

# Flavonoids and Their Biological Secrets



M. I. Rashid, M. I. Fareed, H. Rashid, H. Aziz, N. Ehsan, S. Khalid,  
I. Ghaffar, R. Ali, A. Gul, and Khalid Rehman Hakeem

## Introduction

### *Flavonols*

3-Hydroxy flavones or flavonols, one major subclass of flavonoids, are polyaromatic secondary plant metabolites. Their structure consists of general three-ring backbone of flavonoids, i.e., rings A, B, and C. Flavones are classified as flavanones when there is a hydroxyl group attached to the 3-position of C ring. Structures of flavonol and flavone molecules are shown in the figure.

In higher plants, flavonols are present in glycosylated form; most abundant are the *O*-glycosides. The sugar residues commonly found in flavonols are glucose, galactose, rhamnose, and glucuronic acid. Glycosylation is reported at 3-, 7-, 3-, and 4'-positions (Table 1).

Flavonols are present in various parts of plants including leaves, fruits, and vegetables. Among different plants tested for flavonols, their highest concentration was found in strawberry (*Fragaria* spp.), peepal (*Ficus religiosa*), spinach (*Spinacia oleracea*), and cauliflower (*Brassica oleracea*) (Sultana and Anwar 2008). Like

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M. I. Rashid · M. I. Fareed · H. Rashid · H. Aziz · N. Ehsan · S. Khalid · A. Gul (✉)  
Atta-ur-Rahman School of Applied Biosciences (ASAB), National University of Sciences and  
Technology (NUST), Islamabad, Pakistan  
e-mail: [alvina\\_gul@asab.nust.edu.pk](mailto:alvina_gul@asab.nust.edu.pk)

I. Ghaffar  
University College of Pharmacy (UCP), University of the Punjab, Lahore, Pakistan

R. Ali  
Institute of Basic Medical Sciences, Khyber Medical University, Peshawar, Pakistan

K. R. Hakeem  
Department of Biological Sciences, Faculty of Science, King Abdulaziz University,  
Jeddah, Saudi Arabia

**Table 1** The relative substitutions among the 15 different flavonoids discussed in the paper

Sr.#	Flavonols	Position									
		2'	3'	4'	5'	3	5	6	7	8	
1	3-Hydroxyflavone	H	H	H	OH	H	H	H	H	H	
2	Azaleatin	H	OH	OH	H	OH	OCH <sub>3</sub>	H	OH	H	
3	Fisetin	H	H	OH	OH	OH	H	H	OH	H	
4	Galangin	H	H	H	H	OH	OH	H	OH	H	
5	Gossypetin	H	OH	OH	H	OH	OH	H	OH	OH	
6	Isorhamnetin	H	OCH <sub>3</sub>	OH	H	OH	OH	H	OH	H	
7	Kaempferide	H	H	OCH <sub>3</sub>	H	OH	OH	H	OH	H	
8	Kaempferol	H	H	OH	H	OH	OH	H	OH	H	
9	Morin	OH	H	OH	H	OH	OH	H	OH	H	
10	Myricetin	H	OH	OH	OH	OH	OH	H	OH	H	
11	Natsudaidain	H	H	OCH <sub>3</sub>	OCH <sub>3</sub>	OH	OCH <sub>3</sub>	OCH <sub>3</sub>	OCH <sub>3</sub>	OCH <sub>3</sub>	
12	Pachypodol	H	H	OH	OCH <sub>3</sub>	OCH <sub>3</sub>	OH	H	OCH <sub>3</sub>	H	
13	Quercetin	H	OH	OH	H	OH	OH	H	OH	H	
14	Rhamnazin	H	OCH <sub>3</sub>	OH	H	OH	OH	H	OCH <sub>3</sub>	H	
15	Rhamnetin	H	OH	OH	H	OH	OH	H	OCH <sub>3</sub>	H	

other flavonoids, flavonols are most apparent antioxidant in higher plants. Antioxidative activity of flavonols has been shown experimentally to prevent nuclear DNA damage by hydrogen peroxide in plants (Melidou et al. 2005). Studies on *Arabidopsis* plant have shown that flavonols are involved in providing protection to plant leaves against oxidative damage due to excessive visible radiation (Havaux and Klopstech 2001). They are also involved in providing defense against fungal infection to plant leaves (Treutter 2006).

Despite their role in plant survival, biological activities of flavonols also contribute to human health. Antiviral activities of flavonoids were discovered in the first half of the twentieth century. Hydroxyl group at 3-position makes flavonols more effective against herpes simplex virus type 1 than flavones (Cody et al. 1986; Selway 1986). Anti-inflammatory response of flavonol has also been reported on animal models for both chronic and acute inflammation (Lee et al. 1993). Flavonols also involved in antithrombogenic effect by preventing platelet aggregation (Gryglewski et al. 1987).

## *Fisetin*

Fisetin is a special class of flavonoid compounds defined as 3,3',4',7-tetrahydroxyflavone, 6-desoxyquercetin, and fisidenolon; its empirical formula is C<sub>15</sub>H<sub>10</sub>O<sub>6</sub>. In plants it is present as glycoside fisetin-8-glucoside. Chemically it is defined as -(3,4-dihydroxyphenyl)-3,7-dihydroxy-4H-1-benzopyran-one and 3,3',4',7-tetrahydroxy-2-phenylchromen-4-one. Fisetin usually is found in plants as the glycoside fisetin-8-glucoside.

It is a basic 15-carbon structure also known as diphenylpropane molecule having two aromatic rings which is linked through three carbon atoms. Flavonoids make difference because of the saturation of the heteroatomic ring C, in place of B at position C-2 or C-3 of ring C and throughout patterns of methoxylation (Nijveldt et al. 2001).

## Biological Properties

Natural polyphenolic compounds including flavonoids are present in fruits, vegetables, and some beverages (Aherne and O'Brien 2002). They have role in pharmaceuticals and have the potential of treating cancer and heart diseases (Havsteen 2002; Hill et al. 1989; Lopez-Lazaro 2002; Middleton et al. 2000; Monasterio et al. 2004). It has been discovered that few flavonoids have also a role in the organization of cytoskeleton especially in the assembly of tubulin.

