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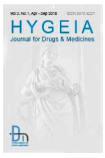
Review

.

Research article section: Health &Nutrition/Pharmacology



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IMPORTANCE OF FLAVONOIDES IN THERAPEUTICS

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Abstract

This review covers ,various categories of structurally novel therapeutically active flavonoids and their derivatives used in therapeutics, their chemical structures, crude drug sources, mechanisms of action, and interactions with different classes of synthetic drugs.

Introduction

Flavonoids (or bioflavonoid), collectively known as Vitamin P and citrin, are a class of plant secondary metabolites which are ubiquitous in photosynthesizing cells and are commonly found in fruits, vegetables, nuts, seeds, stems, flowers, tea, wine, propolis and honey. For centuries, preparations containing these compounds as the principal physiologically active constituents have been used to treat human diseases.

The function of flavonoids in flowers is to provide colors attractive to plant pollinators [1,3]. In leaves, these compounds are increasingly believed to promote physiological survival of the plant, protecting it from, for example, fungal pathogens and UV- radiation [2,3]. In addition, flavonoids are involved in photosensitization, energy transfer, the actions of plant growth hormones and growth regulators, control of respiration and photosynthesis, morphogenesis and sex determination [1,2].

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The basic structural feature of flavonoid compounds is the 2-phenyl-benzopyrane or flavane nucleus, which consists of two benzene rings (A and B) linked through a heterocyclic pyrane ring (C).

Increasingly, this class of natural products is becoming the subject of anti-infective research, and many groups have isolated and identified the structures of flavonoids possessing antifungal, antiviral and antibacterial activity.

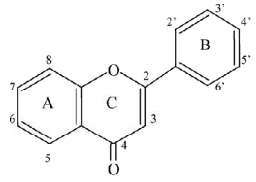
The flavonoids inhibit a perplexing number and variety of eukaryotic enzymes and have a tremendously wide range of activities. In the case of enzyme inhibition, this has been postulated to be due to the interaction of enzymes with different parts of the flavonoid molecule, e.g. carbohydrate, phenyl ring, phenol and benzopyrone ring [4].

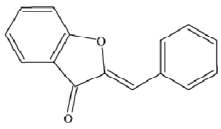
The vasodilator property of flavonoids is highly useful for the treatment of heart diseases. Literature search indicated that biflavones and isoflavones are potential blood circulation enhancers in brain. Several reviews showed that flavonoides possess wide spectrum of biological activities in cardio vascular system, which include anti oxidant, anti thrombotic, anti apoptic, anti ischemic, anti arrhythmic, and anti hypertensive activities.

Major dietary sources of Flavonoides in the form of flavonols, flavones, isoflavones, flavonones, biflavones are, tea , red wine , apple, tomato, cherry, onion, thyme, parsley, soyabeans, and other legumes, grape fruit, orange, lemon, ginkgo, and neem. The flavonoid groups of poly phenolic compounds have low toxicity in mammals and are widely distributed in plant kingdom. They have been shown to inhibit the growth of various cancer cell lines *invitro* and reduce tumor development.

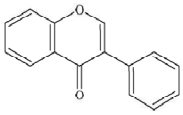
Flavonoides like kaempferol, myricetin, and quercetin are strong inhibitors of xanthine oxidase, and indicated in the treatment of gout, hyperuricemia, and reperfusion injury. The aldoreductase inhibition property of flavonoids found to be useful in diabetes induced retinopathy and cataract.Catechins acts as an antiulcer agent by inhibiting the H^+/ K ATPase .Liquritigenin administration in experimental animals showed significant fall in serum cholesterol. The cardio toxicity of doxorubicin can be countered by flavonoides like luteolin. Silymarin is proved as an effective hepatoprotective agent. Tyrosinase inhibitors like Butein (2', 4', 3, 4-Tetrahydroxychalcone)and other chalcones have become increasingly important in the cosmetic and medicinal products used in the prevention of hyperpigmentaion.

Usually HPLC, HPTLC and UV spectrophotometric methods can be used effectively for the qualitative and quantitative estimation of Flavonoides and related compounds in crude drugs. Researches are underway to study the effect of several flavonoids in diseases such as pneumonia, cancer, amoebic dysentery, worm infestations through bioinformatics studies of docking flavonoides on different protein structures involved in these diseases.

