BIOFLAVONOIDS CLASSIFICATION, PHARMACOLOGICAL, BIOCHEMICAL EFFECTS AND THERAPEUTIC POTENTIAL

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SUMMARY Flavonoids belong to a group of polyphenolic compounds, which are classified as flavonols, flavonones, flavones, flavanols, flavan-3-ols and isoflavones according to the positions of the substitutes present on the parent molecule. Flavonoids of different classes have several pharmacological activities. Flavonoids have also been known to posses biochemical effects, which inhibit a number of enzymes such as aldose reductase, xanthine oxidase, phosphodiesterase, Ca^{+2}-ATPase, lipoxygenase, cycloxygenase, *etc.* They also have a regulatory role on different hormones like estrogens, androgens and thyroid hormone. In view of their wide pharmacological and biological actions, they seem to be having a great therapeutic potential.

KEYWORDS Flavonoids biochemistry pharmacology therapeutic potential

INTRODUCTION

Flavonoids are a group of polyphenolic compounds, which are widely distributed through out the plant kingdom. To date about 3000 varieties of flovonoids are known[1]. Many have low toxicity in mammals and some of them are widely used in medicine for maintenance of capillary integrity[2]. Flavonoids exhibit several biological effects such as antiinflammatory, anti hepatotoxic and anti-ulcer actions[3,4]. They also inhibit enzymes such as aldose reductase and xanthine oxidase. They are potent antioxidants and have free radical scavenging abilities. Many have antiallergic, antiviral actions and some of them provide protection against cardiovascular mortality[5,6]. They have been shown to inhibit the growth of various cancer cell lines *in vitro*, and reduce tumour development in experimental animals[7]. In this review we have attempted to describe the present status of their classification, pharmacological/biochemical effects and their therapeutic potential.

Structure and classification of flavonoids:

Flavonoids occur as aglycones, glycosides and methylated derivatives. The flavonoid aglycone consists of a benzene ring (A) condensed with a six-membered ring (C), which in the 2-position carries a phenyl ring (B) as a substituent (Figure 1). Six-member ring condensed with the benzene ring is either a α-pyrone (flavonols and flavonones) or its dihydroderivative (flavanols and flavanones). The position of the benzenoid substituent divides the flavonoid class into flavonoids (2-position) and isoflavonoids (3-position). Flavonols differ from flavonones by hydroxyl group the 3-position and a C_2-C_3 double bonds[8]. Flavonoids are often hydroxylated in position 3,5,7,2',3',4',5'. Methylethers and acetylesters of the alcohol group are known to occur in nature. When glycosides are formed, the glycosidic linkage is normally located in positions 3 or 7 and the carbohydrate can be L-rhamnose, D-glucose, glucor-hamnose, galactose or arabinose[9]. The most common flavonoids are listed in Table 1.

I. Pharmacological Effects of Flavonoids

1. CNS Activity:

Synthetic flavonoids like 6-bromoflavone and 6-bromo-3'-nitro- flavones were shown to displace [3H] flumazenil binding to membranes from rat

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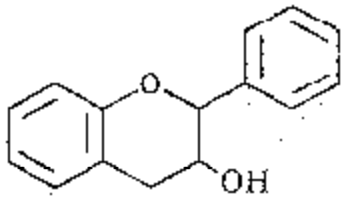
Table 1. Nomenclature of the subclasses of flavonoids based on the position of their substituents.

