidase and xanthine dehydrogenase. Under normal physiological conditions xanthine dehydrogenase is present in the form of an enzyme which gets interconverted to xanthine oxidase (source of free radicals) during oxidative stress. In the reoxygenation phase superoxide free radicals are released as a result of reaction of xanthine oxidase with available molecular oxygen. Flavonoids, quercetin and silibin have been proved to decrease oxidative injury by inhibiting xanthine oxidase activity.[62,63] Luteolin (3',4'5,7- tetrahydroxyflavone) has been reported to be a potent inhibitor of xanthine oxidase.[64]

Leukocyte Immobilization Mechanism

An another crucial mechanism for the production of reactive oxygen species, release of mediators of inflammation (bradykinin, PGE2) and cytotoxic oxidants is the strong adhesion of leukocytes to the endothelial wall. This route is responsible for further activation of the complement system as well.[41,45] Unlike during normal conditions where leukocytes roam freely, at the time of inflammation and ischemia several complement factors and endothelium derived mediators make leukocytes adhere to the endothelial wall. Because of this leukocytes get immobilized and degranulation of neutrophils starts. As an outcome, inflammatory mediators and oxidants are released which cause damage to various cells and tissues. The concentration of immobilized leukocytes in ischemia-reperfusion injury was reported to downturn after oral administration of fraction of purified micronized flavonoid.[41,45,65] Administration of flavonoids resulted in lowering of the concentration of immobilized leukocytes which is assumed to be related to the decline in total serum complement. This can be considered as a defensive mechanism against inflammation associated disorders (e.g.: reperfusion injury).[65,66] Stimulation of degranulation of neutrophils can be inhibited by many flavonoids without having any affect on production of superoxide.[67] Modulation of Ca^{2+} channels of the plasma membrane by flavonoids seem to have inhibitory effect on degranulation of mast cells.[68]

Interaction with Other Enzyme Systems

The main effects of flavonoids are an outcome of their radical scavenging property.[69] Interaction of flavonoids with several enzyme functions is an another route via which flavonoids perform their action. Moreover, some effects can be an outcome of combination of two mechanisms i.e. interaction with enzyme systems and radical scavenging. Lipid peroxidation occurs when reactive chemical species containing oxygen are present in the vicinity of iron.[70] Some flavonoids have been recognized to chelate iron,[71] by that they inhibit the formation of free radicals. Quercetin is one such flavonoid which is acknowledged for its iron-stabilizing and iron-chelating properties. Directly inhibiting lipid peroxidation is one more protective action which flavonoids perform.[72] Explicit flavonoids decrease inflammation by scaling down the adhesion and confinement of inflammatory cells to the endothelial wall by decreasing complement activation.[66,73] Diminishing the peroxidase release is another characteristic of flavonoids. Diminished production of peroxidase impede the production of reactive oxygen species by neutrophils by meddling with the activation of α1-antitrypsin.[74,75] Thereafter a gradual deactivation of proteolytic enzymes was reported to occur in neutrophils.[75] Flavonoids, having ability to obstruct various enzyme systems, hamper arachidonic acid's metabolism as well.[76] This characteristic of flavonoids allows them to perform their antithrombogenic and antiinflammatory actions. Process of inflammation starts with the production and release of arachidonic acid. Chemotactic agents (movement towards a chemical gradient) are formed from neutrophils consisting of lipoxygenase. Release of cytokines is provoked by them as well.[41,77]

PHARMACOLOGICAL PROPERTIES

Anti-Parkinson

It is a progressive degenerative disorder. Progressive degeneration of neurons occurs in substantia nigra pars compacta and nigrostriatal tract.[78] The etiology of Parkinson's disease is extremely complicated with various factors playing roles such as environment, genetics and aging.[79] Neurodegeneration occurs as a result of several biological processes involving oxidative stress,[80-83] augmented iron deposition,[84-86] DNA damage,[87,88] lipid peroxidation,[89] reduced glutathione (GSH) levels,[90,91] oxidation of protein,[88] and elevated superoxide dismutase level.[92,93] Lipopolysaccharide, an external stimuli could generate ROS which can alleviate the endogenous antioxidant enzymes specifically glutathione peroxidase, catalase and superoxide dismutase and leads to upswing in lipid peroxidation and cell death.[94,95] Mitochondrial metabolism can get affected by ROS directly. ROS causes lipid peroxidation that progressively causes cytochrome-c's leakage from mitochondria and ultimately cell death. External stimuli also trigger proapoptotic caspases by activating MAPK-induced inflammatory medi-

