Polyphenols and their role in obesity management: A systematic review of randomized clinical trials

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List of abbreviations: *AMPK: AMP-activated protein kinase; CVD: Cardiovascular diseases; ECP: Ecklonia cava polyphenols; HSE: Hibiscus sabdariffa extract; Licorice flavonoid oil; RCTs: Randomized clinical trials; WC: Waist circumference*

Abstract

Polyphenols have been suggested to reduce body weight and modify body composition through different mechanisms. These effects have been extensively studied in animals and in vitro and to a lesser extent in humans. The aim of this review is to consider the association between polyphenols and body weight status by focusing on human intervention studies. We conducted a systematic literature search in MEDLINE (via EBSCOhost), ProQuest CENTRAL and Cochrane CENTRAL without time restrictions. Randomized controlled trials (RCTs) assessing the effect of polyphenols on weight and/or body composition in the overweight and/or obese population were included. Nineteen studies met our inclusion criteria. Results suggest that further research is required before supporting a potential role of polyphenols in reducing weight in overweight and obese individuals (9 studies showed a significant decrease in weight by a mean of 1.47±0.58 Kg). Nevertheless, several studies indicated that polyphenols might be effective in preventing small increases in weight during periods of overfeeding rather than reducing weight as such. The outcomes noted do not yet support polyphenol supplementation as a complementary approach in weight-loss diets. Further larger trials with duration of 12 months or more are needed to elucidate the effect of polyphenols on body weight status.

Introduction

Polyphenols are vastly diverse phytochemicals with complex chemical structures. They are found in a variety of commonly consumed foods such as chocolate, tea, coffee, wine, olive, dry legumes, and some vegetables (like lettuce and cabbage) and fruits (like apples and berries) (Manach et al., 2004; D'archivio et al., 2007). Around 8000 structures of polyphenols have been already identified (Martin et al., 2010). Polyphenols are classified into four groups: flavonoids, lignans, stilbenes and phenolic acids (Manach et al., 2004). **Figure 1** summarizes the most common polyphenols and their subtypes.

Polyphenols have been extensively studied over the past decade because of their potential antioxidant and anti-inflammatory roles and their possible role in the prevention and management of several diseases such as cardiovascular diseases (CVD), hypertension, diabetes, cancer, and neurodegenerative diseases (Manach et al., 2004; D'archivio et al., 2007; Michalska et al., 2010; Serban et al., 2015). Most recently, polyphenols have attracted media interest and research community because of their potential role in reducing obesity, an increasingly serious health issue in different population age ranges (Zaki et al., 2015; WHO 2016). Polyphenols such as catechins, anthocyanins, curcumin and resveratrol were suggested to exert beneficial effects on lipid and energy metabolism (Meydani et al., 2010; Min et al., 2013; Gu et al., 2014; Kunnumakkara et al., 2016; Smeriglio et al., 2016) and

potentially on weight status. Multiple mechanisms of action have been proposed

mostly as a result of animal and cell studies, such as inhibition of the differentiation

of adipocytes (Min et al., 2013), increased fatty acid oxidation (Dulloo et al., 1999;

Shimoda et al., 2009), decreased fatty acid synthesis (Matsui et al., 2005), increased

thermogenesis and energy expenditure (Nagao et al., 2007; Osakabe et al., 2013;

Stohs and Badmaev, 2016) and inhibition of digestive enzymes (McDougall et al.,

2005; Gu et al., 2011). Despite the popularity of this topic, the biggest contribution to

this research remains through animal and in vitro studies. Few cohort studies have

looked at the association between polyphenol consumption and body weight in

humans (Wu et al., 2003; Hughes et al., 2008; Golomb et al., 2012), and human

intervention studies are outnumbered by animal and cell studies and remain

relatively limited. Results from animal and in vitro studies have mostly indicated an

effect of polyphenols on reducing obesity, and have considerably contributed to the

obesity-lowering effects of polyphenols discussed in the media. However, many

factors could affect the replication of these outcomes to humans. Firstly, there are

many differences in the metabolism and mechanism of actions of polyphenols

between animals and humans (Natsume et al., 2003). For example, there is lack of

clear evidence of the presence of biologically active brown adipose tissue in adults,

the latter being demonstrated to be primarily triggered by cold exposure in humans

(Chen et al., 2013). This has explained a part of the weight lowering effect of cocoa

and tea polyphenols in animals (Matsui et al., 2005; Nomura et al., 2008). Secondly,

there is a difference in body weight control between animals and free living humans.

The latter exhibit large differences in daily levels of physical activity and energy

balance (Leibel, 2008). Thirdly, the complexity of substituting in vitro studies for

humans studies relies in the limitations in assessing polyphenol bioavailability in cell

studies (Etcheverry et al., 2012). Also, the doses of polyphenols that exert a significant effect on obesity in cells (such as the inhibition of adipogenesis (Min et al., 2013; Ejaz et al., 2009)) can be higher than the physiological levels. In view of these potential differences, and for the aim of helping the public make informed choices and directing future research, we attempt to consider the association between polyphenols and body weight status through conducting a systematic review of human intervention studies.

Methods

The review preparation was completed in 7 steps**:** Identification of research question, definition of inclusion and exclusion criteria, literature search, selection of eligible studies, data extraction, evaluation of the risk of bias (through *the Cochrane RoB Tool*) and presentation of results (Cornell 2016). The review was prepared according to the Prisma guidelines (Moher et al., 2009).

Search strategy

We (GF, EAD) independently conducted a systematic literature search in MEDLINE (via EBSCOhost), ProQuest CENTRAL and Cochrane CENTRAL (from 11 November 2016 to 10 December 2016) without any time restrictions. We used the following keywords: Polyphenol AND (Body weight OR Waist circumference OR Fat). We also searched the reference list of selected studies for more relevant research. Disagreements in the assessment of data were resolved by discussion and consensus was reached in all cases.