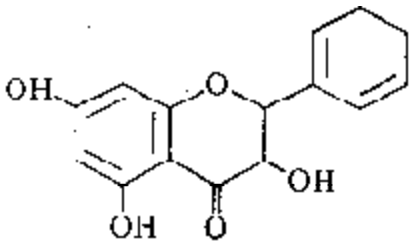
	3	5	7	2'	3'	4'	5'
Flavonols:							
Kaempferol	OH	OH	OH	H	H	OH	H
Morin	OH	OH	OH	OH	H	OH	H
Rutin	O-R[1]	OH	OH	H	OH	OH	H
Myricetin	OH	OH	OH	H	OH	OH	OH
Quercetin	OH	OH	OH	H	OH	OH	H
Quercetrin	O-Rh	OH	OH	H	OH	OH	H
Myricitrin	O-Rh	OH	OH	H	OH	OH	OH
Spirenoside	OH	OH	OH	H	OH	O-Glu	H
Galangin	OH	OH	OH	H	H	H	H
Robinin	O-R[1]	OH	OH	H	H	OH	H
Kaempferide	OH	OH	OH	H	H	O-Me	H
Fisetin	OH	H	OH	H	OH	OH	H
Rhamnetin	OH	OH	O-Me	H	OH	OH	H
Flavonones:							
Hesperitin	H	OH	OH	H	OH	O-Me	H
Naringin	H	OH	O-R	H	H	OH	H
Naringenin	H	OH	OH	H	H	OH	H
Eriodictyol	H	OH	OH	H	OH	OH	H
Hesperidin	H	OH	O-Me	H	OH	O-Me	H
Pinocembrin	H	OH	OH	H	H	H	H
Likvirtin	H	H	OH	H	H	O-Glu H	H
Flavones:							
Rpoifolin	H	OH	O-R	H	H	OH	H
Apigenin	H	OH	OH	H	H	OH	H
Tangeretin	H	O-Me	O-Me	H	H	O-Me	H
Flavone	H	H	H	H	H	H	H
Baicalein	H	OH	OH	H	H	H	H
Luteolin	H	OH	OH	H	OH	OH	H
Chrysin	H	OH	OH	H	H	H	H
Techtochrysin	H	OH	O-Me	H	H	H	H
Diosmetin	H	OH	OH	H	OH	O-Me	H
Diosmin	H	OH	O-R[1]	H	OH	O-Me	H
Flavanolols:							
Silibinin	OH	OH	OH	H	H	O-L-O -	H
Silymarin	OH	OH	OH	H	H	O-L-O -	H
Taxifolin	OH	OH	OH	H	OH	OH	H
Pinobanksin	OH	OH	OH	H	H	H	H
Flavan-3-o1s:							
Catechin	OH	OH	OH	H	OH	OH	H
Isoflavones:							
Genistein	-	OH	OH	H	H	OH	H
Daidzin	-	H	O-Glu	H	H	OH	H

-O-Me = Methoxy -O-Glu = Glucosyl -O-R' = Alkoxy -O-L-O = Selane

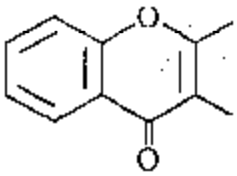
Figure 1. Basic structure of various flavonoids and related compounds.