According to the reported data, fisetin is the most active member of flavonoid compounds and shows a role in the modification of morphology of endothelial cells that is related to the stabilization of microtubule and to the  $\alpha$ -tubulin acetylation which is known to be a distinctive marker for the stabilization of tubulin. Such type of presented data has been useful for us in the selection of food which has such type of active flavonoids acting against cancer and other diseases.

Flavonoid compounds showed responses against inflammation, allergy, and bacterial infection (Melgarejo et al. 2007; Middleton et al. 2000; Williams and Grayer 2004). Fisetin is an important class of flavonoid compounds found in a variety of fruits and vegetables which is responsible for decreasing the process of degranulation of mast cells (Arai et al. 2000).

It has been discovered that fisetin has a role in the differentiation of nerve cells and also protects them from death due to oxidative stress (Ishige et al. 2001; Sagara et al. 2004). It has been studied that fisetin possesses also the properties of antiaging. Fisetin has also a role in rising the serotonin and non-adrenaline levels in the brain which results in the production of effect against depression (Zhen et al. 2012).

Fisetin also has a role in the promotion of growth and maintenance of nerve cells without the help of neurotropic factors. These are important factors because if those factors are removed, it will result in the death of nerve cells. In the absence of those factors, fisetin is involved promotion of growth and survival of nerve cells (Maher 2006, 2008).

NF-kappa B pathway plays an important role in inflammation which results in the progression of cancer. Fisetin and some other flavonoids perform an important role in the suppression of numerous inflammatory pathways most importantly NF-kappa B pathway which is important in many remedies against cancer (Gupta et al. 2010; Prasad et al. 2010; Sung et al. 2007).

Fisetin has also a role in the prevention of Huntington's disease which is an important neurodegenerative disorder affecting various brain functions (Maher et al. 2011a). Wnt signaling pathway has an important role in the proliferation and

progression of cancer; fisetin compound performs function in inhibition of this pathway (Teiten et al. 2012).

It has been studied that fisetin performs function against pulmonary inflammation infection, against asthma specifically doing by downregulation of NF-kappa B pathway (Wu et al. 2011). Many other flavonoids including fisetin decrease the activation of mast cell which reduces the histamine level as a result of which inhibition of many allergies occurs. Because when mast cells become active, they tend to secrete histamine and many other pro-inflammatory compounds (Park et al. 2008).

Fisetin makes the high expression of glyoxalase 1 which is an important enzyme and plays a significant role in the exclusion of substances and reducing the levels of glycated proteins responsible for diabetes (Maher et al. 2011b). In contrast if the expression of glyoxalase 1 becomes low, it leads to the increased level of glycation and complications in diabetes (Miyata et al. 2001).

Also by decreasing the secretion of glucose from the liver, fisetin hinders the hyperglycemia which is induced due to the glucose secretion from the liver (Constantin et al. 2010).

## *Galangin*

Galangin is an important class of flavonoid compounds; they are found in honey, propolis, *Helichrysum aureonitens*, and *Alpinia officinarum* in greater amount. This compound has an important role in pharmaceuticals; also it performs function against oxidation, against mutations, and against cancer (Cushnie and Lamb 2006; Gwak et al. 2011; Heo et al. 2001).

It has three hydroxyl groups on its carbon ring, and it has the capability of enzyme modulation and can decrease the chemical toxicity (Chen et al. 2008). It has been reported earlier that galangin has a role in the inhibition of aryl hydrocarbon receptor; in organisms these compounds are also involved in certain biological activities at nontoxic levels (Murray et al. 2006).

## **Biological Properties**

By using the agar dilution assay, it was studied that galangin also showed its activity against the 17 strains of *Staphylococcus aureus* species which was resistant against quinolone. In a specific strain when there is a change in the amino acid in the GrlB subunit of topoisomerase IV, it results in its increase receptiveness toward galangin. Therefore topoisomerase IV enzyme plays an important role in the function of galangin against bacterial infection (Cushnie 2006).

The activity of galangin was also discovered against 17 strains of *Campylobacter jejuni* and several gram-positive and gram-negative strains, but the highest galangin activity was found against the 17 strains of *Campylobacter jejuni* (Campana et al. 2009).

In colorectal and liver cancer, the transcriptional process of beta-catenin is increased; galangin reduces its transcription by the elimination of beta-catenin inside the cell. This compound also decreases the levels of beta-catenin by making the mutations inactive of adenomatous polyposis coli (Gwak et al. 2011).

According to the *in vivo* and *in vitro* studies, it has been reported that galangin has the capability of performing functions in the regulation of enzyme activity and in decreasing the toxic effect of chemicals and against oxidation (Heo et al. 2001). Galangin has been found in liposomes; these liposomes have been analyzed for their activities against oxidation, and results have showed that liposomes which have greater concentration of galangin have more antioxidative activity (Landi-Librandi et al. 2011).

The effect of galangin was studied in rat liver which was fed on fructose; the high expression of plasma glucose, triglycerides, and insulin was prohibited by galangin; and furthermore it also increases the sensitivity of insulin, while galangin also plays an important role in decreasing the expression of cytokines. It also prohibited the high translocation of NF-kappa B (Sivakumar and Anuradha 2011).

HPLC and MS have been used in finding the quantification of galangin in biological samples, and results showed that these compounds are aggregated more in the nucleus than cytoplasm (Mukai et al. 2009). According to chromatographic studies, galangin is also available in propolis of *Lactobacillus fermentum* (Saavedra et al. 2011). It has been discovered after the analysis of seven different types of Slovenian honey that it contains the greater amount of galangin (Bertoncelj et al. 2011).

Extracts of different plants have galangin which is considered to be the most active compound (Yang et al. 2011b). Concentration of polyphenol in fruits and leaves of *Ficus carica* has shown the occurrence of galangin as a major constituent (El-Shobaki et al. 2010).

By using the technique of HPLC, seven different phenolic components were discovered in bee pollen sample, among which galangin was the most active and also galangin was found in different fruits which were taken from Italy (Grippi et al. 2007; Šarić et al. 2009). Galangin was also discovered from the 120 samples of Chinese propolis which were detected by using the fingerprint method (Chen et al. 2008).

