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CHEMISTRY AND PATHOPHYSIOLOGY OF 2–PHENYL–4H–CHROMEN–4–ONE DERIVATIVES AS HOLISTIC FLORA IN THE FORM OF GLYCOSIDIC AGLYCONE

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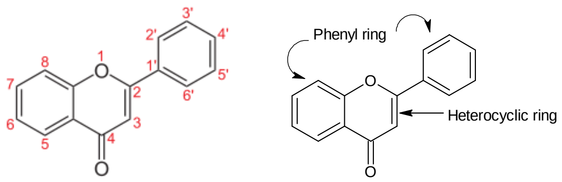
ABSTRACT

Flavones are flavonoids characterized by a nonsaturated 3–C chain and have a double bond between C–2 and C–3, like flavonols, with which they differ by the absence of hydroxyl in the 3–position. It appears that this simple difference in structure between flavones and flavonols has very important consequences in the biogenesis, physiological, and pharmacological roles, and the phylogenetic and chemotaxonomic signification of these compounds. Flavones are widely distributed among the higher plants in the form of aglycones of glycosides. Flavonols are molecules present in most plants that are an important component of some human diets. Epidemiological evidence shows the beneficial effects of these molecules in cardiovascular and neuropathological diseases. Experimental evidence in–vitro and in–vivo has confirmed the neuroprotective effects in neurons in culture against oxidative insults and in models of focal ischemia and experimental parkinsonism. Nevertheless, the active concentration range in–vitro is very narrow, and effects on brain pathology have been shown mostly after chronic administration. Although the preventive effects of flavones and flavonols in brain pathology could be considered mostly substantiated, the positive neuroprotective activity after acute administration still deserves more research.

KEYWORDS: Benzopyran, Chromen, Flavones, Flavonoids, Polyphenols.

INTRODUCTION

Flavones (flavus = yellow), are a class of flavonoids based on the backbone of 2–phenylchromen–4–one (2–phenyl–1–benzopyran–4–one). Flavones are mainly found in spices and red or purple plant foods. The estimated daily intake of flavones is about 2 mg per day. Flavones have proven physiological effects in the human body and have sufficient antioxidant food value. Following ingestion and metabolism, flavones, other polyphenols, and their metabolites are absorbed poorly in body organs and are rapidly excreted in the urine, indicating mechanisms influencing their presumed absence of metabolic roles in the body.[1–5]



Figure–1: Skeleton of flavone.

Flavones from natural sources

1. Primuletin [5–Hydroxy–2–phenyl–4H–chromen–4–one]

2. Chrysin [5,7–Dihydroxy–2–phenyl–4H–chromen–4–one] is a flavone found in honey, propolis, the passion flowers, *Passiflora caerulea* and *Passiflora incarnata*, and in *Oroxylum indicum*. It is extracted from various plants, such as the blue passion flower (*Passiflora caerulea*). Following oral intake by humans, chrysin has low bioavailability and rapid excretion. It is under basic research to evaluate its safety and potential biological effects.

3. Techtochrysin [5–hydroxy–7–methoxy–2–phenylchromen–4–one] is a chemical compound. It is an O–methylated flavone, a flavonoid isolated from *Prunus cerasus*, the sour cherry, a plant native to much of Europe and southwest Asia.

4. Primetin [5,8–dihydroxy–2–phenylchromen–4–one]

5. Apigenin (5,7–Dihydroxy–2–(4–hydroxyphenyl)–4H–1–chromen–4–one), found in many plants, is a natural product belonging to the flavone class that is the aglycone of several naturally occurring glycosides. It is a yellow crystalline solid that has been used to dye wool.

6. Acacetin [5,7–dihydroxy–2–(4–methoxyphenyl)–4H–1–chromen–4–one] is an O–methylated flavone found in *Robinia pseudoacacia* (black locust), *Turnera diffusa* (damiana), *Betula pendula* (silver birch), and in the fern *Asplenium normale*.

7. Genkwanin [5–hydroxy–2–(4–hydroxyphenyl)–7–methoxychromen–4–one] is an O–methylated flavone, a type of flavonoid. It can be found in the seeds of *Alnus glutinosa*, and the leaves of the ferns *Notholaena bryopoda* and *Asplenium normale*.

8. Echioidinin [5–Hydroxy–2–(2–hydroxyphenyl)–7–methoxy–4H–chromen–4–one]

9. Baicalein (5,6,7–Trihydroxy–2–phenyl–chromen–4–one) is a flavone, a type of flavonoid, originally isolated from the roots of *Scutellaria baicalensis* and *Scutellaria lateriflora*. It is also reported in *Oroxylum indicum* (Indian trumpetflower) and *Thyme*. It is the aglycone of baicalin. Baicalein is one of the active ingredients of Sho–Saiko–To, a Chinese herbal supplement believed to enhance liver health.

10. Oroxylon [5,7–dihydroxy–6–methoxy–2–phenyl–chromen–4–one]

11. Negletein [5,6–Dihydroxy–7–methoxy–2–phenyl–4H–chromen–4–one]

Figure–2: Flavonoids.

