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Flavonoids in Grapefruit and Commercial Grapefruit Juices: Concentration, Distribution, and Potential Health Benefits

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Florida is the main producer of grapefruit (*Citrus paradisi* Macf.) in the world. Grapefruit provide not only the traditional nutrients (carbohydrates, proteins, vitamins, minerals), but also phytochemicals such as flavonoids, which are not essential for life, but may provide many health benefits. Flavanones are the dominant flavonoids, and account for about 98% of the total flavonoids in grapefruit. Major flavanones in grapefruit are present as glycosides. In grapefruit, identified flavanone glycosides include didymin, dihydrokaempferol glucoside, eriocitrin, naringin, poncirin, hesperidin, neohesperidin, neoeriocitrin, narirutin, narirutin-4'-glucoside, naringin-6''-malonate (open form), and naringin-6''-malonate (closed form). Flavones or flavonols found in grapefruit include apigenin 6,8-di-*C*-glucoside, apigenin 7-(malonylapiosy)-glucoside, kaempferol glycoside, luteolin, myricetin, neodiosimin, quercetin, rutin, and rhoifolin. Reported polymethoxylated flavones in grapefruit include heptamethoxyflavone, nobiletin, and tangeretin. The presence of naringenin (an aglycone form of naringin and narirutin) in grapefruit remains controversial. Naringin is present at the highest concentration followed by narirutin, hesperidin, poncirin, neohesperidin, didymin, and quercetin. The presence and their concentrations of individual flavonoids vary with grapefruit variety, fruit tissue, juice extraction method, and geographic location. Flavonoids have been linked to many health benefits including antioxidant, anti-inflammatory, and anti-tumor activity. Grapefruit and grapefruit juice are a rich source of flavonoids, especially naringin. By consuming grapefruit and grapefruit juice, individuals not only will obtain essential nutrients but also will get health-beneficial flavonoids.

Florida is the main producer of grapefruit (*Citrus paradisi* Macf.) in the world, and accounts for about 48% of the world's grapefruit production (USDA Data, 2004). During the 2003–04 crop year, about 41% and 59% of Florida's grapefruit was marketed as fresh and juice, respectively, in the world. Overseas shipments accounted for approximately 54% of Florida's fresh grapefruit shipments. Japan is the major importer of Florida fresh grapefruit, accounting for about 55.4% of all overseas shipments during the 2003–04 season. Grapefruit consist of several white and pigmented varieties including 'Marsh', 'Flame', and 'Ruby Red'.

Citrus fruits and juices are among the most important nutrient-dense foods (Rampersaud, 2007). They contain a range of important nutrients for human health such as vitamin C, vitamin A, folate, and minerals. In addition, citrus fruits and juices contain many phytochemicals including flavonoids, carotenoids, glucarates, coumarins, terpenes and limonoids. Unlike the traditional nutrients (carbohydrates, proteins, vitamins, minerals), phytochemicals are not essential for life, but they may provide many health benefits, such as anti-inflammatory and anti-tumor activity as well as inhibiting blood clots (Baghurst, 2003; Manthey and Guthrie, 2002; Middleton et al., 2000). Bioactive phytochemicals may also protect against some of the common chronic diseases such as cancer, cardiovascular diseases, degenerative eye diseases, cognitive impairment, and general damage caused by aging (Manthey and Guthrie, 2002; Middleton et al., 2000; Nair et al., 2004). This review primarily discusses the chemistry, concentration, distribution, and potential health benefits of flavonoids in grapefruit and commercial grapefruit juice products.

Chemistry and Classification of Flavonoids

Flavonoids are a group of phenolic compounds with antioxidant activity that have been identified in fruits, vegetables, and other plant foods and have been linked to a reduced risk of major chronic diseases (Liu, 2004). Flavonoids are low molecular weight compounds composed of a three-ring structure with various substitutes (Middleton et al., 2000). They consist of two benzene rings (A and B), which are connected by an oxygen-containing pyrone ring (C) (Fig. 1). Differences in the generic structure of the oxygenated heterocycle C ring classify them into six subclasses: flavones, flavonols, flavanones, flavanols (catechins), anthocyanins, and isoflavonoids (Fig. 2) (Liu, 2004).