Galangin was significantly found in the chemical composition of propolis which was taken from arid and semiarid areas of Sonora, Mexico, Europe, China, and Argentina (Gardana et al. 2007). Galangin was also found from the extracts of apple and parsley (Abdel-Rahim and El-Beltagi 2010).

## **Gossypin**

Gossypin (3,3',4',5,7-pentahydroxy-8-*O*-glucosylflavone) is a flavonol and a derivative of gossypetin. It is a monoglucoside. On complete methylation and hydrolysis, it gives an *O*-pentamethyl gossypetin (Rao and Seshadri 1946b). The presence of

glucose moiety in the eighth position of hexahydroxyflavone makes it water soluble (Gautam and Vijayaraghavan 2007).

It was initially extracted from *Gossypium indicum* (Neelakantam and Seshadri 1936). However, the species *Gossypium indicum* did not yield sufficient amount of gossypin to carry out further experimentation. It was then found out that *Hibiscus vitifolius* was a rich source of gossypin (Rao and Seshadri 1946a). A detailed study of the structure and function of the flavonol has been carried out since.

## Biological Properties

Major focus of today's research is finding a cure for cancer. To avoid the harms of chemotherapy and radiotherapy, scientists now look toward natural products with higher efficacy and fewer side effects. In this regard, the anticancer activity of gossypin has been investigated by many researchers. A study by Babu et al. (2003) demonstrated the anticarcinogenic activity of the bioflavonoid gossypin against the carcinogens such as DMBA which causes skin papillomas in mouse. Moreover it was shown to decrease the tumor burden in solid tumors and inhibition of angiogenesis. The antitumor activity of gossypin is attributed somewhat to its ability to inhibit the key enzymes in DNA replication, the topoisomerase I and II (Babu et al. 2003). In another study conducted on human glioma, U251 cells treated with gossypin showed promising results. Gossypin caused cell cycle arrest at G2/M phase involving the phosphorylation of cell division cycle 25C (Cdc25C) tyrosine phosphatase through the stimulation of checkpoint kinase 1 (Chk1) (Shi et al. 2012). Additionally gossypin has been found to block cell multiplication in L929, HT29, and K562 tumor cell lines in vitro (Babu et al. 2003). Another possible mechanism underlying anti-tumorigenic capability of gossypin was demonstrated by Kunnumakkara et al. (2007). They analyzed the effect of gossypin on NF-kappa B, a master regulator involved in inflammation, carcinogenesis, hyper-proliferation, invasion, and angiogenesis. The results supported the hypothesis of possible NF-kappa B inhibition by gossypin (Kunnumakkara et al. 2007).

Gossypin's role as a potent antioxidant was examined in a study involving lead toxicity. Lead is known to cause generation of reactive oxygen species (ROS) and destruction of antioxidant reserves in the body (Patrick 2006; Silbergeld et al. 2000). Gautam et al. demonstrated the significance of co-administrating gossypin during lead exposure. They concluded that gossypin prevents lead-induced oxidative stress by chelating lead, stimulating the enzymes involved in protecting antioxidant reserves, and by inducing delta-aminolevulinic acid dehydratase, which is primarily targeted by lead (Gautam and Flora 2010).

Not only gossypin is effective in its antitumor activities, but its potential role in alleviating many other pathologies is also under consideration. Many of the current orally administered hypoglycemic drugs for the treatment of diabetes mellitus induce harmful side effects. A study was conducted to evaluate the antidiabetic effect of gossypin in streptozotocin (STZ)-induced experimental diabetes in rats.

Results revealed a strong antidiabetic activity of gossypin against STZ-induced experimental diabetes (Venkatesan and Sorimuthu Pillai 2012).

Epilepsy is a set of neurological disorders characterized by recurrent or single seizures accompanied by alterations in the brain (Chang and Lowenstein 2003; Fisher et al. 2005). To avoid the drug interactions caused by the many antiepileptic drugs, researchers are investigating natural alternatives with fewer side effects. In this pursuit, gossypin was used in a set of experiments to evaluate its anticonvulsant activity. The results obtained emphasized the importance of gossypin against convulsions probably by influencing the GABA aminergic and glycine inhibitory mechanism (Rasilingam et al. 2008).

Mast cell degranulation and release of histamines and other inflammatory cytokines underlie severe allergic reactions. Gossypin was shown to inhibit anaphylaxis in a rat model of allergy (Ganapaty et al. 2010). The anti-inflammatory activity of gossypin is thought to be the consequence of inhibition of arachidonic acid breakdown through blocking of the cyclooxygenase and lipoxygenase enzymes (Ferrandiz and Alcaraz 1991). Gossypin also has a potent effect against sulfur mustard (SM), a blistering agent, possibly through its anti-inflammatory action (Gautam and Vijayaraghavan 2007).

Gossypin has also been shown to relieve pain in mice, acting as an analgesic possibly through the induction of opiate receptors (Viswanathan et al. 1984).

## *Isorhamnetin*

Isorhamnetin (3'-methoxy-3,4',5,7-tetrahydroxyflavone) is an *O*-methylated flavonol occurring naturally in plants but is also a metabolic product of quercetin (isorhamnetin is methylated quercetin) ([phytochemicals.info](http://phytochemicals.info)). It can be extracted from *Tagetes lucida* (Bohm and Stuessy 2001). It is mostly found in fruits and medicinal herbs (Kim et al. 2011). Isorhamnetin is a metabolite of quercetin, a widely distributed natural flavonol (Anderson 2004).

## **Biological Properties**

Isorhamnetin has found its promising role in treatment of various diseases such as cardiovascular disorders, rheumatism, and hemorrhage (Gupta et al. 2010; Ma et al. 2007a; Suomela et al. 2006). Isorhamnetin is known to have cardiovascular effects. Isorhamnetin and its parent compound quercetin caused endothelium-independent vasodilatation in the aorta, mesenteric arteries, portal vein, and porcine coronary arteries of rat (Ibarra et al. 2002).

Anti-inflammatory activity of isorhamnetin was observed in murine RAW264.7. Analysis was performed based on the expression of pro-inflammatory markers in lipopolysaccharide-stimulated murine macrophages (Boesch-Saadatmandi et al.

