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FLAVONOIDS

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ABSTRACT

Flavonoids are the most abundant **polyphenols** in human diet, representing about 2/3 of all those ones ingested. Like other phytochemicals, they are the products of secondary metabolism of plants and currently, it is not possible to determine precisely their number, even if over 4000 have been identified. In fruits and vegetables, they are usually found in the form of glycosides and sometimes as acylglycosides while acylated, methylated and sulfate molecules are less frequent and in lower concentrations. They are water-soluble and accumulate in cell vacuoles. Their basic structure is a skeleton of **diphenylpropane.** They can be subdivided into different subgroups depending on the carbon of the C ring on which B ring is attached, and the degree of unsaturation and oxidation of the C ring. Flavonoids in which B ring is linked in position 3 of the ring C are called **isoflavones;** those in which B ring is linked in position 4, **neoflavonoids**, while those in which the B ring is linked in position 2 can be further subdivided into several subgroups on the basis of the structural features of the C ring. These subgroup are: **flavones, flavonols, flavanones, flavanonols, flavanols or catechins and anthocyanins.** Finally, flavonoids with open C ring are called chalcones.

KEYWORDS: Flavonoids, polyphenols, flavones, flavonols, flavanones, flavanonols, flavanols or catechins and anthocyanins.

INTRODUCTION

Flavonoids are the most abundant polyphenols in human diet, representing about 2/3 of all those ones ingested. Like other phytochemicals, they are the products of secondary metabolism of plants and, currently, it is not possible to determine precisely their number, even if over 4000 have been identified. In fruits and vegetables, they are usually found in the form of glycosides and sometimes as acylglycosides, while acylated, methylated and sulfate molecules are less frequent and in lower concentrations. They are water-soluble and accumulate in cell vacuoles.

Chemical structure of flavonoids

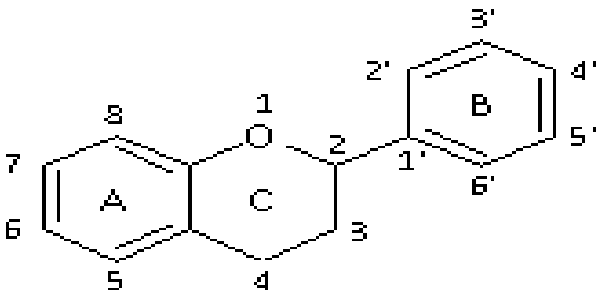


Fig. 1 – Skeleton of Diphenylpropane

Their basic structure is a skeleton of **diphenylpropane**, namely, two benzene rings (ring A and B, see figure) linked by a three carbon chain that forms a closed pyran ring (heterocyclic ring containing oxygen, the C ring) with benzenic A ring. Therefore, their structure is also referred to as C6-C3-C6.

In most cases, B ring is attached to position 2 of C ring, but it can also bind in position 3 or 4; this, together with the structural features of the ring B and the patterns of glycosylation and hydroxylation of the three rings, makes the flavonoids one of the larger and more diversified groups of phytochemicals, so not only of polyphenols, in nature. Their biological activities, for example they are potent antioxidants, depend both on the structural characteristics and the pattern of glycosylation.

Classification of flavonoids

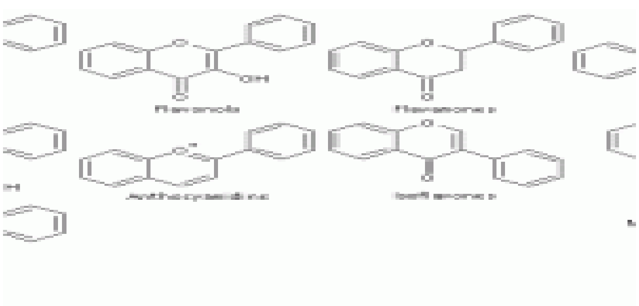


Fig. 2 – Flavonoid Subgroups

They can be subdivided into different subgroups depending on the carbon of the C ring on which B ring is attached, and the degree of unsaturation and oxidation of the C ring. Flavonoids in which B ring is linked in position 3 of the ring C are called **isoflavones**; those in which B ring is linked in position 4, **neoflavonoids**, while those in which the B ring is linked in position 2 can be further subdivided into several subgroups on the basis of the structural features of the C ring. These subgroup are: **flavones, flavonols, flavanones, flavanonols, flavanols or catechins and anthocyanins**. Finally, flavonoids with open C ring are called chalcones.