12. Norwogonin [5,7,8–trihydroxy–2–phenylchromen–4–one], is a flavone, a naturally occurring flavonoid–like chemical compound which is found in *Scutellaria baicalensis* (Baikal skullcap). It has been found to act as an agonist of the TrkB, the main signaling receptor of brain–derived neurotrophic factor (BDNF), and appears to possess roughly the same activity in this regard to that of the closely related but more well–known 7,8–dihydroxyflavone (7,8–DHF).

13. Wogonin [5,7–Dihydroxy–8–methoxy–2–phenyl–4H–chromen–4–one] is an O–methylated flavone, a flavonoid–like chemical compound which was found in *Scutellaria baicalensis*. The glycosides of wogonin are known as wogonosides. For example, oroxindin is a wogonin glucuronide isolated from *Oroxylum indicum*. It is one of the active ingredients of Sho–Saiko–To, a Japanese herbal supplement.

14. Geraldone [7,4′–Dihydroxy–3′–methoxy–2–phenyl–4H–chromen–4–one]

15. Tithonine [7,4′–Dimethoxy–3′–hydroxy–2–phenyl–4H–chromen–4–one]

16. Luteolin [2–(3,4–Dihydroxyphenyl)–5,7–dihydroxy–4–chromenone] is a flavone, a type of flavonoid, with a yellow crystalline appearance. Luteolin is the principal yellow dye compound that is obtained from the plant *Reseda luteola*, which has been used as a source of the dye since at least the first millenium B.C. Luteolin was first isolated in pure form, and named, in 1829 by the French chemist Michel Eugène Chevreul.

17. 6–Hydroxyluteolin [5,6,7,3′,4′–Pentahydroxy–2–phenyl–4H–chromen–4–one]

18. Chrysoeriol [5,7–Dihydroxy–2–(4–hydroxy–3–methoxyphenyl)chromen–4–one] is a flavone, chemically the 3'–methoxy derivative of luteolin.

19. Diosmetin [5,7–dihydroxy–2–(3–hydroxy–4–methoxyphenyl)chromen–4–one], also known as 5,7,3'–trihydroxy–4'–methoxyflavone, is an O–methylated flavone, a chemical compound that can be found in the Caucasian vetch.

20. Pilloin [5–hydroxy–2–(3–hydroxy–4–methoxyphenyl)–7–methoxy–4H–1–chromen–4–one]

21. Velutin [5–Hydroxy–2–(4–hydroxy–3–methoxyphenyl)–7–methoxychromen–4–one]. Velutin is a chemical compound isolated from açaí fruit. It is classified as a flavone.

22. Norartocarpetin [2–(2,4–dihydroxyphenyl)–5,7–dihydroxychromen–4–one] is a flavone. It is found in *Artocarpus dadah*.

23. Artocarpetin [2–(2,4–dihydroxyphenyl)–5–hydroxy–7–methoxy–4H–1–chromen–4–one]

24. Scutellarein [4′,5,6,7–tetrahydroxy–2–phenyl–4H–chromen–4–one] is a flavone that can be found in *Scutellaria lateriflora* and other members of the genus *Scutellaria*, as well as the fern *Asplenium belangeri*.

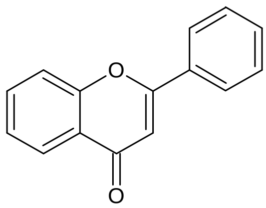
25. Hispidulin [5,7–dihydroxy–2–(4–hydroxyphenyl)–6–methoxy–4H–chromen–4–one] is a naturally occurring flavone with potential antiepileptic activity in rats and gerbils. It is found in plants including *Grindelia argentina*, *Arrabidaea chica*, *Saussurea involucrate*, *Crossostephium chinense*, *Artemisia*, and *Salvia*.