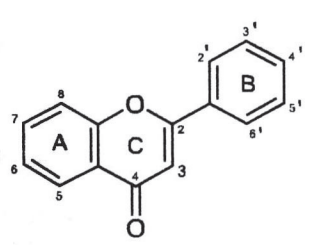

Fig. 1. The generic structure of flavonoids.

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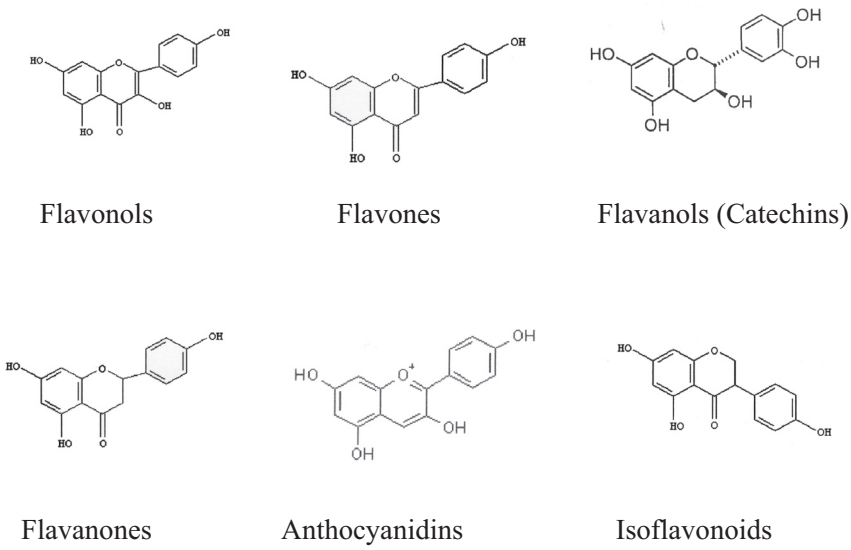

Fig. 2. Structures of main classes of dietary flavonoids.

When sugar molecules are attached to the flavonoid nucleus, the compounds are called glycosides. When the sugars are not present, the term "aglycone" is used. Flavonoids are mainly present in plants as flavonoid glycosides. At least eight different saccharides (such as β-neohesperidose and β-rutinose) or combinations of these can bind to the various hydroxyl groups of the flavonoid aglycone. The glycosides are usually *O*-glycosides, with the sugar moiety bound to the hydroxyl group at the C-3 or C-7 position (Fig. 1) (Erlund, 2004).

More than 5000 different flavonoid compounds have been identified in plants (Holden et al., 2005). Flavonoids are found in most fruits and vegetables, but the types of flavonoids obtained from different dietary sources vary (Erlund, 2004). Four types of flavonoids occur in citrus: flavanones, flavones, flavonols, and anthocyanidins (Benavente-Gaecia et al., 1997). Citrus fruit are a rich source of health promoting flavonoids, especially flavanones (Vanamala et al., 2006, Baghurst, 2003; Horowitz and Gentili, 1977; Peterson et al., 2006). The principal citrus flavanones occur less frequently as the free aglycones but are combined through the C-7 hydroxyl group with either β-neohesperidose or β-rutinose. Anthocyanins, so important in other plants as pigments of flowers and fruits, are of minor importance in citrus and are known only as constituents of the blood oranges (Horowitz and Gentili, 1977).

Flavonoids Identified in Grapefruit

Based on the literature reviewed, flavonoids that have been identified in grapefruit and/or grapefruit juices are listed in Table 1. It has been noted that apigenin 6,8-di-*C*-glucoside and apigenin 7-(malonylapiosyl)-glucoside are two new flavones that were identified in grapefruit (Dugo et al., 2005).

Taste of Flavanones

Flavanones are the dominant flavonoids, and account for about 98% of the total flavonoids in grapefruit (Peterson et al., 2006). Some flavanones are bitter compounds, which contribute to the bitterness of grapefruit and grapefruit juice. These bitter

Table 1. Flavonoids identifed in grapefruit and/or grapefruit juices.