Eligibility criteria

Studies included were human RCTs investigating as a main outcome the link between polyphenols and obesity (through measurement of body weight and/or waist circumference (WC), waist/hip ratio, or body fat at least twice during the study). There were no restrictions on the type of studies (parallel or crossover studies). Eligible studies included overweight and/or obese adults with no history of known diseases (diabetes, CVD or hypertension) and no intake of medications that could influence lipid, carbohydrate or energy metabolism. Studies involving exercise regimens and/or hypocaloric diets in addition to the polyphenol intervention were excluded. In addition, eligibility of studies was restricted to duration no less than 4 weeks and to English language. To avoid confounding effects, studies investigating the combined effects of polyphenols and other components (such as tyrosine, fibre etc...) on anthropometric measures were excluded. Missing data and further information were requested from the authors.

Study selection and data extraction

References were checked for eligibility by two independent authors. Full texts were then verified against the inclusion criteria. Risk of bias was assessed and data about study design, participant information (BMI, age, gender) and outcome measures (Body weight, BMI, WC, waist-to-hip ratio and/or body fat percentage or mass) were extracted. Baseline and post intervention values and mean difference from baseline data were collected.

Results

The search identified 19 eligible studies. The study selection process is summarised in **Figure 2**.

Risk of bias

The allocation concealment was considered to be suitable in 2 studies and unclear in 17. Eighteen studies reported blinding participants and outcome assessors. Three studies described measures used to blind participants and outcome assessors. Data analysis of the main outcomes was reported by 15 studies. Incomplete outcome data was considered to be adequately handled in 10 studies. The two authors (GF, EAD) have reached a consensus on not to conduct a meta-analysis in this review for the following reasons 1) heterogeneity of the studies and the different types of polyphenols administered 2) missing outcome data that we failed to obtain from authors 3) missing information regarding allocation concealment and handling outcome data which makes it difficult to evaluate the risk of bias in studies. This might likely produce inappropriate summary and biased conclusions. Therefore, this review mainly aimed to clarify the effects of polyphenols on anthropometric measures and to provide directions for future research.

Study characteristics

Studies were conducted in Japan (N=5), USA (N=4), Germany (N=2), Spain (N=1), Taiwan (N=2), France (N=1), China (N=1), Denmark (N=1), Poland (N=1) and UK

(N=1). Studies investigated the effect of green tea (N=6), oolong tea (N=1), Licorice flavonoid oil (LFO) (N=3), apple juice (N=2), citrus extract (N=1), Hibiscus sabderiffa extract (N=1), grape juice (N=1), quercetin (N=1), Ecklonia cava (N=1), resveratrol (N=1) and orange juice (N=1). Samples sizes ranged from 22 to 240 participants. Sixteen studies were parallel, while 3 were crossover. All studies assessed body weight, 14 assessed waist circumference and 12 assessed body fat (percentage or mass). Four studies used a polyphenol-rich drink that provided energy, while 15 studies used capsules or drinks that provided a negligible amount of calories. Four studies assessed the effect of different doses of polyphenols on anthropometric measures. Ten studies disclosed funding from industry, and 3 studies gave no indication of funding. **Table 1** provides an overall summary of study details.

Weight loss and BMI

Out of the 19 selected studies, 10 reported a significant decrease in body weight from baseline in the experimental group (**Table 1**). While one of the studies noted a significant decrease in weight only during the first intervention period of the crossover study (Brown et al., 2011), the 9 remaining studies (8 studies lasted for 12 weeks and one study lasted for 8 weeks) showed a significant decrease in body weight by a mean of 1.47 ± 0.58 Kg. Three of these studies used a phenolic compound that provided energy (between 85-350 Kcal) (Hollis et al., 2009; Shin et al., 2012; Rangel-Huerta et al., 2015). Seventeen studies assessed BMI, of which 7 demonstrated a decrease by a mean of 0.65 ± 0.55 Kg/m^2 from baseline in the experimental group. On the other hand, three studies reported a significant increase in weight only in the placebo (control) group (mean increase: 1.04 ± 0.54 Kg).

Changes in waist circumference

Fourteen studies assessed the effect of polyphenols on WC. Nine studies found a significant lowering effect on WC (mean decrease: 2.58 ± 1.33 cm). Eight studies lasted for 12 weeks while one study lasted for 8 weeks (noted a significant decrease in WC by 0.63 cm) (**Table 1**).

Changes in body fat percentage and body composition

Twelve studies assessed fat composition as either body fat percentage (N=10) or body fat mass (N=2). While 4 studies showed no significant effects on body fat percentage, 6 studies showed a decrease in fat percentage by a mean of 1.86 ± 0.98%. One study reported a significant decrease in fat mass (by 1.03 ± 0.24 Kg depending on the polyphenol dose). Three studies assessed fat visceral area and noted a significant decrease by 9.18 ± 1.2 cm (**Table 1**).

Discussion

Main findings

The aim of this review was to assess existing human research on polyphenols and body weight status. Eligible studies involved the incorporation of polyphenols (in different forms) in the context of a normocaloric diet and not as a part of a reduced-calorie diet or in addition to exercise. This eliminated the effect of weight loss

strategies which would mask the effect of polyphenols on weight and body composition. Demonstrating a potential effect of polyphenols on obesity would be helpful towards integrating polyphenols in weight loss regimens or coupled to exercise.

The similarities in the mechanisms of action of polyphenols on obesity provided a justification for including different types of polyphenols in the same review. For example, phlorotannins, quercetin and phenolic acids have been shown to be involved in the inhibition of adipocyte differentiation (Hsu et al., 2007; Jung et al., 2014; Seo et al., 2015). Anthocyanins, quercetin and phenolic acids have been reported to increase AMPK (adenosine monophosphate-activated protein kinase), which is involved in fatty acid oxidation (Pfeuffer et al., 2013; Chang et al., 2014). Some polyphenols have been implicated in increasing satiety, reducing energy intake (Panickar et al., 2013) and increasing thermogenesis (Meydani et al., 2010; Stohs and Badmaev, 2016). The latter mechanisms are involved in body weight control. The limited understanding of the mechanisms of actions requires further research.

