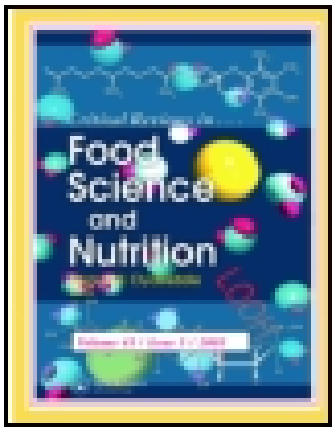

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Effects of Flavanols on the Enteroendocrine System: Repercussions on Food Intake

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Abstract

Flavanols are plant-derived bioactive compounds for which several beneficial effects have been described. When ingested, they reach the gastrointestinal tract, where they can interact with the enteroendocrine cells. In this paper, we consider the possibility that flavanols modulate enterohormone secretion. Because the regulation of food intake is among the principal functions of the hormones that are secreted in the gastrointestinal tract, we also compile the literature that covers how the effects of flavanols on food intake are measured. Although there are some papers showing the effects of flavanols on the regulation of enterohormones, there are very few papers that have addressed the specific effects at the food intake level. Instead, most of the findings are secondary to the study of the action of flavanols on body weight, which makes it difficult to reach a clear conclusion regarding the effects of flavanols on food intake.

Keywords

Catechins, proanthocyanidins, enterohormones, hunger, satiety, body weight

Introduction

Plant-derived foods have many minor components that have the capacity to alter enzymatic and chemical reactions, which exert biological responses in mammalian systems and, therefore, impact health both positively and negatively. One of the largest groups of these bioactive components is the flavonoids, a subclass of polyphenols (Beecher, 1999, 2003). In turn, flavonoids are divided into 6 subclasses, with flavanols (also known as flavan-3-ols) being the most structurally complex subclass of the flavonoids. Flavanols can scavenge free radicals, complex with metal ions, interact with proteins, modulate signaling cascades and modify gene expression. Through these mechanisms, flavanols can exert protective effects against cardiovascular diseases (reviewed in (Rasmussen et al., 2005)) and act as antioxidant (Puiggros et al., 2005), anti-inflammatory (Terra et al., 2009), and anti-carcinogenic (Nandakumar et al., 2008) molecules. Additionally, they can improve lipid homeostasis (Bladé et al., 2010) and modulate glucose homeostasis (Pinent et al., 2012). Despite all of these well-described effects, the bioavailability of these compounds remains a controversial point. Most of them are detected in several tissues (Manach et al., 2004) inside the organism. However, the enormous diversity of chemical structures that can arise after their metabolization makes it difficult most of the time to identify the compound(s) that are responsible for the described effect. In contrast, it is very clear that flavonoids reach the gastrointestinal tract, where they can directly interact with the enteroendocrine system, which controls several digestive and metabolic processes as well as food intake.

The enteroendocrine system is one of the highest endocrine systems of the organism (Janssen & Depoortere, 2012). On the intestinal surface, there are absorptive enterocytes, bactericidal Paneth cells, mucus-producing goblet cells and hormone-secreting enteroendocrine cells. These last cells are fully differentiated cells that, together with the goblet and Paneth cells, constitute the secretory lineages in the intestine, composing 10% of the epithelium (Moran-Ramos et al., 2012). The different enteroendocrine cell types have been classified according to their epithelial localization: first, the ñclosed cellsò that do not reach the gut lumen, and second, the ñopen cellsò that project a tuft of apical microvilli into the intestinal lumen and extend to the basal lamina (lamina propria) (Sternini et al., 2008). The open type cells are considered to be primary chemoreceptors, responding to the luminal nutrients by releasing their secretory products, which activate neuronal pathways, nearby cells or distant targets. Closed cells can be regulated by luminal content indirectly through neural and humoral mechanisms (Sternini et al., 2008). Enteroendocrine cells have also been classified into at least 10 types based on their morphology, principal hormone product(s) and distribution along the intestinal tract (Janssen & Depoortere, 2012) (summarized in Table 1). The most studied enteroendocrine cells are I-, L-, and K-cells due to their secreted products, which are cholecystokinin (CCK), glucagon-like peptides, and GIP, respectively (Moran-Ramos et al., 2012).

Food intake is controlled by the brain, which receives hormonal, neural and metabolic signals that reflect the energetic status; the brain then responds to these inputs by coordinating adaptive alterations of energy intake and expenditure. There are several signals that emanate from the gastrointestinal system, such as pancreatic and intestinal satiation peptides. Panickar (2012) recently reviewed the effects of dietary polyphenols on neuroregulatory pathways that modulate

food intake. They concluded that some polyphenols clearly appear to have the potential to modulate neuropeptides that are involved in food intake and satiety, but they remark that the studies that allow such conclusions are scarce (Panickar, 2012).