Flavonoids	References
Flavanones	
Didymin	1, 2, 3, 8
Dihydrokaempferol glucoside	1
Eriocitrin	2, 5, 6
Neoeriocitrin	1, 3, 5
Naringenin	7, 13
Naringin	1, 2, 3, 4, 5, 6, 7, 8, 13
Poncirin	1, 2, 3, 6
Hesperidin	1, 2, 3, 4, 5
Neohesperidin	1, 2, 3, 4, 5, 6, 8
Narirutin	1, 2, 3, 4, 5, 6, 8
Narirutin-4'-glucoside	8
Naringin-6''-malonate (open form)	8
Naringin-6''-malonate (close form)	8
Flavones/flavonols	
Apigenin 6,8-di-C-glucoside	3
Apigenin 7-(malonylapiosyl)-glucoside	3
Isorhoifolin	8
Kaempferol	1, 9
Myricetin	9
Diosmin	8
Luteolin	9
Neodiosimin	6
Quercetin	9, 11, 12
Rutin	1, 6
Rhoifolin	1, 6
Polymethoxylated flavones	
Heptamethoxyflavone	1, 6, 10
Nobiletin	1, 6, 10
Tangeritin	1, 10

[1]Horowitz and Gentili, 1977; [2]Peterson et al., 2006; [3]Dugo et al., 2005; [4]Rouseff et al., 1987; [5]Mouly et al., 1994; [6]Nogata et al., 2006; [7]Ho et al., 2000; [8]Berhow et al., 1998; [9]USDA, 2007; [10]Stremple, 1998; [11]Vanamala et al., 2006; [12]Ross et al., 2000; [13]Wanwimolruk and Marquez, 2006.

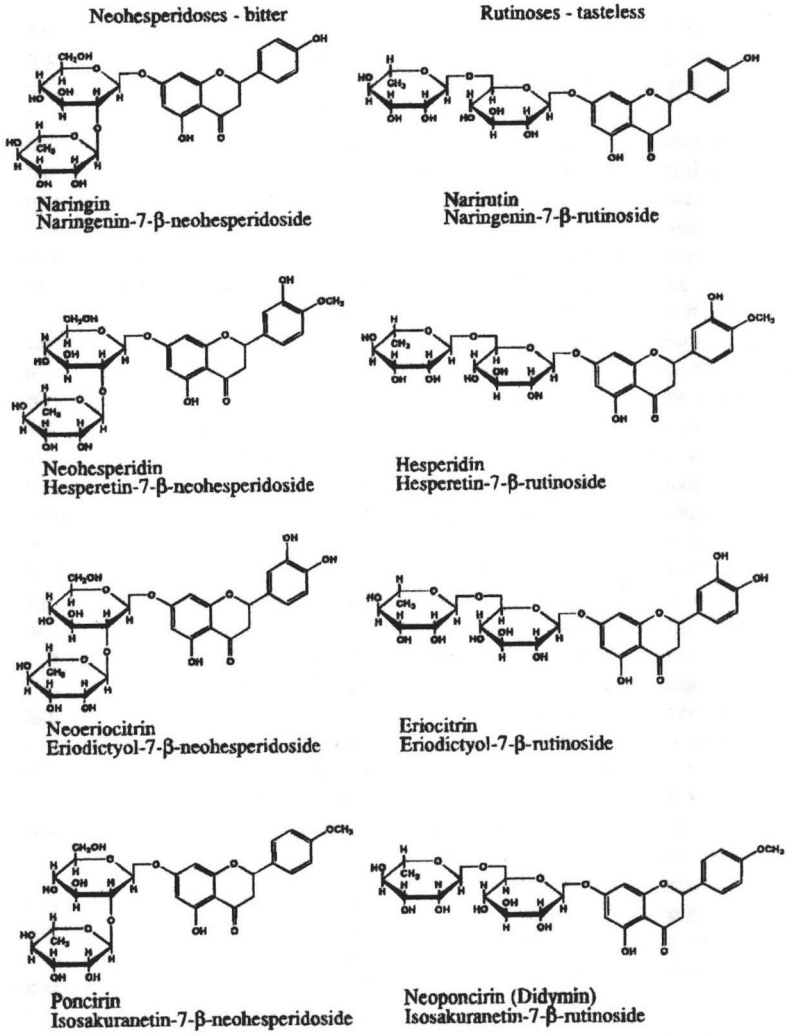

Fig. 3. Some flavanone glycosides found in grapefruit.