2011). The possible way by which isorhamnetin blocks inflammation is not yet clear; however the study by Boesch-Saadatmandi et al. suggested the inhibition of NF-kappa B to have a significant role in this regard (Boesch-Saadatmandi et al. 2011).

A derivative of isorhamnetin, isorhamnetin 3-*O* neohesperidoside (I3ON), has potential antioxidant activity and protective capability against DNA damage caused by hydroxyl free radical (Bouhleb et al. 2009).

Osteoporosis is mainly attributed to estrogen deficiency in postmenopausal women (Richelson et al. 1984). Different flavonols were examined for their estrogen receptor agonist activity. Isorhamnetin along with other flavonols under study exhibited stimulatory activity for estrogen receptors, thereby producing the required osteogenic effects (Yang et al. 2011a).

Isorhamnetin has been found useful in treating obesity as it has an anti-adipogenic action. Differentiation of human adipose tissue-derived stem cells into adipocytes is controlled in different ways. Wnt signaling, being one of the chief regulatory mechanisms in the differentiation process, is targeted by isorhamnetin mainly by the stabilization of  $\beta$ -catenin (Lee et al. 2010).

As for the role of isorhamnetin in cancer, it is shown to exert antitumor activity. One of the possible mechanisms for this anticancerous activity was delineated by Kim et al. (2011) in a study of skin cancer. In this study isorhamnetin blocked epidermal growth factor (EGF)-induced neoplastic cell transformation by suppressing the expression of COX-2 protein. COX-2 is a major inflammatory mediator and exerts pro-tumorigenic activity (Méric et al. 2006). Furthermore it exerted a negative effect on anchorage-dependent and anchorage-independent growth of A431 human epithelial carcinoma cell line (Kim et al. 2011). Many other evidences support isorhamnetin's role in reducing cell growth and weight and size of tumors (Ma et al. 2007a; Steffen et al. 2008). Another set of experiments revealed antitumor role of isorhamnetin by inhibition of the cell cycle protein, farnesyl protein transferase (FPTase) (Oh et al. 2005). Previously, quercetin was shown to be a potent anticancer agent, but newer studies have signified the increased potential of isorhamnetin an effective anticancer entity. Such isorhamnetin showed elevated levels of cytotoxicity against cancerous cells as compared to quercetin. It induces necrosis and apoptosis in human colon cancer cell line (HCT-116) (Jaramillo et al. 2010). Moreover in another research aflatoxin B1 (AFB1)-mediated oxidative stress was lessened considerably by isorhamnetin more than quercetin in hepatocellular carcinoma cells (Choi et al. 2010).

Isorhamnetin was shown to reduce proliferation and stimulate apoptosis in gastric cancer. These functions were mediated through the activation of peroxisome proliferator-activated receptors (PPAR- $\gamma$ ) which is known to be involved in promoting tumorigenesis in gastric cancer. The results by Ramachandran et al. provide a strong basis for establishment of combination therapy involving the use of isorhamnetin to reduce the side effects and enhance treatment efficacy for gastric cancer (Ramachandran et al. 2012).



## ***Kaempferol/Kaempferide***

3,5,7-Trihydroxy-2-(4-hydroxyphenyl)-4H-1-benzopyran-4-one kaempferol is a class of flavonol compounds (Calderon-Montano et al. 2011). It is abundantly found in edible plants and one of the most important flavonoid compounds (Miean and Mohamed 2001a). These plants include tea (Park et al. 2006a), broccoli (Calderon-Montano et al. 2011), cabbage (Calderon-Montano et al. 2011), and strawberries (Calderon-Montano et al. 2011; Hakkinen et al. 1999), and other dietary plants (Calderon-Montano et al. 2011). Previously during epidemiological research, it has been observed that these dietary plants also used for human health betterment and during various preclinical and clinical trials have revealed that kaempferol-rich diet overcomes the human malignancy development (Kim et al. 2003). Many naturally occurring glycosides of kaempferol are extracted from different plants. These glycosides are kaempferitrin (kaempferol 3,7-dirhamnoside) (Vishnu Prasad et al. 2009), astragalín (Wei et al. 2011), afzelin (kaempferol 3-rhamnoside) (Markham et al. 1992), kaempferol 7-*O*-glucoside (Ibrahim et al. 2008), robinin (kaempferol-3-*O*-robinoside-7-*O*-rhamnoside) (March et al. 2004), sophoraflavonolósido (kaempferol 3-*O*-sophoroside) (Kim et al. 2012), and trifolin (kaempferol-3-*O*-galactoside) (Nowak and Wolbis 2002). Kaempferol-3-*O*- $\beta$ -D-glucopyranoside-7-*O*- $\alpha$ -L-rhamnopyranoside is one of the most bitter-tasting glycoside compounds and has been isolated from the methanolic plants (Gohar et al. 2000; Ragasa et al. 2005). During the metabolism process by the activity of enzyme transferase, these flavonoid kaempferol compounds can transfer the product of kaempferol and *S*-adenosyl methionine to kaempferide (Calderon-Montano et al. 2011; Curir et al. 2001). Kaempferide is defined as 4'-*O*-methylkaempferol which is also included in chemical flavonoid compound (Curir et al. 2001). These isolated flavonoid and chemical compounds have an antimicrobial (Yang et al. 2010), antioxidant (Choi et al. 2013), anticancer (Calderon-Montano et al. 2011), neuroprotective (Filomeni et al. 2012), antidiabetic (Habtemariam 2011), immunomodulatory (Kim et al. 2008), anti-osteoporotic, antiestrogenic (Oh et al. 2006), anxiolytic (Vissiennon et al. 2012), analgesic (Tsiklauri et al. 2011), and anti-allergic activities (Kim et al. 2008). Therefore naturally occurring plants are usually used as medicinal plants and for pharmaceutical products. The study of immunopharmacological properties of these plants has clearly shown the result to inhibit the cell growth, oxidative low-density lipoprotein (LDLP) suppression, viral inhibition, and reduction of apoptosis and strengthen the immune system (Kim et al. 2008). Kaempferol and kaempferide are developed by the metabolic activities of bioactive plants and are agents to treat many disorders (Kim et al. 2008). *Ginkgo biloba*, *Moringa oleifera*, *Equisetum* spp., *Tilia* spp., propolis, and *Sophora japonica* are the species of medicinal productivity (Calderon-Montano et al. 2011). For the cure of free radical damages and different infectious diseases, these pharmacokinetics species have often been utilized (Calderon-Montano et al. 2011). It was indicated that kaempferol compound in plants can be used as an agent of chemo-protection (Chen and Chen 2013). Recently it was observed that hypertension stress that associated with cardiac risks