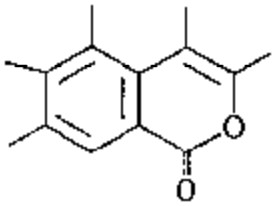
Flavan-3-ols



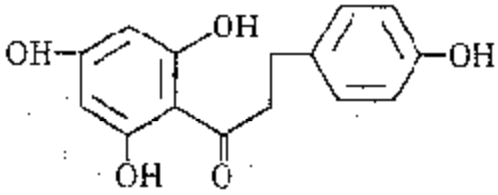
Flavanolols



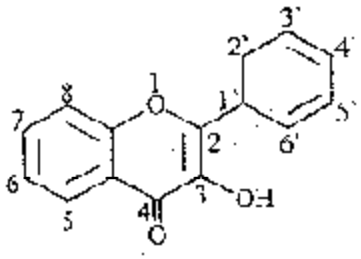
Benzo-γ-pyrone



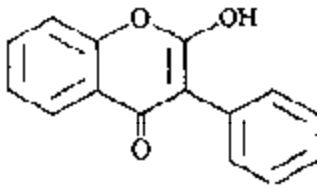
Coumarin



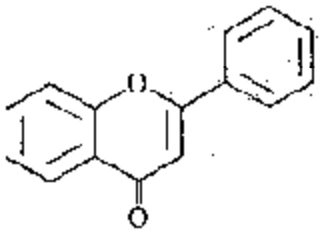
Chalchone



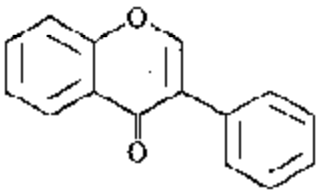
Flavonol



Isoflavenol



Flavone



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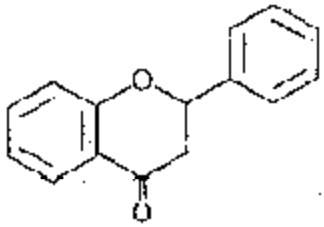
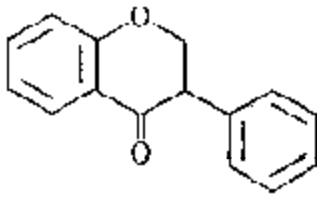
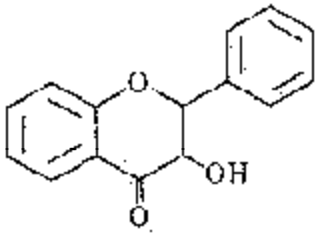


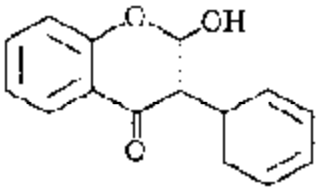
Flavanone



Isoflavanone



Flavononol



Isoflavanenol

cerebellum but not from spinal cord, indicating selectivity for the BZ-Omega receptor subtype, but latter was very potent than 6-bromoflavone. Results from two conflict tests in rats showed that these synthetic flavonoids possess anxiolytic like properties similar or superior to that of diazepam[10].

2. Cardiotonic activity:

Flavonoids have been reported to have action on the heart. The unsubstituted parent flavone exerts coronary dilatory activity and was commercially available under the name 'Chromocor' and its combination with routine and isoquercetin was also available with brand name 'flavoce', useful in the treatment of atherosclerosis. 3-methyl quercetin has positive chronotropic effect on guinea pig right atrium and antiarrhythmic effect on left atrium[11]. In recent report the cardiotoxicity (negative inotropic effect) of doxorubicin on the mouse left atrium has been inhibited by flavonoids, 7-monohydroxy ethyl rutoside and 71,3',4'- trihydroxyethyl rutoside. In a recent review Huesken *et al*. gave detailed discussion on the cardioprotective effects of flavonoids[12].

The glycosides of luteolin, apigenin and genistein produced antihypertensive activity even more than the reference drug papaverine. Three flavonoids showed vasorelaxant effect in order of potency, luteolin > eriodictyol > naringenin on rat thoracic aorta.

Luteolin, apigenin and genistein exhibited their action through different mechanisms by inhibition of the calcium release from sarcoplasmic reticulum, enzymatic systems such as protein kinase-C and the calcium influx[13]. Different flavonoids were tested for a positive inotropic effect on guinea pig papillary muscle placed at 0.2 Hz in a Kerbs-Henseleit solution at 30° C. Quercetin showed the most potent intrinsic activity, and produced the strongest inotropic responses among the different flavonoids. The relative order of potency of the tested flavonoids was, quercetin > morin = kaempferol > luteolin = apigenin > fisetin = galangin[14].

3. Lipid lowering activity:

Oxidative modification of low-density lipoproteins (LDL) by free radicals is an early event in the pathogenesis of atherosclerosis. The rapid uptake of oxidatively modified LDL *via* a scavenger receptor leads to the formation of foam cells. Oxidized LDL also has a number of other atherogenic properties. A number of mechanisms are likely to contribute to inhibition of LDL oxidation by flavonoids. Flavonoids may directly scavenge some radical species by acting as chain-breaking antioxidants[15]. In addition, they may recycle other chain-breaking antioxidants such as α-tocopherol by donating a hydrogen atom to the tocopheryl radical[16]. Transition metals such as iron and copper are important pro-oxidants, and some flavonoids can chelate divalent metal ions, hence preventing free radical formation. The ability of quercetin, and the quercetin glycosides, to protect LDL against oxidative modification has shown a significant protective effect [17-19]. Liquiritigenin showed a significant fall in serum cholesterol, LDL-cholesterol and atherogenic index. Influence of flavonoids on blood coagulation has been studied. The anticoagulant action of heparin was antagonized by flavonoids extracted from *T. hircanicum*. Ability of different flanovoids to inhibit the procoagulant activity of adherent human monocyties has been studied recently and hinokiflavone, a bioflavonoid has been found to be very most active in inhibiting the interleukin-1β induced expression of tissue factor on human monocytes[20]. Silymarin counteracts ethanol-induced lipid peroxidation injury by reducing liver MDA and raising GSH levels [22].