flavanones generally have a chemical structure where neohesperidose (sugar moiety) binds to the C-7 position (Fig. 3) (Robards et al., 1997). These compounds include naringin, neohesperidin, neoeriocitrin and poncirin (Sinclair, 1972). Naringin is by far the most dominant bitter flavonoid compound in grapefruit (Lee and Kim, 2003; Hagen et al., 1966). Narirutin, hesperidin, eriocitrin and neoponcirin (didymin), which are the isomers of naringin, neohesperidin, neoeriocitrin and poncirin, respectively, are tasteless, and have a chemical structure where rutinose (sugar moiety) binds to the C-7 position (Fig. 3). Thus, flavanone neohesperidosides can be distinguished from the flavanone rutinosides by taste (Horowitz and Gentili, 1977). Naringin and poncirin are the most bitter, followed by neohesperidin and neoeriocitrin. Maurer et al. (1950) indicated that when the naringin concentration in the juice samples exceeded 0.07%, the juice had a bitter taste, while juice containing less than 0.05% naringin appeared to have superior flavor quality. Other factors, such as sugars, acids, total soluble solids, pH, and oil content, also affect the juice flavor (Sinclair, 1972).

Flavonoids in Commercial Grapefruit Juices

Vanamala et al. (2006) measured flavonoid concentrations in five commercial brands of grapefruit juice using reverse phase high-pressure liquid chromatography (HPLC) and showed that naringin, narirutin, and poncirin were the major flavonoids in all five brands of grapefruit juices. The average concentration of naringin, narirutin and poncirin was 30.4, 10.1, and 1.24 mg/100 mL of juice, respectively. The results showed differences in the concentrations of naringin and narirutin among the five brands of grapefruit juice. Two additional flavonoids reported in this study were neohesperidin and quercetin with an average concentration of 0.59 and 0.64 mg/100 mL of juice, respectively (Vanamala et al., 2006).

Ross et al. (2000) studied the variability of several flavonoids in six brands of grapefruit juice using HPLC. The concentrations of seven flavonoid glycosides, naringin, narirutin, hesperidin, neohesperidin, didymin, poncirin and quercetin, were determined. Naringin (14.6 to 63.8 mg/100 mL) was found to be the major flavonoid, followed by narirutin (2.6 to 12.2 mg/100 mL) and hesperidin (1.4 to 3.1 mg/100 mL).

Naringin and naringenin concentrations were measured in different commercial grapefruit juices sold in California and New Zealand using HPLC (Ho et al., 2000; Wanwimolruk and Marquez, 2006). Their results showed that all tested commercial grapefruit juice products contained both naringin and naringenin. The concentration of naringin (a glycoside form) is much higher than that of naringenin (an aglycone form). The content of narin-

gin varied among the products, ranging from 10.4 mg/100 mL to 74.2 mg/100 mL. The content of naringin in pink and Ruby Red grapefruit juice products were significantly lower than that in white grapefruit juice products. The content of naringenin also varied from brand to brand, and ranged from 0.4 mg/100 mL to 12.6 mg/100 mL. The study conducted by Wanwimolruk and Marquez (2006) in California indicated that there were no significant differences in naringenin contents among the three types. It should be indicated that, based on the information in this review, these are the only two publications that show detectable level of naringenin in grapefruit juice, while most publications indicate that naringenin is not detectible in grapefruit juice.

Rouseff et al. (1987) measured the concentrations of four flavanone glycosides in five major grapefruit cultivars commercially grown in Florida using HPLC. Juice samples were obtained by hand-squeezing the fruit harvested from the Florida Citrus Arboretum in Winter Haven, FL. The data indicated that grapefruit juices from different cultivars contained all four flavanone glycosides naringin, narirutin, hesperidin and neohesperidin with naringin as the predominant flavanone glycoside. Their data also showed that commercially canned grapefruit juices obtained from commercial extractors contained higher amounts of these four flavanones than those obtained from hand-squeezing fruits. This was largely due to the fact that the fruit peel and segment membrane contained higher amounts of these flavonoids, and more flavonoids in fruit peel and membrane were expressed into the juices by commercial extractors compared to the hand-squeezing method.