We hypothesize that flavonoid effects on food intake could be mediated by its interaction with the ñopen cellsò in the gastrointestinal epithelium. To further analyze this hypothesis, we next review the described effects of flavonoids on gastrointestinal signals that regulate food intake and their described bioactivity that is related to food intake.

Flavanol structure and metabolism

Flavanols range from simple monomers, (+)-catechin and its isomer (-)-epicatechin, to complex structures that include the oligomeric and polymeric proanthocyanidins, which are also known as condensed tannins. The monomeric forms can be hydroxylated to form gallocatechins, and monomers can also undergo esterification with gallic acid (Crozier et al., 2009). Catechins are found in many fruits, but the richest sources of catechins are green tea, chocolate, and red wine (DôArchivio et al., 2007). Catechin and epicatechin are the main flavanols in fruit, whereas gallocatechin (GC), epigallocatechin (EGC), and epigallocatechin gallate (EGCG) are found in certain seeds of legumes, in grapes, and in tea. In contrast to other classes of flavonoids, flavanols are not glycosylated in food (Manach et al., 2004). Although the exact flavanol content is difficult to determine due to the wide range of structures, they are major components in the human diet due their widespread presence in fruits, berries, nuts, beans, some spices, cocoa-based products, wine, and beer (Gu et al., 2004).

The biological properties of polyphenols depend on their bioavailability. The chemical structure of polyphenols determines their rate, the extent of intestinal absorption and the nature of the metabolites that circulate in the plasma (reviewed in (Scalbert & Williamson, 2000; Aron & Kennedy, 2008)). Moreover, the degree of polymerization and galloylation of flavan-3-ols are factors that affect their bioavailability. Monomeric flavan-3-ols are absorbed in the small intestine, where they are extensively metabolized into glucuronide conjugates. Flavan-3-ols can also enter the liver, where they are mainly sulfated and methylated (Monagas et al., 2010). Then, conjugated flavanols enter into systemic circulation or can be returned to the intestinal lumen via bile (entero-hepatic circulation) (Aura, 2008). Approximately 90-95% of the total consumed polyphenols cannot be absorbed by the small intestine; as a result, they pass to the colon and, in addition to the compounds returned by the entero-hepatic circulation, they are metabolized by the colonic microflora (Clifford, 2004). The microbial metabolites are absorbed by the colonocytes and arrive at the liver, where they are subjected to glucuronidation, methylation and sulphatation. Then, they enter into systemic circulation or to the kidneys, where they are excreted in the urine (Monagas et al., 2010). Flavonoids have been detected in a wide range of tissues in mice and rats, including the brain, endothelial cells, heart, kidney, spleen, pancreas, prostate, uterus, ovary, mammary gland, testes, bladder, bone, and skin (Manach et al., 2004). Numerous studies in animals and humans have shown that polymeric proanthocyanidins are not absorbed. The majority of them pass unaltered through the small intestine and are then metabolized by the colonic microflora to yield a number of simple phenolic acids (Déprez et al., 2000). However, procyanidin dimers and trimers have been detected in rat urine (Tsang et al., 2007) and plasma

(Serra et al., 2010) following administration of grape seed procyanidins. Additionally, oligomers (up to pentamer size) were detected in rat plasma following administration of a procyanidin extract from apples (Shoji et al., 2006). Some *in vitro* assays that mimic gastrointestinal conditions have demonstrated the degradation of procyanidin oligomers to yield bioavailable monomers (Spencer et al., 2000). However, *in vivo* studies rejected the notion that procyanidins contribute to the pool of circulating flavanols via their breakdown into monomers in rats (Tsang et al., 2007) and humans (Ottaviani et al., 2012). The detection of dimeric procyanidins in human plasma has been reported in some studies (Sano et al., 2003; Holt et al., 2002; Urpi-Sarda et al., 2009).

Effects of flavonoids on enterohormone release

GLP-1 is secreted by L-cells of the intestine and participates in the regulation of food intake, although its main role is as incretin, a hormone that promotes insulin secretion. The modulation of incretins by procyanidins has been partly evaluated. In healthy rats, an acute oral dose of grape seed extract (1 g/kg bw) has been shown to increase GLP-1 levels after an oral glucose load. The mechanisms that exert this effect could arise from their capacity to inhibit Dpp4, their ability to modulate GLP-1 secretion from L-cells, as shown in the enteroendocrine cell line STC-1, and/or by altering the number of enteroendocrine cells in the intestine (submitted results). Similarly, a dose of 10 g/kg bw of the procyanidin tetramer cinnamtannin A2 also increases plasma active GLP-1 when it is acutely administered to fasted mice (Yamashita et al., 2013).