The results of the selected studies do not mostly favour a weight-lowering effect of polyphenols in overweight and obese individuals. The weight loss reported by 9 out of 19 selected studies ranged between 1.47 ± 0.58 Kg. The duration of the studies (4-12 weeks) might provide an explanation for the results obtained. It has been indicated that larger longer-term trials with duration of 12 months or more are needed to understand the effect of an intervention on weight loss and weight management (Headland et al., 2016). The nine studies showed a small body weight

reduction, less than previously considered clinically relevant weight loss at 5% (Stevens et al., 2006). However, one study showed that a loss of 1 Kg of weight could potentially reduce diabetes risk by 16% (Hamman et al., 2006). Therefore, the outcomes may not be insignificant in relation to many health outcomes. It is worth noting that all these studies were double-blinded which eliminated the expectation bias. Nevertheless, there was no sufficient detail on allocation concealment in most of the studies.

A clinically relevant decrease in WC constitutes more than 3 % over the long term (Verweij et al., 2013). The mean decrease in WC in selected studies was 2.58 ± 1.33 cm. As all selected studies included overweight and obese participants, and assuming that they have an elevated WC (at least 80 cm), changes reported might not be clinically relevant in all studies.

Among studies that analysed both body weight and body fat composition, 7studies showed a significant decrease in both body weight and body fat, while two studies reported a significant decrease only in body weight and one study reported a significant decrease in body fat percentage (by 1% , *p< 0.05*), but not body weight. Further studies are needed to explain the association between body weight and body fat in relation to polyphenol consumption, particularly because the majority of mechanisms by which polyphenols are suggested to reduce obesity is through their effects on lipid metabolism, such as inhibition of fatty acid oxidation (Dulloo et al., 1999; Shimoda et al., 2009), and decrease of fatty acid synthesis (Matsui et al., 2005).

This review suggests that further research is needed before considering polyphenols a complementary approach to aid in weight loss. This hypothesis might be helpful in avoiding misleading advertisement currently describing polyphenols as anti-obesity

agents. Nevertheless, the effects of polyphenols on cardiovascular risk seem to be more established (Dudzińska et al., 2015). Therefore, it could be suggested that polyphenols can lower CVD risk by targeting components of the metabolic syndrome such as blood pressure and HDL cholesterol (Serban et al., 2015; Santini and Novellino, 2016; Ganjali et al., 2017; Patti et al., 2017), while their implication in weight loss is less plausible. Meanwhile, a diet rich in polyphenols can be recommended as having protective effects on risk factors for CVD but their effects on weight loss in humans require further research.

Among polyphenols, flavonoids and phenolic acids appear to be the most involved in obesity and weight control. Subtypes of flavanoids that have been implicated in weight loss or change in body composition in the selected studies are catechins, phlorotannins, glabridin, anthocyanins, procyanidins and quercetin. Although the study by Rangel and Huerta (2015) showed a significant decrease in weight following the consumption of orange juice (at two different concentrations of flavanones), it is suggested that flavanone is not involved in weight loss. The decrease in weight was explained by the decrease in energy intake during the study (Rangel-Huerta et al., 2015). However, the latter study lacked a control group which could have provided more clarification on the effects of flavanones on body weight. Further studies investigating the effect of flavanones on body weight status are needed.

Other polyphenols such as curcumin, flavanols and ellagic acids have also been involved in attenuating obesity (Meydani et al., 2010) and are known to exist in several commonly consumed foods such as turmeric, grapes, nuts, pomegranate, berries, cocoa and chocolate (Daniel et al., 1989; Meydani et al., 2010; Akaberi and Hosseinzadeh, 2016; Kunnumakara et al., 2016). As far as we know, limited or no

human studies primarily investigating the potential implication of the latter polyphenols on obesity and body weight. Cocoa and dark chocolate have been the subject of extensive animal and in vitro studies due to their high flavanol content (epicatechin, procyandins and quercetin) (Hurst et al., 2008). Although a human study demonstrated that 7 days of cocoa supplementation with 2000 mg of polyphenols reduced WC (by 1.24±1.45cm, p≤ 0.05) without affecting weight (Di Renzo et al., 2013), this significance remains under question due to the short study duration and the absence of a control group. Hence, this study was not included in the systematic review.

Catechins in green tea have been the most popular polyphenols studied. Research is mostly in favour of their potential effects on lowering weight and adiposity (Nagao et al., 2005; Nagao et al., 2007; Wang et al., 2010; Hsu et al., 2008). Nonetheless, a meta-analysis suggested that the effects of green tea catechins on body weight are more plausible in the Asian population due to a genetic polymorphism that leads to differences in the thermogenic effect of green tea (Hursel et al., 2009). This explains the consistent results obtained in the Asian populations (Nagao et al., 2005; Nagao et al., 2007; Wang et al., 2010; Hsu et al., 2008), while the effects are less consistent in western studies (Basu et al., 2010; Brown et al., 2011; Sulliburska et al., 2012). Therefore, it is important to find out whether findings about tea and polyphenols can be applicable to different regions. However, It seems that when the amount of caffeine is controlled, the treatment effect of green tea catechins on obesity was no longer apparent (Basu et al., 2010; Brown et al., 2011). This has been reinforced by a Dutch study which showed that the effect of green tea was not significant in participants with a habitual high caffeine intake (Westerterp-Plantenga et al., 2005).

The potential effect of caffeine or a synergistic effect between polyphenols and caffeine deserve further investigation.