4. GIT:

a) Antiulcer Activity:

Some recent reports have indicated that many flavonoids possess antiulcerogenic activity. Oral treatment with the ether fraction of the flavonoid extract demonstrated a good level of gastric protection. Mucous content was increased and accompanied by proportionate increase in proteins and hexosamines[21]. β Hydroxy ethyl rutosides, gossypin, naringin, naringenin and (+)-Cyanidanol-3 were shown to exhibit anti-ulcer activity[22]. Quercetin, rutin and kaempferol administered intraperitoneally (25-100 mg/kg) inhibited dose-dependent gastric damage produced by acidified ethanol in rats. Flavone was inactive while naringin was active at a higher dose (200 mg/kg). Quercetin, kaempferol, morin, myricetin and rutin when tested were found to inhibit the mucosal content of platelet activating factor (P AF) in a dose dependent manner suggesting that the protective role of these substances may be

mediated by endogenous PAF[22]. Qurcetin, kaempferol, rutin produced an inhibitory effect on intestinal functions, and that their actions are mediated through α_2-adrenergic and calcium systems[23]. This result may show the beneficial effects in diarrhea and other intestinal secretions. Lorenz *et al* [25]. Showed that (+)-Cyanidanol-3 has histidine decarboxylase inhibitory activity and hence anti-ulcer activity[25]. 3-Methoxy-5,7,3',4'-tetra hydroxy flavan (Meciadanol), a congener of (+)-cyanidanol-3 exhibited significant anti-ulcer activity in pylorus ligated rats, restraint ulcers and gastric mucosal damage induced by aspirin models[22].

b) Hepatoprotective activity:

Many flavonoids have also been found to possess hepato-protective activity. In a study carried out to investigate silymarin, apigenin, quercetin and naringenin as putative therapeutic agents against microcrystin LR- induced hepatotoxicity, silymarin was found to be the most effective one[24]. Rutin and venorutin showed regenerative and hepato-protective effects in experimental cirrhosis[25]. The results of several clinical investigations showed the efficacy and safety of flavonoids in the treatment of hepato-biliary dysfunction and digestive complaints, such as sensation of fullness, loss of appetite, nausea and abdominal pain. Silymarin normalizes cell phospholipid synthesis without showing any demonstrable effect on undamaged cells where by counteracting fatty liver. Moreover, earlier findings on a hepato-protective effect and the prevention of NSAIDs-induced gastropathy may be confirmed[26,27].

5. Antioxidant activity:

Free radical production in animal cells can either be accidental or deliberate. With the increasing acceptance of free radicals as common place and important biochemical intermediates, they have been implicated in a large number of human diseases[28,29].

Quercetin, kaempferol, morin, myricetin and rutin by acting as antioxidants exhibited several beneficial effects, such as antiinflammatory, antiallergic, antiviral as well as an anticancer activity. They have also been suggested to play a protective role in liver diseases, cataracts, and cardiovascular diseases. Quercetin and silybin acting as free radical scavengers were shown to exert a protective effect in reperfusion ischemic tissue damage[30-32]. The scavenging activity of flavonoids has been reported to be in the order: myricetin > quercetin > rhamnetin > morin > diosmetin > naringenin > apigenin > catechin > 5,7-dihydroxy-3',4',5'-trimethoxyflavone > robinin > kaempferol > flavone[33]. Stabilization of meat lipids with flavonoids has been studied and morin, myricetin, kaempferol and quercetin at a level of 200 ppm were found to be most effective[34]. Induction period of lipid oxidation in canola oil was delayed with the flavonoid myricetin by upto fifteen days. Formation of oxidation products was also inhibited by 69%, during this period. Morin, myricetin, kaempferol and quercetin have also been suggested as stabilizers for fish oil as an alternative to synthetic antioxidants[35].