Furthermore, Törrönen et al., working with healthy humans, showed that a single administration of a berry purée (800 mg polyphenols including anthocyanins, flavonols, phenolic acids, proanthocyanidins, and ellagitannins, corresponding to 12mg/kg bw) administered together with sucrose tended to increase GLP-1 (Törrönen et al., 2011). Not only acute doses, but also a preventive dose of 25 mg/kg bw of the grape seed procyanidin extract, for 12 weeks, prevented the cafeteria-induced decrease in colon GLP-1 producing cells (submitted results).

Other monomeric polyphenols have also been shown to modulate GLP-1 levels. Chlorogenic acid, which is a major phenol found in coffee, was shown to improve plasma GLP-1 levels in humans (Johnston et al., 2003) and increase GLP-1 secretion and production in STC-1 cells, a murine enteroendocrine cell line (Rafferty et al., 2011). Berberine, which is a major active constituent of *Rhizomacoptidis*, has been reported to increase portal active GLP-1 levels in healthy and streptozotocin-induced diabetic rats (STZ) and to enhance GLP-1 secretion and biosynthesis in NCI-H716 cells, a human enteroendocrine cell line (Lu et al., 2009; Yu et al., 2010). Genistein and daidzein isoflavonoids, which are derived from soybean fermentation, have been reported to increase GLP-1 secretion from NCI-H716 cells (Kwon et al., 2011); glyceollins and phytoalexins that are derived from daidzein in soybean with a fungi infection showed the same effect *in vitro* (Park et al., 2010). Resveratrol, a polyphenolic compound produced by fruits such as red grapes or berries, was found to increase portal active GLP-1 levels and intestinal biosynthesis in high-fat diet-fed rats (HFD) (Dao et al., 2011). Finally, a recent paper has reported that curcumin, a phenolic compound that is isolated from the rhizomes of *Curcuma*

longa L., can increase GLP-1 secretion in the murine enteroendocrine cell line, GLUTag (Takikawa et al., 2013).

Ghrelin is produced by X-cells of the stomach, and its main role is highly related to the regulation of food intake. Ghrelinôs modulation by isoflavones has been evaluated, while there is less information regarding other types of flavonoids. Soy isoflavones decreased plasma ghrelin, increased CCK, and increased, although not significantly, PYY when administered to ovariectomized rats that were fed a high-fat diet for 4 weeks. These changes were found at 3 doses of isoflavones: low (26 mg/kg bw), medium (74 mg/kg bw), and high (206 mg/kg bw). However, the body weight was increased at the lower dose and was reduced at the other two doses. At the higher doses, the energy intake was reduced (Zhang et al., 2009). A similar effect was found in female mice by Ryökkynen et al. In this case, 8 mg/kg bw/day of the isoflavone genistein administered to mice for 8 weeks reduced plasmatic ghrelin in females, while it had no effect in males. In these mice, food consumption was reduced at weeks 1 and 5 but not at the end of the experiment because these animals had pups that were in the lactation period (Ryökkynen et al., 2006). Thus, animal studies suggest that some isoflavones can modify the levels of ghrelin, and it appears that such a modification precedes changes in body weight. Similar studies in humans do not clearly show this effect, but these results could be due to the different doses that were administered. In healthy postmenopausal women, 80 or 120 mg (i.e., 1.19 or 1.79 mg/kg bw) of soy isoflavones for 12 months did not modify the fasting levels of appetitive hormones (ghrelin, insulin, leptin, and adiponectin). In the same sense, the body composition was not affected by soy isoflavones. Food intake was not assessed (Matvienko et al., 2010). Similarly, in

another study in healthy postmenopausal women, 50 mg/day of isoflavones neither affected preprandial ghrelin plasma levels, nor insulin, glucose body weight or energy intake. Instead, PYY was increased by isoflavones, and the authors concluded that this hormone level is not a major factor in the regulation of body weight (Weickert et al., 2006). In a smaller study (Nikander et al., 2004), isolated isoflavonoids (114 mg/day) for three months inhibited the age-dependent rise of fasting plasma ghrelin in postmenopausal women with a history of breast cancer, although this finding was not accompanied by modifications in the lipid profile or insulin sensitivity, and the body composition and food intake were not assessed.

