



## Critical Review

## A comprehensive review on flavanones, the major citrus polyphenols

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## ABSTRACT

The consumption of *Citrus* fruits and juices has been widely investigated for its possible role in the prevention of cardiovascular disease and cancer. These beneficial effects are mainly attributed to flavanones, the typical polyphenols of *Citrus* species. Major flavanones in plant species include hesperetin, naringenin, eriodictyol, isosakuranetin and their respective glycosides. Hesperetin and its derivatives are characteristic flavanones of sweet orange, tangelo, lemon and lime, while naringenin and its derivatives are those of grapefruit and sour orange. Advances in analytical techniques like ultra high performance liquid chromatography (UPLC) coupled with mass spectrometry has facilitated (a) the estimation of flavanone contents in other plant species and in humans after ingestion and (b) the determination of flavanone metabolites more rapidly and with greater efficiency. The present review will summarize the current knowledge about flavanones from their occurrence in plants to the bioactivity of their metabolites in humans.

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## 1. Introduction

It is now well accepted that a low consumption of fatty foods, a regular physical activity and a high consumption of plant-derived foods help to maintain a good health status. In particular, there is an association between an increased level of fruit and vegetables in the diet and a reduced risk of some life-threatening diseases such as cardiovascular disease and cancer (Parr and Bolwell, 2000). There is also growing acceptance that many phenolic secondary metabolites (polyphenols) present in plant-derived foods exert beneficial effects in the prevention of these degenerative diseases (Benavente-García and Castillo, 2008; Del Rio et al., 2010). Moreover, *Citrus* fruit and juices are highly consumed worldwide and this consumption has significantly increased during the past few years. Global production of *Citrus* fruit reached 82 million tons in the years 2009–2010, of which oranges – commercially the most important citrus fruit – accounts for about 50 million tons (USDA, 2010). Worldwide *Citrus* consumption has thus stimulated research on the most abundant *Citrus* phenols, i.e. flavanones. Based on the criterion of flavanone content, *Citrus* plants belonging to the *Rutaceae* family appear especially important. This review will cover the updated literature available on the chemistry and biochemistry of the main *Citrus* flavanones, hesperetin and naringenin.

## 2. Structures and classification

A few decades ago, flavanones were considered as only minor flavonoids (Bohm, 1994), like chalcones, dihydrochalcones, dihydroflavonols and aurones. However, during the past 15 years, the total number of known flavanones has increased to the point that they are now considered a major flavonoid class like flavones, isoflavones, flavanols, flavonols and anthocyanidins (Veitch and Grayer, 2006). Up to now about 350 flavanone aglycones and 100 flavanone glycosides have been identified in nature (Iwashina, 2000).

Generally, polyphenols are classified into two major classes: flavonoids and nonflavonoids. The latter include structurally simple molecules such as phenolic acids (hydroxybenzoic acids and hydroxycinnamic acids) and stilbenes, and highly complex molecules such as stilbene oligomers, tannins and lignins (Cheynier, 2005). The former, the most studied class of polyphenols, includes more than 9000 identified compounds (Martens and Mithöfer, 2005; Pietta, 2000). Flavonoids commonly share the same generic structure, the flavan nucleus, consisting of two aromatic rings (A and B) linked by a pyran ring (C). Differences in the location of the B-ring to C-ring linkage make it possible to distinguish between flavonoids (2-phenylbenzopyrans), isoflavonoids (3-phenylbenzopyrans), and neoflavonoids (4-phenylbenzopyrans). The by far the most abundant 2-phenylbenzopyran group may be further divided into 3-hydroxyflavonoids (flavonols, flavanols, anthocyanidins, dihydroflavonols), and flavonoids without substituent at C3 (flavanones and flavones). Flavones differ from flavanones by a C2–C3 double bond (Marais et al., 2006). The flavanone class encompasses a wide array of compounds with

O- and/or C-substitutions at the A- or B-ring, e.g., hydroxy, methoxy, methylenedioxy, O- and C-glycosyl, C-methyl, C-benzyl, C-hydroxymethyl, C-formyl, C-isoprenyl substituents (including furano or dihydrofurano rings), conjugations to stilbene, anastatin, phenolic acid, and diarylheptanoid moieties (Fig. 1) (Veitch and Grayer, 2006, 2008).

## 3. Biosynthesis of flavanones in plants

Due to the diverse physiological functions in plants and beneficial effects on human health, flavonoids are now attractive targets for genetic engineering strategies. In most plant species, the flavonoid biosynthetic pathway has been almost completely elucidated. In general, the biosynthesis of flavonoids is initiated by the two precursors, malonyl-CoA and *p*-coumaroyl-CoA, which are originated from carbohydrate metabolism and the phenylpropanoid pathway, respectively. After condensation of three molecules of malonyl-CoA with one molecule of *p*-coumaroyl-CoA, the yellow 2',4,4',6'-tetrahydroxychalcone is formed. This step is catalyzed by chalcone synthase (CHS). The unstable chalcone is then cyclized to the corresponding 4',5,7-trihydroxyflavanone by the enzyme chalcone isomerase (CHI). Flavanones may be regarded as the cornerstone of flavonoid biosynthesis as they are the precursors of all other flavonoid classes (Fig. 2) (Martens and Mithöfer, 2005; Schijlen et al., 2004). Moreover, in *Citrus* species, UDP-glucose flavanone-7-O-glucosyltransferase (UFGT) and UDP-rhamnose flavanone glucoside rhamnosyltransferase (UFGRT) sequentially convert the flavanone aglycones into their 7-O-β-D-glucosides and rhamnoglucosides (Lewinsohn et al., 1989) (Fig. 3).

Naturally occurring flavanones display the (*S*) configuration at C<sub>2</sub> (Tomas-Barberan and Clifford, 2000) as a consequence of the enantioselectivity of the chalcone isomerase (CHI)-catalyzed intramolecular Michael addition within the chalcone precursor (Jez and Noel, 2002a). However, mixtures of (2*R*)- and (2*S*)-hesperidin epimers in an approximate molar ratio of 1/6 was detected in orange juice (Si-Ahmed et al., 2010), possibly because of the propensity of flavanone glycosides to undergo epimerization at C<sub>2</sub> via the chalcone form. In the CHI-catalyzed cyclization, the enone moiety of 2',4,4',6'-tetrahydroxychalcone is locked in an *s-trans* conformation. Electrophilic activation of the C=O group involves a water molecule bound to the Tyr106 phenolic OH group and to the OH group of the Thr48 side chain. The main hydrogen bonds established between CHI and the flavanone product are represented on Fig. 4 (Jez et al., 2002b).

The concentrations of biosynthesis enzymes may play an important role in defining the distribution of flavanones in the different parts of the fruit. For instance, in the peel of *Solanum lycopersicum* (a tomato variety), the level of gene expression is lower for CHI than for CHS and flavanone 3-hydroxylase, which results in a high accumulation of naringenin chalcone (Iijima et al., 2008). This biosynthetic pathway is extensively investigated to outline the role of flavonoids in different physiological functions of plants such as insect–plant interactions (Simmonds, 2001), pigmentation (Mato et al., 2000), heavy metal tolerance (Keilig and Ludwig-Müller,

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