The USDA's Database for Flavonoid Content of Selected Food (2007) provided some data of individual flavonoid compounds that were detected in four different grapefruit juices. In the USDA's database, citrus flavonoid glycosides were expressed as aglycone forms by mathematical conversion based on the molecular weights of individual flavonoids. The concentrations of naringenin, hesperetin, and eriodictyol (aglycone forms) were calculated from flavonoid glycoside forms. However, it has been known that these aglycone forms (naringenin, hesperetin and eriodictyol) of the flavonoids are naturally not present or are at very low levels in grapefruit and grapefruit juices. They are mainly present as glycoside forms (naringin, narirutin, hesperedin and neoeriocitrin) in grapefruit and grapefruit juice. Therefore, the USDA's data could easily mislead the readers in understanding the real occurrence and concentrations of certain flavonoids in citrus fruit and juices. A similar comment can be made for a recent review of the published flavanone concentrations in grapefruit from 1968 to 2002 (Peterson et al., 2006).

The concentrations of individual flavonoids in grapefruit juices, as they are affected by fruit variety, fruit maturity, and juice extraction methods, are summarized in Table 2.

Distribution of Flavonoids in Different Tissues of Grapefruit

Nogata et al. (2006) analyzed the flavanones, flavones, and polymethoxylated flavones in juice vesicle, flavedo, albedo, and segment epidermis of 'Marsh' grapefruit grown in Japan. Flavonoids found in different fruit parts of 'Marsh' grapefruit were as follows: Flavanones: eriocitrin, narirutin, naringin, neohesperidin, neoponcirin and poncirin; Flavones: rutin, rhoifolin and neodiosmin; Polymethoxylated flavones: nobiletin and heptamethoxyflavone. In 'Marsh' grapefruit, naringin was present at the highest concentration, followed by poncirin, narirutin, neohesperidin, neodiosmin, eriocitrin, rhoifolin, neopocirin and rutin. The albedo contained the highest concentrations of naringin, poncirin, and narirutin compared to other tissues in the same grapefruit. The flavedo contained the highest concentrations of rhoifolin and nobiletin, while the albedo contained more neoponcirin and neodiosmin. Hesperidin was not detected in any fruit tissues of this 'Marsh' grapefruit cultivar under the test conditions.

Jourdan et al. (1983) examined the distribution of naringin within different 'Ruby Red' grapefruit tissues using a radioimmunoassay method. Their approach was that a 1-cm-thick cross-section of tissue was cut from the middle of a 'Ruby Red' grapefruit, and the individual tissues were dissected, extracted, and analyzed for the concentration of naringin. Their results showed that the order of naringin concentration of different tissues within a 'Ruby Red' grapefruit is: core tissue (11.4 mg/g fresh weight) > sac membrane (9.4 mg/g fresh weight) > albedo (6.2 mg/g fresh weight) > flavedo (3.5 mg/g fresh weight > seeds (1.4 mg/g fresh weight) > juice (0.2 mg/g fresh weight).

De-Castro et al. (2006) measured the concentrations of naringin in flavedo, albedo, pulp and seeds of white and red grapefruit using HPLC. The data indicated that the albedo tissue contained the highest concentration of naringin, followed by flavedo, pulp and seeds. In this study, naringin concentration appeared to be higher in white grapefruit compared to that in red grapefruit.

Maurer et al. (1950) measured naringin concentration within different grapefruit tissues among six grapefruit varieties grown in Texas. The pink and red grapefruit varieties tended to have less naringin than the light-fleshed 'Marsh' and 'Duncan' grapefruit varieties. In all varieties, the percentage of naringin in the grapefruit decreased as the season progressed. The most significant decrease of naringin during the 1948 harvest season was between 13 Oct. and 17 Nov., when the naringin content of the juice dropped by 66%. Throughout the fruit season the juice contained much less naringin than did the peel, membrane, or core tissues.

Another study conducted by Del Rio et al. (1997) also showed that immature grapefruit contained much higher concentration of naringin than mature fruit. They reported that the mean concentration of naringin in a whole immature grapefruit (3–7 mm diameter) was 37.8 g/100 g of dry tissue compared to 7.2 g/100 g dry tissue for a mature grapefruit (70–80 mm diameter). In addition, other flavonoids such as hesperidin and neohesperidin were also higher in immature grapefruit than in mature fruit (Del Rio et al., 1997).

Table 2. Flavonoid concentrations of commercial grapefruit juices from different studies.