An extract of *Citrus grandis* that is rich in naringenin was administered for 12 weeks at different concentrations (300, 600, 1200 mg/kg bw) in Zucker fatty rats that were fed a high fat/high cholesterol diet and did not induce significant changes in the body weight nor in the food intake, although the authors suggested that there was a tendency to reduce the body weight accompanied by an increased energy intake. The hormones were analyzed, and the extract appeared to counteract the HFD-induced decrease in ghrelin. The extract also decreased the plasma GLP-1 (which was not affected by the diet), while it did not change the insulin, PYY, leptin nor amylin (Raasmaja et al., 2013). In type 2 diabetic humans, a decaffeinated green tea extract (11.12 mg EGCG/kg bw) for 16 weeks did not show any difference in plasma ghrelin or leptin compared to the placebo group. Treatment also did not modify the body weight or plasmatic parameters (insulin, glucose, HOMA-IR) (Hsu et al., 2011). Finally, in healthy humans, carob pulp reduced the acylated but not the total ghrelin. The effects on ghrelin might account for the observed reduction in NEFA and TAG and the change in the substrate utilization toward lipid oxidation (decrease in RQ) (Gruendel et al., 2006). The effects on plasma acylated ghrelin and fat

oxidation after a meal were maintained 24-hour after carob pulp intake (Gruendel et al., 2007). Because the treatment was acute, no report on hunger or energy intake was made. Moreover, carob pulp is rich in insoluble dietary fiber and polyphenols, mainly gallic acid, gallotannins and flavonol glycosides, and from these experiments, it cannot be deciphered whether the effects were due to the fiber or the polyphenols (Gruendel et al., 2006).

There are very few studies that evaluate flavonoid effects on PYY; these studies were cited above. Raasmaja et al. showed no effects of an extract that was rich in naringenin given simultaneously with a HFD in Zucker fatty rats (Raasmaja et al., 2013). Zhang et al. reported that an isoflavone treatment of ovarectomitzed rats increased PYY (Zhang et al., 2009). Finally, Weickert et al. described that soy isoflavone supplementation for eight weeks did not significantly reduce the energy intake or body weight, even though plasma PYY increased during the isoflavone treatment (Weickert et al., 2006).

The relation of CCK with flavonoids is indeed less analyzed. The scarce existing studies are already indicated above.

Taking these studies together, flavonoids have been shown to modulate GLP-1 levels. Other polyphenols also modulate GLP-1 and ghrelin. There is very little data that concerns the effects on other enterohormones. In all of these studies, whether such modulation involves effects on food intake has not been assessed.

Effects of flavanols on food intake

There are few studies that evaluate the effect of flavonoids on food intake, and most of them evaluate it secondarily in studies that were designed to analyze the effects on body weight and energy balance.

Tea catechins

Among the most studied flavanols are the tea catechins, of which EGCG is the most abundant polyphenol. A few animal studies showed the inhibition of food intake by tea catechins (summarized in Table 2a). Kao et al. showed that, in Sprague Dawley rats, intraperitoneal EGCG injection (~85 mg/kg bw) reduced food intake within 2-7 days of treatment. Instead, other catechins (catechin, epigallocatechin, epicatechingallate) did not modify food intake. Such effects were also reproduced in Zucker fatty rats, which suggests that the inhibition of food intake by EGCG is leptin-receptor independent. Treated animals also showed a significant reduction in body weight, which the authors attributed mainly to the reduced food intake. EGCG when orally administered led to a lower reduction in food intake compared to the intraperitoneally treated rats, and no effects on the body weight were found (Kao et al., 2000). Long-term studies in mice also showed a reduction in the food intake. Female mice that were fed a diet that contains 4% green tea powder for 16 weeks showed suppressed body weight gain and food intake (Sayama et al., 2000). Additionally, Murase et al. showed that in C57Bl/6J mice that were fed 0.5% (estimated intake: 592 mg EGCG/kg bw) tea catechins with a high-fat diet for 11 months, the energy intake was reduced. However, the authors suggested that these effects are due

to the reduction in body weight that was induced by this catechin dose, because a decreased body weight was observed prior (12 weeks) to the decreased energy intake. Lower (0.1% and 0.2%) catechin doses had no effects on the food intake, although they did reduce the body weight (Murase et al., 2002).

Human studies also show the effect of inhibiting the food intake (summarized in Table 2b). In overweight men, an intake of 1500 mg (17.8 mg/kg bw) of green tea extract reduced energy consumption in a 4-hours test. However, at the same time, green tea extract enhanced the desire to eat something sweet and something fatty (Belza et al., 2007). Intake inhibitory effects have been observed when a combination of catechins and other substances was tested; in these cases, it is difficult to conclude whether the effects are due to the individual components or due to additive/synergic effects. In overweight humans, a study of a preload of a beverage that contained fiber ± caffeine and EGCG followed by a test lunch and a recording of motivational ratings and food consumption showed that the beverage and caffeine was more satiating and led to a lower calorie intake at lunch than the beverage that had only fiber (Carter & Drewnowski, 2012). Additionally, in overweight subjects, an oily complex of EGCG (50 mg/capsule) and 85 mg N-oleyl-phosphatidilethanolamine (NOPE), a naturally occurring phospholipid, administered for 2 months together with a restricted energy intake, promoted diet compliance and an increased feeling of fullness and satiety and reduced feelings of hunger compared to the placebo group. Weight change, which was reduced by the low calorie diet, was not different between the treated group and the placebo (Rondanelli et al., 2009). Finally, in healthy humans who were under a three-week positive-balance intake, the ingestion of green tea plus capsaicin (a total daily intake

of catechins: 1795.5 mg) for five separate days significantly reduced their energy intake. These components individually showed a tendency toward reduction, but it was not significant. When individuals were subjected to a negative energy balance, the treatments did not significantly alter their energy intake. Hunger, the desire to eat and fullness were reduced, and satiety was increased, due to the combination of ingredients, in both positive and negative energy-balance experiments (Reinbach et al., 2009).