26. Sorbifolin [5,6–dihydroxy–2–(4–hydroxyphenyl)–7–methoxy–4H–1–chromen–4–one]

27. Pectolinarigenin [5,7–Dihydroxy–6–methoxy–2–(4–methoxyphenyl)chromen–4–one] is a *Cirsium vulgare* isolate with anti–inflammatory activity and belongs to the flavones.
28. Mikanin [5–hydroxy–6,7–dimethoxy–2–(4–methoxyphenyl) –3–[(2R,5R,6R)–3,4,5–trihydroxy–6–(hydroxymethyl) oxan–2–yl] oxychromen–4–one]
29. Isoscutellarein [5,7,8–trihydroxy–2–(4–hydroxyphenyl) chromen–4–one] is a flavone found in Cupuaçu (*Theobroma grandiflorum*) and in the liverwort *Marchantia berteroana*. Theograndin I is a sulfated glucuronide of isoscutellarein.
30. Zapotinin [2–(2,6–dimethoxyphenyl)–5–hydroxy–6–methoxychromen–4–one]
31. Zapotin [2–(2,6–Dimethoxyphenyl)–5,6–dimethoxy –4H–chromen–4–one] is a natural chemical compound, classified as a flavone, isolated from White sapote (*Casimiroa edulis*). Several recent *in–vitro* studies have shown that zapotin has potential anti–carcinogenic effects against isolated colon cancer cells.
32. Cerrosillin [2–(3,5–dimethoxyphenyl)–5,6–dimethoxychromen–4–one]
33. Alnetin [5–Hydroxy–6,7,8–trimethoxy–2–phenyl–4H–1–benzopyran–4–one]. Alnetin is a flavone isolated from *Lindera lucida*.
34. Tricetin [5,7–dihydroxy–2–(3,4,5–trihydroxyphenyl) chromen–4–one] is a flavone, a type of flavonoid. It is a rare aglycone found in the pollen of members of the Myrtaceae, subfamily Leptospermoideae, such as *Eucalyptus globulus*. This compound shows anticancer effects on human breast adenocarcinoma MCF–7 cells.
35. Tricin [5,7–dihydroxy–2–(4–hydroxy–3,5–dimethoxyphenyl) –4H–chromen–4–one] is a chemical compound. It is an O–methylated flavone, a type of flavonoid. It can be found in rice bran and sugarcane.
36. Corymbosin [5–hydroxy–7–methoxy–2–(3,4,5–trimethoxyphenyl) chromen–4–one]
37. Nepetin [2–(3,4–dihydroxyphenyl)–5,7–dihydroxy–6–methoxychromen–4–one] is the 6–Methoxy derivative of the pentahydroxyflavone 6–Hydroxyluteolin, an O–methylated flavone. It can be found in *Eupatorium ballotaefolium*.
38. Pedalitin [2–(3,4–dihydroxyphenyl)–5,6–dihydroxy–7–methoxychromen–4–one]
39. Nodifloretin [5,6,7–trihydroxy–2–(4–hydroxy–3–methoxyphenyl)chromen–4–one]
40. Jaceosidin [5,7–dihydroxy–2–(4–hydroxy–3–methoxyphenyl)–6–methoxychromen–4–one]
41. Cirsiliol [2–(3,4–dihydroxyphenyl)–5–hydroxy–6,7–dimethoxychromen–4–one]
42. Eupatilin [2–(3,4–Dimethoxyphenyl)–5,7–dihydroxy – 6 –methoxychromen–4–one] is 5,7–Dihydroxy–3',4',6–trimethoxyflavone is an O–methylated flavone, a type of flavonoids. It can be found in *Artemisia asiatica* (Asteraceae).
43. Cirsilineol [5–Hydroxy–2–(4–hydroxy–3–methoxyphenyl) –6,7–dimethoxychromen–4–one] is a bioactive flavone isolated from Artemisia and from *Teucrium gnaphalodes*.
44. Eupatorin [5–hydroxy–2–(3–hydroxy–4–methoxyphenyl)–6,7–dimethoxychromen–4–one]
45. Sinensetin [2–(3,4–dimethoxyphenyl)–5,6,7–trimethoxychromen–4–one] is a methylated flavone. It can be found in *Orthosiphon stamineus* and in orange oil.
46. Hypolaetin [2–(3,4–dihydroxyphenyl)–5,7,8–trihydroxychromen–4–one] is a flavone. It is the aglycone of hypolaetin 8–glucuronide, a compound found in the liverwort *Marchantia berteroana*. Hypolaetin 8–glucoside can be found in *Sideritis leucantha*.
47. Onopordin [2–(3,4–dihydroxyphenyl)–5,7–dihydroxy –8–methoxychromen–4–one]
48. Wightin [5,3′–Dihydroxy–7,8,2′–trihydroxy–2–phenyl–chromen–4–one]
49. Nevadensin [5,7–dihydroxy–6,8–dimethoxy–2–(4–methoxyphenyl)chromen–4–one]
50. Xanthomicrol [5–hydroxy–2–(4–hydroxyphenyl)–6,7,8–trimethoxychromen–4–one]
51. Tangeretin [5,6,7,8–tetramethoxy–2–(4–methoxyphenyl)–4H–1–benzopyran–4–one] is an O–polymethoxylated flavone that is found in tangerine and other citrus peels. Tangeretin strengthens the cell wall and acts as a plant's defensive mechanism against disease–causing pathogens.
52. Serpyllin [5–hydroxy–7,8,2′,3′,4′–pentamethoxy–2–phenyl–chromen–4–one]
53. Sudachitin [5,7–dihydroxy–2–(4–hydroxy–3–methoxyphenyl)–6,8–dimethoxychromen–4–one]
54. Acerosin [5,7–dihydroxy–2–(3–hydroxy–4–methoxyphenyl)–6,8–dimethoxychromen–4–one]
55. Hymenoxin [2–(3,4–dimethoxyphenyl)–5,7–dihydroxy–6,8–dimethoxychromen–4–one]
56. Gardenin D [5–hydroxy–2–(3–hydroxy–4–methoxyphenyl)–6,7,8–trimethoxychromen–4–one]
57. Nobiletin [2–(3,4–Dimethoxyphenyl)–5,6,7,8–tetramethoxychromen–4–one] is a flavonoid isolated from citrus peels. It is an O–methylated flavone that has the activity to rescue bulbectomy–induced memory impairment.
58. Scaposin [5,7–dihydroxy–2–(3–hydroxy–4,5–dimethoxyphenyl)–6,8–dimethoxychromen–4–one]