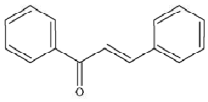




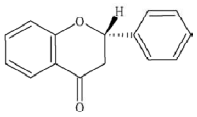
Aurone



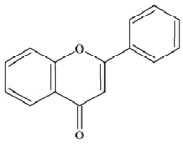
Isoflavone



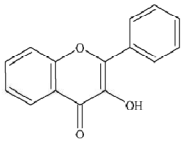
Chalcone



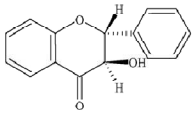
Flavanone



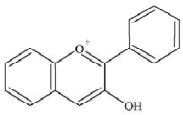
Flavone



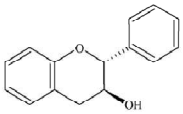
Flavonol



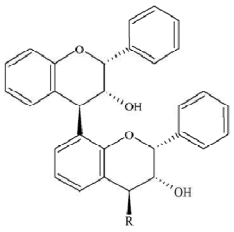
Flavanon-3-ol (also known as 3-hydroxyflavanone or dihydroflavonol)



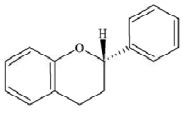
Anthocyanidin



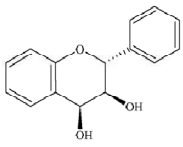
Flavan-3-ol (also known as catechin)



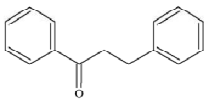
Proanthocyanidin (also known as flavolan or condensed tannin)



Flavan



Flavan-3,4-diol (also known as leucoanthocyanidin)