6. Effect on heat shock proteins:

Heat shock proteins (HSP) have been recognized against physiological stress such as heat shock, heavy metals and glucose starvation. Recent progress has revealed the role of HSPs in various diseases. HSP27 has been shown to be involved in the acquired resistance of tumour cells, hyperthermic and chemotherapeutic treatment. Aberrant expression of HSP could cause various autoimmune diseases. Flavonoids inhibited the expression of HSP27, HSP47, and HSP72/73[36]. The results suggested the pharmacological possibilities of flavonoids in diseases derived from abnormal expression of J-ISPs.

7. Anti-inflammatory activity:

A number of flavonoids are reported to possess anti-inflammatory activity. Hesperidin, a citrus flavonoid possesses significant antiinflammatory and analgesic effects[37]. Recently, apigenin, luteolin and quercetin have been reported to exhibit antiinflammatory activity. Quercetin, gallic acid ethyl ester and some as yet unidentified flavonoids might account for the antinociceptive action reported for the hydroalcoholic extract of *Phyllanthus caroliniensis*. Treatment with silymarin demonstrated reversal of the carrageenin induced biochemical changes. Detailed biochemical studies to establish mechanism of action of flavonoids have been carried out[38,39].

8. Antineoplastic activity:

Quite a number of flavonoids have exhibited antineoplastic activity. Recent reviews have highlighted this activity[40-42]. Detailed studies have revealed that quercetin exerted a dose dependent inhibition of cell

growth and colony formation. The flavonoids kaempferol, catechin, toxifolin and fisetin also suppressed cell growth[43,44]. On screening antileukaemic efficacy of 28 naturally occurring and synthetic flavonoids on human promyelocytic leukaemic HL-60 cells, genistein, an isoflavone was found to have strong effect. Genistein is also reported to inhibit in a dose dependent manner the growth of HGC-27 cells derived from human gastric cancer. Of the 14 flavonoids tested against murine and human cancer cell lines, 2',6'-diacetoxy -4,4' -dimethoxydihydro chalcone was the most potent and showed selectivity for the cell line P-388[45-50]. Trifolirhizin tetraacetate showed greater selectivity for the human cell lines.

9. Effects on blood vessels:

Quercetin and rutin have been used as effective constituents of several pharmaceuticals used for treatment of capillary fragility and phlebosclerosis. The activities of certain flavonoids in inhibiting capillary permeability and Arthus phenomenon were found to be in the following order, hesperitin > rutin > quercetin > naringenin > kaempferol > isoquercitol[51-54]. It has been suggested that flavonoids, which contain free hydroxyl groups at 3, 3' and 4' positions exert beneficial physiological effects on capillaries.

Flavonoids tangeratin, hesperidin, quercetin, and rutin have been found to reduce aggregation of horse erythrocytes. The decrease in blood cell aggregation produced by most of the flavonoids may explain the reported beneficial effects of these compounds on abnormal capillary permeability and fragility, the reduction of disease symptoms and their protection against various traumas and stresses[55]. The flavonoids O-(β- hydroxyethyl) rutoside, (+)- catechol, trihydroxyethylrutoside increased the negative charge density of the blood vessel wall *in vitro* and were markedly antithrombogenic[56]. Quercetin also has been reported to inhibit aggregation of human platelets by several authors. Other antiaggregatory flavonoids reported were 3-methyl quercetin, toxerutin, fisetin, dihydroquercetin and flavone. Nobeletin and sinensetin decreased erythrocyte aggregation and sedimentation *in vitro* and might be useful in dietary control of high blood viscosity syndrome[51-58]. Orally administered flavonoids weakly inhibit the vascular permeability and prevent pulmonary haemorrhage. Acacetin at 25-100 mg/kg oral dose to mice reduced capillary fragility and at 50-100 mg/kg it reduced vascular permeability[57,58]. Patuletin reduced the capillary permeability and was also reported to have antispasmodic and hypotensive effects.