- **Flavones:** They have a double bond between positions 2 and 3 and a ketone in position 4 of the C ring. Most flavones of vegetables and fruits has a hydroxyl group in position 5 of the A ring, while the hydroxylation in other positions, for the most part in position 7 of the A ring or 3′ and 4′ of the B ring may vary according to the taxonomic classification of the particular vegetable or fruit. Glycosylation occurs primarily on position 5 and 7, methylation and acylation on the hydroxyl groups of the B ring. Some flavones, such as nobiletin and tangeretin, are polymethoxylated.

- **Flavonols:** Compared to flavones, they have a hydroxyl group in position 3 of the C ring, which may also be glycosylated. Again, like flavones, flavonols are very diverse in methylation and hydroxylation patterns as well, and, considering the different glycosylation patterns, they are perhaps the most common and largest subgroup of flavonoids in fruits and vegetables. For example, quercetin is present in many plant foods.

- **Flavanones:** Flavanones, also called dihydroflavones, have the C ring saturated; therefore, unlike flavones, the double bond between positions 2 and 3 is saturated and this is the only structural difference between the two subgroups of flavonoids. The flavanones can be multi-hydroxylated and several hydroxyl groups can be glycosylated and/or methylated. Some have unique patterns of substitution, for example, furanoflavanones, prenylated flavanones, pyranoflavanones or benzylated flavanones, giving a great number of substituted derivatives. Over the past 15 years, the number of flavanones discovered is significantly increased.

- **Flavanonols:** Flavanonols, also called dihydroflavonols, are the 3-hydroxy derivatives of flavanones; they are an highly diversified and multisubstituted subgroup.

- **Isoflavones**

As anticipated, isoflavones are a subgroup of flavonoids in which the B ring is attached to position 3 of the C ring. They have structural similarities to estrogens, such as estradiol, and for this reason they are also called phytoestrogens.

- **Neoflavonoids**

They have the B ring attached to position 4 of the C ring.

- **Flavanols or flavan-3-ols or catechins:** Flavanols are also referred to flavan-3-ols as the hydroxyl group is almost always bound to position 3 of C ring; they are called **catechins** as well.

Unlike many flavonoids, there is no double bond between positions 2 and 3. Another distinctive features, e.g. compared to flavanonols, with which they share a hydroxyl group in position 3, is the lack of a carbonyl group, that is, a keto group, in position 4. This particular chemical structure allows flavanols to have two chiral centers in the molecule, on positions 2 and 3, then four possible diastereoisomers. Epicatechin is the isomer with the *cis* configuration and catechin is the one with the *trans* configuration. Each of these configurations has two stereoisomers, namely, (+)-epicatechin and (-)-epicatechin, (+)-catechin and (-)-catechin.

(+)-Catechin and (-)-epicatechin are the two isomers most often present in edible plants. Another important feature of flavanols, particularly of catechin and epicatechin, is the ability to form polymers, called proanthocyanidins or condensed tannins. The name "proanthocyanidins" is due to the fact that an acid-catalyzed cleavage produces anthocyanidins.

Proanthocyanidins typically contain 2 to 60 monomers of flavanols. Monomeric and oligomeric flavanols (containing 2 to 7 monomers) are strong antioxidants.

- **Anthocyanidins:** Chemically, anthocyanidins are flavylium cations and are generally present as chloride salts. They are the only group of flavonoids that gives plants colors (all other flavonoids are colorless).

Anthocyanins are glycosides of anthocyanidins. Sugar units are bound mostly to position 3 of the C ring and they are often conjugated with phenolic acids, such as ferulic acid.

The color of the anthocyanins depends on the pH and also by methylation or acylation at the hydroxyl groups on the A and B rings.

- **Chalcones:** Chalcones and dihydrochalcones are flavonoids with open structure; they are classified as flavonoids because they have similar synthetic pathways.