Dihydrochalcone

Compound	Substituents at carbon position:											
	2	3	4	5	6	7	8	2′	3′	4′	5′	6′
Flavones and their glycosides												
Acacetin	–	–	–	OH	–	OH	–	–	–	OCH_3	–	–
Apigenin	–	–	–	OH	–	OH	–	–	–	OH	–	–
Baicalin	–	–	–	OH	OH	OR1	–	–	–	–	–	–
Baicalein	–	–	–	OH	OH	OH	–	–	–	–	–	–
Chrysin	–	–	–	OH	–	OH	–	–	–	–	–	–
Gardenin A (demethylated)	–	–	–	OH	OH	OH	OH	–	OH	OH	OH	–
Genkwanin	–	–	–	OH	–	OCH_3	–	–	–	OH	–	–
Luteolin	–	–	–	OH	–	OH	–	–	OH	OH	–	–
Luteolin 7-glucoside	–	–	–	OH	–	OR2	–	–	OH	OH	–	–
7,8-Dihydroxyflavone	–	–	–	–	–	OH	OH	–	–	–	–	–
5,5′-Dihydroxy-8,2′,4′-trimethoxyflavone	–	–	–	OH	–	–	OCH_3	OCH_3	–	OCH_3	OH	–
5-Hydroxy-7,4′-dimethoxyflavone	–	–	–	OH	–	OCH_3	–	–	–	OCH_3	–	–
5,7,4′-Trihydroxy-3′,5′-dimethoxyflavone	–	–	–	OH	–	OH	–	–	CH_3	OH	CH_3	–
6,7,4′-Trihydroxy-3′,5′-dimethoxyflavone	–	–	–	–	OH	OH	–	–	CH_3	OH	CH_3	–
Isoflavones												
6,8-Diprenylgenistein	–	–	–	OH	R3	OH	R3	–	–	OH	–	–
Sophoraisoflavone A	–	–	–	OH	–	OH	–	*	*	OH	–	–
Flavonols and their glycosides												
Galangin	–	OH	–	OH	–	OH	–	–	–	–	–	–
Kaempherol	–	OH	–	OH	–	OH	–	–	–	OH	–	–
3-*O*-methylquercetin	–	OCH_3	–	OH	–	OH	–	–	OH	OH	–	–
Morin	–	OH	–	–	–	OH	–	OH	–	OH	OH	–
Myricetin	–	OH	–	OH	–	OH	–	–	OH	OH	OH	–
Quercetagetin	–	OH	–	OH	OH	OH	–	–	OH	OH	–	–
Quercetagetin-7-arabinosyl-galactoside	–	OH	–	OH	OH	OR4	–	–	OH	OH	–	–
Quercetin	–	OH	–	OH	–	OH	–	–	OH	OH	–	–
Quercetin-3-*O*-(2″-galloyl)-α-L-arabinopyranoside	–	OR5	–	OH	–	OH	–	–	OH	OH	–	–
Quercetrin	–	OR6	–	OH	–	OH	–	–	OH	OH	–	–
Robinetin	–	OH	–	–	–	OH	–	–	OH	OH	OH	–
Rutin	–	OR7	–	OH	–	OH	–	–	OH	OH	–	–
3,2′-Dihydroxyflavone	–	OH	–	–	–	–	–	OH	–	–	–	–
3,6,7,3′,4′-Pentahydroxyflavone	–	OH	–	–	OH	OH	–	–	OH	OH	–	–
Flavan-3-ols												
Catechin	–	OH	OH	–	–	OH	–	–	OH	–	OH	–
Epicatechin gallate	–	R8	–	OH	–	OH	–	–	OH	OH	–	–
Epigallocatechin	–	OH	–	OH	–	OH	–	–	OH	OH	OH	–
Epigallocatechin gallate	–	R8	–	OH	–	OH	–	–	OH	OH	OH	–
3-*O*-octanoyl-(+)-catechin	–	R9	–	OH	–	OH	–	–	OH	OH	–	–
3-*O*-octanoyl-(−)-epicatechin	–	R9	–	OH	–	OH	–	–	OH	OH	–	–
Flavanon-3-ols												
Dihydrofisetin	–	OH	–	–	–	OH	–	–	OH	OH	–	–
Dihydroquercetin	–	OH	–	OH	–	OH	–	–	OH	OH	–	–
Flavanones and their glycosides												
Lonchocarpol A	–	–	–	OH	R3	OH	R3	–	–	OH	–	–
Naringenin	–	–	–	OH	–	OH	–	–	–	OH	–	–
Naringin	–	–	–	OH	–	OR7	–	–	–	OH	–	–
Pinocembrin	–	–	–	OH	–	OH	–	–	–	–	–	–
Ponciretin	–	–	–	OH	–	OH	–	–	–	OCH_3	–	–
Sophoraflavanone G	–	–	–	OH	–	OH	R10	OH	–	OH	–	–
3-Methyleneflavanone	–	CH_2	–	–	–	–	–	–	–	–	–	–
5,7,4′-Trihydroxy-8-methyl-6-(3-methyl-[2-butenyl])-(2*S*)-flavanone	–	–	–	OH	R3	OH	CH_3	–	–	OH	–	–
Chalcones												
Licochalcone A	–	R11	OH	–	OCH_3	–	–	–	–	OH	–	–
Licochalcone C	–	–	OH	R3	OCH_3	–	–	–	–	OH	–	–
2,4,2′-Trihydroxychalcone	OH	–	OH	–	–	–	–	OH	–	–	–	–
2.4.2′-Trihydroxy-5′-methylchalcone	OH	–	OH	CH_3	–	–	–	OH	–	–	–	–
Flavan-3,4-diols and anthocyanidins												
Leucocyanidin	–	OH	OH	OH	–	OH	–	–	OH	OH	–	–
Pelargonidin chloride	–	Cl	–	OH	–	OH	–	–	–	OH	–	–
Flavans												
6,4′-Dichloroflavan	–	–	–	–	Cl	–	–	–	–	Cl	–	–
7-Hydroxy-3′,4′-(methylenedioxy)flavan	–	–	–	–	–	OH	–	–	#	#	–	–

R1: Glucuronic acid; R2: glucose; R3: prenyl group; R4: arabinose–galactose; R5: (2″-galloyl)-α-L-arabinopyranoside; R6: rhamnose; R7: rhamnose–glucose; R8: gallic acid; R9: octanoyl; R10: lavandulyl; R11: 3-methyl-1-butene.

–, no substitution; *, pyran ring between positions 2′ and 3′; #, O-CH_2-O between positions 3′ and 4′.

Note: Hinokiflavone and robustaflavone are biflavonoids (also known as biflavonyls) consisting of two apigenin molecules joined through I-6-*O*-II-4′ and I-6-II-3′ linkages, respectively.

