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Citrus bioactive phenolics: Role in the obesity treatment

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ABSTRACT

Adipose tissue performs many functions in the body, being considered an endocrine organ due to substances secreted, called adipokines. The excess of adipose tissue is called obesity, and it is associated with a state of chronic subclinical inflammation. Various strategies and products have been evaluated in an attempt to prevent and treat obesity, standing out the importance of polyphenols from citrus fruits. This paper aims to review studies developed to evaluate the role of these compounds in obesity and some general trends can be highlighted. The *in vitro* studies indicate that citrus polyphenols could assist in the management of obesity, since they cause a reduction in adipocyte differentiation, lipid content in the cell and adipocyte apoptosis. The biological assays are not entirely consistent; however, most of them indicated a reduction in adipose tissue; increased genes expression indicating a stimulus to β-oxidation; improved lipid profile and glycemia; as well as some evidence of improvement in inflammatory status. Several clinical trials have demonstrated the positive effect of citrus flavonoids in the reduction of proinflammatory cytokines in humans, being beneficial to alleviate the complications present in obesity. However, there are few clinical trials developed to examine its role in reducing adiposity.

1. Introduction

Adipose tissue has long been considered only as a site of energy storage, however it is now known that it performs many functions in the body. This tissue is considered an endocrine organ due to paracrine substances secreted, called adipokines (Grundy, Brewer Jr., Cleeman, Smith, & Lenfant, 2004). Also there are other cells present in adipose tissue, besides the adipocytes, that release active substances involved in metabolic pathways, such as macrophages (Weisberg et al., 2003). In parallel, the adipose tissue has receptors for afferent signals emitted by other endocrine systems, enabling a communication with the central nervous system. This network interaction explains the coordinating activity of adipose tissue in energy metabolism, neuroendocrine and immune function (Kershaw & Flier, 2004).

Obesity is a disease characterized by excess body weight, associated with a state of chronic subclinical inflammation, caused by an increased secretion of adipokines that modulate certain responses in the body (Balistreri, Caruso, & Candore, 2010). Overall, the vast majority of adipokines studied have a role in the development of chronic diseases associated with obesity causing insulin resistance, increased blood pressure, abnormal blood lipids, increased inflammatory response, and thrombus formation (Grundy et al., 2004).

In addition to many complications associated with obesity, the high prevalence of the disease made it a public health problem. Accordingly, various strategies and products have been evaluated in an attempt to prevent and treat excessive body weight. Among the compounds studied, stands out the importance of polyphenols in plant food.

A source of polyphenols widely studied is citrus fruits. This group of fruits is important source of bioactive compounds, mainly flavonoids, being target of many studies concerning the adipose tissue and obesity. Therefore, this paper aims to review studies developed to evaluate the role of these compounds in the obesity and associated changes.

2. Phenolics in citrus fruits

Phenolic compounds or polyphenols refers to a group of molecules found in plants, that exert photoprotection function, defense against microorganisms and insects, being responsible for pigmentation and some food organoleptic characteristics (Escarpa & Gonzalez, 2001). Among the various classes that comprise the phenolics, flavonoids are considered important for human consumption due to its wide distribution in plant foods.

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The flavonoid structure is based on the flavylium nucleus, which consists of three phenolic rings (Fig. 1). The first benzene ring (A) is condensed with the sixth carbon of the third ring (C), which in the 2-position carries a phenyl group (B) as a substituent (Aherne & O'Brien, 2002).

The biochemical activities of flavonoids and their metabolites depend on their chemical structure, which may vary with one or more hydroxyl substituents, including derivatives. Flavonoids and isoflavones commonly occur as esters, ethers or derivatives glycosides, or a mixture of them. Except the group of leucoanthocyanins, other flavonoids occur in plants usually accompanied by carbohydrates thus receiving the name of glycosylated flavonoids. The glycidic substituents include: D-glucose, L-rhamnose, glucose-rhamnose, galactose and arabinose (Birt, Hendrich, & Wang, 2001). When the flavonoid is free of carbohydrates, the structure is called aglycone.

Citrus fruits are rich in various nutrients, such as vitamins A and C, folic acid and dietary fiber. Furthermore, these fruits are source of bioactive compounds, as flavonoids, coumarins, limonoids and carotenoids (Ding et al., 2012; Turner & Burri, 2013).

Among the flavonoids, citrus present considerable amounts of flavanones, flavones, flavonols and anthocyanins, however the main flavonoids are the flavanones (Benavente-García, Castillo, Marin, Ortuño, & Del Río, 1997). In this class of compounds, the most frequent ones are hesperidin, narirutin, naringin and eriocitrin (Ghasemi, Ghasemi, & Ebrahimzadeh, 2009; Sun et al., 2013). Other phenolics often found in citrus are p-coumaric, ferulic, caffeic and sinapic acids (Manthey & Grohmann, 2001; Sun et al., 2013).

Gattuso, Barreca, Garguilli, Leuzzi, and Caristi (2007) reviewed the flavonoid composition of citrus, and some of their results are summarized at the Table 1.

The genus *Citrus* comprises several orange species – *Citrus sinensis* (sweet orange), *Citrus aurantium* (sour oranges), *Citrus reticulata* (tangerine or mandarin) – and their hybrids – tangors, which are orange-tangerine hybrids, and tangelos, which are tangerine-grapefruit or tangerine pummelo hybrids. Many of these species or hybrids can have different varieties (Gattuso et al., 2007).

