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Commentary

Functional benefits of citrus fruits in the management of diabetes

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Citrus fruits are important fruit tree crops in the world and are among the most consumed fruits after mangoes, tomatoes and bananas. Citrus fruits (Fig. 1 and Table 1) not only provide ample supply of vitamins, minerals, dietary fibers and pectins but they contain active phytochemicals including phytophenolics (e.g. flavanones, flavones, flavonols, phenolic acids, etc.) that are widely suggested to protect health due to their biological properties, which include anti-atherogenic, anti-inflammatory and anti-tumor activities, inhibition of blood clots, antimicrobial activity and strong antioxidant activity (Middleton and Kandaswami, 1994; Montanari et al., 1998; Samman et al., 1998; Fattouch et al., 2007). Citrus is consumed mostly as fresh produce and juice and most often the peel is discarded. This represents a huge waste as citrus peels are reported to possess the highest amounts of flavonoids compared to other parts of the fruit (Manthey and Grohman, 2001). According to the USDA National Nutrient data base, the peel of some fruits contains considerable amounts of minerals and vitamins, especially in guava and citrus fruits. The peel of certain fruits like an orange contains more vitamin C (ascorbic acid) than its juice. The peel provides 136 mg per 100 g of vitamin C whereas the same in its pulp is only about 71 mg. Likewise, the peel is a rich source of vitamin A, B-complex vitamins, minerals such as calcium, selenium, manganese, zinc…etc. containing several folds more than that in its pulp. Citrus peels are subdivided into the epicarp, or flavedo and mesocarp, or albedo. The flavedo is the colored peripheral surface of the peel, while the albedo is the white soft middle layer of the peel (Fig. 1).

Most citrus species accumulate substantial quantities of flavonoids during the development of their different organs (Castillo et al., 1992). Four types of flavonoids occur in *Citrus* species, namely the flavanones, flavones, flavonols and anthocyanins, with the latter group occurring only in blood oranges. Flavanones are among the flavonoids that predominate in all species of the genus and they occur as glycosides, in which the aglycones are linked to a sugar moiety (Fig. 2) (Lewinsohn et al., 1989; Horowitz and Gentili, 1977). Flavones and flavonols occur at lower concentrations in *Citrus* tissues, but they are associated with powerful antioxidant actions with methoxylated flavones exhibiting the highest biological activity (Benavente-Garcia et al., 1997). The total polyphenols in the peels of lemons, oranges and grapefruits are significantly higher than in the peeled fruits (Ramful et al., 2010a,b, 2011; Gorinstein et al., 2001).

Citrus fruits contain a wide range of flavonoid constituents which are encompassed in the flavanones, flavones and flavonol sub-classes (Nogata et al., 2006; Matabilbao et al., 2007; Tomás-Barberán and Clifford, 2000; Merken and Beecher, 2000) (Fig. 2). A study by Ramful et al. (2010a,b) have shown that citrus fruits contain flavanone glycosides poncirin, didymin, narirutin and flavone glycosides diosmin and isorhoifolin in the flavedo extracts, with the amounts of flavonoid glycosides in the pulp extracts being lower than in the flavedo and albedo extracts. This trend is consistent with the phenolic and vitamin C contents, as well as the antioxidant activities of citrus fruits (Ramful et al., 2011). Berhow et al. (1998) that have shown that the concentration of flavanones is greater in the citrus albedo whilst the levels of flavones and flavonols vary in the flavedo and juice sacs. The dominant rutinosyl flavanones include hesperidin, eriocitrin and narirutin. Hesperidin is abundant in lemon, lime, mandarin and sweet orange. Although the flavanone profile of sweet orange is relatively simple and varies little among cultivars, orange fruit and juice contain hesperidin, narirutin and didymin (Anis and Aminuddin, 1981; Rouseff and Nagy, 1994; Rousseff et al., 1987; Matsubara et al., 1985).