Nonetheless, there is evidence to suggest that the role of polyphenols might be limited to the prevention of weight gain rather than reducing weight per se. This is in line with the majority of animal studies which demonstrated that polyphenols reduce weight gain caused by diet-induced obesity. For instance, extracts of epicatechin and quercetin and polyphenols in green tea, cocoa, resveratrol, pomegranate and curcumin have prevented an increase in weight in animals administered a hypercaloric diet, compared to those given a placebo control (no polyphenols) (Lei et al., 2007; Ahn et al., 2008; Shao et al., 2012; Gulvady et al., 2013; Tian et al., 2013; Dorenkott et al., 2014). This hypothesis provides an explanation for the results obtained in the study by Hollis et al. (2009) who showed a significant increase in weight only in the group administered grape juice with a negligible amount of polyphenols (by 1.6 ± 0.3 Kg, $p>0.05$). Participants who consumed grape juice with polyphenols (934 mg) did not display a significant increase in weight (mean difference from baseline: 0.8 ± 0.6 Kg, $p<0.05$). In their study on licorice flavonoid oil (LFO), Bell et al. (2011) noted a significant increase in weight only in the control group and suggested that LFO can be helpful in reducing weight gain in periods of overfeeding. Additionally, a study that did not meet the inclusion criteria for this systematic review showed that one month of pomegranate juice supplementation prevented an increase in weight, BMI and body fat mass in obese participants (mean difference from baseline: -0.5 ± 2.3 Kg, -0.2 ± 0.5 Kg/m^2, -1.4 ± 3%, respectively, p> 0.05) compared to the group administered the control juice (weight, BMI and body fat mass increased by 1.1 ± 1.3 Kg, 0.4 ± 0.5 Kg/m^2, 1.1 ± 1.1%, respectively, p< 0.05) (Gonzàlez-Ortiz et al., 2011). Moreover, the results noted by Brown et al. (2011) led

to conclude that tea catechins may be involved in preventing weight gain during periods of positive energy imbalance such as increase in weight during seasonal changes, for instance during winter. The current authors have also shown that 400 mg of flavanols in dark chocolate avoided the increase in weight at the end of a 4-week study (Mean difference from baseline: -0.01 ± 0.9 Kg, *p=0.98*) compared to the control group (0.44 ± 0.86 Kg, *p= 0.009*) administered dark chocolate with low amount of flavanols (<60 mg) (Farhat et al., 2015). Similar results were noted by another study which included overweight and obese individuals and suggested that polyphenols can counter the effect of fat and energy contents of the diet (Al Moosawi et al., 2012), although there was no data to support this. In view of the outcomes noted, further investigation is needed before suggesting a significant effect of polyphenols on reducing weight gain in the overweight and obese population. This effect could be of importance as it was shown that an increase of 1 Kg of body weight can rise coronary mortality risk by 1 - 1.5 % (Jousilhati et al., 1996). With the increasing obesity prevalence, mainly due to a positive energy balance (Krzysztoszek et al., 2015), polyphenols could then be helpful in preventing small increases in weight such as during winter or periods of overfeeding.

Further larger long-term studies (at least 12 months) controlled for energy intake and physical activity are required to determine the role of polyphenols in weight management. Studies comparing the effect of different polyphenols in periods of overfeeding and in periods of steady weight are needed in the overweight and obese population. In addition, further research investigating the effects of different doses of polyphenols will be helpful to determine the optimal dose of polyphenols for maximum benefit. Also, because of the serious effects of certain herbs and the herb-

drug interactions (Izzo et al., 2016), it is important to consider these side effects while recommending some herbal products because of their high polyphenol content. It would be important to determine whether polyphenols administered in different forms can have different effects. For example, a placebo-controlled study with three arms analyzing the effect of polyphenol-rich juice or food (introduced in the context of an energy-balanced diet) versus polyphenol extract capsules on body weight and composition in the overweight population would be valuable. Based on the results of the selected studies in this review, we can hypothesize that the administration of polyphenols in various forms does not differently affect their weight-lowering properties.

Furthermore, studies with complete data, including information about concealment and data analysis are needed. Breakdown of the amount of polyphenols in both experimental and control group is required. It is also worth noting that polyphenols can be affected by several factors such as the timing of intake, as one of the mechanisms by which polyphenols reduce obesity is through their potential effects on digestive enzymes such as inhibition of protease and lipase (McDougall et al., 2005). Therefore, it is important to test match for these differences in future studies. Lastly, it would be important to determine whether there is a combination effect of different polyphenols or polyphenol-rich foods on body weight status, especially since many of these polyphenols are available combined in nature, and whether an adaptation to the effect of polyphenols occurs over time. This would be helpful to establish conclusions regarding different foods and beverages such as apple juice, green tea as well as polyphenol extracts.

Strength and limitations

One of the review's potential weaknesses is that the comparison of significant effects between studies was based on different statistical comparisons used. In fact, 9 studies considered between-group differences, while 10 studies considered within-group differences. This has possibly affected the generation of hypotheses and conclusions. For instance, in the study by Chang et al. (2014), paired-t-tests showed a significant difference in body weight, BMI and waist-to-hip ratio ($p< 0.05$), while between-group analysis showed significant difference only in WC, waist-to-hip ratio and body fat percentage ($p<0.05$). In addition, Tominaga et al. (2009) did not analyse whether there is a significant interaction between different doses of polyphenols and time on the effects noted. This is an important point that needs to be emphasized in both future systematic reviews and trials. Another limitation is the duration of the studies (4-12 weeks) which might not have been sufficient to understand the effect of polyphenol on body weight. Furthermore, most of the studies measured the outcomes on limited time points (baseline and week 12 were considered in 8 studies). Five other studies have taken measurements at multiple time points but did not include these data in the analysis. This an important point to consider in future studies. A suggestion would be to analyse the study parameters at 2-week interval in long term studies. Also, diet advice to participants was not properly described in the majority of selected studies. A further limitation is the restriction of the review to the English language, as the studies on polyphenols are popular in the Asian population.

Conclusion

This review of selected studies suggests that further research is needed before supporting the implication of polyphenols in weight loss and recommending polyphenols as a potential complementary approach in weight-loss diets. There is an indication to suggest that the benefits of polyphenols might only be restricted to the counteraction of the small increases in body weight and fat resulting from seasonal changes (such as during winter) or periods of overfeeding. Long-term studies involving a large cohort and controlling for diet and exercise are needed in order to confirm the potential effect of polyphenols on obesity in humans. The genetic differences between populations also need to be considered.