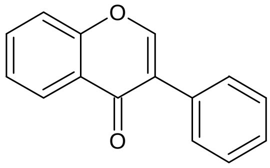
Flavones are common in the food supply, mainly from spices, and red–purple fruits and vegetables. Common flavones include apigenin (4',5,7–trihydroxyflavone), luteolin (3',4',5,7–tetrahydroxyflavone), tangeritin (4',5,6,7,8– pentamethoxyflavone), chrysin (5,7–dihydroxyflavone), and 6–hydroxyflavone.

Flavonoids are a group of plant metabolites thought to provide health benefits through cell signaling pathways and antioxidant effects. These molecules are found in a variety of fruits and vegetables.[6–10]



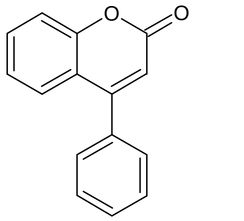
2-phenyl-4*H*-chromen-4-one

Flavone



3-phenyl-4*H*-chromen-4-one

Isoflavone



4-phenyl-2*H*-chromen-2-one

Neoflavone

Figure–2: Flavone isomeric structures.

Flavonoids are polyphenolic molecules containing 15 carbon atoms and are soluble in water. They consist of two benzene rings connected by a short three carbon chain. One of the carbons in this chain is connected to a carbon in one of the benzene rings, either through an oxygen bridge or directly, which gives a third middle ring. The flavonoids can be divided into six major subtypes, which include chalcones, flavones, isoflavonoids, flavanones, anthoxanthins and anthocyanins. Many of these molecules, particularly the anthoxanthins give rise to the yellow color of some petals, while anthocyanins are often responsible for the red color of buds and the purple–red color of autumn leaves.

Flavonoids are abundant in plants, in which they perform several functions. They are essential pigments for producing the colors needed to attract pollinating insects. In higher order plants, flavonoids are also required for UV filtration, nitrogen fixation, cell cycle inhibition, and as chemical messengers. Flavonoids secreted by a plant's roots aid the symbiotic relationship between rhizobia and certain vegetables such as peas, clover and beans. The rhizobia present in soil produce Nod factors in response to the presence of flavonoids. Nod factors (nodulation factors or NF), are signaling molecules produced by soil bacteria known as rhizobia during the initiation of nodules on the root of legumes. A symbiosis is formed when legumes take up the bacteria. The rhizobia produce nitrogen for the plant, and the legumes produce leghemoglobin to carry away any oxygen that would inhibit nitrogenase activity. These Nod factors are then recognized by the plant, which induces certain responses such as ion fluxes and root nodule formation. Nodulation factors (Nod factors) act as signalling molecules between symbiotic bacteria and plants in response to flavonoids secreted by legume root hairs. Rhizobium refers to bacteria that include: Rhizobia, Bradyrhizobia, Azorhizobia, and Sinorhizobia. Members of these genera are capable of forming endosymbiotic interactions with leguminous plants. These bacteria have the ability to fix nitrogen into a form that plants can utilize. The enzyme that is used for this process is nitrogenase and it has the ability to reduce atmospheric nitrogen (N_2) to ammonia (NH_3) at normal temperatures and atmospheric pressure. Nod factors are secreted by rhizobia during a tightly regulated signalling pathway which results in formation of root nodules in leguminous plants, resulting in the rhizobia becoming bacteroids. Some flavonoids also inhibit certain spores to protect against certain plant diseases. Flavonoids are ubiquitous in plants and are the most common type of polyphenolic compound found in the human diet. The abundance of flavonoids coupled with their low toxicity relative to other plant compounds means they can be ingested in large quantities by animals, including humans. Examples of foods that are rich in flavonoids include onions, parsley, blueberries, bananas, dark chocolate and red wine.

Health benefits to humans: Flavonoids are important antioxidants, and promote several health effects. Aside from antioxidant activity, these molecules provide the following beneficial effects: Anti–viral, Anti–cancer, Anti–inflammatory, Anti–allergic anti–inflammatory, anti–allergic, hepatoprotective, anti–thrombotic, anti–viral, and anti–carcinogenic activities etc. One flavonoid called quercetin can help to alleviate eczema, sinusitis, asthma, and hay fever. Some studies have shown that flavonoid intake is inversely related to heart disease, with these molecules inhibiting the oxidation of low–density lipoproteins (LDL) and therefore reducing the risk of atherosclerosis developing. Flavonoids are also abundant in red wine, which some have theorized is the reason why the incidence of heart disease may be lower among the French (who have a relatively high red wine intake) compared with other Europeans, despite a higher consumption of foods rich in cholesterol (French paradox). Many studies have also shown that one to two glasses of wine a day can help protect against heart disease.