Sl no:	Name of crude drugs	Parts of plant used	Family	Major active constituents	Nature of therapeutic action
1	Crannbery	Fruits	Ericaceae	Flavonol glycosides	Colon and prostrate cancer.
2	Acacia greggii	Seeds and branch	Fabaceae	Fisetin, catechins and quercetin	Anticarcinogenic
3	Grapefruits	Fruits	Rutaceae	Kaempferol , myricetin	Breast cancer, pancreatic cancer
4	Brussels sprout	Leafy green buds	Brassicaceae	Kaempferol	Anticancer activity
5	Apple	Fruits	Rutaceae	Kaempferol myricetin	Colon ,prostrate and lung cancer
6	Basil	Seeds and leaves	Lamiaceae	Apigenin	Breast cancer
7	Celery	seeds	Apiaceae	Apigenin	Skin cancer
8	Chamomile	Flowers	Asteraceae	Apigenin	Anticancer activity
9	Strawberry	Fruits	Rosaceae	Catechins , anthocyanins	Lung cancer
10	Turmeric	Rhizomes	Zingiberaceae	Curcumin	Pancreatic and colon cancer
11	Dalandan	Fruits	Rutaceae	Hespiridine	Slows the proliferation of cancer cells
12	Buck wheat	Seeds	Polygonaceae	Quercetin, rutin	Decrease the proliferation of cancer cells
13	Milk thistle	Herbs and flowers	Asteraceae	Silymarin	Anti cancer
14	Acai palm	Fruits	Arecaceae	Taxifolin	Reduce the proliferation of cancer cells
15	Soybean	Beans and flowers	Fabaceae	Genistein , daidzein	Brain, colon, prostrate, breast and cervical cancer.
16	Green tea	Leaves	Theaceae	Catechins	Breast cancer
17	Psoralea	Roots	fabaceae	Genistein	Anticancer
18	Black Raspberry	Fruits	Rosaceae	Anthocyanin	Effective in the initiation and progressoion stage of tumor
19	Garlic	Bulbs	Alliaceae	Apigenin	Breast cancer
20	Citrus fruits	Citrus peels.	Rutaceae	Tangeritin	Anti cancer
21	Pinto beans	Beans and flowers	Fabaceae	Genistein	Prostrate , breast cancer
22	Blue berry	Fruits and flowers	Ericaceae	Anthocyanins	Against cancer cell development

Common Dietary Flavonoids		
Flavonoid Subclass	Dietary Flavonoids	Some Common Food Sources
Anthocyanidins	Cyanidin, Delphinidin, Malvidin, Pelargonidin, Peonidin, Petunidin	Red, blue, and purple berries; red and purple grapes; red wine
Flavanols	Monomers (Catechins): Catechin, Epicatechin, Epigallocatechin Epicatechin gallate, Epigallocatechin gallate Dimers and Polymers: Theaflavins, Thearubigins,Proanthocyanidins	Catechins: Teas (particularly green and white), chocolate, grapes, berries, apples Theaflavins, Thearubigins: Teas (particularly black and oolong) Proanthocyanidins: Chocolate, apples, berries, red grapes, red wine
Flavanones	Hesperetin, Naringenin, Eriodictyol	Citrus fruits and juices, e.g., oranges, grapefruits, lemons
Flavonols	Quercetin, Kaempferol, Myricetin, Isorhamnetin	Widely distributed: yellow onions, scallions, kale, broccoli, apples, berries, teas
Flavones	Apigenin, Luteolin	Parsley, thyme, celery, hot peppers,
Isoflavones	Daidzein, Genistein, Glycitein	Soybeans, soy foods, legumes

Conclusion

The present review covers the important flavonoids and related derivatives used in therapy for various ailments, their structures, crude drug sources and their mechanism of action and also involve the compilation and search for structurally novel therapeutically active flavonoids. The data indicated that flavonoids possess many pharmacological activities like anti ulcer, anti ageing, anti bacterial, anti oxidant, anti fungal, anti-inflammatory, anti diabetic, anti hepatotoxic, anti allergic anti cacer,anti tumor and vasodilator properties .Also flavonoids show potential vitamin C sparing activity and activities of lipoxygenase , cyclooxygenase, proteinkinase C, tyrosine kinase, etc.

Majority of flavonoids are powerful antioxidants that help neutralize harmful free radicals and prevent oxidative stress which damage cells and DNA, and which can lead to aging and degenerative diseases like cancer and Alzheimer's or Parkinson's disease. Flavonoides normally enhances the effects of the other

antioxidant vitamins, and increases levels of glutathione, an important and powerful antioxidant, normally works with vitamin C to strengthen and protect blood vessel structure, and reduce prolonged bleeding, bruising, and nosebleeds. Flavonoides may help prevent and treat cataracts, reduces the risk of cardiovascular disease and heart attack by lowering LDL cholesterol level and stopping blood platelets from clumping, which minimizes blood clotting and prevents build-up of atherosclerotic plaque on artery walls . Quercetin has natural anti-histamine and anti-inflammatory properties, and taken with bromelin may be useful in preventing and treating asthma and other allergies also has got antibiotic-like effect due to anti-viral and anti-bacterial activity, and also anti-allergic and anti-inflammatory properties and proved clinically in the treatment of hemorrhoids and varicose veins.