has been suppressed by the consumption of this anticancer compound in tea and broccoli (Calderon-Montano et al. 2011). It has been concluded that kaempferol also plays a vital role to overcome the inflammatory response (Choi et al. 2013). Kaempferol also suppresses the translational activity of particular protein that may help to inhibit the growth of inflammatory lesions (Choi et al. 2013). Kaempferol has been isolated from *B. pinnatum* which is a medicinal herb used as drug for the antimicrobial activity (Tatsimo et al. 2012). It also inhibits the aggregation of the foam-producing cells, and these foam-producing cells increase the low-density lipoprotein oxidation (Li et al. 2013). These naturally occurring compounds are also used to eliminate cholesterol and lipids from macrophages (Li et al. 2013). Therefore it can reduce the effect of atherosclerotic disorder (Li et al. 2013) and toxicity of neurodegenerative Parkinson's disease (Filomeni et al. 2012). Secondary glycosidic metabolites of kaempferoid have the ability to develop products like kaempferol as anticancer, antioxidant, and anti-glycine (Al-Musayeib et al. 2011). While these metabolites not only target the tumorous cells but are also capable of minimizing the side effects of the combination of both radio- and chemotherapies (Al-Musayeib et al. 2011). Productivity of kaempferol and phytochemically active compound kaempferide has a key importance to act as antiestrogenic property (Hung 2004). Photochemicals inhibit the estrogen and progesterone receptors to control the proliferation of inflammatory cancerous cells (Frigo et al. 2002). Kaempferide has structural capability to suppress the attack of fungal infections (Curir et al. 2001). It was hypothesized that kaempferol reduces the effect of vascular endothelial growth factor receptors too. VEGF receptor increases the risk of ovarian cancer; it can be controlled by taking dietary fruits and vegetables having flavonoid products (Luo et al. 2010). In vivo investigations induced the role of flavonoid kaempferide acting as an antioxidant to treat the liver patients by the use of isoforms such as P450 (Otake and Walle 2002). Another side in vitro studies show that kaempferide has anti-plasmodium and antimalarial activity against the strains of *Plasmodium falciparum* (De Monbrison et al. 2006). Therefore in this study it was analyzed that naturally occurring flavonol and chemically active compounds can be used as therapeutic agents. These therapeutic products play an important role to save human life and suppress the activity of various infectious diseases with the help of development of these compounds.

These plants include tea (Park et al. 2006b), broccoli, cabbage (Calderon-Montano et al. 2011), and strawberries (Häkkinen et al. 1999; Calderon-Montano et al. 2011). These isolated flavonoid and chemical compounds have an antimicrobial (Yang et al. 2010), antioxidant (Choi et al. 2013), anticancer (Calderon-Montano et al. 2011), neuroprotective (Filomeni et al. 2012), antidiabetic (Habtemariam 2011), immunomodulatory (Kim et al. 2008), anti-osteoporotic, antiestrogenic (Oh et al. 2006), anxiolytic (Vissiennon et al. 2012), analgesic (Tsiklauri et al. 2011), and anti-allergic activities (Kim et al. 2008). Therefore in this study it was analyzed that naturally occurring flavonoid and chemically active compounds can be used as therapeutic agents. These therapeutic products play an important role to save human life and suppress the activity of various infectious diseases with the help of development of these compounds.

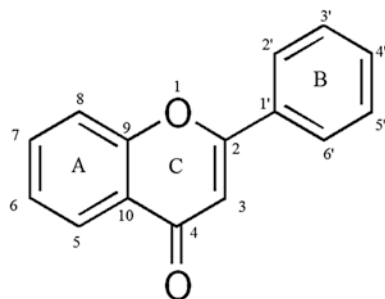
## Rhamnetin and Rhamnazin

Rhamnetin is also one of the chemical *O*-methylated flavonoid compounds (Ozipek et al. 1994; Yun et al. 2000). It was recognized as rhamnetin 3-*O*-[3'''-*O*-(*p*-coumaroyl)- $\alpha$ -L-rhamnopyranosyl(1 $\rightarrow$ 3)- $\alpha$ -L-rhamnopyranosyl(1 $\rightarrow$ 6)]- $\beta$ -D-galactopyranoside (Ozipek et al. 1994). It can be isolated from various plant sources such as cloves, green vegetables, and fruits (Yun et al. 2000). Chemical structure of this natural compound has been discovered by Austrian chemist Josef Herzig. Basically this molecule having flavonol nuclei consisted of two benzene rings (Zhen et al. 2012). And these rings have been combined by O<sub>2</sub>-containing pyran rings as shown in Fig. 1 (Zhen et al. 2012).

### Biological Properties

Rhamnazin was synthesized through the activity of enzyme 3-methylquercetin 7-*O*-methyltransferase (Khouri et al. 1988; Ozipek et al. 1994). This transferase enzyme uses *S*-adenosyl methionine and isorhamnetin to produce *S*-adenosylhomocysteine and rhamnazin (Khouri et al. 1988). Basically rhamnazin is known as 3,5-dihydroxy-2-(4-hydroxy-3-methoxyphenyl)-7-methoxychromen-4-one (Khouri et al. 1988). It is also the naturally occurring 3',7-dimethylquercetin flavonoid compound (Joe et al. 2010). Like other naturally occurring chemical compounds, rhamnetin and rhamnazin also have anticancerous (Lee et al. 2011; Ma et al. 2012), antioxidant (Pande 2001), and anti-infectious activities (Ahmed et al. 2001), etc. The *O*-methylated flavonoid compounds are chemically methylated on hydroxyl groups. Chemical formation of this methoxy bond is difficult because methoxylation is possible in any position of molecule (Lee et al. 2011). So the usage of specific enzyme *O*-methyltransferase plays an important role which interacts substrate on specific position of molecule (Mattarei et al. 2010). That enzyme implies the *O*-methylation on a specific hydroxyl (3-OH) position. Multiple hydroxal functional groups greatly contribute towards the therapeutic potential of polyphenols (Mattarei et al. 2010). In the metabolism these substrate molecules are rapidly being converted into sulfates, glucuronides, and methyl ethers (Biasutto et al. 2007;