ators which cause cellular apoptosis.[96] Commencement of proinflammatory cytokine genes (iNOS, TNF-α and IL-1β) expressions induced by NF-κB, is also caused by MAPK family.[96,97] Flavonoids for example emodin,[98] kaempferol,[99] genistein[100] and morin[101] have been proved to suppress secretion of TNF-α. Naringenin has been reported to alleviate expression of NF-κB, iNOS and COX-2.[102]

Anti-Ulcer

Peptic ulcer occurs in that part of the gastrointestinal tract which is exposed to gastric acid and pepsin. It results probably due to an imbalance between the aggressive (acid, pepsin, bile and *H. pylori*) and defensive (gastric mucus, nitric oxide and bicarbonate secretion) factors.[103] The probable anti-ulcer effect of hesperidin has been due to its antioxidant and mucoprotective effect. Hesperidin impedes oxidative cell injury by augmenting the levels of certain enzymes (superoxide dismutase, catalase and glutathione) in gastric mucosa. Free radicals play major role in formation of stomach ulcers. Hesperidin allows the regeneration of ulcerated tissue and prevented hemorrhagic injury of gastric mucosa.[104] Quercetin has been found to have antiulcer activity in animals.[105-107] It acts by inhibiting the enzyme histidine decarboxylase[108, 109] and thus reduce the formation of histamine in the gastric mucosa, which stimulates the parietal cells and pepsinogen responsible for the secretion of hydrochloric acid and pepsin respectively.[110] Manuka honey, which is rich in flavonoids, preserves the gastric mucosal GSH.[111] GSH and gastric mucus both act as a barrier against gastric mucosal injury.[112] *Matricaria chamomilla*, which contains apigenin-7-O-β-glucoside-6"acetate, apigenin-7-O-galactoside-6" acetate and apigenin-7-O-β-glucoside, has been found to exhibit antiulcer effect.[113]

Spasmolytic

Spasmolytic effect occurs by blocking M_3 receptor (visceral smooth muscle contraction is elicited through M_3 receptor).[114] Catechin promotes vasodilation by activating muscarinic receptors on the endothelium and hence stimulates endothelium-dependent nitric oxide production.[115] Studies have shown that catechin has been reported to have a vasodilator effect mediated through numerous pathways including reduction in Ca^{2+} uptake, upturn of cyclic adenosine monophosphate (cAMP) levels and inhibition of protein kinase C.[116] Probable Ca^{2+} channel blocking action adds to the already compelling profile of catechin.[115] Thyme extract and flavones inhibit responses of particular receptors like histamine, L-noradrenaline and acetylcholine by inhibiting responses to such agonists which stimuate these receptors.[117] Flavonoids suppress contraction of smooth muscles caused by influx of extra-cellular Ca^{2+} into the guinea-pig longitudinal muscle.[118]

Anti-Depressant

In depression, monoaminergic transmission in the brain gets affected (5-HT and/or NE gets depleted).[119] Several flavonoids including quercetin have shown inhibitory action against MAO-A.[120,121] Monoamine oxidase-A is responsible for oxidative deamination of 5-HT and NA. Hence, manifestations of depression can be ameliorated by inhibiting MAO-A.[122] Intake of reserpine repeatedly causes cognitive deficit and elevate cellular oxidative stress. Quercetin shows a protective effect against reserpine induced dysfunctions.[123] A downturn in the levels of SOD and CAT was noted in groups that were provided with reserpine. Mice treated with *Hypericum hookerianum* (EEHh) and its glycosidic flavonoid enriched extract (GFHh) were able to maintain normal levels of SOD and CAT enzymes.[124] Flavonoids, quercetin and rutin, act against dysfunctions induced by reserpine by scavenging upon reserpine generated oxygen-derived free radicals.[125] Antidepressant property of hesperidin was displayed by inhibiting L-arginine/ nitric oxide/ cyclic-GMP pathway and by elevating levels of BDNF in the brain, specifically in hippocampus.[126,127] A study showed antidepressant action of vitexin which was mediated through heightened levels of catecholamines (dopamine, adrenaline and noradrenaline) in the synaptic cleft and by interacting with dopaminergic, serotonergic and noradrenergic receptors.[128] Other flavonids including fisetin,[129] quercetin,[130] naringenin,[131,132] nobiletin (a dietary flavonoid),[133] luteolin[134] and kaempferitrin[135] also have reported antidepressant activity.