Citrus fruits and their potential benefits in the management of diabetes

Oxidative stress (the imbalance of the physiologic antioxidant protective mechanism and the extent of oxidative burden)-induced

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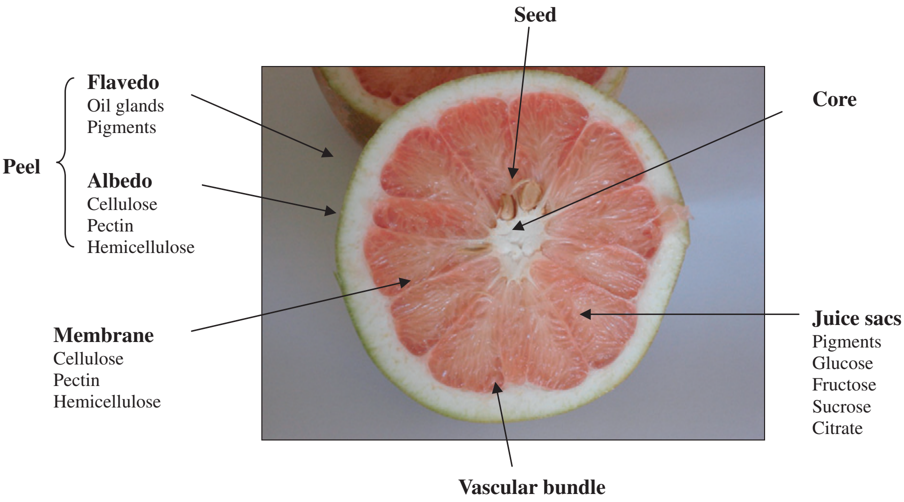


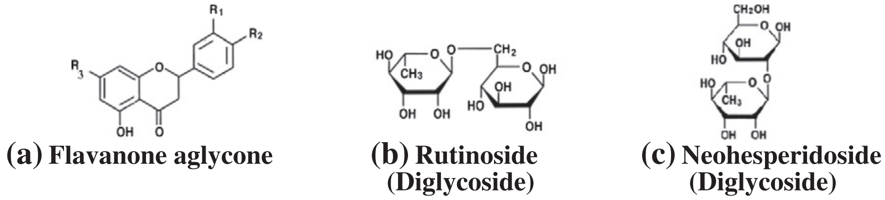
Fig. 1. Equatorial cross-section through a citrus fruit.
Adapted from Ramful et al. (2010a,b).

cell damage has been implicated in a variety of chronic diseases. The mechanisms of action of naturally occurring antioxidants can be diverse in vivo, a demonstration of which requires assessment of a multiplicity of biomarkers (Aruoma, 1994, 2003; Perez-Jimenez et al., 2008). Chemoprevention by dietary means continues to attract major attention for the management of chronic degenerative diseases primarily due to the dramatic rise of cancer and type 2 diabetes mellitus and the increasing incidence of cardiovascular diseases as major and interlinked healthcare problems (Aruoma et al., 2007). The level of antioxidant enzymes along with potential antioxidant vitamins are decreased in diabetic experimental animals and in humans, thus weakening the endogenous antioxidant defense homeostasis. For example, there is demonstrated evidence for the inactivation of glutathione synthesis in erythrocytes from type 2 diabetic patients and also a total reduction in antioxidant activity in both type 1 and type 2 diabetic patients. A free radical is any chemical species (capable of independent existence) possessing one or more unpaired electrons, an unpaired electron being one that is alone in an atomic or molecular orbital. Free radicals are formed from molecules via the breakage of a chemical bond such that each fragment keeps one electron (free radicals may also be formed by collision of the non-radical species by a reaction between a radical and a molecule—which must then result in a radical since the total number of electrons is odd), by cleavage of a radical to give another radical and, finally via redox reactions. Radicals are generally less stable than non-radical species, although their reactivity varies (Aruoma et al., 2007). Indeed several clinical disorders including rheumatoid arthritis, cancer, inflammatory bowel diseases, neurodegenerative diseases, cardiovascular problems, diabetes and the process of aging are associated with chronic inflammatory reactions. Chemoprevention, which involves the use of pharmaceuticals, dietary biofactors, phytochemicals and even whole plant extracts to prevent, arrest or reverse the cellular and molecular processes of carcinogenesis has been proposed due to its multiple intervention strategies. The emerging important mechanisms of action of selected citrus flavonoids are demonstrated in animal models as summarized in Fig. 3 (Bahorun et al., 2012). Oxidative stress and alterations in glucose metabolism are important risk factors for diabetes and its related complications. Advanced glycation end products (AGEs) and their carbonyl derivatives contribute to the pathogenesis of type 2 diabetes by their interaction with specific cell membrane receptors triggering, for instance, the nuclear factor-*Kappa* B signaling pathway to induce the expression of pro-inflammatory mediators and elicit oxidative stress, which exacerbate diabetic complications (Stern et al., 2002). Thus inhibitors of protein AGEs delay or prevent glycation so as to alleviate the phenotype of these diseases (Pashikanti et al., 2010). Given that numerous AGEs inhibitors, including aminoguanidine, improved diabetic complications in animal models and clinical trials with, however, a number of adverse effects (Ho et al., 2010), AGEs inhibitors from natural foods/dietary biofactors may serve as valuable adjuvants. Pursuant of this, Ramful et al. (2010a,b) have shown that extracts of citrus fruits from the tangor and tangelo varieties can delay the free-radical-induced hemolysis in the hemolysis test, thus providing complementary evidence of their antioxidant potency.