Flavonoid	Mean (mg/100 mL)	Range (mg/100 mL)	Reference
Naringin	40.5	10.1–86.7	1, 2, 3, 4, 5, 6, 7, 8
Narirutin	10.7	2.6–12.2	3, 4, 6, 7
Naringenin	2.8	0–12.6	2, 8
Poncirin	1.2	0.1–1.9	3, 4, 7
Hesperidin	1.9	1.6–3.1	3, 4, 6
Didymin	1.0	0.3–1.7	3, 4
Neohesperidin	0.9	0.2–1.1	3, 4, 6, 7
Quercetin	0.6	0.2–0.9	4, 7

[1]De-Castro et al., 2006; [2]Ho et al., 2000; [3]Mouly et al., 1994; [4]Ross et al., 2000; [5]Rouseff et al., 1980; [6]Rouseff et al., 1987; [7]Vanamala at al., 2006; [8]Wanwimolruk and Marquez, 2006.

Table 3. Flavonoid concentration ranges in grapefruit based on available scientific publications.

Flavonoids	Commercial juices (mg/100 mL)	Hand-extracted juices (mg/100 mL)	Albedo (mg/100 g)	Flavedo (mg/100 g)	Core (mg/100 g)	Segment epidemis (mg/100 g)
Flavanones						
Didymin	0.3–1.7	na[z]	0[y]	0	na	na
Dihydrokaempferol glucoside	na	na	na	na	na	na
Eriocitrin	na	0-tr[x]	0	0–25.8	na	13.6
Neoeriocitrin	na	na	0–10	0	na	0
Naringenin	0–12.6	0–2.7	na	na	na	na
Naringin	10.1–86.7	7.3–30.7	490–4100	50–1050	1070–2240	1130–1140
Poncirin	0.1–1.9	na	0–638	0–140	na	301
Hesperidin	1.6–3.1	0.4–1.6	0	0	na	0
Neohesperidin	0.2–1.1	0.4–0.8	0–20	tr–29.5	na	16.2
Narirutin	2.6–12.2	2.3–10.6	40–231	10–114	na	118
Narirutin-4'-glucoside	na	na	tr–30	0	na	na
Naringin-6''-malonate (open form)	na	0–tr	10.0–70.0	0	na	na
Naringin-6''-malonate (closed form)	na	tr	20.0–70.0	0	na	na
Flavones/flavonols						
Apigenin 6,8-di-C-glucoside	na	na	na	na	na	na
Apigenin 7-(malonylapiosyl)-glucoside	na	na	na	na	na	na
Diosmin	na	na	0	0	na	0
Isorhoifolin	na	na	0	0	na	0
Kaempferol glycoside	na	na	na	na	na	na
Luteolin	na	na	na	na	na	na
Myricetin	na	0–0.1	na	na	na	na
Neodiosimin	na	14.6	13.6	6.3	na	5.7
Quercetin	0.2–0.9	na	na	na	na	na
Rutin	na	5.4	7.9	0	na	5.5
Rhoifolin	na	10.6	2.7	46.9	na	2.1
Polymethoxylated flavones						
Heptamethoxyflavone	na	0	0	2.2	na	0
Nobiletin	na	0	1.1	11.1	na	0
Tangeritin	na	0	0	0	na	0

[z]na = no data available for its concentration based on the current literature search.
[y]Single value based on one publication.
[x]tr = detected at trace amount level.

Flavonoids in Different Grapefruit Cultivars

The USDA conducted a survey of phenolic compounds in citrus (Berhow et al., 1998). It provided estimated amounts of flavanones and flavones/flavonols in the flavedo, albedo, and juice vesicle tissues of different grapefruit cultivars using HPLC with a UV detector. Flavanones were the dominant flavonoids, and accounted for at least 97% of the total flavonoids. Within a grapefruit, the albedo had the highest concentration of flavanones compared to flavedo and juice. However, the flavedo in 'Star Ruby' grapefruit had the highest concentration of flavones/flavonols when compared to albedo and juice (Berhow et al., 1998). Peterson et al. (2006) also reported that flavanones accounted for about 98% of the total flavonoids in grapefruit.