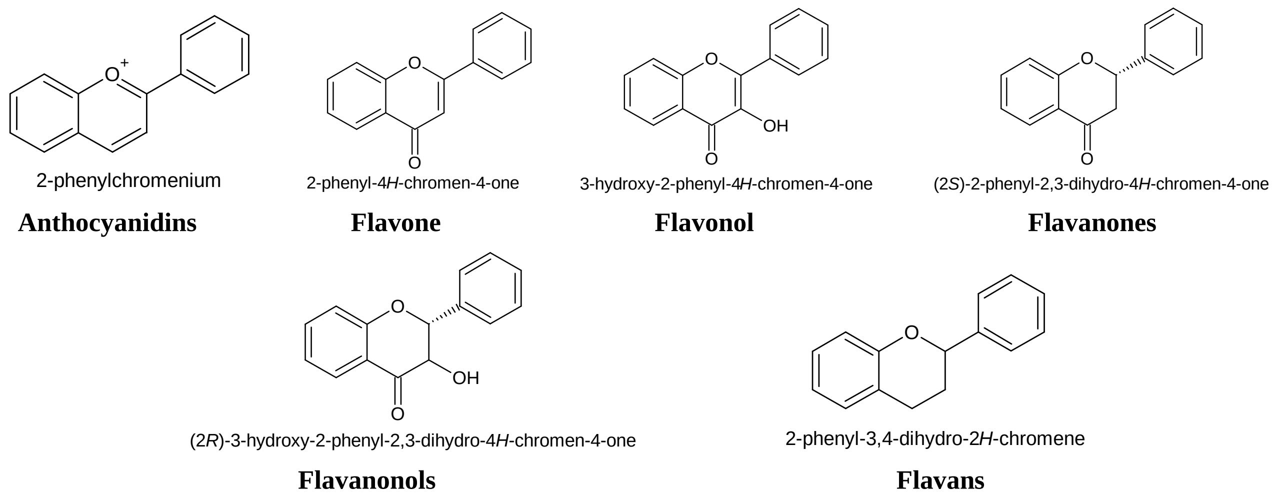
Some types of tea are also rich in flavonoids and their consumption is thought to lower levels of triglycerides and cholesterol in the blood. Soy flavonoids or isoflavones also lower cholesterol, as well as protecting against osteoporosis and alleviating the symptoms of menopause. The daily intake of dietary flavonoids typically ranges from anywhere between 50 and 500 mg, meaning the contribution to antioxidant activity varies widely between individuals.

Food sources: Almost all fruits, vegetables and herbs contain a certain amount of flavonoids. They can also be found in other food sources including dry beans, grains, red wine and green and black teas. The general rule is that the more colorful a food item is, the richer it will be in flavonoids. Oranges, however are an exception to the rule because the flavonoids contained in this fruit are mainly found in the white and pulp interior of the skin.

The best way to ensure a good intake of flavonoids is to consume plenty of fresh fruit and vegetables on a daily basis. Experts advise eating five servings of vegetables and four of fruit. Regarding the intake of red wine, men are advised not to drink more than two glasses per day and women should not drink more than one glass per day.Flavonoid supplements are also available, but people who buy these should note that experts have not confirmed what the ideal flavonoid intake is and an excess intake may even be harmful.[11–13]

Interactions: Certain drugs do interact with flavonoids. Studies have shown that the enzyme cytochrome P450, which is involved in the metabolism of drugs, is inhibited by flavonoids. An efflux transporter called P–glycoprotein, which decreases the absorption of certain drugs, is also affected.

Flavonoids have also been shown to interact with certain nutrients. They can bind to nonheme iron, thereby decreasing its absorption in the intestine. Some flavonoids also inhibit cellular uptake of vitamin C and some experts advise avoiding flavonoid–rich foods or drinks when taking vitamin C. Flavonoids (or bioflavonoids) (from the Latin word flavus, meaning yellow, their color in nature) are a class of plant and fungus secondary metabolites.



Figure–3: Chemical class of benzopyrans.

Chemistry: Chemically, flavonoids have the general structure of a 15–carbon skeleton, which consists of two phenyl rings (A and B) and a heterocyclic ring (C). This carbon structure can be abbreviated C6–C3–C6. According to the IUPAC nomenclature, they can be classified into: (a) flavonoids or bioflavonoids derived from 2–phenylchromen–4–one (2–phenyl–1,4–benzopyrone) structure, (b) isoflavonoids, derived from 3–phenylchromen–4–one (3–phenyl–1,4–benzopyrone) structure, (c) neoflavonoids derived from 4–phenylcoumarine (4–phenyl–1,2–benzopyrone) structure. The three flavonoid classes above are all ketone–containing compounds and as such, anthoxanthins (flavones and flavonols). This class was the first to be termed bioflavonoids. The terms flavonoid and bioflavonoid have also been more loosely used to describe non–ketone polyhydroxy polyphenol compounds, which are more specifically termed flavanoids. The three cycles or heterocycles in the flavonoid backbone are generally called ring A, B, and C. Ring A usually shows a phloroglucinol substitution pattern.[14–16]

Chemical class

1. Anthocyanidins: Anthocyanidins are the aglycones of anthocyanins; they use the flavylium (2–phenylchromenylium) ion skeleton: Cyanidin, Delphinidin, Malvidin, Pelargonidin, Peonidin, Petunidin

2. Anthoxanthins:

(a) Flavone [2–phenylchromen–4–one]: Luteolin, Apigenin, Tangeritin

(b) Flavonol [3–hydroxy–2–phenylchromen–4–one]: Quercetin, Kaempferol, Myricetin, Fisetin, Galangin, Isorhamnetin, Pachypodol, Rhamnazin, Pyranoflavonols, Furanoflavonols.