Flavonoid-Drug –Food interactions

Crude drug	**Name of flavonoids present**	**Enzyme**	**Class of synthetic drugs**	**Action of enzyme**	**interactions**
grapefruit	dihydroxybergamottin	cytochrome P450 (CYP) 3A4	atorvastatin, lovastatin, and simvastatin felodipine, nicardipine, nisoldipine, nitrendipine, verapamil terfenadine amiodarone cyclosporine saquinavir diazepam, midazolam sildenafil	inhibit the intestinal drug metabolizing enzyme, cytochrome P450 (CYP) 3A4	increase the bioavailability and the risk of toxicity of drugs
Grapefruit Green tea Red and Yellow onions	Quercetin, naringenin, and the green tea flavanol, epigallocatechin gallate (EGCG)	P-glycoprotein	digoxin, antihypertensive agents, antiarrhythmic agents, anticancer agents, antifungal agents, HIV protease inhibitors, immunosuppressive agents, H2 receptor antagonists	P-glycoprotein is an efflux transporter that decreases the absorption of a number of drugs. Flavonoides inhibits the activity of P-glycoprotein	potentially increasing the toxicity of drugs
from purple grape juice, dark chocolate			Increase the risk of bleeding when taken with anticoagulant drugs, such as warfarin (Coumadin), and antiplatelet drugs, such as clopidogrel (Plavix), dipyridamole (Persantine), non-steroidal anti-inflamatory drugs (NSAIDs), aspirin.	inhibit plateletaggregation	increase the risk of bleeding
flavonoid-rich beverages	normal flavonoides		flavonoid-rich beverages or flavonoid supplements should not be taken along with meals	.	Flavonoids can bind nonheme iron, inhibiting its intestinal absorption

Sl no.	Enzymes and Flavonoids	Mechanism of action
1.	**Kinases**	
	a) Quercetin	Acted as a competitive inhibitor of ATP binding and was more effective as an inhibitor of the enzyme.
	b) Fisetin	Inhibitor of nonactivated phosphorylase kinase
	c) Hesperetin	Stimulate the enzyme protein tyrosine kinase.
2.	**Phospholipase A_2**	
	a) Quercetin	Effective inhibitor of PLA_2
3.	**ATPases**	
	a) Quercetin	Competitive inhibitor of ATP binding to the enzyme
4.	**Lipoxygenases and cyclooxygenases**	
	a) Silymarin	Inhibition of cyclooxygenase
	b) Quercetin	Effective inhibitor of 12-LO activity in human platelets.
5.	**Phospholipase C**	
	a) Genistein	Blocks PLC activation and formation of inositol triphosphate (IP_3) and diacylglycerol (DAG)
6.	**Adenylate Cyclase**	
	a) Apigenin	Decreases the platelet cAMP response to prostacyclin, an effect attributed to inhibition of adenylate cyclase.
	b) Chrysin	
7.	**Ornithine Decarboxylase**	
	a) Quercetin	Suppress the stimulatory effect of ODC activity and on skin tumor formation.
8.	**Glyoxalase**	
	a) Fisetin	Glyoxalases detoxify glyoxalase I by facilitating
	b) Myricetin	their oxidation to inert glyoxalase II.
	c) Quercetin	