Anti-Bacterial

An Antibacterial agent is the one which interrupts the propagation and growth of bacteria.[136] Apigenin-7-O-triglycoside, apigenin, luteolin-7-O-neohesperidoside, lucenin-2, saponarine and vitexin are some of the flavonoids which are isolated from mosses and have been proved to possess inhibitory effect against various bacterias. They have been shown to have antibacterial effect against several bacterias including *Enterobacter cloaceae* and *Pseudomonas aeruginosa*.[137] Golnar extract has played a successful role in preventing food poisoning as it exhibited antibacterial action against both gram positive and gram negative food poisoning causing bacterias.[138]

Anti-Hypertensive

When given chronically, Quercetin showed a gradual dose dependant and sustain fall in BP of rats.[139] Quercetin inhibits oxygen-derived free radicals and exer-

cises its inhibitory action against several transcription factors, enzymes and ion channels as well.[140] Hence several changes in cell functioning and gene expression are caused by quercetin by interfering with different signal rely pathways. Thus quercetin's vasodilatory action is a possible mechanism via which it shows its antihypertensive effect. ROS have been assumed to have pathophysiological role in essential hypertension and therefore decrease in cellular oxidative stress by quercetin could be considered as a possible mechanism via which it shows its antihypertensive effect. In spontaneously hypertensive rats (SHRs) quercetin alleviated superoxide ions which is related to down regulation of NADPH oxidase subunits.[141] Assessment of BP in rats at the end of 5 weeks treatment demonstrated that quercetin exhibited remarkable reduction in diastolic, systolic and mean arterial BP in SHRs. Quercetin markedly decreased both heart rate and BP in spontaneously hypertensive rats.[142] In male wistar rats antihypertensive action of flavonoids chrysin and luteolin was efficiently investigated. Chrysin and luteolin both have the capability to reduce BP and heart rate of diabetic rats which is associated with their vasorelaxation action.[143,144] Kaempferol does not need functional endothelium to initiate vasodilation of blood vessels and hence considered as endothelium-independent vasodilator which acts similar to sodium nitroprusside. Epicatechin and myricetin both flavonoids showed their inhibitory action against vasoconstrictors (endothelin-1 and angiotensin II).[146,147] The fall in blood pressure has been accomplished by various flavonoids via their effects on functions of epithelium. Different classes of flavonoids such as flavanones (naringin and hesperidin), flavanols (epicatechin) and flavones (luteolin, buddleoside and chrysin), all have exhibited vasodilatory effect.[145,148-150] Many studies have showed that naringin, hesperidin, quercetin and epicatechin have augmented nitric oxide synthase activity and bioavailability in the endothelium which enhanced endothelial function.[151-155] Acetylcholine-induced vasodilation was improved *invitro* by naringin, hesperidin, luteolin and epicatechin.[144,146,155]