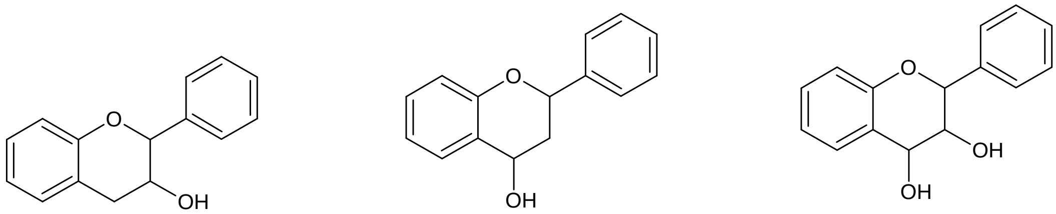
3. Flavanones [2,3–Dihydro–2–phenylchromen–4–one]: Hesperetin, Naringenin, Eriodictyol, Homoeriodictyol

4. Flavanonols [3–hydroxy–2,3–dihydro–2–phenylchromen–4–one]: Taxifolin (or Dihydroquercetin), Dihydrokaempferol

5. Flavans [Include flavan–3–ols (flavanols), flavan–4–ols and flavan–3,4–diols].

Flavan–3–ols (flavanols): Flavan–3–ols have 2–phenyl–3,4–dihydro–2H–chromen–3–ol skeleton.

Examples: Catechin (C), Gallocatechin (GC), Catechin 3–gallate (Cg), Gallocatechin 3–gallate (GCg), Epicatechins (Epicatechin (EC)), Epigallocatechin (EGC), Epicatechin 3–gallate (ECg), Epigallocatechin 3–gallate (EGCg).



2-phenyl-3,4-dihydro-2*H*-chromen-3-ol 2-phenyl-3,4-dihydro-2*H*-chromen-4-ol 2-phenyl-3,4-dihydro-2*H*-chromene-3,4-diol

Figure–4: Flavans.

Theaflavin: Theaflavin (TF) and its derivatives, known collectively as theaflavins, are antioxidant polyphenols that are formed from the condensation of flavan–3–ols in tea leaves during the enzymatic oxidation (sometimes erroneously referred to as fermentation) of black tea. Theaflavin–3–gallate, theaflavin–3'–gallate, and theaflavin–3–3'–digallate are the main theaflavins. Theaflavins are types of thearubigins, and are therefore reddish in color. Epigallocatechin gallate (EGCG) will metabolize into some theaflavins in the liver. Those molecules contain a tropolone moiety. Examples: Theaflavin–3–gallate, Theaflavin–3'–gallate, Theaflavin–3,3'–digallate.

Thearubigin: Thearubigins are polymeric polyphenols that are formed during the enzymatic oxidation and condensation of two gallocatechins (epigallocatechin and epigallocatechin gallate) with the participation of polyphenol oxidases during the fermentation reactions in black tea. Thearubigins are red in colour and are responsible for much of the staining effect of tea. Therefore, a black (fully oxidized) tea often appears red while a green or white tea has a much clearer appearance. The colour of a black tea, however, is affected by many other factors as well, such as the amount of theaflavins, another oxidized form of polyphenols. Proanthocyanidins are dimers, trimers, oligomers, or polymers of the flavanols.

6. Isoflavonoids: Isoflavonoids are a class of flavonoid phenolic compounds, many of which are biologically active. Isoflavonoids and their derivatives are sometimes referred to as phytoestrogens, as many isoflavonoid compounds have biological effects via the estrogen receptor. Isoflavones have 3–phenylchromen–4–one skeleton (with no hydroxyl group substitution on carbon at position 2). Examples: Genistein, Daidzein, Glycitein.

Isoflavones are substituted derivatives of isoflavone, a type of naturally occurring isoflavonoids, many of which act as phytoestrogens in mammals. Isoflavones are produced almost exclusively by the members of the bean family, Fabaceae (Leguminosae).

(i) Isoflavandiols [3–phenyl–3,4–dihydrochromene–2,2–diol]

(ii) Isoflavanes are a class of isoflavonoids, which are themselves types of polyphenolic compounds. They have the 3–phenylchroman. *Lonchocarpus laxiflorus* contains two isoflavanes: lonchocarpane and laxiflorane. Example: Equol.

(iii) Isoflavenes: Isoflavanes are a class of isoflavonoids, which are themselves types of polyphenolic compounds. They have the 3–phenylchroman Glabrene, found in the roots of liquorice, is also a xenoestrogen. 2–Methoxyjudaicin found in the roots of *Cicer bijugum*, Haginin D, Idronoxil, also known as phenoxodiol, which is used for anticancer purposes.