In general, the data where the specific *C. sinensis* variety analyzed is reported show that different varieties present approximately the same flavonoid composition pattern. Commercial orange juices present a similar composition to freshly squeezed ones, with the appearance of some unexpected compounds. Naringin and diosmin hint at the possibility that some of the samples analyzed are not pure orange juices, or, as in the case of hand-squeezed juices, the presence of PMFs in variable quantities suggests that they could be essentially derived from the flavedo and confirm that the amounts of polymethoxyflavones found in industrial juices are a consequence of the pressing process used (Gattuso et al., 2007).

It is also important to consider that the flavanones in citrus can be glycosylated or aglycone. The glycosylated forms are also divided

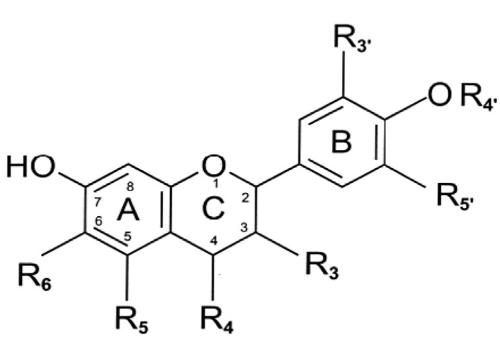

Fig. 1. General structure of food flavonoids.

into neohesperidosides that contain a neohesperidose (ramnosil-α-1,2 glucose) and have a bitter taste; and rutinosides that contain a flavanone and a disaccharide residue, and do not have taste (Macheix, Fleuriet, & Billot, 1990). Naringin, neohesperidin and neoeriocitrin are examples of neohesperidosides; while hesperidin, narirutin and didymin are examples of rutinosides (Tripoli, Guardia, Giammanco, Majo, & Giammanco, 2007). Naringenin and hesperetin are the most common aglycones, often found in trace concentrations.

Concerning the quantity of the compounds, Miller and Rice-Evans (1997) detected the presence of hesperidin (141 ± 49 μmol/L) and narirutin (62 ± 16 μmol/L) in longlife orange juice. Klimczak, Małecka, Szlachta, and Gliszczyńska-Świgło (2007) also evaluated longlife orange juice, verifying the presence of some hydrocinnamic acids as caffeic (8.2 mg/L), p-coumaric (0.5 mg/L), ferulic (0.6 mg/L) and sinapic (0.7 mg/L). However, as mentioned above, the flavanones were found in greater quantity, being detected the presence of narirutin (70.2 mg/L), hesperidin (76.9 mg/L) and dydymin (9.9 mg/L). Of the flavanones analyzed, naringin and neohesperidin were not detected.

Stuetz, Prapamontol, Hongsibsong, and Biesalski (2010) evaluated the polyphenol content of *C. reticulata* Blanco cv. Sainampueng, to verify the difference between hand-pressed juice and the peeled fruit. The peeled fruit had low content of polymethoxyflavones, while the hand-pressed juice presented high content of tangeritin (5.99–31.8 mg/L), nobiletin (5.49–28.2 mg/L) and sinensetin (0.30–2.00 mg/L). The authors observed that the polymethoxyflavones were present in the peel of the fruit, and a simple squeezing can cause the transfer of these compounds from the peel to the juice. Besides this class of polyphenol, it was also detected the presence of the flavanones didymin (4.44–9.50 mg/L), narirutin (17.7–43.4 mg/L) and hesperidin (123.3–206.7 mg/L) in the hand-pressed juice. On the other side, the peeled fruit had high content of didymin (45–112 mg/kg), narirutin (181–600 mg/kg) and hesperidin (841–1898 mg/kg).

Some researchers also study the peels and peels extract of citrus fruits, as Ramful, Bahorun, Bourdon, Tarnus, and Aruoma (2010) that evaluated orange, clementine, mandarine, tangor, tangelo and pamplemousses peels. The flavonoids detected in this matrix were poncirin (2.49–18.85 mg/g FW), rhoifolin (4.54–10.39 mg/g FW), didymin (3.22–13.94 mg/g FW), rutin (8.16–42.13 mg/g FW), diosmin (4.01–18.06 mg/g FW), isorhoifolin (1.72–14.14 mg/g FW), neohesperidin (3.20–11.67 mg/g FW), hesperidin (83.4–234.1 mg/g FW), neoeriocitrin (8.8–34.65 mg/g FW) and narirutin (5.05–21.23 mg/g FW). Naringin (19.49 mg/g FW) was only detected in mandarine.

Londoño-Londoño et al. (2010) identified using HPLC-MS the presence of hesperidin, neohesperidin, diosmin, nobiletin and tangeritin in orange peel; hesperidin and neohesperidin in tangerine peel; and hesperidin, neohesperidin and diosmin in lime peel. Reinforcing the information above, none of the peels presented the aglycone hesperitin in their composition.

Ghasemi et al. (2009) evaluated the total polyphenol and flavonoid content of peels and tissues from three varieties of *C. sinensis*, three of *C. reticulata*, three of *Citrus unshiu*, one of *Citrus limon*, one of *Citrus paradisi* and two of *C. aurantium*. For most citrus analyzed the total polyphenols content was higher in the peel (104.2–223.2 mg gallic acid equivalent/g of extract powder) in comparison to tissue (66.5–396.8 2 mg gallic acid equivalent/g of extract powder), excepting all *C. reticulata* varieties, and one *C. sinensis* variety (var. Washington Navel). The total flavonoid content was also higher in the peel (0.3–31.1 mg quercetin equivalent/g of extract powder) in relation to tissue (0.3–17.1 mg quercetin equivalent/g of extract powder) in most of the samples, excepting four varieties (*C. sinensis* var. Sungin, *C. unshiu* var.