Anti-Inflammatory

The antiinflammatory activity of flavonoids is mediated through a number of mechanisms including inhibition of proinflammatory enzymes like lipooxygenase, Cyclooxygenase-2 and iNOS. At molecular level, flavonoids stimulate protein kinase C, phase II antioxidant and detoxifying enzymes and mitogen activated protein kinase (MAPK). Flavonoids also show inhibitory action against NF-kβ.[156-158] In peritoneal macrophages of rats, kaempferol and quercetin inhibit COX-2.[159] Catechin quite infirmly inhibits Cyclooxygenase-2 and that too at an extremely large concentration.[160] Whereas some flavonoids like myricetin, kaemferol, quercetin and morin act by inhibiting lipooxygenase. Apigenin, quercetin and luteolin inhibit COX-2 at very high concentrations and inhibit NO production.[161] Catechin and quercetin showed synergistic inhibitory action against tumor necrosis factor alpha (TNF-α) and Interleukin 1 beta (IL-1β) and augment the release of IL-10, also known as human cytokine synthesis inhibitory factor.[156] Genistein has been proved to inhibit TNF-α, IL-1β and IL-6 in LPS induced RAW cells.[156] Quercetin showed its affect on iNOS and TNF-α in RAW cells treated with LPS by blocking MAPK and AP-1 DNA binding.[163,164]

Anti-Diabetic

Diabetes mellitus is a metabolic disorder indicated by conditions such as hyperglycaemia, negative nitrogen balance, hyperlipidaemia, glycosuria and sometimes ketonaemia. Two major types of diabetes mellitus are-Type-I Insulin-dependent diabetes mellitus (IDDM) and Type-II Noninsulin-dependent diabetes mellitus (NIDDM).[165]

Various researchers have proved that flavonoids scale down diabetes mellitus either by avoiding glucose absorption or by improving glucose tolerance.[166] *Invitro* experiments have stated that isoflavones of soyabean extract (daidzein and genistein) impede absorption of glucose in the small intestinal brush-border-membrane (BBM) vesicles of rabbits.[167] Naringenin also decreased the level of uptake of glucose into the BBM vesicles of diabetic rats equivalent to normal rats.[168] Several flavonoids including (−)- epigallocatechin, (−)-epigallocatechin gallate, myricetin, quercetin, apigenin and (−)-epicatechin gallate ameliorate diabetes mellitus by inhibition of Na^+ dependent glucose transporter-1 (SGLT-1).[169] In both *invivo* and *in vitro* conditions of animal tissues, non-glycosylated flavonoids showed reduction in glucose absorption under Na^+ dependent conditions.[170,171] Flavonoids alleviate diabetes mellitus via several mechanisms. Most common being reduction in glucose absorption. Another mechanism via which flavonoids act is by inhibiting the activity of α-glucosidase in the small intestine. Kaempferol, luteolin, galangin and chrysin showed α-glucosidase inhibitory activity in both *invivo* and *invitro* conditions when used to study their roles in absorption and metabolism of glycosides.[172]

Amentoflavone, daidzein, luteolin and luteolin 7-O-glucoside have been proved to be the strongest inhibitors of α-glucosidase among the twenty-one tested compounds.[173] Orientoside too was shown to impede

α-glycosidase function. The lowest possible level of blood glucose is achieved after 4 h of dosing of quercetin.[174] A research has proved that rutin has higher activity as compared to ellagic acid, boswellic acid and quercetin. They act by upsurging the peripheral utilization of glucose and by obstructing the glucose transporter function in intestine. Hypoglycemic activity of these four flavonoids were noticed in this mentioned order- Rutin> Quercetin >Ellagic acid> Boswellic acid.[175] Diosmin stimulates the production of insulin from β-cells of pancreas.[176-178] Studies revealed that in contrast with casein, soya protein isolate show better hypotriglyceridemic effect. This proposed that partly isoflavones are responsible for this activity.[179] Another study has reported that genistein improves hyperglycemia, promotes cAMP/PKA signaling pathway and causes human vascular endothelial inflammation *ex vivo*.[180] Several reports have shown that genistein ameliorates glucose tolerance, hyperglycemia and blood insulin level in obese diabetic mice without having any affect on fat deposit, peripheral insulin sensitivity, body weight gain, plasma lipid profile and food intake.[181] Intake of genistein resulted in improved cardiac remodeling advancement in experimentally induced diabetes which was mediated partly by inhibiting the actions of CRP (C-reactive protein), TGF- β1 (Transforming growth factor β1) and TNF-α (Tumor necrosis factor-α).[182] By controlling intracellular signaling mechanism of AMPK (AMP-activated kinase), genistein, EGCG and capsaicin improve obesity.[183]