Acknowledgments

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Table 1: Overall details of included studies

Study/participants characteristics	Length (weeks)	Intervention	Energy content /day	Polyphenol content per day//type (s)	Anthropometric measurements	Baseline	Post-intervention (Mean change from Baseline)
Dallas et al., 2014 *(26)* *France* double-blinded controlled parallel study N=95 (42% men) Age: 22-45 years BMI: 26 - 29.9 kg/m^2	12	Two capsules of a) citrus polyphenolic extract with red orange, grapefruit, sweet orange and guarana (Sinetrol-Xpur) or b) maltodextrin placebo)	NEGL	a)900 mg / Catechin (~810 mg), Flavanones (at least 20% (naringin) b) NEGL	Body weight BMI WC Waist-to-hip ratio BF %	EG: 78.14 ±1.35 CG: 77.39 ± 1.23 EG: 27.58 ± 0.16 CG: 27.27 ± 0.14 EG: 88.68 ± 1.05 CG: 88.44 ± 1.09 EG: 0.813 ± 0.113 CG: 0.809 ± 0.113 EG: 37.97 ± 1.59 CG: 36.87 ± 1.48	**EG: 75.52 ± 1.25*** (-2.62) CG: 75.78 ± 1.23 (-1.58) EG: 26.39 ± 0.33 (-1.19) CG: 26.12 ± 0.35 (-1.15) **EG: 83.53 ± 0.87*** (-5.15) CG: 87.02 ± 1.02 (-1.42) EG:0.784 ± 0.155 (-0.03) CG:0.808 ± 0.101 (-0.001) **EG: 34.36 ± 1.49*** (-3.01) CG: 35.85 ± 1.51 (-1.02)
Chang et al., 2014 *(27) Taiwan* double-blinded controlled parallel study N= 36 (58% men) Age: 18-65 years BMI ≥ 27 kg/m^2	12	6 capsules of a) Hibiscus sabdariffa extract (HSE) or b) starch (placebo)	NEGL	a)152 mg / Flavonoids (~39mg) Anthocyanins (68 mg) Phenolic acids (46 mg) b) NEGL	Body weight BMI WC Waist-to-hip Ratio BF %	EG: 88.52 ± 15.96 CG:84.93 ± 12.79 EG:31.51 ± 4.01 CG:30.91 ± 3.71 EG:98 ± 11.75 CG:95.32 ± 10.43 EG:0.91 ± 0.07 CG:0.9 ± 0.06 EG:37.37 ± 6.22 CG: 38.44 ± 9.8	**EG: 87.28 ± 16.02*** (-1.24) CG: 84.27 ± 13.14 (-0.66) **EG: 31.09 ± 4.23*** (-0.42) CG: 30.65 ± 3.76 (-0.26) EG: 97.16 ± 10.94 (-0.84) CG: 95.94 ± 10.25 (0.62) **EG: 0.9 ± 0.06*** (-0.01) CG: 0.9 ± 0.06 (0) EG:36.67 ± 6.61 (-0.7) CG: 39.08 ± 9.82 (0.64)
Hollis et al., 2009 *(28)* *USA* double-blinded controlled parallel study N= 76 (61% men) Age: 18-50 years BMI 25-29.9 kg/m^2	12	a) 480 ml of Concord Grape Juice (CGJ) or b) 480 ml of substitute (polyphenol-free) grape flavored drink (SGD; control) or c) no beverage (NTG)	CGJ: 350 Kcal; SGJ: 350 Kcal	a)934 mg / anthocyanins (191 mg), procyanidins (307 mg) catechin, quercetin, & myricetin. b) NEGL c) NEGL	Body weight BMI WC	EG: 79 ± 8.4 CG: 79 ± 10.7 EG: 27 ± 1.6 CG: 27 ± 1.5 EG: 83.31 ± 6.6 CG: 84.07 ± 7.62	EG : 79.7 ± 9.5 (0.7) **CG: 80.6 ± 11.2*** (1.6**)** EG: :27.1 ± 2.0 (0.1) CG: 27.2 ± 1.9 (0.2) EG: **82.04 ± 7.1*** (-1.57) CG: 83.31 ± 8.64 (-0.76)

Study	Duration	Intervention	Kcal	Dose	Outcome	Baseline	Results
Pfeuffer et al, 2013 *(29)* *Germany* double-blinded crossover study N= 49 (100 % males) Age: 48 ± 68 years BMI: 26.3 ± 0.3 kg/m²	Two 8-week treatment (3 week washout period)	Six capsules of a) quercetin dihydrate (150 mg/day) or b) placebo	NEGL	a)150mg / quercetin b) NEGL	Body weight BMI WC	+ + +	NS+ NS+ + (-0.63)*
Shin et al., 2012 *(30)* *USA* double-blinded parallel controlled study N= 97 (34% males) Age: 40.5 ± 9.2 years BMI: 26.5 ± 1.6 kg/m²	12	246 ml of a)Ecklonia cava Polyphenol extract (ECP) drink low dose b) ECP high dose or c) control drink (sugars, sodium chloride, citric acid, vit C and lemon flavour)	~ 85 Kcal (a, b,c)	a)ECP low dose: 72 mg/ Phlorotannins (unique polyphenols) b) ECP high dose: 144 mg) / Phlorotannins c) NEGL	Body weight BMI Body fat % WC Waist-to hip ratio	ECP HD: 71.2 ± 9.4 ECP LD: 70.5 ± 10 CG: 71.3 ± 9.4 ECP HD: 31.4 ± 5.4 ECP LD: 26.4 ± 1.7 CG:26.5 ± 1.5 ECP HD: 31.4 ± 5.4 ECP LD: 30.8 ± 5.3 CG: 31.7 ± 5.2 ECP HD: 90.7 ± 7.1 ECP LD: 90.4 ± 6.8 CG: 90.8 ± 6.3 ECP LD:90.2 ± 5.9 ECP LD: 89.9 ± 5.6 CG: 90.3 ± 4.9	**ECP HD: 69.9 ± 9.6*** (-1.3) **ECP LD: 69.6 ± 9.6*** (-0.9) CG: 70.9 ± 9.7 (-0.4) **ECP HD: 29.3 ± 5.4*** (-2.1) **ECP LD: 26.2 ± 1.7*** (-0.2) CG: 26.4 ± 1.8 (-0.1) **ECP HD: 29.3 ± 5.4* (-2.1)** **ECP LD: 29.9 ± 5.4* (-0.9)** **CG: 31.3 ± 5.3* (-0.4)** **ECP HD: 89.3 ± 6.3*** (-1.4) **ECP LD: 89.6 ± 5.9*** (-0.8) **CG: 90.3 ± 6*** (-0.5) **ECP LD: 88.8 ± 5.5* (-1.4)** **ECP LD: 88.9 ± 5.8* (-1)** CG: 89.7 ± 5 (-0.6)
Rangel-Huerta et al., 2015 *(31)*, *Spain* Double-blinded crossover study N= 100 (8 % males) Age: 50 ± 3 years 25≤ BMI < 40 kg/m²	Two 12-week period (7 week washout period)	500 ml of orange juice a)normal polyphenol concentration (NPJ) b) high polyphenol concentration (HPJ)	NPJ: 245 Kcal ; HPJ : 303 Kcal	a)NPJ : 299.5 mg/ Flavanones (237 mg of hesperidin 45 mg) of narirutin, and 17 mg of didymin) b)HPJ: 742.5 mg/ Flavanones (582.5 mg mg of hesperidin, 125 mg of narirutin, and 34 mg didymin)	Body weight BMI WC	NPJ: 90.4 ± 1.5 HPJ: 90.6 ± 1.5 NPJ: 32.5 ± 0.4 HPJ: 32.6 ± 0.4 NPJ: 99.1 ± 1.3 HPJ: 99.4 ± 1.1	**NPJ: 89.1 ± 1.5 *** (-1.3) **HPJ: 88.88 ± 1.5 *** (-1.8) **NPJ: 32.0 ± 0.4*** (-0.5) **HPJ: 31.9 ± 0.4*** (-0.7) **NPJ: 95.1 ± 1.2 ***(-4.0) **HPJ: 95.6 ± 1.1*** (-3.8)