However, several other studies in animals, acute tests in humans or longer feeding studies in humans did not find changes in food intake due to tea catechins, although in many of these studies a reduction in body weight was observed. Concerning animal studies, in female mice feeding on a diet with 2% (estimated intake: 2368 mg EGCG/kg bw) green tea powder for 16 weeks, there was a reduced body weight gain without any effects on energy intake. A combination of 0.3% catechins + 0.05% caffeine showed similar effects, and the catechins alone modified neither the energy intake nor the body weight (Zheng et al., 2004). Often, antiobesity effects are observed when there is an impedance of body weight gain rather than a reduction in the body weight. In obesity-prone NZB mice, TEAVIGO (green tea extract with an estimated daily dose of EGCG of 1.3 mg/kg bw and less than 0.1% caffeine) consumption for 29 days dependently reduced the increase in body weight observed after the feeding of an HFD, which was exclusively due to a reduction in body fat and without any effects on food intake (Klaus et al., 2005). Male Sprague Dawley rats that were fed a high-fat diet together with green tea extract (estimated dose: 2300 mg/kg bw) showed a reduction in body fat gain without having any effects on the energy intake (Choo, 2003). In C57BL/6J mice that were fed a high-fat diet (60% energy

as fat), supplementation with dietary EGCG treatment (3.2 g/kg diet; estimated dose: 425.6 mg/kg bw) for 16 weeks reduced the body weight gain and the percent body fat. Additionally, 3-month-old high-fat-induced obese mice that received short-term EGCG treatment (3.2 g/kg diet, 4 weeks) had decreased mesenteric fat weight and tended to have a lower body weight. However, any of these experiments showed a modified energy intake that was due to EGCG treatment (Bose et al., 2008). No effect on the food intake was found in male C57BL/6 mice that were fed a high-fat/Western-style diet together with a 3.2 g EGCG/kg diet (~ 10 cups/day of green tea) for 17 weeks. Although after 9 weeks of treatment, a significantly lower body weight gain in EGCG-treated rats was observed, at the end of the experiment, these animals weighed 9% less than the non-treated mice (Chen et al., 2011).

Concerning human studies, Gregersen et al. designed a study to analyze the effect of tea catechins ± caffeine on energy expenditure and fat oxidation, which included testing subjective appetite sensation by visual analogue scales. The study, a one-day test that was conducted on normal-weight healthy males who received capsules of caffeine mixed with tea catechins (600 mg), failed to show any effects on their appetite sensations (Gregersen et al., 2009). In obese subjects, the intake of a green tea extract that is rich in catechins (689.9 mg/day) for 12 weeks, without any modifications in lifestyle, induced a reduction in body weight without affecting the food intake (Nagao et al., 2007). In the same sense, in overweight Asian populations, a daily consumption of 500-900 mg of green tea catechins (with low-moderate amounts of caffeine) for 90 days exerted positive effects on the body composition and abdominal fat mass, but a reduction in the body weight was not accompanied by changes in the reported energy intake (Wang et al.,

2010). Combinations of tea catechins and other substances have also shown a lack of effect on hunger, e.g., in overweight humans, EGCG together with NOPE enhanced compliance to a low calorie diet for 4 weeks but did not have any significant effects on weight loss or feelings of hunger (Mangine et al., 2012).

Importantly, some studies have also found increased energy intake due to tea catechin consumption. A population of sedentary, middle-aged, overweight or obese men was given 530 mg decaffeinated green tea extract (DGT) twice daily for 6 weeks during 2 intervention periods. During the first intervention period, the body weight of the placebo group increased while that of the DGT group decreased, without any differences in food intake. During the second treatment period, the DGT showed increased energy intake compared with the placebo group, while the body weight was reduced in both groups, without significant differences due to the DGT treatment (Brown et al., 2011). Increased hunger and prospective food consumption was also observed after green tea treatment in overweight females who were eating a low-energy diet (weight loss intervention). The dose that was administered was 1125 mg tea catechins + 225 mg caffeine/day for 83 days, and no effect of the treatment on the body weight was observed (Diepvens et al., 2005). Increased hunger and lower satiety has been described in response to green tea-caffeine mixtures in overweight and moderately obese subjects who were first subjected to weight loss followed by a weight maintenance period. The dose that was administered, which also promoted weight maintenance, was 270 mg EGCG + 150 mg caffeine/day) (Hursel & Westerterp-Plantenga, 2009). These studies suggest that the effects of tea

catechins promote weight maintenance but not weight loss and could lead to increased energy intake.