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No.	Herb/ source	Ref.no.	Phytoconstituents	Therapeutic uses	Mechanism of action	Enzymes involved
1	*Tagetes minuta*	5	quercetagetin-7-arabinosyl-galactoside	to treat infectious disease	-	-
2	*Eysenhardtia texana*	7	5,7,4_-trihydroxy-8- methyl-6-(3-methyl-[2-butenyl])-(2*S*)-flavanone	against the pathogen *Candida albicans*	-	-
3	*Terminalia bellerica*	8	7-hydroxy-3^1,4^1 (methylenedioxy)flavan,	against *C. albicans*	-	-
4	*Artemisia giraldi*	32,9	6,7,4_-trihydroxy-3^1,5^1 dimethoxy flavone and 5,5- dihydroxy-8,2,4 – trimethoxyflavone , together with 5,7,4_- trihydroxy-3,5 - dimethoxyflavone	against *Aspergillus flavus*	-	-
5	Propolis	10,9	Galangin,	against *Aspergillus tamarii*, *A. flavus*, *Cladosporium sphaerospermum*, *Penicillium digitatum* and *Penicillium italicum*	-	-
6	*Rhus succedanea* and *Garcinia multiflora*	38,11	Baicalein robustaflavone and hinokiflavone	inhibits HIV-1 infection and replication	Inhibit HIV-1 reverse transcriptase.	HIV-1 reverse transcriptase.
7	*Acer okamotoanum*	12,13	Robinetin, myricetin, baicalein, quercetagetin [12] and quercetin 3-*O*-(2__-galloyl)--l-arabinopyranoside	inhibits HIV-1 infection	Inhibit HIV-1 integrase.	HIV-1 integrase.
8	Flavone containing plants	12	caffeic acid phenethyl ester (CAPE)	inhibits HIV-1 infection	Inhibit HIV-1 integrase.	HIV-1 integrase.
9	Plant flavones and flavans	1,14	quercetin, morin, rutin, dihydroquercetin, dihydrofisetin, leucocyanidin, pelargonidin chloride and catechin	against herpes simplex virus (HSV), respiratory syncytial virus, poliovirus and Sindbis virus	binding of viral nucleic acid or viral capsid proteins .	inhibition of viral polymerase
10	Plant flavonoides	14	kaempferol and luteolin	Against HSV(herpes simplex virus).	Synergism	-
11	synthetic	1	6,4-dichloroflavan	anti viral		
12	Synthetic & natural	15	Quercetin, and 5-ethyl-2-dioxyuridine and acyclovir	potentiation	against HSV and pseudo rabies infection	
13	Synthetic & natural	15	Apigenin and acyclovir	antiviral	against HSV and pseudo rabies infection	
14	Normal plant flavovonoides	16,17,118, 19, 20,21	apigenin, galangin, pinocembrin,ponciretin, genkwanin, sophoraflavanone G and its derivatives, naringin and naringenin,	Anti bacterial	-	-

		, 22,23 , 24,25 , 26	epigallocatechin gallate and its derivatives, luteolin and luteolin 7-glucoside, quercetin, 3-*O*-methylquercetin and kaempferol			
15	Flavonoides with transition metals	27	5-hydroxy- 7, 4-dimethoxyflavone with a number of transition metals	increased antibacterial activity	-	-
16	Flavonoides with bromine or chlorine substituents	28	3-methyleneflavanones with the B ring contains bromine or chlorine substituents	increased antibacterial activity	-	-
17		29	sophoraisoflavone- A and 6,8-diprenylgenistein	significant protection to mice challenged with colony-forming units (CFUs) of *Salmonella typhimurium*	*Inhibit Salmonella typhimurium*	-
18	Structure activity relationship of flavonoides	30	2,4- or 2^1,6^1dihydroxylation of the B ring and 5,7-dihydroxylation of the A ring in the flavanone structure was important for anti-MRSA activity.	Anti- Methicillin Resistant *Staphylococcus aureus*.	-	-
19	Structure activity relationship of flavonoides	30	Substitution at the 6 or 8 position with a long chain aliphatic group such as lavandulyl (5-methyl 2- isopropenyl-hex-4-enyl) or geranyl (trans-3,7-dimethyl-2,6- octadienyl) also enhanced activity	Anti- Methicillin Resistant *Staphylococcus aureus*	-	-
20	Structure activity relationship of flavonoides	31	with C8 and C10 chains of flavonoids belonging to the flavan- 3-ol class	antistaphylococcal activity	-	-
21	Structure activity relationship of flavonoides	32	5-hydroxyflavanones and 5-hydroxyisoflavanones with one, two or three additional hydroxyl groups at the 7, 2^1 and 4^1 positions	Inhibit the growth of *Streptococcus mutans* and *Streptococcus sobrinus*.	-	-
22	Structure activity relationship of flavonoides	39	importance of a hydroxyl group at position 5 of flavanones and flavones	Required for the activity against MRSA.	-	-
23	Structure activity relationship of flavonoides	33	importance of hydroxylation at the 2-position for antibacterial activity of chalcones, found that 2, 4, 2-	inhibit the growth of 15 strains of cariogenic streptococci	-	-