**Fig. 1** Core structure of flavonols



Mattarei et al. 2010). The effect of *O*-methylation depends on the solubility of flavonoids (Mattarei et al. 2010). In vivo experiments induced that chemical modification of these molecules were to enhance the solubility effect while reduces the metabolic effects to provide the low bioavailability of polyphenols (Biasutto et al. 2007; Manach et al. 2005; Silberberg et al. 2006; Williamson and Manach 2005). These studies observed the overall survival of polyphenol OHs (Mattarei et al. 2010). As shown in Fig. 1, structurally rhamnetin is a monoethyl ether of quercetin while rhamnazin is identified as quercetin dimethyl ether (Martini et al. 2004). Therapeutic potential could be attributed to functional groups i.e. C-ring of 3'-hydroxyl and 4'-hydroxyl groups contribute towards redox activity (Metodiewa et al. 1999), while 3-OH act as inhibitor (Sarno et al. 2002). On the other hand, 7-OH and 5-OH are having weak and less acidic activity because of intramolecular hydrogen bonding to the 4-carbon of carbonyl compound (Van Dijk et al. 2000). This study reports that acetylated 3-OH bond has enzymatic activity and is used as protective chemical reaction of catecholic OHs (Mattarei et al. 2010). They also suggest that this mitochondrial-targeted compound has a free OH at the specific 3-position (Mattarei et al. 2010).

## *Quercetin*

Quercetin is one of the major dietary flavonoids. It is present in various plant parts including fruits, vegetables, and beans. Although exact concentration of quercetin in food stuff is not known, it is estimated that it makes 50% of the total dietary flavonoids. Depending on various factors including plant varieties, growth conditions, processing, etc., quercetin content may vary, but onions are experimentally shown to have highest concentrations of quercetin, i.e., about 200–600 mg/kg.

Quercetin contains five hydroxyl residues which are responsible for its activity and possible derivatives. Quercetin has two main groups of derivatives, i.e., glycosides and ethers. Some quercetin derivatives also contain sulfate and prenyl substituents but they are less frequent (Williams and Grayer 2004).

Quercetin *O*-glycosides are widely distributed in plants. They may either contain one or two *O*-glycoside residues. The most common derivative is quercetin 3-*O*-glycosides which contain OH-group at C-3 carbon. The commonly found sugar residues in quercetin 3-*O*-glycoside derivatives include glucose, galactose, rhamnose, and xylose. Another derivative is quercetin 7-*O*-glucoside which contains glucose residue at the hydroxyl group of C-7 carbon (Chang and Wong 2004).

Quercetin ethers make the second major group of quercetin derivatives. They may contain up to five ether bonds along with other substituents such as sugar residues and alkyl groups. Quercetin molecules are lipophilic but become hydrophilic by the glycosidation of at least one OH-group (Materska 2008).

## Biological Properties

Quercetin is an ubiquitous antioxidant and is shown beneficial in maintaining good health. Quercetin acts as anticancer agent by regulating cell cycle human breast cancer MCF-7 cells (Chou et al. 2010). Antiviral activity of quercetin has been reported against various viral strains along with other flavonoids (Cody et al. 1986). Pharmacologic effects of quercetin in various diseases including neurodegenerative disorders, cardiovascular diseases, inflammation, bacterial and fungal infections, and liver disorders have also been reported (Tanwar and Modgil 2012).

## Morin

Morin (2',3,4',5,7-pentahydroxyflavone) is a yellow-colored naturally occurring substance in *Maclura tinctoria* (old fustic) and *Maclura pomifera* (Osage orange) wood and from *Psidium guajava* (common guava) leaves (Rattanachaiunsopon and Phumkhachorn 2007). By the circular dichroism spectrum, the change in both confirmations after the binding of morin with high affinity to site II (subdomain IIIA) of bovine serum albumin (BSA) has been observed (Hu et al. 2012).

Morin having comparatively high bimolecular rate constant ( $k_2$ ) value for its interaction with the 1,4-dinitrobenzene (1,4-DNB) electrochemical system presents to its less intermolecular hydrogen bonding and more acidic nature (Arshad et al. 2012). Circular dichroism (CD) and UV-vis spectroscopy results showed that the binding of bovine serum albumin (BSA) to morin and other flavonol compounds induces some conformational changes in BSA (Shahabadi and Mohammadpour 2012).

## Biological Properties

Morin is known to have the antihypertensive and antioxidant effects in deoxycorticosterone acetate (DOCA)-salt-induced hypertension in rats (Prahalthan et al. 2012a, b). Morin has found its role in the treatment of many diseases. A significant interaction of flavonoid drug or flavonoid xenobiotic has been observed during test regarding to b5 reductase inhibition that shows a promising role in therapeutic and toxicological outcomes for certain drugs and xenobiotic (Çelik and Koşar 2012; Çelik et al. 2013). In cases of colon cancer and hepatocellular carcinoma, 3,5,7,2',4'-pentahydroxyflavone has been observed to possess chemopreventive potential in animal models. Antiproliferative and anticarcinogenic effects also have been determined against 7,12-dimethylbenz(a)-anthracene (DMBA)-induced experimental mammary carcinogenesis (Nandhakumar et al., 2012). In tumor cells, downregulation of STAT3-dependent chemosensitization and gene expression was led by the suppression of the signal transducer and activator of transcription 3 (STAT3) pathway after the application of morin (Gupta et al. 2012).