All of the previous data show that although there are several studies that report the effects of tea catechins on food intake, and some of them support a positive effect, the exact effects and mechanisms remain unresolved. In general, these studies suggest that a role of increasing energy expenditure and fat oxidation as well as inhibition of nutrient absorption might be more relevant than limiting the food intake in the reduction of body weight gain by green tea extract, according to the literature (reviewed in (Rains et al., 2011)).

Other flavanols besides tea catechins

Grapes, especially grape seed and skin, and their derivate beverages, such as wine, are another source of flavanols that have well-defined beneficial health effects (Puiggros et al., 2005; Bladé et al., 2010; Pinent et al., 2012; Terra et al., 2011). The type of flavanols in which grapes, and especially grape seeds and skin, are enriched differ from those found in tea. Grapes contain mainly catechin, epicatechin and their polymerized forms, and the content of EGCG in grapes is low (Quiñones et al., 2013).

For grape flavanols, the effects on food intake have not been studied as extensively as for tea catechins (summarized in Table 3). In fact, most of the studies focus on the effects on body weight and not specifically on food intake control. Several studies, which were mostly on animals, also point to a role of grape flavanols at impairing weight gain. In rats that were fed a

hypercaloric diet for 8 weeks, moderate wine consumption (voluntary consumption) prevented an increase in body weight. This result was associated with a decreased food intake (Vadillo et al., 2006). Tebib et al. first described that feeding grape seed tannins at a dietary level of 7.1 mg/kg bw for a 12-weeks period in male Sprague Dawley rats resulted in a reduced body weight gain. The authors hypothesized that this finding might be due to a delayed absorption that is caused by flavanol polymers because a monomer-enriched diet did not induce such an effect. None of the diets modified the food intake (Tebib et al., 1996). It has been suggested that not only the effects on food absorption but also other mechanisms could lead to a reduction in weight gain. A monomer-rich grape seed extract at 0.5 or 1% in an HFD for 12 weeks reduced the increase in body weight in C57BL/6J mice without modifying the food intake, and the authors point to an increase in fatty acid oxidation as being responsible for the reduced weight gain (Ohyama et al., 2011). Grape seed procyanidins that were administered together with a high-fat diet (1 mg PE/g of feed) prevented the body weight gain that was induced by the diet, without modifying the total energy intake, and it prevented low-grade inflammation (Terra et al., 2011). A grape seed extract of 50.1% total flavanols, 49.08% procyanidins, and 1.02% monomeric flavanols was administered together with a high-fructose diet (at 0.5% and 1%) to male Sprague Dawley rats for 8 weeks. Both of the doses led to a reduced body weight without changes in the food intake. Grape seed procyanidins at a dose that is achievable by the human diet (25 mg/kg bw) and for a subchronic period of time (15 days) reduced the body weight gain in hamsters that were fed either a control or a high-fat diet. Such effects were not explained by a food intake reduction because the food intake was not modified. Instead, increased oxidation and the glycerol/fatty acid cycle in adipose tissue might explain the antiobesity effects (Caimari et al.,

2013). In humans, compensatory effects of the polyphenols on thermogenesis and substrate oxidation were also suggested for concord grape juice, which is a source of catechin, myricetin, quercetin, anthocyanidins, and proanthocyanidins; when administered to healthy males for 12 weeks (480 ml/day), there were no differences in the food intake (as reported by the participants) or appetite sensations when compared to a polyphenol-free drink or a non-treatment control. The polyphenol-rich juice also did not lead to significant differences in the weight gain compared to the non-treatment controls, while the polyphenol-free juice did increase the weight gain (Hollis et al., 2009). Additionally, other studies report no effects on food intake while they also fail to find a modulation in the body weight. Grape seed extract (50 mg/kg bw) or fractions that were extracted in different solvents (30 mg/kg) were administered to male and female db/dbmice (C57BL/KsJ-lepr^{db}/lepr^{db}) for 8 weeks, but this administration did not modify the body weight or food intake of the diabetic mice (Hwang et al., 2009). Additionally, no changes in the body weight were observed when two grape extracts (of the seed and skin) were tested for their potential toxicity. They were supplied together with the diet to outbred albino rats at 0.63, 1.25, and 2.5% (w/w). No effect on the food consumption was observed in the female rats. Instead, at the 2.5% dose of both extracts (mean equivalent to 1780 mg/kg bw per day), the male rats showed a small but significant increase in their food intake from day 7 until the end of the study (3 months) compared to controls (Bentivegna & Whitney, 2002). Although it does not appear that inhibition of energy intake is a mechanism that explains the effects of grape flavanols avoiding weight gain, a short-term study on healthy humans taking grape seed procyanidin extract (300 mg containing > 90% procyanidins, in two intervention periods of 3 consecutive days separated

by a washout period) showed a reduced 24-hour energy intake in subjects with an energy requirement Óthe median of 7.5 MJ/day, without affecting satiety (Vogels et al., 2004).