Study	Weeks	Intervention		Dose	Outcome	Baseline	Final (change)
Poulsen et al., 2013 *(32)* *Denmark* double-blinded parallel controlled study N= 24 (100 %males) Age: 38.4 ± 2.6 years BMI: 34.2 ± 0.7 kg/m^2	4	Four capsules of a) resveratrol or b) placebo		a) 500 mg of resveratrol b) NEGL	Body weight	EG: 107.1 ± 2.7 CG: 115. 9 ± 3.6	NS
					BMI	EG: 32.5 ± 0.6 CG: 35.9 ± 1.2	NS
					BF %	EG:30. 2 ± 0.7 CG: 32.3 ± 1.4	NS
					Visceral fat volume	EG: 4996 ± 876 CG: 4285 ± 585	NS
Nagao et al., 2005 *(33)* *Japan* Double-blinded parallel controlled study N= 35 (100 % males) Age: 24-46 years BMI: 24.9 ± 0.4 (EG) BMI: 25 ± 0.4 (CG) (Kg/m^2)	12	One bottle (340 ml) of a) Oolong tea with amount of catechins or b) Oolong tea with low amount of catechins	NEGL	a) 690 mg of catechins b) 22 mg of catechins / CT, CG, GC, GCG, EC, ECG, EGC, EGCG	Body weight	EG: 73.9 ± 1.8 CG: 73.8 ± 1.3	**EG: 71.5 ± 1.7** * (-2.4) CG: 72.5 ± 1.4 (-1.3)
					BMI	EG: 24.9 ± 0.4 CG: 25 0 ± 0.4	**EG: 24.1 ± 0.4** *(-0.8) CG: 24.6 ± 0.4 (- 0.4)
					WC	EG: 87. 9 ± 1.4 CG: 87.8 ± 1.1	**EG: 84.5 ± 1.3***(- 3.4) CG: 86.2 ± 1.2 (-1.6)
					Body Fat mass	EG: 19.7 ± 0,8 CG: 19.5 ± 1	**EG: 18.3 ± 0.9*** (-1.4) CG: 18.8 ± 1.1 (-0.6)
Nagao et al., 2007 *(11)* *Japan* Double-blinded controlled study N= 240 (58% males) Age: 41.7 ± 9.9 years BMI: 26.8 ± 2.0 kg/m^2	12	One can of a) Green tea (340 ml) high in catechins or b) Greetn tea low in catechins	NEGL	a)583 mg catechins b) 96 mg of catechins/ CT, CG, GC, GCG, EC, ECG, EGC, EGCG	Body weight	EG: 73.3 ± 9.7 CG:72.1 ± 10	**EG: 71.6 ± 9.8*** (-1.7) CG: 72.1 ± 10.3 (-0.1)
					BMI	EG: 26.9 ± 1.9 CG:26.7 ± 2.1	**EG: 26.2 ± 1.9*** (-0.6) CG: 26.6 ± 2.2 (-0.0)
					WC	EG:87.2 ± 5.2 CG:86.5 ± 6.1	**EG: 84.7 ± 5.5*** (-2.5) CG: 86.5 ± 6.7 (0)
					BF %	EG:30.7 ± 6.4 CG:30.7 ± 5.4	**EG: 28.3 ± 6.1*** (-2.5) CG: 30 ± 5.6* (-0.7)
					Visceral fat area	EG:109.2 ± 42.3 CG: 107.7 ± 44	**EG: 98.9 ± 38.6*** (-10.3) CG: 103.8 ± 38.9 (-3.9)
Wang et al., 2010 *(34)* *China* Double-blinded parallel controlled study N= 182 (27%males) Age: 18-55 years BMI: 24-35 kg/m^2	~12	Tea bags infusion : a) Green tea 1 (GT1); b) GT2 c) GT3 or c) control	NEGL	GT1: 458 mg; GT2: 468 mg ; GT3: 886 mg: Control: 30mg/ CT, CG, GC, GCG, EC, ECG, EGC, EGCG	Body weight	GT3: 71.1 ± 11.9 GT2: 71.5 ± 11.8 GT1: 71.4 ± 9.8 CG: 69.7 ± 8.9	**GT3: 69.9 ± 12.1***(-1.2) GT2: 70.7 ± 11.7 (-0.8) GT1: 70.7 ± 10.1 (-0.7) CG: 69.8 ± 9.1 (0.1)
					WC	GT3: 95.5 ± 6.9 GT2: 95.9 ± 7 GT1: 96.1 ± 5.8 CG: 94.5 ± 6	**GT3: 93.6 ± 7*** (-1.9) GT2: 94.6 ± 7 (-1.3) GT1: 95 ± 6.2 (-1.1) CG: 94.3 ± 5.8 (-0.2)
					BF %	GT3: 32.7 ± 5.3 GT2: 33.1 ± 5 GT1: 32.7 ± 5.1 CG: 33.2 ± 4.7	GT3: 32.2 ± 5.2 (-0.5) GT2: 32.2 ± 4.9 (-0.9) **GT1: 32 ± 5.1 * (-0.7)** CG: 33 ± 4.7 (-0.2)
					Intra-abdominal fat	GT3: 83.6 ± 3.2 GT2: 84.7 ± 3.1 GT1: 85 ± 2.8	**GT3: 78 ± 3.4*** (-5.6) GT2: 81.1 ± 3.1 (-3.6) GT1: 81 ± 3 (4.1)