Anti-Cancer

In cancer uncontrolled cellular function occurs. Cancerous cells escape normal cellular functions and normal homeostasis via suppression of tumor suppressor gene and alteration of normal cellular physiological functions and structure. Flavonoids of tea obstruct epidermal growth factor and platelet-derived growth factor mediated signal relay pathways. Malignant cells affect various events such as angiogenesis.[184] Tyrosine kinase is mediator of signal transduction process which causes cell proliferation, migration, differentiation and apoptosis. This tyrosine kinase is inhibited by flavonoids quercetin and genistein.[185,186] Flavonoids namely apigenin, luteolin and quercetin arrest cell growth and cause apoptosis mediated via p53 as stated by different reports.[187] These flavonoids have inhibitory and protective action against breast tumor as reported by several researchers. Genistein administration has improved the early maturation and differentiation of the mammary glands, which is assumed to be the mechanism of tumor obstructing activity of soya. Tumor inhibitory activity of isoflavones has been demonstrated through various studies conducted on different models.[188] Women who eat up high amount of tofu have been observed to have lower incidence of breast cancer.[189] Seventh Day Adventists and Japanese studies have stated that consumption of high amount of soya milk and tofu is correlated with less chances of prostate cancer.[190,191] Flavonoids in tea have been proved to have anti-cancer effect as stated by different studies.[192,193] Antitumor effect has been shown by oncamex, a new flavonoid, in animal models of breast carcinoma.[194]

Apigenin was observed to posess skin papillomas inhibitory activity and was seen to prevent their conversion to cancer as well.[195] Luteolin acts by penetrating into the skin for treatment and prevention of skin cancer.[196] Quercetin has also been reported to have activity against hepatic-cancer.[197] Kaempferol showed productive results in ovarian cancer by lowering vascular endothelial growth factor (VEGF) expression which causes increment in vascular proliferation and permeability.[198] Myricetin and baicalein showed cytotoxic activity against leukemia, an another type of cancer.[199] Quercetin was reported to impede thyroid cell growth by inhibiting insulin modulated AKT kinase activity. It downturns TSH- inflected RNA levels in sodium iodide sympoter (NIS) gene and therefore considered to be a new disrupter of thyroid function which can be used in thyroid cancer.[200] Proliferation of KAT 18 and HTH 7 have been inhibited by Chrysin both time and dose dependently. An upturn in cleaved polyADP ribose polymerase (responsible for DNA repair, genomic integrity and apoptosis), cleaved caspase-3, along with a downturn in Mcl-1, cyclin D1 and XIAP (play role in the control of mitotic cell death) was detected.[201] Via the mechanism of induction of differentiation, human U937 leukemia cell line is inhibited by a novel flavonoid III-10.[202,203] Several researchers have reported the anticancer activity of alcoholic extracts of *Gracilaria tenuistipitata* in squamous cell carcinoma of mouth. Programmed cell death is induced by the alcoholic extract by enhancing ROS initiation, mitochondrial depolarization and DNA damage.[204,205] Another flavonoid Epigallocatechin-3-gallate (EGCG) has demonstrated to inhibit angiogenesis in the chorioallantoic membrane.[206-208]

CONCLUSION

Flavonoids are naturally occurring compounds present in plants. The major dietary sources of flavonoids within the reach of human beings are vegetables and fruits including tea and wine. In the present study we discussed the chemistry and pharmacological activities such as anti-parkinson, anti-ulcer, spasmolytic,

anti-depressant, anti-bacterial, anti-hypertensive, anti-diabetic, anti-inflammatory and anti-cancer. This review intent to give healthy information for formation of new flavonoid based pharmaceutical formulation to act against various diseases.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

LDL: Low density lipoprotein; **ROS:** Reactive oxygen species; **PGEA2:** Prostaglandin E2; **MAPK:** Mitogen-activated protein kinase; **TNF:** Tissue necrotic factor; **SOD:** Superoxide dismutase; **BDNF:** Brain-derived neurotrophic factor.

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