The interest in defining the beneficial effects of flavanols has led to the study of several other sources that are enriched in such bioactive compounds. Because most of the studies that analyze food intake do aim to demonstrate a putative antiobesity effect, they are conducted in animal models of diet-induced obesity. The polyphenols of a lingonberry extract (5.8% flavanols, 2.9% flavonols, 1.9% phenolic acids, and 1.5% anthocyanins) were analyzed, and the effect on this extract was assayed in rats that were fed a high-cholesterol, high-fat diet. The effects on the energy intake appeared to be dependent on the dose because the lowest dose (8 mg/day) significantly reduced the energy intake, while the highest dose (50.6 mg/day) increased it. A lower intake correlated with a reduced body weight gain in the low dose, but the high dose did not show any significant difference (Mane et al., 2011). Instead, there are more studies that show the effects of reducing the body weight without altering the food intake. Extracts from acacia bark, which is rich in flavan-3-ols such as robinetinidol and fisetinidol, were assessed in KKAy mice that were fed a high-fat diet, to induce severe obesity. Acacia polyphenols (2.5% or 5% (w/w) for 7 weeks) suppressed HF-induced body weight, and no effect on the food intake was found (Ikarashi et al., 2011). Hop (*Humulus lupulus* L.) is an herb that is used in beer production and contains flavonoids such as procyanidins and prenylflavonoids. Purified hop pomace polyphenols (60% procyanidins, 15% other flavonoids, 3% astragalin, 2% isoquercitrin and 20% unknown phenolic compounds) were administered to OLETF rats (a model of obesity and type 2 diabetes) at 1% for 70 days. Polyphenol-treated rats tended to show reduced final body weight and weight of the mesenteric adipose tissue, while the food intake did not change between the

groups (Yui et al., 2013). Additionally, different plant extracts that are rich in polyphenols were tested for their putative antiobesity effects in a model of Wistar rats that were fed a high-fat sucrose diet for 56 or 64 days. Several extracts (apple, cinnamon, hamamelis and birch) lowered the body weight gain and improved the HOMA-IR index, and among them, apple and cinnamon were the most promising for being antiobesogenic because they also prevented the increase in total white adipose tissue, and no changes in the food intake were found (Boqué et al., 2013). Thus, no clear evidence shows a modulation in the food intake by non-tea flavanols, although the number of studies for each extract was too low to establish firm conclusions. On the other hand, some action of the flavanols that are present in natural sources toward reducing body weight gain are described, and the underlying mechanisms could be similar to those described for tea and grape flavanols, such as a reduction in the fat absorption, a reduction in the inflammation (Boqué et al., 2013) and a regulation of fatty acid metabolism (Yui et al., 2013).

General conclusions

After having collected all of the available studies in which food intake is reported, the main conclusion is that there is a lack of reliable data that allows clear effects to be described. Flavanols are a large group of compounds, and the studies on their effects on food intake and the enteroendocrine system are scarce and diversified. From all of these studies, the involvement in the modulation of food intake from the effects of flavanols is not evident. However, the fact that there are some controversial studies that show positive or negative effects on food intake,

together with the ability of some of these compounds to modulate some enterohormones, singles them outas possible candidates for acting through mechanisms that exert regulatory effects on food intake, which is a hypothesis that requires further work to be elucidated.

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Table 1. Summary of the different subset of enteroendocrine cells, localization and hormone(s) secreted (adapted from Janssen and Depoortere (2012))

Cell Type	**Highest density**	**Peptide released**
G cells	Stomach	Gastrin
D cells	Stomach	Somatostatin
P or X/A cells	Stomach	Ghrelin
I cells	Duodenum	Cholecystokinin (CCK)
K cells	Duodenum	GIP
L cells	Duodenum, and colon	GLP-1, PYY
EC cells	Entire GI tract	5-HT (5-hydroxytryptamin)