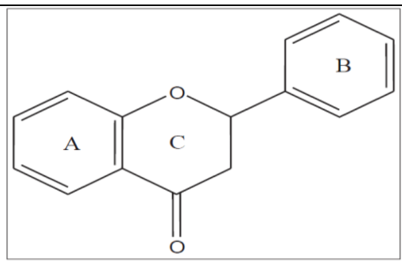
Biosynthesis

Functions of flavonoids in plants: Flavonoids are widely distributed in plants, fulfilling many functions. Flavonoids are the most important plant pigments for flower coloration, producing yellow or red/blue pigmentation in petals designed to attract pollinator animals. In higher plants, flavonoids are involved in UV filtration, symbiotic nitrogen fixation and floral pigmentation. They may also act as chemical messengers, physiological regulators, and cell cycle inhibitors. Flavonoids secreted by the root of their host plant help *Rhizobia* in the infection stage of their symbiotic relationship with legumes like peas, beans, clover, and soy. Rhizobia living in soil are able to sense the flavonoids and this triggers the secretion of Nod factors, which in turn are recognized by the host plant and can lead to root hair deformation and several cellular responses such as ion fluxes and the formation of a root nodule. In addition, some flavonoids have inhibitory activity against organisms that cause plant diseases, e.g. *Fusarium oxysporum*.[3]

Subgroups: Over 5000 naturally occurring flavonoids have been characterized from various plants. They have been classified according to their chemical structure, and are usually subdivided into the following subgroups (for further reading see[4])

Table.1 Anthoxanthins

Anthoxanthins are divided into two groups[5]

Group	Skeleton				Examples
	Description	Functional groups		Structural formula	
		3-hydroxyl	2,3-dihydro		
Flavone	**2-phenylchromen-4-one**	✗	✗	 X Fig. 1: Flavanone (2-phenylchroman-4-one).	Luteolin, Apigenin, Tangeritin

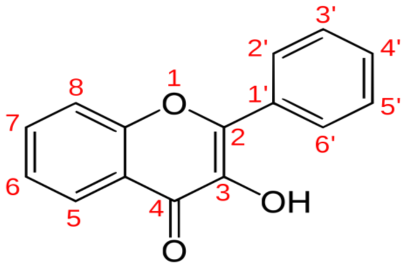
Flavonol or **3-hydroxyflavone**	**3-hydroxy-2-phenylchromen-4-one**	✓	✗		Quercetin, Kaempferol, Myricetin, Fisetin, Galangin, Isorhamnetin, Pachypodol, Rhamnazin, Pyranoflavonols, Furanoflavonols,

Table.2 Flavone

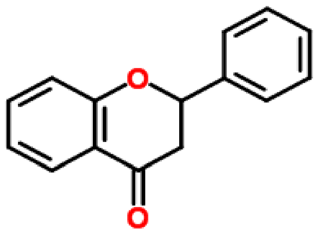
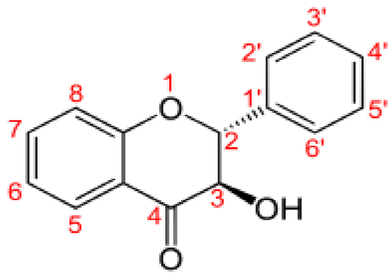
Group	Vice Versa				Examples
	Description	Functional groups		Structural formula	
		3-hydroxyl	2,3-dihydro		
Flavanone	**2,3-dihydro-2-phenylchromen-4-one**	✗	✓		Hesperetin, Naringenin, Eriodictyol, Homoeriodictyol

Table.3 Flavanones

Group	Vice Versa				Examples
	Description	Functional groups		Structural formula	
		3-hydroxyl	2,3-dihydro		
Flavanonol or **3-Hydroxyflavanone** or **2,3-dihydroflavonol**	**3-hydroxy-2,3-dihydro-2-phenylchromen-4-one**	✓	✓		Taxifolin (or Dihydroquercetin), Dihydrokaempferol

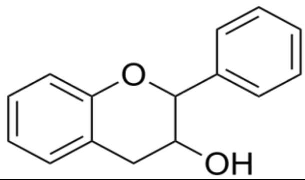
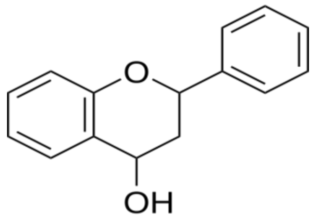
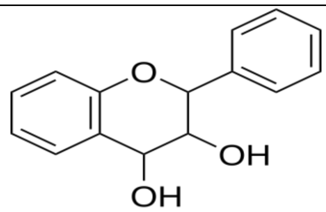
Flavans

Flavan structure

Include flavan-3-ols (flavanols),

flavan-4-ols and flavan-3,4-diols.