Morin inhibited the expression of matrix metalloproteinase-3 (MMP-3) and matrix metalloproteinase-13 (MMP-13), and it also has increased the expression of tissue inhibitors of metalloproteinase-1 (TIMP-1) in interleukin-1 $\beta$  (IL-1 $\beta$ ) which induced rat chondrocytes (Chen et al. 2012a). Morin has decreased in asymmetric dimethylarginine (ADMA) level, while dimethylarginine dimethylaminohydrolase (DDAH) activity in the liver was significantly higher in rats (Merwid-Lad et al. 2013). Morin is also been reported to be indirectly involved in insulin signalling and functionality (Paoli et al. 2013).

In vivo study in murine model, for osteoarthritis (OA) induced by anterior cruciate ligament transection (ACLT), the results clearly indicated suppression of cartilage degradation by orally administered morin. So morin has been observed to be used for the treatment of osteoarthritis (OA) as therapeutic agent (Chen et al. 2012a). Human inhibits the formation of amyloid by hydrate of morin (2',3,4',5,7-pentahydroxyflavone). The polypeptide hormone islet amyloid polypeptide (IAPP, amylin) and disaggregates preformed IAPP amyloid fibers observed under right-angle light scattering and transmission electron microscopy (TEM) (Noor et al. 2012). Nitric oxide (NO) and prostaglandin E2 (PGE-2) production was inhibited by morin as well as the expression of inducible NO synthase (iNOS) and cyclooxygenase (COX-2) in interleukin-1-beta (IL-1 $\beta$ )-induced chondrocytes. Morin also suppressed the degradation of inhibitor of nuclear factor- $\kappa$ B (I $\kappa$ B- $\alpha$ ) as well as the translocation of nuclear factor kappa B (NF-kappa B).

In rats, an IL-1 $\beta$ -induced osteoarthritis (OA) model, morin also exerted anti-inflammatory properties during in vivo study (Chen et al. 2012b). Morin exhibits antioxidant potential and offers enhancement in antioxidant levels simultaneously showing protection that clearly reduce in urea, ammonia, lipid peroxidation (Subash and Subramanian 2009). It has also been clarified that a lower concentration of morin in carcinomas than normal oral mucosa inhibited the activation of activated protein kinase AKT, whereas Jun N-terminal kinase (JNK), p38 kinase, and polyclonal antibodies (GADD45) all induced the same dose-response parallel curves in normal oral mucosa and carcinomas (Brown et al. 2003).

## *Myricetin*

Myricetin (3,5,7-trihydroxy-2-(3,4,5-trihydroxyphenyl)chromen-4-one) (figure) is a major plant secondary metabolite; these are commonly found particularly in the whole plant kingdom and in majority of human foods, i.e., different fruits, berries, grapes, herbs, vegetables, and many other plants. A rich source of myricetin is walnuts; traces can be found as glycosides (Miean and Mohamed 2001b).

Myricetin is one of the phenolic compounds which are found in red wine (Maggiolini et al. 2005). It is found on the leaf surface of wild tomato (*Solanum habrochaites*) plants that contain 3,7,3',5'-tetramethyl myricetin, 3,7,3'-trimethyl myricetin, and 3,7,3',4',5'-pentamethyl myricetin, with secreting glandular trichomes (gland types 1 and 4) containing abundantly than storage glandular tri-

chomes (type 6) and with the tetramethylated compound predominating in all types 1, 4, and 6 (Schmidt et al. 2011). Myricetin contains a three-ring structure with a central oxygenated heterocyclic and two aromatic centers (Gee and Johnson 2001) that serve as multiple functions like antioxidant activities and pigmentation (Hertog et al. 1994).

## Biological Properties

Myricetin and other polyphenolic compounds are absorbed in human gut, remaining larger fraction in the lumen, thus the major proportion of mucosa from gastrointestinal. These compounds also show considerable biological effects at cellular level. These myricetin with some other phenolic compounds control the cellular cycles, apoptosis (programmed cell death), and differentiation after interaction with cellular signal pathways (Gee and Johnson 2001). A wide range of bioactivities have been reported for this molecule i.e. Allelochemic; Antioxidant; Antibacterial; Anti-feedant; Anti-HIV; Antihistaminic; Anti-gingivitic; Antiallergenic; Anti-gastric; Anti-gonadotrophic; COMP-Inhibitor; Antihistaminic; Antiseptic; Anti-inflammatory; Anti-mutagenic; Anti-periodontic; Antiplaque; Antiviral; Diuretic; Topoisomerase-I-Inhibitor; Hypoglycemic; Vasodilator; Cancer-Preventive; Mutagenic; Candidicide; Larvostat; Lipoyxygenase-Inhibitor; Oxidase-Inhibitor; Quinone-Reductase-Inducer; Pesticide; Tyrosine-Kinase-Inhibitor; Topoisomerase-II-Inhibitor (<http://www.ars-grin.gov/duke/>, accessed).

Myricetin can cause muscle paralysis by inhibiting acetylcholine release at the neuromuscular junction. When compared to *Clostridium botulinum* neurotoxin (BoNT/A) the myricetin effect on muscle paralysis was unpretentious (Yang et al. 2011c). It is also claimed myricetin has antibiotic effects on *R. leguminosarum* by *trifolii* (Fottrell et al. 1964). Myricetin is known to have DNA damage (strand breakdown and oxidized pyrimidines/purines) effect in human hepatocellular carcinoma (HepG2) cells which is induced by taking it as a diet to have a significant protective effect against *N*-nitrosopyrrolidine (NPYR)-, *N*-nitrosodimethylamine (NDMA)-, and benzo(*a*)pyrene (BaP)-induced DNA damage (Delgado et al. 2008). Myricetin and rosmarinic acid are inhibited by amyloid- $\beta$  (A $\beta$ ) protein, and by site-specific binding, there were also observed aggregation and synaptic dysfunction (Ono et al. 2012).