Study	Duration	Intervention		Dose	Outcome	Baseline	End
						CG: 80.4 ± 3.1	CG: 79.3 ± 2.9 (-1.1)
Brown et al., 2011 *(35)* *UK* Double-blinded cross-over controlled study N= 69 (100% males) Age: 40-69 years 28 ≤ BMI ≤38 kg/m²	Two 6-week period (2 week washout period)	Capsules of a) decaffeinated green tea extract (530mg) b) lactose (placebo)	NEGL	530 mg catechins/ CT (6.15 mg), CG (0.16 mg), GC (10.7 mg), GCG (6.7 mg), EC (46 mg), ECG (32 mg), EGC (86 mg), EGCG (216 mg) b) NEGL	Body weight	EG: 101.3 ± 11.4 CG: 100.2 ± 11.1	EG: ┼ (-0.64)* ‡ CG: ┼ (0.53)* ‡
Basu et al., 2010 *(36)* *USA* Single-blinded controlled parallel study N=35 (23% men) Age: 42.5 ± 1.7 years BMI 36.1 ± 1.3 kg/m²	8	a)Four cups of decaffeinated green tea beverage or b) 2 capsules of green tea extract capsules or c) water (4 cups)	NEGL	a)928mg of catechins b)870 mg/ CT, CG, GC, GCG, EC, ECG, EGC, EGCG c) NEGL	Body weight BMI WC BF %	GT: 96.4 ± 4.7 GTE: 106.2 ± 7.5 Control: 102.7 ± 6.6 GT:34.6 ± 1.5 GTE: 38 ± 2.3 Control: 36.4 ± 2.8 GT:105 ± 2.8 GTE: 115 ± 6.4 Control: 108 ± 5.08 GT: 42 ± 2.8 GTE: 42 ± 2.8 Control: 44 ± 3.4	┼ #
Hsu et al., 2008 *(37)* *Taiwan* Double-blinded controlled parallel study N=100 (0 % men) Age: 43 ± 11.8 years BMI: 30.8 ± 4.1 kg/m²	12	Three capsules of a) Green tea extract (GTE) b) cellulose (placebo)	NEGL	a) 205 mg of catechins/ CT (2.76 mg) , CG (2.05 mg), GC (20.5 mg), GCG (9.16 mg), EC (23 mg), ECG (10.6 mg), EGC (12.3 mg), EGCG (125 mg) b) NEGL	Body weight BMI WC	EG: 78.5 ± 10.3 CG:76.3 ± 14.5 EG: 31.2 ± 3.5 CG: 30.5 ± 4.6 EG: 94.7 ± 7.7 CG: 93 ± 12.6	EG: 78.3 ± 10.6 (-0.15) CG: 76.2 ± 14.4 (-0.03) EG: 31.1 ± 3.7 (-0.06) CG: 30.5 ± 4.6 (-0.006) EG: **93 ± 8.5** *(-1.7) CG: 91.7 ± 11.5 (1.3)
Sulliburska et al., 2012 *(38)* *Poland* Double-blinded controlled parallel study N=46 (50 % men) Age: 30-60 years	12	One capsule of a) Green tea extract (GTE) or b) placebo capsules	NEGL	a) 379 mg/ CT, CG, GC, GCG, EC, ECG, EGC, EGCG (208 mg) b) NEGL	BMI WC	EG: 32.7 ± 2.4 CG: 33.45 ± 2.7 EG: 101.8 ± 6.4 CG:105 ± 6.5	EG: 31.7 ± 2.29 (-1) CG: 33.36 ± 2.66 (-0.09) EG: 101.15 ± 6.42 (-0.65) CG: 105.02 ± 6.1 (-0.02)