ApoE, which is a component of lipoproteins, e.g., chylomicrons, very low-density lipoprotein, intermediate-density lipoproteins, and high-density lipoprotein, is mainly produced and secreted by the liver (Beisiegel et al., 1988). ApoE is known to regulate both cellular and systemic cholesterol, as well as triglyceride metabolism (Mahley, 1988; Tarnus et al., 2009), and has been extensively studied for its potential role in the etiology of atherosclerosis, diabetes, and obesity. ApoE, which exhibits anti-inflammatory, anti-atherogenic, and antioxidant properties (Miyata and Smith, 1996; Davignon, 2005), has been found to be highly expressed by adipose tissue and

Table 1
Scientific and common names, variety of citrus fruits.

Scientific name	Common name	Variety
Citrus sinensis	Orange	Valencia late Washington Navel
Citrus unshiu	Satsumah	Owari
Citrus clementina	Clementine	Commune
Citrus reticulata	Mandarin	Fairchild Dancy Beauty Suhugan Fizu
C. reticulata × *C. Sinensis*	Tangor	Elendale
Citrus aurantium ssp. bergamia	Bergamot	–
Citrus meyeri	Lemon	Meyer
C. reticulata × *C. paradisis*	Tangelo	Mineola Orlando Ugli
Fortunella margarita	Kumquat	Nagami
Citrus mitis	Calamondin	–
Citrus maxima	Pamplemousses (Pummelo)	Rainking Kaopan Pink Chandler



(a) Flavanone aglycone

(b) Rutinoside (Diglycoside)

(c) Neohesperidoside (Diglycoside)

Flavanone	R_1	R_2	R_3
Didymin	H	OMe	ORut [a]
Eriodictyol	OH	OH	OH
Hesperetin	OH	OMe	OH
Hesperidin	OH	OMe	ORut
Naringenin	H	OH	OH
Naringin	H	OH	ONeo [b]
Narirutin	H	OH	ORut
Neoeriocitrin	OH	OH	ONeo
Neohesperidin	OH	OMe	ONeo
Poncirin	H	OMe	ONeo

[a] rutinoside, [b] neohesperidoside

Fig. 2. Flavanone skeleton with substitution pattern.
Adapted from Merken and Beecher (2000).

adipocytes (Wassef et al., 2004; Zechner et al., 1991). Significant reductions in apoE secretions were observed in citrus albedo- and pulp-extract-treated SW872 human liposarcoma cells (Ramful et al., 2011). An increase in apoE secretion at the adipocyte level may represent a defense response to oxidative stress (Tarnus et al., 2009). The decrease in apoE secretion in cells incubated with citrus extract seems to be an adaptive response to the presence of the exogenous citrus antioxidants.

The mechanism of action of citrus phytophenolics in models of diabetes suggest that naringenin is able to reduce glucose uptake and inhibit intestinal and renal Na^+-glucose co-transporter (Li et al., 2006) (and that both naringin and hesperidin significantly increased the glucokinase mRNA level, while naringin reduced the mRNA expression of phosphoenolpyruvate carboxykinase and glucose-6-phosphatase in the liver (Jung et al., 2006). The extracts from Dangyuja (a Korean citrus fruit), containing high levels of flavanone glycosides, could be used to control the blood glucose level of diabetic patients by inhibiting α amylase and α glucosidase in the intestinal tract (Gyo-Nam et al., 2009). The neuroprotective action of naringenin has been reported (Zbarsky et al., 2005) and this could benefit the management of diabetic neuropathies.