As for the role of myricetin in cancer, myricetin and scutellarin are potently shown to inhibit the severe acute respiratory syndrome coronavirus (SARS-CoV) helicase protein (Yu et al. 2012). Myricetin has been found to protect neurons' discrete and multiple pathways and inhibited glutamate-induced excitotoxicity (Shimmyo et al. 2008). Myricetin was exerted as potent chemopreventive activity mainly by targeting activity of Fyn kinase straightly and afterward attenuated UVB-induced cyclooxygenase-2 (COX-2) expression (skin carcinogenesis) (Jung et al. 2008). Myricetin (20  $\mu$ M) when treated with macrophages derived from U937 has been significantly observed to inhibit the expression of mRNA and surface protein CD36 cells, which means myricetin might play an important role in ameliorating



atherosclerosis (Lian et al. 2008). During the experimental result of Perls' iron staining, it has made an evidence in the substantia nigra by the enhancement of iron-staining cells; myricetin prevented the 6-hydroxydopamine (6-OHDA) (Ma et al. 2007b). It has also been observed that antiproliferative potential of flavonoids decreased in the order isorhamnetin > kaempferol > myricetin > rutin, while their antioxidant properties decreased in the order rutin > myricetin > kaempferol > isorhamnetin. When combined the treatment of isorhamnetin, kaempferol, and myricetin with AraC has led to synergism in their antiproliferative activities (Nadova et al. 2007).

However, the result of myricetin on pharmacokinetics of carvedilol has not been reported in vivo. The enhanced oral bioavailability of carvedilol may result from both inhibition of CYP2C9 or CYP2D6-mediated metabolism and P-gp-mediated efflux of carvedilol in the small intestine and/or in liver by myricetin rather than reducing renal elimination (Lee et al. 2012).

### *Natsudaïdai*

Natsudaïdai (2-(3,4-dimethoxyphenyl)-3-hydroxy-5,6,7,8-tetramethoxychromen-4-one) was isolated from *Citrus reticulata* for the first time (Qian and Chen 1998). The name of the molecule comes from *Citrus natsudaïdai* (Natsumikan, lit. "summer tangerine") (Matsui et al. 2009).

### **Biological Properties**

Natsudaïdai exhibited less inhibitory effect on the pro-matrix metalloproteinase-9 (proMMP-9)/in HT-1080 cells and progelatinase B production (Miyata et al. 2008). Natsudaïdai has been shown to inhibit cyclooxygenase-2 and tumor necrosis factor- $\alpha$  production by p38 MAPK phosphorylation suppression, while there was no p65 NF- $\kappa$ B phosphorylation suppression observed, and that inflammatory diseases were also mitigated by natsudaïdai (Matsui et al. 2009).

Two flavonoids, natsudaïdai isolated and 3,5,6,7,8,3',4' heptamethoxyflavone (HEPTA) that are extracted from *Citrus* plants, in guinea pig papillary muscle produced a positive inotropic effect (PIE). It has also been observed (pD<sub>2</sub> 4.98  $\pm$  0.07) that natsudaïdai was more intense than (pD<sub>2</sub> 4.33  $\pm$  0.08) HEPTA (Itoigawa et al. 1994). Hydroxyl C-3 and C-8 methoxyl groups were necessary for efficient activity of natsudaïdai and other flavonols; on the other hand in B-ring ortho-catechol moiety and C-2, C-3 bonds were essential for the antiproliferative activity (Kawaii et al. 1999a). Natsudaïdai when treated with HL 60 cells in dose-dependent manner has exerted its activity as to differentiate into repertoire of macrophage and monocytes (Kawaii et al. 1999b).



## Drug Leads and Pharmacophores from Flavonols

Association of different bioactivities to flavonols has triggered computational studies to study and understand the mechanisms and interactions involved for obtaining new drug leads. Such studies involved molecular docking, three-dimensional structure-activity relationship, and pharmacophore modeling. Investigations have reported the interactions and pharmacophoric models for flavonols based on their interactions with cellular proteins. Using theoretical and computational approaches and the antioxidant activity of structure-activity relationship of flavonoids has been calculated (Butkovic et al. 2004; Ghiotto et al. 2004; Lee et al. 2009; Om and Kim 2008; Teixeira et al. 2005). A pharmacophore map based on flavonols suggested anti-angiogenic and thus antitumor drug leads as human vascular endothelial growth factor receptor 2 (hVEGFR2) antagonists (Yang et al. 2008). Therapeutic potential of flavonoids has been explained for genetic/metabolic disorders (i.e. xanthinuria, gout, and diabetes mellitus by inhibition of respective enzymes xanthine oxidase, aldose reductase, and liposygenase), but also for viral infections as well using computational approaches (Alves et al. 2001; Liu et al. 2012).

A study focused on inhibition of hVEGFR2 signaling for antitumor effects developed receptor-based pharmacophore model using crystal structures of inhibitor-hVEGFR2 complex and cyclin-dependent kinase 6 (CDK6) and flavonoid fisetin complex. Superimposition of these complexes helped in the identification of interactions between fisetin and hVEGFR2 and resulted in pharmacophore map. Hydrogen bond acceptors (HBAs), hydrogen bond donors (HBDs), and lipophilicity (Lipo) features were used to conclude the map. Resultant map had four features, two HBD, one Lipo, and one HBA. Virtual screening was performed, and the model yielded five out of nine hits with each hit flavonol having hydrogen bonding 3- and 4'-OH interacting with ATP binding site of hVEGFR2 (Yang et al. 2008).

A NS5B inhibitor pharmacophore model (Hypo 1) was developed using common feature-based pharmacophore and structure-based docking approaches for identification of novel antivirals for HCV. Discovery Studio's Common Feature pharmacophore generation protocol was used to develop the model with best conformational generation choice. The model was evaluated using decoy set of 1040 molecules of which 40, active against NS5B, were selected from the literature, while 1000 were randomly selected may bridge database. The model Hypo 1 was used to screen in-house database commercially available natural products with 3D structures and yielded 246 hits. These hits were investigated by docking studies and the list was reduced to 31. These results were validated in wet lab and showed inhibition of NS5B HCV enzyme (Liu et al. 2012).

## Conclusions

Attaining the spotlight since the 2000s, flavonols have been rigorously investigated for exploring their roles in metabolism, as antioxidant and also as potential drug leads. Being natural products, these are considered as much safer than the other pharmaceutical products. Current studies are focusing on evaluating the effects of flavonols on human/mammalian cells for developing more effective therapeutic agents. Sophisticated and sensitive techniques have enabled us to mine out and exploit more and more information shedding lights on curing of diseases. Multiple studies conducted have revealed the possibilities of flavonoids as leading to improved drugs for most of the clinically difficult to treat diseases in future.

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