10. Antimicrobial activity:

Flavonoids and esters of phenolic acids were investigated for their antibacterial, antifungal and antiviral activities. All samples were active against the fungal and gram-positive bacterial test strains and most showed antiviral activity[59].

i) *Antibacterial Activity:* Antibacterial activity has been displayed by a number of flavonoids. Twenty-five out of one hundred and eighty two flavonoid studies were found to be active against many bacteria. Most of the flavonones having no sugar moiety showed antimicrobial activities where as none of the flavonols and flavonolignans tested showed inhibitory activity on the microorganisms[59].

ii) *Antifungal Activity:* Number of flavonoids isolated from peel of tangerine orange, when tested for fungistatic activity towards Deuterophoma tracheiphila showed promising activity. Chlorflavonin was the first chlorine-containing flavonoid type antifungal antibiotic produced by strains of *Aspergillus candidus*[60].

iii) *Antiviral Activity:* Flavonoids also displayed antiviral, including anti-HIV activity. It has been found that flavonols are more active than flavones against herpes simplex virus type 1 and the order of importance was galangin > kaempferol > quercetin[61]. Recently, a natural plant flavonoid polymer of molecular weight 2100 Daltons was found to have antiviral activity against two strains of type-1 herpes type simplex virus, including a thymidine-kinase deficient strain and type -2 herpes simplex virus[62]. Out of twenty-eight fiavonoids tested, flavan-3-o1 was more effective than flavones and flavonones in selective inhibition of HIV-1, HIV-2 and similar immunodeficiency virus infections[63]. Details of the flavonoids and their antimicrobial activity were given in Table 2.

Table 2. Antibacterial, antifungal and antiviral activity of various flavonoids.

Organism	Flavonoids	References
Antibacterial activity:		
Staphylococcus aureus	Quercetin, Baicalin, Quercetogetin, Hespertin, Fisetin, iso-liquiritigenin[83], Naringin+rutin, Naringin+ Hespertin	64
Staphylococcus albus	Fisetin	65
Streptococcus pyogenes	Apigenin	66
Streptococcus viridans	Apigenin	67
Streptococcus jaccalis	Chrysin	68
Streptococcus baris	Chrysin	69
Streptococcus pneumoniae	Chrysin	70
Shigella boydii	Hespertin, Naringin+Rutin, Naringenin+Hespertin	71
Pseudomonas aeruginosa	Rutin, Naringin, Baicalin, Hydroxyethylrutosine	72
Escherichia coli	Quercetin	73
Bacillus subtilis	Quercetin	73
Bacillus anthracis	Rutin	74
Proteus vulgaris	Datisetin	76
Clostridium perfingens	Hydroxyethylrutoside	77
Antiviral activity:		
Rabies virus	Quercetin, Quercetrin, Rutin	84
Herpes Virus	Quercetin	85
Para influenza virus	Quercetin, Rutin	86
Herpes simplex virus type	Galangin, Quercetin, Kempferol	87
	Apigenin, Chrysin	88
Potato virus	Morin, Rutin+Quercetin	89
Influenza virus	Rutin+Quercetin	89
Herpes simplex virus type 2	Quercetin	90
Respiratory syncytial virus	Quercetin, Naringin	90
Immuno-deficiency virus infection	Apigenin	91
Auzesky virus	Quercetin, Quercetrin, Morin, Apigenin, Luteolin	92
Polio virus	Quercetin	93
Mengo virus	Quercetin	93
Pseudorabies virus	Quercetin	93
Antifungal activity:		
Candida albicans	Chloroflavonin	78
Candida tropicalis	Quercetin	79
Fusarium solani	Chrysoeriol	80
Botrytis cinerea	Chrysoeriol	80
Verticillium dahliae	Chrysoeriol	80
Azotobacter vinelandii	Quercetin, Rutin, Epicathenin	81
Alternacia tennisima	Apigenin, Echinacin	82
Cladosporium herbarum	Phaseolinisoflavan	83

II. Biochemical effects of flavonoids:

(i) On enzymes:

Flavonoids are known to inhibit a number of enzymes such as aldose reductase[107], xanthine oxidase[108], phosphodiesterase[109], Ca^{2+} A TPase[110], lipo-oxygenase[111] and cyclooxygenase[112]. Flavonols like quercetin, myricetin and kaempferol inhibit the activity of the adenosine deaminase of endothelial cells, while flavones are inactive[94]. Quercetin, morin, myricetin and kaempferol are effective in antagonizing bradykinin responses[95]. Effects of luteolin and quercetin on inhibition of tyrosine kinase, on cell growth and metastasis[96]. They have inhibitory properties on the 5'-nucleotidase (5'- ribonucleotide phosphohydrolase) activity[97]. Flavonoids inhibit intracellular Ca^{2+} elevation by reducing phospholipase-C activity[98] and they possess potent inhibitory effects on several enzyme systems such as protein kinase-C, protein tyrosine kinase, phospholipase A2 and others[99]. Flavonoids have high potencies and selectivities for inhibition of CYPIA isoenzymes[100]. Silymarin acts a strong antioxidant by virtue of its ability to act as an acceptor of O_2 or CCl_3 radicals. By trapping O_2 related free radicals silymarin hinders their interaction with polyunsaturated fatty acid and abolishes the enhancement of lipid peroxidation. Some flavonoids are predominant inhibitors of either cyclo-oxygenase or lipoxygenase, others are equally effective against both enzymes[101,102].

Numerous reports of a high standard have appeared on the inhibition by flavonoids of a perplexing number and variety of enzymes, *e.g.* hydrolases (such as α-glucuronidase), hyaluronidase, alkaline phosphatase, arylsulphatase, H^+-ATPases of lysosomal and granular membranes, Na^+/K^+-ATPase of the plasma membrane, α-galactosidase, c-AMP phosphodiesterase, lipases, lyases (such as DOPA- decarboxylase), transferases (like catechol-O-methyltransferase), hydroxylases (like aryl hydroxylase), oxidoreductases (like aldose reductase) and kiriases (*e.g.* hexokinase)[103-106]. Apigenin inhibits phosphodiesterase (PDE) and the effect was greater on cAMP-PDE than cGMP-PDE levels by 40 percent and cGMP level remained unchanged. Thus the cardiotonic action is due to the inhibition of cardiac cAMP-PDEI[13-114]. When one examines these enzymes, which are all influenced by a group of compounds of a rather homogeneous structure, one notices that they seem to have little in common. Therefore, they apparently interact with different parts of the flavonoid molecule, parts of flavonoid interact with enzymes were given in Table 3.

(ii) On hormones:

Flavonoids have also been shown to have regulatory activity of hormones, by binding to 17 beta-hydroxy steroid dehydrogenases, which regulates estrogen and androgen levels in humans and to 3 beta-hydroxy steroid dehydrogenase, which regulates progestin and androgen levels in humans[115]. Quercetin, myricetin, rutin, kaempferol affect the transport, metabolism and action of thyroid hormones. Quercetin myricetin, rutin, kaempferol, galangin, spirenoside and robinin are potent non-toxic ITH deiodinase inhibitors in microsomal membranes, and intact rat hepatocytes. Myricetin, rutin, kaempferol are specific high affinity competitors for L- T4-binding to human TBPA, weaker antagonists in the T3-5'-deiodinase reaction, and very poor inhibitors of T3 binding to the nuclear T3 receptor. Further investigation needs the role of ITH deiodination for tissue specific expression of thyroid hormone action as well advance the knowledge of specific interaction of flavonoids with antithyroidal agent with extra-thyroidal mechanism of action in the process of T_4 bioactivation to the thyromimetically active T_3[116].

(iii) Therapeutic potential of flavonoids:

The use of flavonoids in the treatment of diseases is to a large extent is much older than the science of chemistry. In view of the need for safe and effective treatment a study of the role of silymarin in the management of non-B acute viral hepatitis was investigated, which showed significantly earlier recovery from hepatomegaly and enlarged spleen in patients receiving silymarin. Both meciadiol and sofalcone have been studied for antiulcer effectiveness and found to be effective in clinical trials[22]. Sofalcone has been used clinically in Japan for treatment of gastroduodenal ulcers[122-125]. Treatment with hydroxy ethyl rutosides significantly improved the sensation of limb swelling, 'bursting' pain, heaviness, tension and mobility. They have been administered to a small number of patients with Raynaud's syndrome and produced reductions in the number of episodes, relief of pain and healing of ulcers. Improvements in fluorescein angiography-documented skin blood flow, heating

Table 3. Part of flavonoid molecule and its binding with enzymes.