(iv) Coumestans: Coumestan [Benzoxolo [3,2–c]chromen–6–one] is a heterocyclic organic compound. Coumestan forms the central core of a variety of natural compounds known collectively as coumestans. Coumestans are oxidation products of pterocarpan that are similar to coumarin. Coumestans, including coumestrol, a phytoestrogen, are found in a variety of plants. Food sources high in coumestans include split peas, pinto beans, lima beans, and especially alfalfa and clover sprouts. Coumestrol has about the same binding affinity for the ER–β estrogen receptor as 17β–estradiol, but much less affinity than 17α–estradiol, although the estrogenic potency of coumestrol at both receptors is much less than that of 17β–estradiol.

(v) Pterocarpans: Pterocarpans are derivatives of isoflavonoids found in the family Fabaceae. It is a group of compounds which can be described as benzo–pyrano–furano–benzenes (i.e. 6H–[1]benzofuro[3,2–c]chromene skeleton) which can be formed by coupling of the B ring to the 4–one position. 2'–hydroxyisoflavone reductase is the enzyme responsible for the conversion in *Cicer arietinum* and glyceollin synthase for the production of glyceollins, phytoalexins in soybean.

(vi) Rotenoids: These are naturally occurring substances containing a cis–fused tetrahydrochromeno[3,4–b]chromene nucleus. Many have insecticidal activity, such as the prototypical member of the family, rotenone. Rotenoids are related to the isoflavones.

7. Neoflavone: Neoflavonoids are a class of polyphenolic compounds. While flavonoids (in the narrow sense) have the 2–phenylchromen–4–one backbone, neoflavonoids have the 4–phenylchromen backbone with no hydroxyl group substitution at position 2. Neoflavonoids include 4–arylcoumarins (neoflavones), 4–arylchromanes, dalbergiones and dalbergiquinols. Neoflavones are derived from the 4–phenylcoumarin (or 4–aryl–coumarin) backbone ($C_{15}H_{12}O_2$). The first neoflavone isolated from natural sources was calophyllolide from *Calophyllum inophyllum* seeds. It is also known to found in bark and timber of Sri Lankan endemic plant *Mesua thwaitesii*. Neoflavenes possess the 4–phenylchromen backbone

($C_{15}H_{10}O_2$). Dalbergichromene, extracted from the stem–bark and heartwood of *Dalbergia sissoo*, is an example of such compounds.

Diet source: Flavonoids (specifically flavanoids such as the catechins) are the most common group of polyphenolic compounds in the human diet and are found ubiquitously in plants. Flavonols, the original bioflavonoids such as quercetin, are also found ubiquitously, but in lesser quantities. The widespread distribution of flavonoids, their variety and their relatively low toxicity compared to other active plant compounds (for instance alkaloids) mean that many animals, including humans, ingest significant quantities in their diet. Foods with a high flavonoid content include parsley, onions, blueberries and other berries, black tea, green tea and oolong tea, bananas, all citrus fruits, *Ginkgo biloba*, red wine, sea–buckthorns, buckwheat, and dark chocolate (with a cocoa content of 70% or greater). Parsley, both fresh and dried, contains flavones. Blueberries are a dietary source of anthocyanidins. Black tea is a rich source of dietary flavan–3–ols. Citrus flavonoids include hesperidin (a glycoside of the flavanone hesperetin), quercitrin, rutin (two glycosides of the flavonol quercetin), and the flavone tangeritin. Wine, Cocoa.

Flavonoids exist naturally in cocoa, but because they can be bitter, they are often removed from chocolate, even dark chocolate. Although flavonoids are present in milk chocolate, milk may interfere with their absorption; however this conclusion has been questioned. Peanut (red) skin contains significant polyphenol content, including flavonoids.

In–vitro: Flavonoids have been shown to have a wide range of biological and pharmacological activities in *in–vitro* studies. Examples include anti–allergic, anti–inflammatory, antioxidant, anti–microbial (antibacterial, antifungal, and antiviral), anti–cancer, and anti–diarrheal activities. Flavonoids have also been shown to inhibit topoisomerase enzymes and to induce DNA mutations in the mixed–lineage leukemia (MLL) gene in *in–vitro* studies. However, in most of the above cases no follow up *in–vivo* or clinical research has been performed, leaving it impossible to say if these activities have any beneficial or detrimental effect on human health. Biological and pharmacological activities which have been investigated in greater depth are described below.

Table 1: Flavone contents.

Food source	Flavones	Flavonols	Flavanones
Red onion	0	4–100	0
Parsley	24–634	8–10	0
Thyme	56	0	0
Lemon juice	0	0–2	2–175

Antioxidant activity: Research at the Linus Pauling Institute and the European Food Safety Authority shows that flavonoids are poorly absorbed in the human body (less than 5%), with most of what is absorbed being quickly metabolized and excreted. These findings suggest that flavonoids have negligible systemic antioxidant activity, and that the increase in antioxidant capacity of blood seen after consumption of flavonoid–rich foods is not caused directly by flavonoids, but is due to production of uric acid resulting from flavonoid depolymerization and excretion.