			trihydroxy-5_-methylchalcone and 2, 4, 2- trihydroxychalcone			
24	Structure activity relationship of flavonoides	33	Substitution of the B ring was found to enhance antibacterial activity, with 3-chloro, 4- chloro and 4_-bromo analogues	twice as effective as their parent compound against *S. aureus*, and four times more active against *Enterococcus faecalis*		
25	*Proteus vulgaris*,	34	robinetin, myricetin and (−)-epigallocatechin.	Anti bacterial action	the B ring of the flavonoids may play a role in intercalation or hydrogen bonding with the stacking of nucleic acid bases and this may explain the inhibitory action on DNA and RNA synthesis	
26	yellow onions, scallions, red onions	35	quercetin	Anti bacterial action	binds to the GyrB subunit of *E. coli* DNAgyrase and inhibits the enzyme's ATPase activity	*E. coli* DNAgyrase
27	Ruta graveolens and related plants	36	rutin	Anti bacterial action	Induce topoisomerase IV-mediated DNA cleavage leads to an SOS response and growth inhibition of *E. coli* cells	Topoisomerase IV Topoisomerase IV is essential for cell survival.
28	Green tea	37	Epigallo catechin gallate	against Gram-positive than Gram-negative bacteria	epigallocatechin gallate induced leakage & aggregation of small molecules from the intraliposomal space and results in the damage of bacterial membrane	
29	Roots of *Glycyrrhiza inflata*	38	licochalcones A and C	against *S. aureus* and *Micrococcus luteus*	Licochalcones A and C	NADH-cytochrome *c*

					effectively inhibited NADH-cytochrome *c* reductase	reductase
30	Parsley, thyme, celery, hot peppers,	40	Vitexin,quercetin	Maintain capillary permeability, capillary resistance due to the substances like hyaluronic acid or chondroitin, which are subjected to attack by hyaluronidase enzyme	Inhibitor of hyaluronidase.	Hyaluronidase.
31	Flavonoides	41,42	Most of the flavonoides	Ability of flavonoids to chelate (bind) metal ions like iron, copper, appears to contribute to their antioxidant activity in vitro	-	-
32	Parsley, thyme, celery, hot peppers,	43,44	Luteolin	inhibits vascular endothelial growth factor-induced angiogenesis; inhibition of endothelial cell survival and proliferation by targeting phosphatidylinositol 3'-kinase activity	Inhibiting tumor invasion and angiogenesis	Phosphatidyl inositol 3'-kinase
33	black tea polyphenols	45,46	polyphenols	Endothelial nitric oxide synthase (eNOS) activity is the enzyme that catalyzes the formation of nitric oxide by vascular endothelial cells. Nitric oxide is needed to maintain arterial relaxation (vasodilatation). Impaired nitric oxide-dependent vasodilatation is associated with increased risk of cardiovascular disease	Activation of endothelial nitric-oxide synthase	nitric-oxide synthas
35	Green tea polyphenolic compounds in the diet	47,48, 49	epigallocatechin-3-gallate	Inhibiting platelet aggregation ,there by preventing the primary and secondary cardiovascular disease	Platelet aggregation is one of the first steps in the formation of a blood clot that can occlude a coronary or cerebral artery, resulting in myocardial infarction or stroke. Flavonoides like epigallocatechin gallate inhibit platelet aggregation	-
36	Green tea polyphenolic compounds	50	epigallocatechin-3-gallate	Daily consumption of 4-5 cups (900-1,250 ml) of black tea for four weeks significantly improved endothelium-dependent vasodilatation in patients with coronary artery disease	Green tea poly phenols promote the production of nitric oxide, that facilitate arterial relaxation (vasodilatation)	-