Enzyme	Part of flavonoid	Reference
Adenosine deaminase	Benzopyrone ring	94
Tyrosine kinase	Phenyl ring	96
5'-Ribonucleotide phosphohydrolase	Carbohydrate	97
Phospholipase-C	Phenyl ring	98
Protein kinase-C	Phenyl ring	98
Protein tyrosine kinase	Benzopyrone ring	99
Phospholipase-A_2	Phenyl ring	99
Cyclooxygenase	Benzopyrone ring	99
Lipoxygenase	Benzopyrone ring	101,102
β-galactoside	Carbohydrate	103,104
β-galactoside	Carbohydrate	105
β-galacturonidase	Carbohydrate	103
Hyaluronidase	Carbohydrate	106
Alkaline phosphatase	Phenyl ring	103
Aryl sulphatase	Phenyl ring or Benzopyrone ring	107
DOPA Decarboxylase	Phenyl ring	110
Lipase	Phenol {Mg^{2+} Chelator)	112
ATPase	Benzopyrone ring	112
c-AMP Phosphodiesterase	Benzopyrone ring	113
Catechol-O-Methyl transferase	Phenyl ring	96
Aryl hydroxylase	Benzopyrone ring	96
Aldose reductase	Methylation of Hydroxy group at C_6/C_8	123
Proline hydrolases	Bcnzopyrone ring	96,98
Dehydrogenases	Phenyl ring	99, 111
Xanthine Oxidase	Free hydroxyl group at C_5 & C_7	145, 146
Phosphodiseterase	Free hydroxyl group at C_5 & C_7	112
Ca^{2+} ATPase	Free hydroxyl group at C_5 & C_7	113, 103, 106
Lipoxygenase	Free hydroxyl group at C_5 & C_7	114

Table 4. Diseases treated with flavonoids.

Flavonoids	Target	Disease	Reference
Hydroxyethylrutosides, Quercetin,silymarin.	PG synthesis	Pain and Inflammation, Night cramps, tiredness/heavy legs, oedema/swollen legs, Ankle/leg circumference.	37, 38, 39
Quercetin	Aldose reductase.	Diabetes mellitus	107
Rutin/citrin.	Capillary wall (pG)	Allergy	112
Disodium cromoglycate	H^+ ATPase	Allergy	103-106
Quercetin	Mast cell	Allergy	112
Quercetin	Capillary wall (PG)	Parodentosis	38
Quercetin	Na^+/K^+ATPase	Cancer	40-42
Quercetin	H^+ ATPase of lysosomal membrane.	Virus infection, Common cold	103-106
Quercetin	Arylhydroxylase, Epoxide hydroxylase	Chemical oncogenesis	
Sofalcone, Quercetin	PG synthesis	Oral surgery, Stomach, Head ache, Duodenal ulcers.	21,37,40
Rutin, Quercetin			
Kaempferol	PAF	Antiulcer	41
(+)-Cyandidanol-3 Meciadanol, Catechins	Gastic H^+/K^+ ATPase	Antiulcer	42

and resting pain have been reported in patients with severe arterial insufficiency of the lower legs receiving oral anticoagulants together with short term intravenous hydroxyethyl-rutosides therapy. Considering the number of flavonoids existing, the probability that the choice was less than optimal was high. Some of the diseases in which therapeutic attempts have been made with flavonoids are listed in Table 4.

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LOW DOSE ASPIRIN MAY HELP TO PREVENT PRE-ECLAMPSIA DURING PREGNANCY

A study in BMJ shows that antiplatelet drugs, largely low dose aspirin, have small to moderate benefits when used for prevention of pre-eclampsia and its complications during pregnancy.

Duley and colleagues reviewed 39 trials, involving over 30,000 women at risk of developing pre-eclampsia. Their findings suggest that antiplatelet drugs are associated a moderate (15%) reduction in the risk of pre-eclampsia, a 14% reduction in the risk of stillbirth or neonatal death, and an 8% reduction in the risk of preterm birth.

As the reductions in risk are moderate, relatively large numbers of women will need to be treated to prevent the death of one baby, explain the authors. However, from a public health perspective, even these moderate benefits may be worthwhile. Data from individual women need to be reviewed to identify which women are most likely to benefit, when treatment should be started, and at what dose, they conclude.

Source: Antiplatelet drugs for prevention of pre-eclampsia and its consequences: systematic review, BMJ 10th February 2001. Full article available at http://bmj.com/cgi/content/full/322/7282/329