Conclusion

The philosophy that food can be health promoting beyond its nutritional value is gaining acceptance within the public arena and among the scientific community as mounting research links diet/food components to disease prevention and treatment. The efficacy of citrus extracts is supported by conclusive evidence from animal models which have provided the concepts for underlying mechanisms of action suggesting that citrus fruit extracts represent an excellent candidate for nutraceuticals and functional foods geared towards the management of diabetes, cardiovascular diseases and cancer. The development will center on the use of a selection of citrus fruit varieties with high polyphenolic content and antioxidant activities for the novel prophylactic beverage/functional foods.

Conflict of interest statement

The authors declare no conflict of interest.

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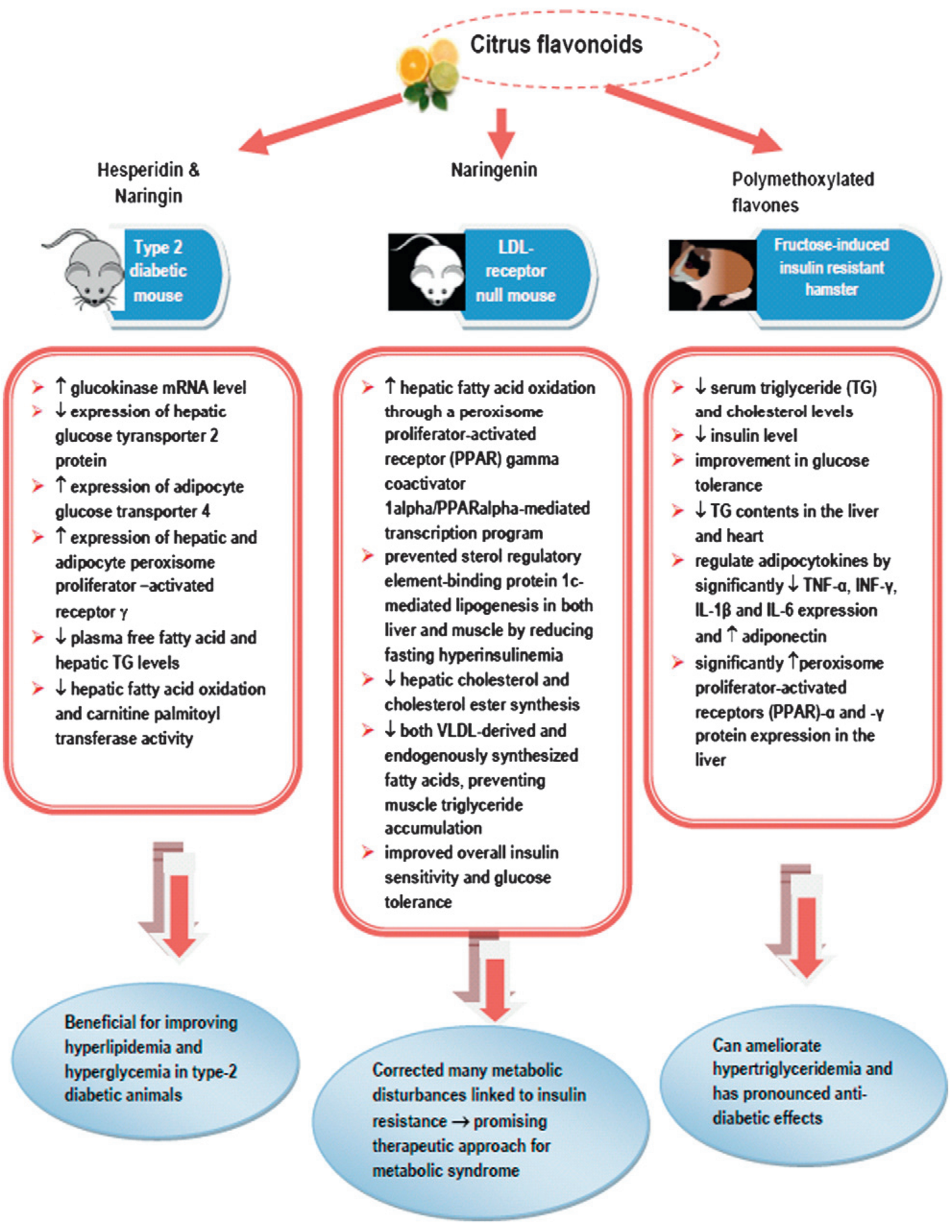

Fig. 3. Mechanisms of action of selected citrus flavonoids in animal models of diabetes. Adapted from Bahorun et al. (2012).

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