37	flavonols and flavones ,flavonoid-rich diets	51	flavonols and flavones	Inflammation, oxidative stress, and transition metal accumulation appear to play a role in the pathology of several neuro degenerative diseases, including Parkinson's disease and Alzheimer's disease	flavonoides have anti-inflammatory, antioxidant, and metal-chelating properties.	
38	Onions,citrous fruits	52	Quercetin,kaempferol,hesperidin,naringin	Protein kinase C (PKC), , largely Ca^{2+}- and phospholipid-dependent, multifunctional serine- and threonine-phosphorylating enzyme, is involved in a wide range of cellular activities, including tumor promotion, mitogenesis, secretory processes, inflammatory cell function, and T lymphocyte function	Inhibit protein kinase C	Protein kinase C (PKC)
39	Yellow and red Onions	53	Quercetin	Phospholipase A_2 (PLA_2) releases arachidonic acid for the metabolism via the cyclooxiginase (CO) and lipoxigenase (LO) pathways. PLA_2 is likely an important intra- and extracellular mediator of inflammation	Quercetin was found to be an effective inhibitor of PLA_2	Phospholipase A_2
40	Red and yellow onins, citrous fruits Oxalis corniculata	54	Hesperidin, vitexin, quercetin	cAMP and cGMP are formed from ATP and GTP by the catalytic activity of adenylate and guanylate cyclases. Their activity is terminated by the cyclic nucleotide phosphodiesterases (PDE).	Flavonoides are found to be inhibitors of this enzyme PDE due to the structural mimicry of the pyrimidine ring in cAMP and the pyranone ring of flavonoides	cyclic nucleotide phosphor diesterases
41	Widely distributed: yellow onions, scallions, kale, broccoli, apples, berries, teas	55,56	Gardenin A, myricetin, morin, quercetin, and fisetin	The enzyme HIV-1 Proteinase and HIV-1 Integrase is the necessary component for the processing and replication of HIV- 1.inhibited by flavonoides	inhibitors of the enzymes HIV-1 Proteinase HIV-1 Integrase	HIV-1 Proteinase HIV-1 Integrase
42	yellow onions, scallions, kale, broccoli, apples,	57	quercetin, chrysin, apigenin	Inhibit the enzyme aromatase	The conversion of androstenedione to estrone is catalyzed by aromatase. Inhibition of aromatase contribute to the control of estrogen-dependent conditions, such as breast cancer.	aromatase
43	Widely distributed: yellow onions, scallions, kale, broccoli, apples, berries, teas	58	Quercetin, fisetin, myricetin,	Glyoxalase substrates may be important in the regulation of cell division.	potent inhibitors of glyoxalase I	Glyoxalase
44	Rhododendron dauricum [Chinese Alpenrose])	59	3′-hydroxyfarrerol	For the pharmacotherapy of chronic lung disorders characterized by leukocytic infiltration.	inhibit human neutrophil elastase, reduce tumor necrosis factor	neutrophil elastase
		60,61		Reverse transcriptases are enzymes that enable	Anti viral	Reverse transcriptases

45	Scutellaria baicalensis (Baikal skullcap)		Baicalein (5,6,7-trihydroxyflavone)	viruses to invade healthy cells and duplicate themselves Baicalein has been described as the most significant non-nucleoside reverse transcriptase inhibitors		
46	parsley, artichoke, basil, Roman chamomile and celery	62	Apigenin	Anti leukemic	Inhibit topo isomerase enzyme	topo isomerase
47	Black cohosh, chaste berry and red clover	63	Genistein, biochanin and formonometin ,aucubin (phyto estrogens)	Reduction in the effects of ageing, including the improvement of the quality of the skin and the delay of osteoporosis. Phyto-estrogens are frequently suggested for HRT (Hormone Replacement Therapy), to overcome menopausal disorders such as osteoporosis, hot flushes, etc.	Reduction in the effects of ageing	-
48	*Felmingia vestita*	64	Genistein	exerts its anthelmintic activity by inhibiting the enzymes of glycolysis and glycogenolysis, and disturbing the Ca2+ homeostasis and NO activity in the parasites	anthelmintic	-
49	passion flower, *Vitex agnus-castus* (chaste tree or chaste berry) and in the *Phyllostachys nigra* bamboo leaves	65	vitexin	Reduce goitre	inhibits thyroid peroxidase	thyroid peroxidase
50	Hepatica nobilis	66	Astragalin isoquercetrin	Used for liver disease,jaundice	-	-
51	Fraxinus exelsior	67	rutin	Analgesic, antiphlogigistic	-	-
52	Drosera rotundifolia	68	Hyperoside,kaempferol	Expectorant, anti spasmodic	-	-
53	Trigonella foenum	69	Iso oientin,iso vitexin,orientin	Inflammation of the skin	-	-
54	Orthosiphon spicatus	70,71	Eupatorin,scutellarine, sinensetin	Urolithiasis (Kidney and bladder stone)	-	-