Table 2a. Effects of tea catechins on murine food intake						
Compound/ extract	**Daily dose (mg/kg bw) (way of administration)**	**Time of treatment**	**Diet**	**Specie**	**Effect on food intake**	**Ref.**
EGCG	85 (i.p.)	7 days	Standard	Male Sprague Dawley rats	Reduced	(Kao et al., 2000)
Green tea extract	2300 *estimated* (in the pellet)	2 weeks	High fat	Male Sprague Dawley rats	No effect	(Choo, 2003)
EGCG	92 (i.p.)	8 days	Standard	Male Zucker fatty	Reduced	(Kao et al., 2000)
EGCG	425.6 *estimated* (in the pellet)	16 weeks	High fat	Male C57BL/6J mice	No effect	(Bose et al., 2008)
EGCG	425.6 *estimated* (in the pellet)	17 weeks	High fat	Male C57BL/6	No effect	(Chen et al.,

				mice		2011)
EGCG	592 *estimated* (in the pellet)	11 months	High fat	Male C57Bl/6J mice	Reduced	(Murase et al., 2002)
Green tea extract	2368 *estimated* (in the pellet)	16 weeks	Standard	Female mice	No effect	(Zheng et al., 2004)
TEAVIGO (94% EGCG)	1.3 (in the pellet)	29 days	High fat diet (corrective)	Male obesity prone NZB mice	No effect	(Klaus et al., 2005)

Table 2b. Effects of tea catechins on human food intake						
Catechin mixture	8.5 *estimated* (pill)	1 dose	Standard	Normal weight healthy males	No effect	(Gregersen et al., 2009)
Green tea plus capsaicin	26.8 *estimated* (in the food)	1 day	Positive balance intake	Healthy humans	Reduced	(Reinbach et al., 2009)
Oily complex of EGCG	0.55 *estimated* (pills)	2 months	Restricted energy intake	Overweight humans	Promoted diet compliance	(Rondanelli et al., 2009)
Green tea extract + other agents	17,8 *estimaded* (orally)	8 weeks	Standard	Overweight men	Reduced	(Belza et al., 2007)
Beverage containing fiber ± caffeine and EGCG	2 *estimated* (orally)	Acute load	Standard	Overweight humans	Satiating effect	(Carter & Drewnowski, 2012)
Green tea extract +	3 *estimated* (mixture	3 months	Maintenance diet ± high	Overweight subjects	Increased hunger and	(Hursel & Westerterp-

caffeine	with diet)		protein		lower satiety	Plantenga, 2009)
Green tea extract rich in catechins	9.44 (test beverage)	12 weeks	Standard	Obese subjects	No effect	(Nagao et al., 2007)
Green tea catechins + caffeine	5-12 *estimated* (test beverage)	90 days	Standard	Overweight subjects	No effect	(Wang et al., 2010)
Green tea extract	10.6 (pill)	6 weeks	Standard	Overweight men	No clear effect	(Brown et al., 2011)
Green tea extract + caffeine	16 *estimated* (synthetic formula)	83 days	Low energy diet	Overweight females	Increased hunger	(Diepvens et al., 2005)

Table 3 Effects of catechins and procyanidins on food intake						
Compound(extract)	**Daily dose (mg/kg bw) (way of administration)**	**Time of treatment**	**Diet**	**Specie**	**Effect on food intake**	**Ref.**
Red wine consumption	14.2 *estimated* (oral)	8 weeks	Hypercaloric diet	Male Zucker lean	Decreased	(Vadillo et al., 2006)
Grape seed procyanidins	30 (in the pellet)	19 weeks	High fat diet	Females Wistar	No effect	(Terra et al., 2011)
Grape seed tannins	7 (in the pellet)	12 weeks	Standard	Male Sprague Dawley rats	No effect	(Tebib et al., 1996)
Two grape extracts (of seed and skin)	1780-2150 (in the pellet)	3 months	Standard	Sprague Dawley	Increase in males. No effect in females	(Bentivegna & Whitney, 2002)
Grape seed procyanidins	25 (in the pellet)	15 days	High fat diet	Male Golden	No effect	(Caimari et al.,

				Syrian hamsters		2013)
Grape seed extract	1.2 *estimated* (in the pellet)	12 weeks	HFD	Male C57BL/6J mice	No effect	(Ohyama et al., 2011)
Grape seed extract	50 (in water, with syringe)	8 weeks	Standard	C57BL/KsJ-lepr^{db}/lepr^{db}	No effect	(Hwang et al., 2009)
Acacia bark	2.5 or 5 *estimated* (in the pellet)	7 weeks	High fat diet	Male mice KKAy	No effect	(Ikarashi et al., 2011)
Polyphenols of a lingonberry extract	23-48 (in the pellet)	6 weeks	High cholesterol high fat diet	Male Wistar rats	Reduced - increased	(Mane et al., 2011)
Hop pomace polyphenols	200 (in the pellet)	10 weeks	Standard	Male OLETF rats	No effect	(Yui et al., 2013)
Concord grape juice	11.67 *estimated* (juice)	12 weeks	Standard	Healthy human males	No effect	(Hollis et al., 2009)

Grape seed procyanidin extract	12 *estimated* (3 pills)	3 days	Standard	Healthy humans, some overweigh t	Reduced in high EI group	(Vogels et al., 2004)