Table.4=Flavanonol

Skeleton	Name
Flavon-3-ol	
Flavon-4-ol	
Flavan-3,4-diol (leucoanthocyanidin)	

- **Flavan-3-ols (flavanols)**

○ Flavan-*3-ols* use the 2-phenyl-3,4-dihydro-2*H*-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)

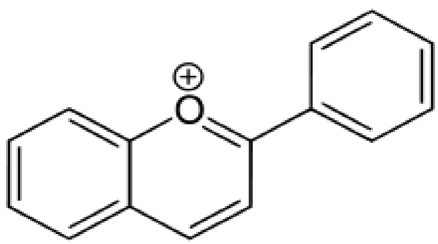
○ Theaflavin

Examples: Theaflavin-3-gallate, Theaflavin-3'-gallate, Theaflavin-3,3'-digallate

○ Thearubigin

○ Proanthocyanidins are dimers, trimers, oligomers, or polymers of the flavanols

Anthocyanidins



Flavylium skeleton of anthocyanidins

- **Anthocyanidins**

Anthocyanidins are the aglycones of anthocyanins; they use the **flavylium** (2-phenylchromenylium) ion skeleton

Examples: Cyanidin, Delphinidin, Malvidin, Pelargonidin, Peonidin, Petunidin

Isoflavonoids

- Isoflavonoids

○ Isoflavones use the 3-phenylchromen-*4-one* skeleton (with no hydroxyl group substitution on carbon at position 2)

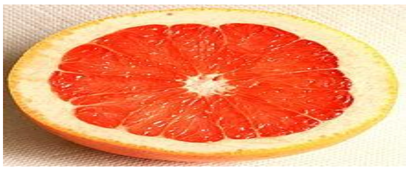
Examples: Genistein, Daidzein, Glycitein

○ Isoflavanes
○ Isoflavandiols
○ Isoflavenes
○ Coumestans
○ Pterocarpans

Dietary sources: 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".[6] 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,[7] onions,[7] blueberries and other berries,[7] black tea,[7] green tea and oolong tea,[7] bananas, all citrus fruits, *Ginkgo biloba*, red wine, sea-buckthorns, and dark chocolate (with a cocoa content of 70% or greater). Further information on dietary sources of flavonoids can be obtained from the US Department of Agriculture flavonoid database.[7]

- **Parsley:** Parsley, both fresh and dried, contains flavones.[7]
- **Blueberries:** Blueberries are a dietary source of anthocyanidins.[7][8]
- **Black tea:** Black tea is a rich source of dietary flavan-3-ols.[7]
- **Citrus**





The citrus flavonoids include hesperidin (a glycoside of the flavanone hesperetin), quercitrin, rutin (two glycosides of the flavonol quercetin), and the flavone tangeritin.

- **Wine**

Main article: Polyphenols in wine

- **Cocoa**

Main article: Health effects of chocolate

Flavonoids exist naturally in cocoa, but because they can be bitter, they are often removed from chocolate, even dark chocolate.[9] Although flavonoids are present in milk chocolate, milk may interfere with their absorption;[10][11] however this conclusion has been questioned.[12]

- **Peanut**

Peanut (red) skin contains significant polyphenol content, including flavonoids.[13][14] [15]

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

Dietary intake: Mean flavonoid intake in mg/d per country, the pie charts show the relative contribution of different types of flavonoids. [16]

Food composition data for flavonoids were provided by the USDA database on flavonoids.[7] In the United States NHANES survey, mean flavonoid intake was 190 mg/d in adults, with flavan-3-ols as the main contributor.[17] In the European Union, based on data from EFSA, mean flavonoid intake was 140 mg/d, although there were considerable differences between individual countries.[16]

Data is based on mean flavonoid intake of all countries included in the 2011 EFSA Comprehensive European Food Consumption Database.[16]

The main type of flavonoids consumed in the EU and USA were flavan-3-ols, mainly from tea, while intake of other flavonoids was considerably lower.[16][17]

Research

Though there is ongoing research into the potential health benefits of individual flavonoids, neither the Food and Drug Administration (FDA) nor the European Food Safety Authority (EFSA) has approved any health claim for flavonoids or approved any flavonoids as pharmaceutical drugs.[18][19][20] Moreover, several companies have been cautioned by the FDA over misleading health claims.[21][22][23][24]

