Citrus Flavonoid Effects on Obesity[1]

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The increased prevalence of obesity in recent decades has sparked tremendous concern worldwide. Obesity is a chronic disease that increases a person's risk for a myriad of disorders including diabetes, hypertension, cardiovascular diseases, as well as certain types of cancers. Obesity results from persistently eating more calories than expended and is characterized by an increase in both adipose (fat) cell size and number. Treatments to date consist of medications that cause various adverse side effects. This has led to the recent shift in research towards investigating natural dietary alternatives to treat obesity (Han, Kimura, and Okuda 2005; Lopes, Martins, and Frare 2005; Moro and Basile 2000).

When included in the diet, numerous extracts from fruits and vegetables, known as phytochemicals, have demonstrated a reduction in body weight that can lead to the prevention of diet-induced obesity (Han, Kimura, and Okuda 2005; Lopes, Martins, and Frare 2005). One subgroup of these phytochemicals, flavonoids, has been shown in clinical trials to provide significant benefits to overall health because of their antioxidant abilities (Cook and Samman 1996). Common in both fruits and vegetables, flavonoids are an important group of polyphenolic compounds that possess varying chemical structures. Over 4,000 types of flavonoids have been identified with functions ranging from protecting plants from parasites, herbivores, pathogens, and cell damage to assisting in pollination (Cook and Samman 1996). They are responsible for the color and taste of edible plants, preventing fat oxidation, and maintaining the integrity of vitamins and enzymes. Flavonoids are organized into seven major classes, all of which are common in the human diet and found in herbs, fruits, vegetables, legumes, and teas (Aherne and O'Brien 2002; Bravo 1998; Peterson and Dwyer 1998).

Among those types found in fruits, flavonoids are especially abundant in citrus species. There are 60 types of citrus flavonoids currently identified, and many can be used in the classification of different citrus species (Benavente-García et al. 1997). Citrus flavonoids include flavonones, flavones, and flavonols, the most abundant being flavonones. These citrus flavonones typically exist as one of two disaccharide (two joined sugars) forms that contribute to the unique taste of citrus (Tripoli et al. 2007). Both the peel and seeds of citrus fruit are rich in flavonoids. Some of the most characteristic of these include hesperidin, naringin, and polymethoxylated flavones (PMFs) (Horowitz and Gentili 1997). Interestingly, the composition of these flavonoids is not consistent among the different citrus fruits, and the flavonoids found in the peel and seeds differ greatly from those found in citrus juices. Typically, citrus flavonoids contribute to product quality by improving fruit appearance, taste, and nutritional value. Unfortunately, the content of these flavonoids can be greatly reduced through juice processing, which includes removing the peel and seeds, and storage conditions, where compounds may leach into or out of containers.

Flavonoids provide numerous health benefits and are most well known for their various antioxidant activities. Research has demonstrated flavanoids to stabilize radicals, stop the breakdown of cell membranes, remove toxic metals from

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the body (Bombardelli and Morazzoni 1993), inhibit aging, and decrease inflammation and prevent antimicrobial activity (Manthey, Guthrie, and Grohmann 2001). Moreover, the use of phytochemicals as a safe and natural alternative to treat obesity is under current investigation because citrus flavanoids have been shown to control calorie intake versus expenditure (Westerterp 2004), regulate lipid metabolism (Han, Kimura, and Okuda 2005; Liu et al. 2011) and adipose tissue (Kim and Park 2011), and inhibit amylase function (Nater and Rohleder 2009). For example, some citrus flavonoids can be used as appetite suppressants by targeting the specific signaling hormones that control appetite. Specifically, a number of flavonoids, such as naringenin, hesperetin, and PMFs, have been shown to suppress appetite by increasing caloric homeostasis through numerous pathways resulting in protein inhibition (Kim and Park 2011; Klok, Jakobsdottir, and Drent 2007). Similarly, naringen and naringenin activate receptors, which, in turn, also suppresses appetite, whereas naringenin and nobiletin have both been shown to upregulate some proteins that increase energy expenditure in heat-producing, brown adipose tissue (Golden, Maccagnan, and Pardridge 1997; Meister 2000; Sahu 2003).

Another anti-obesity strategy is to enhance lipolysis and reduce lipogenesis in an effort to reduce fat deposits. Therefore, flavonoids, including naringin, luteolin, quercetin, kaempferol, taxifolin, and hesteretin, have the potential to be used to target the enzymes, such as acetyl CoA carboxylase (ACC), fatty acid synthase (FAS), and hormone-sensitive lipase (HSL), involved in the mechanisms responsible for both the breakdown of existing or the generation of additional fat cells (Westerterp 2010). In a similar manner, using hesperidin, neohesperidin, and luteolin to inhibit pancreatic lipase (PL) from absorbing triglycerides has strong potential for obesity treatment as well (Yun 2010). Additionally, targeting adipocytes (fat cells) through the process of programmed cell death called apoptosis has been supported in studies using naringenin, hesperidin, naringin, and quercetin to reduce adipocyte populations (Herold, Rennekampff, and Engeli 2013). Lastly, using quercetin and luteolin to inhibit digestion activities, therefore slowing carbohydrate breakdown and subsequent glucose absorption, is yet another natural approach for treating obesity (see Figure 1)(Liu et al. 2011).

Citrus flavonoids possess the potential to target numerous pathways leading to obesity. They are also a natural alternative that has not only been demonstrated to be effective, but also to alleviate the unpleasant and dangerous side effects currently experienced by those using anti-obesity medications. In addition to efficacy and safety, the use of flavonoids in obesity treatment is more cost effective. Thus, with the known overall health benefits, no known side effects, and affordable treatments, there is strong potential for these natural compounds to be developed into anti-obesity agents once thoroughly explored through additional research and clinical trials.

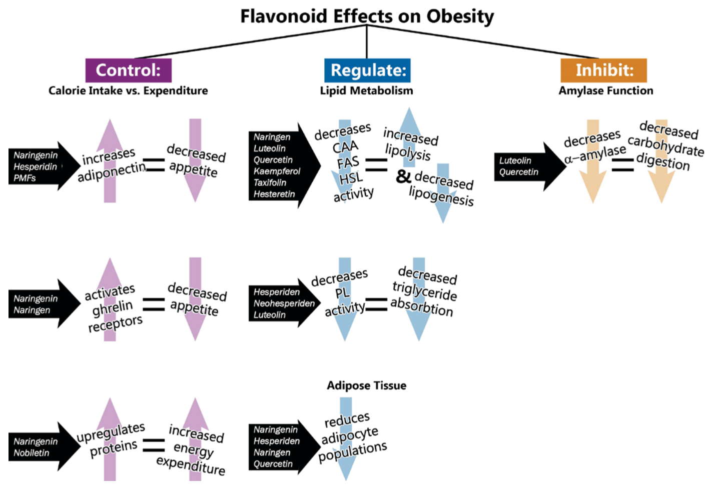

Figure 1. Certain flavonoids affect obesity in different ways. Some flavonoids control the mechanisms leading to obesity, while many regulate metabolism, and others inhibit enzyme function.
Credits: L. Reuss

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