BMI ≥ 30 kg/m^2

Study							
Tominaga et al., 2006 *(39)* *Japan* Double-blinded controlled parallel study N=103 (61% men) Age: 46.1 ± 1.2 years BMI 26.5 ± 0.2 kg/m^2	12	One capsule of a) licorice flavonoid oil (LFO) or b) MCT+ beeswax (placebo)	NEGL	24 mg/ flavonoids (Glabridin)	Body weight	EG: 72.69 ± 1.21 CG: 72.71 ± 1.13	EG: ┼ NS CG: **(1) ***
					BMI	EG: 26.37 ± 0.21 CG: 26.5 ± 0.2	EG: ┼ NS CG: ┼ **(0.5*)** :
Tominaga et al., 2009 *(40)* *Japan* Double-blinded controlled parallel study N=84 (67 % men) Age: 40-60 years BMI 24 - 30 kg/m^2	8	a) 300 mg of licorice flavonoid oil (LFO) b) 600mg of LFO or c) 900 mg LFO d) placebo (MCT+ beeswax)	NEGL	1 % Glabridin per LFO solution	Body weight	CG:71.13 ± 2.2 LFO: 300mg: 71.09 ± 1.98 LFO 600 mg: 71.88 ± 1.71 LFO 900: 72.79 ± 1.82	CG: 73.39 ± 2.22 (2.26) LFO 300 mg: 70.81 ± 1.97 (-0.28) LFO 600 mg: 71.68 ± 1.68 (-0.2) **LFO 900: 72.01 ± 1.81*** (-0.78)
					BMI	CG::26.51 ± 0.34 LFO 300mg: 26.28 ± 0.31 LFO 600 mg: 26.33 ± 0.29 LFO 900mg: 26.22 ± 0.3	CG: 26.59 ± 0.33 (0.08) LFO 300 mg: 26.17 ± 0.32 (-0.11) LFO 600 mg: 26.27 ± 0.3 (-0.06) **LFO 900 mg: 25.97 ± 0.3*** (-0.25)
					Body fat mass	CG::22.65 ± 1.12 LFO 300mg: 22.56 ± 1.29 LFO 600 mg: 21.46 ± 0.92 LFO 900 mg: 22.59 ± 0.9	CG: 22.3 ± 1.24 (-0.35) **LFO 300mg: 21.64 ± 1.31***(-0.92) **LFO 600 mg: 20.53 ± 0.98***(-0.93) **LFO 900 mg: 21.7 ± 0.91*** (-0.89)
					Visceral fat area	CG: 115.26 ± 10.07 LFO 300mg: 120.13 ± 10.6 LFO 600 mg: 117.16 ± 6.3 LFO 900 mg: 122.37 ± 8.2	CG: 110.58 ± 9.67 (-4.68) LFO 300mg:116.03 ± 10.57(-4.1) LFO 600 mg: 117.49 ± 7.1(0.33) **LFO 900 mg:113.02 ± 7.72*** (9.35)
Bell et al., 2011 *(41)* *USA* Double-blinded parallel controlled study N= 22 Age: 20-53 years BMI: 25-36 kg/m^2	8	Three capsules of a) Licorice Flavonoid oil (LFO) (300 mg) or b) placebo (MCT + beeswax)	NEGL	30% polyphenols / flavonoids (3% glabridin)	Body weight	EG:88.7 ± 4 CG:92.3 ± 2.9	EG: 88.6 ± 3.7 (-0.1) CG: 92 ± 3 (-0.3)
					BMI	EG:29.4 ± 1.3 CG:30.2 ± 1.2	EG: 29.4 ± 1.3 (0) CG: 30.1 ± 1.3 (-0.1)
					WC	EG:88.5 ± 3.2 CG: 90.7 ± 2	EG:88.9 ± 3 (0.4) CG: 90.9 ± 2.1 (0.2)
					BF %	EG:33 ± 2.9 CG:32.1 ± 2.1	EG: 32.7 ± 3.2 (-0.3) CG: 32.2 ± 2.1 (0.1)
Barth et al., 2012 *(42)* *Germany* Blinded parallel controlled study	4	a)Polyphenol-rich cloudy apply juice (CLoA) (750 ml) or	a) : 373 Kcal/ b) CB:353 Kcal	a) 802.5 mg/ phenolic acids, quercetin b) NEGL	Body weight	EG: 99 ± 14.2 CG: 97.6 ± 13	EG: 99.3 ± 14.3 (0.3) CG: 97.8 ± 12.9 (0.2)
					BMI	EG:31.1 ± 3.6 CG:30.5 ± 3	EG:: 31.1 ± 3.6 (0) CG 30.6 ± 3.2 (0.1)

N= 68 (100% males) Age: 23-69 years BMI > 27 kg/m²		b)control beverage (CB)			WC	EG:107.3 ± 9.9 CG:106.9 ± 7.9	EG: 107.4 ± 9.7 (0.1) CG: 107.3 ± 7.9 (0.1)
					Body fat %	EG:29.3 ± 3.6 CG:29 ± 2.7	**EG: 28.3 ± 3.9 (-1)*** CG: 28.8 ± 2.7 (-0.2)
Akazome et al., 2010 *(43)* *Japan* double-blinded controlled parallel study N=94 (60 % men) Age: 45.8 ± 8.2 years BMI: 27.2± 1.6 kg/m²	12	Beverage (340 g) containing a)apple polyphenols or b) no polyphenols (placebo)	NEGL	600 mg/	Body weight	EG: 74.1 ± 8.7 CG: 75.2 ± 8.5	**EG: 73.2 ± 8.7*** (-0.9) CG: 75.2 ± 8.2 (0)
					BMI	EG:27 ± 1.7 CG:26.9 ± 1.6	**EG:26.7 ± 1.6*** (- 0.3) CG:26.9 ± 1.5 (0)
					WC	EG: 94.3 ± 5 CG:94.3 ± 4.5	**EG: 92.1 ± 4.7* (-2.2)** CG:94.2 ± 4.2 (-0.1)
					Waist/hip ratio	EG: 0.951 ± 0.041 CG: 0.951 ± 0.041	**EG: 0.942 ± 0.042*** (-0.009) CG: 0.952 ± 0.42 (0.001)
					Body fat %	EG: 28.3 ± 5.8 CG: 28.8 ± 6.2	EG: 28.9 ± 5.6 (0.5) **CG: 29.8 ± 6.1*** (1)
					Visceral fat area	EG: 106.1 ± 34.3 CG: 99.2 ± 31.5	**EG: 98.2 ± 28.2*** (-7.9) CG: 101.3± 35.2 (2.1)

BF: Body Fat; CG: Control group; CT: Catechins; CG: Catechin gallate ;CloA: Polyphenol-rich cloudy apply juice; GC: Gallocatechin; GCG: Gallocatechin gallate; EG: Experimental group; EC: Epicatechin; ECG: Epicatechin gallate; ECP: Ecklonia cava polyphenols; EGG: Epigallocatechin; EGCG: Epigallocatechin gallate; GT: Green tea; GTE: Green tea extract; High polyphenol concentration (HPJ); HSE: Hibiscus sabdariffa extract; LFO: Licorice flavonoid oil; ; MCT: Medium-chain Triglycerides; NEGL: Negligible; Normal polyphenol concentration (NPJ); NS: Non significant; WC: Waist circumference

Body weight (Kg), BMI (kg/m²), Waist circumference (WC), Body fat mass (Kg), visceral/abdominal fat area (cm²), Visceral fat volume area (cm³)

*significant difference p<0.05

┼ missing data

‡ Significant effects (p< 0.05) only in intervention period 1

 # No significant differences in all parameters from baseline between experimental group and control group.