Inflammation: Inflammation has been implicated as a possible origin of numerous local and systemic diseases, such as cancer, cardiovascular disorders, diabetes mellitus, and celiac disease. Preliminary studies indicate that flavonoids may affect anti–inflammatory mechanisms via their ability to inhibit reactive oxygen or nitrogen compounds. Flavonoids have also been proposed to inhibit the pro–inflammatory activity of enzymes involved in free radical production, such as cyclooxygenase, lipoxygenase or inducible nitric oxide synthase, and to modify intracellular signaling pathways in immune cells, or in brain cells after a stroke. Procyanidins, a class of flavonoids, have been shown in preliminary research to have anti–inflammatory mechanisms including modulation of the arachidonic acid pathway, inhibition of gene transcription, expression and activity of inflammatory enzymes, as well as secretion of anti–inflammatory mediators.

Cancer: Clinical studies investigating the relationship between flavonoid consumption and cancer prevention/development are conflicting for most types of cancer, probably because most studies are retrospective in design and use a small sample size. Two apparent exceptions are gastric carcinoma and smoking–related cancers. Dietary flavonoid intake is associated with reduced gastric carcinoma risk in women, and reduced aerodigestive tract cancer risk in smokers.

Cardiovascular diseases: Among the most intensively studied of general human disorders possibly affected by dietary flavonoids, preliminary cardiovascular disease research has revealed the following mechanisms under investigation in patients or normal subjects: inhibit coagulation, thrombus formation or platelet aggregation, reduce risk of atherosclerosis, reduce arterial blood pressure and risk of hypertension, reduce oxidative stress and related signaling pathways in blood vessel cells, modify vascular inflammatory mechanisms, improve endothelial and capillary function, modify blood lipid levels, regulate carbohydrate and glucose metabolism, modify mechanisms of aging.

Antibacterial: Flavonoids have been shown to have (a) direct antibacterial activity, (b) synergistic activity with antibiotics, and (c) the ability to suppress bacterial virulence factors in numerous *in–vitro* and a limited number of *in–vivo* studies. Noteworthy among the *in–vivo* studies is the finding that oral quercetin protects guinea pigs against the Group 1 carcinogen *Helicobacter pylori*. Researchers from the European Prospective Investigation into Cancer and Nutrition have speculated this may be one reason why dietary flavonoid intake is associated with reduced gastric carcinoma risk in European women. Additional *in–vivo* and clinical research is needed to determine if flavonoids could be used as pharmaceutical drugs for the treatment of bacterial infection, or whether dietary flavonoid intake offers any protection against infection.

CONCLUSION

Flavone scaffolds comprehensively discovered heterocyclic ring systems for numerous pathological conditions with antioxidant, antiproliferative, antitumor, and antimicrobial properties. The scaffold has been widely used for multitargeting in complex diseases like cancer, inflammation, cardiovascular disease, diabetes, and various neurodegenerative disorders. Due to the wide range of biological activities of flavones, their structure–activity relationships have generated interest among medicinal chemists. The outstanding development of flavone derivatives in diverse diseases in a very short span of time proves its magnitude for medicinal chemistry research. There has been increasing interest in the research on flavonoids from plant sources because of their versatile health benefits reported in various epidemiological studies. Since flavonoids are directly associated with human dietary ingredients and health, there is need to evaluate structure and function relationship. The bioavailability, metabolism, and biological activity of flavonoids depend upon the configuration, total number of hydroxyl groups, and substitution of functional groups about their nuclear structure. Fruits and vegetables are the main dietary sources of flavonoids for humans, along with tea and wine. Most recent researches have focused on the health aspects of flavonoids for humans. Many flavonoids are shown to have antioxidative activity, free radical scavenging capacity, coronary heart disease prevention, hepatoprotective, anti–inflammatory, and anticancer activities, while some flavonoids exhibit potential antiviral activities. In plant systems, flavonoids help in combating oxidative stress and act as growth regulators. For pharmaceutical purposes cost–effective bulk production of different types of flavonoids has been made possible with the help of microbial biotechnology. This review highlights the structural features of flavonoids, their beneficial roles in human health, and significance in plants as well as their microbial production. Prevention and cure of diseases using phytochemicals especially flavonoids are well known. Fruits and vegetables are natural sources of flavonoids. Variety of flavonoids found in the nature possesses their own physical, chemical, and physiological properties. Structure function relationship of flavonoids is epitome of major biological activities. Medicinal efficacy of many flavonoids as antibacterial, hepatoprotective, anti–inflammatory, anticancer, and antiviral agents is well established. These substances are more commonly used in the developing countries. Therapeutic use of new compounds must be validated using specific biochemical tests. With the use of genetic modifications, it is now possible to produce flavonoids at large scale. Further achievements will provide newer insights and will certainly lead to a new era of flavonoid based pharmaceutical agents for the treatment of many infectious and degenerative diseases.

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