Flavanones identified in flavedo, albedo or juice of 'Duncan' and 'Star Ruby' grapefruit included: narirutin-4'-glucoside, didymin, narirutin, neoeriocitrin, naringin, naringin-4'-glucoside, neohesperidin, naringin-6"-malonate (open form), and naringin-6"-malonate (closed form) (Berhow et al., 1998). The concentrations of flavanones in 'Star Ruby' were higher than those in 'Duncan' grapefruit. Naringin was the dominant flavanone. It accounted for about 83% of total flavanones in juices of both 'Duncan' and 'Star Ruby'. The albedo contained a higher concentration of naringin compared to the flavedo or juice.

Mansell et al. (1983) conducted the analysis of naringin content of 6,686 grapefruit juice samples from three grapefruit cultivars ('Duncan' seedy, 'Marsh' seedless, and 'Pink' seedless) obtained from three Florida State Test Houses from 1980 to 1981. The State Test Houses determine the juice yield and fruit quality characteristics for each load of citrus delivered to a Florida processing plant. A radioimmunoassay method was used to determine the concentration of naringin. The range of naringin concentrations in grapefruit juices was from 0.6 to 211.5 mg/100 mL with an average of 41.2 mg/100 mL. Juice samples from 'Duncan' grapefruit contained the lowest mean concentration of naringin (37.5 mg/100 mL). 'Pink' seedless samples contained an average naringin concentration of 41.2 mg/100 mL, and 'Marsh' seedless contained the highest mean naringin concentration of 45.1 mg/100 mL. As discussed previously, naringin concentrations varied with fruit variety, maturity, and tissue parts within a fruit (Maurer et al., 1950).

Based on the information reviewed at this time, the individual flavonoids, their concentration ranges and distributions in different tissues within the grapefruit are summarized in Table 3.

Potential Health Benefits of Grapefruit Flavonoids

Grapefruit and grapefruit juice are rich sources of flavonoids. Interest in the possible health benefits of flavonoids has increased largely due to their antioxidant and free-radical scavenging activities. The antioxidant activity of flavonoids has been related to their protection against vitamin C oxidation (Middleton, et al., 2000). Flavonoids have long been recognized to possess anti-inflammatory, anti-allergic, hepatoprotective, anti-thrombotic, antiviral, and anti-carcinogenic activities (Havsteen, 1984; Middleton, et al., 2000). Flavonoids have been linked to a reduced risk of certain cancers, inflammation, stroke, heart diseases (Bohm et al., 1998; Manach et al., 2005), asthma (Garcia et al., 2005; Knekt et al., 2002), vision disorders (Cornish et al., 2002; Yarma et al., 1975), and bone loss (Pang et al., 2006).

Naringin is to a large extent unique to grapefruit and grapefruit juice, and has been reported to be associated with many health benefits. It is mainly the naringin aglycone (naringinin) that is bioavailable and it is largely responsible for the beneficial properties of naringin. Research on naringin or naringenin has shown the following effects: Naringin could 1) act as a free radical scavenger and antioxidant (Jeon et al., 2002; Kumar et al., 2003; Naderi et al., 2003); 2) reduce total cholesterol level and enhance lipid metabolism (da-Silva et al., 2001; Shin et al., 1999); 3) enhance ethanol metabolism (Seo et al., 2003); 4) reduce the risk of atherosclerosis (Choe et al., 2001); 5) act as an anti-apoptotic agent (Blankson et al., 2000); 6) protect plasma vitamin E levels (Jeon et al., 2001); 7) reduce radiation-induced chromosome damage in bone marrow (Jagetia and Reddy, 2002; Jagetia et al., 2003) and increase bone cell activity (Wong and Rabie, 2006), and stimulate DNA repair in prostate cancer cells (Gao et al., 2006); and 8) reduce oxidative stress and inflammatory response (Ghanim et al., 2007). So far most of the data on the health benefits of naringin have mainly been obtained from in vitro or animal research. Clinical studies are needed to corroborate the health properties of naringin in humans.

Narirutin is present at the second highest concentration among the flavonoids in grapefruit and grapefruit juice. Naringin and narirutin are closely related in their chemical structures. In commercial grapefruit juice, the total content of naringin and narirutin account for about 90% of the total flavonoids. Both naringin and narirutin (glycosides) will be converted to naringenin (aglycone) in the human body. Therefore, the consumption of grapefruit and grapefruit juice will provide consumers with a considerable amount of the health promoting flavonoid naringenin. However, other flavonoid compounds that are present at relatively low concentrations in grapefruit and grapefruit juice may still be active in providing health benefits to humans.

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