In vitro

Flavonoids have been shown to have a wide range of biological and pharmacological activities in *in vitro* studies. Examples include anti-allergic,[25] anti-inflammatory,[25][26] antioxidant,[26] anti-microbial (antibacterial,[27][28] antifungal,[29][30] and antiviral[29][30]), anti-cancer,[26][31] and anti-diarrheal activities.[32] Flavonoids have also been shown to inhibit topoisomerase enzymes[33][34] and to induce DNA mutations in the mixed-lineage leukemia (*MLL*) gene in *in vitro* studies.[35] 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.

Antioxidant

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.[20][36][37] 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.[38]

Inflammation

Inflammation has been implicated as a possible origin of numerous local and systemic diseases, such as cancer,[39] cardiovascular disorders,[40] diabetes mellitus,[41] and celiac disease.[42]

Preliminary studies indicate that flavonoids may affect anti-inflammatory mechanisms via their ability to inhibit reactive oxygen or nitrogen compounds.[43] 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,[43][44] and to modify intracellular signaling pathways in immune cells,[43] or in brain cells after a stroke.[45]

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.[46]

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.[47] Two apparent exceptions are gastric carcinoma and smoking-related cancers. Dietary flavonoid intake is associated with reduced gastric carcinoma risk in women,[48] and reduced aerodigestive tract cancer risk in smokers.[49]

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:[50][51][52][53][54]

- 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

Listed on the clinical trial registry of the US National Institutes of Health (July 2016) are 48 human studies completed or underway to study the dietary effects of plant flavonoids on cardiovascular diseases.[55]

However, population-based studies have failed to show a strong beneficial effect [56] which might be due to the considerably lower intake in the habitual diet of those investigated.

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.[27][57] Noteworthy among the *in vivo* studies[58][59][60] is the finding that oral quercetin protects guinea pigs against the Group 1 carcinogen *Helicobacter pylori*.[60] 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.[61] 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.

Synthesis, detection, quantification, and semi-synthetic alterations

Color Spectrum

Flavonoid synthesis in plants is induced by light color spectrums at both high and low energy radiations. Low energy radiations are accepted by phytochrome, while high energy radiations are accepted by carotenoids, flavins, cryptochromes in addition to phytochromes. The photomorphogenic process of phytochome-mediated flavonoid biosynthesis has been observed in *Amaranthus*, barley, maize, *Sorgham* and turnip. Red light promotes flavonoid synthesis.[62]

Availability through microorganisms

Several recent research articles have demonstrated the efficient production of flavonoid molecules from genetically engineered microorganisms.[63][64][65]

Tests for detection

Shinoda test

Four pieces of magnesium fillings are added to the ethanolic extract followed by few drops of concentrated hydrochloric acid. A pink or red colour indicates the presence of flavonoid.[66] Colours varying from orange to red indicated flavones, red to crimson indicated flavonoids, crimson to magenta indicated flavonones.

Sodium hydroxide test

About 5 mg of the compound is dissolved in water, warmed and filtered. 10% aqueous sodium hydroxide is added to 2 ml of this solution. This produces a yellow coloration. A change in color from yellow to colorless on addition of dilute hydrochloric acid is an indication for the presence of flavonoids.[67]

p-Dimethylaminocinnamaldehyde test

A colorimetric assay based upon the reaction of A-rings with the chromogen p-dimethylaminocinnamaldehyde (DMACA) has been developed for flavanoids in beer that can be compared with the vanillin procedure.[68]

Quantification

Lamaison and Carnet have designed a test for the determination of the total flavonoid content of a sample ($AlCI_3$ method). After proper mixing of the sample and the reagent, the mixture is incubated for 10 minutes at ambient temperature and the absorbance of the solution is read at 440 nm. Flavonoid content is expressed in mg/g of quercetin.[69]

Semi-synthetic alterations

Immobilized *Candida antarctica* lipase can be used to catalyze the regioselective acylation of flavonoids.[70]

See also

- Phytochemical
- List of antioxidants in food
- List of phytochemicals in food
- Phytochemistry
- Secondary metabolites
- Homoisoflavonoids, related chemicals with a 16 carbons skeleton

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