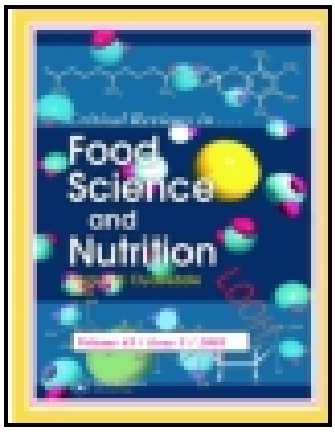

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The Effect of Grapefruits (Citrus paradisi) on Body Weight and Cardiovascular Risk Factors: A Systematic Review and Meta-analysis of Randomized Clinical Trials.

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The effect of grapefruits (*Citrus paradisi*) on body weight and cardiovascular risk factors: a systematic review and meta-analysis of randomized clinical trials.

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ABSTRACT

The aim of this systematic review was to evaluate the evidence for or against the effectiveness of grapefruits (*Citrus paradisi*) on body weight, blood pressure and lipid profile. Electronic searches were conducted in MEDLINE, EMBASE, AMED and the Cochrane Clinical Trials databases to identify relevant human randomized clinical trials (RCTs). Hand searches of bibliographies were also conducted. Only overweight and obese subjects were included. The reporting quality was assessed using the CONSORT checklist, and the strength of the overall body of evidence was rated based on the GRADE criteria. 154 citations were identified and three RCTs with a total of 250 participants were included. The RCTs were of moderate quality. A meta-analysis for change in body weight failed to reveal a significant difference between grapefruits and controls, MD: -0.45 kg (95% CI: -1.06 to 0.16; I^2 = 53%, but analysis revealed a significant decrease in systolic blood pressure, MD: -2.43 mmHg (95%CI: -4.77 to -0.09; I^2 =

0%). Paucity in the number of RCTs, short durations of interventions, and lack of an established minimum effective dose limit the conclusions that can be drawn about the effects of grapefruit on body weight and metabolic parameters. Further clinical trials evaluating the effects of grapefruit are warranted.

Keywords

grapefruit; body weight; body composition; randomized clinical trial; meta-analysis

INTRODUCTION

The increased prevalence of obesity and its associated co-morbidities has resulted in popularity with the use of dietary supplements (Saper et al., 2004). Though a plethora of these supplements are marketed as weight loss pills, the evidence of effectiveness for most of these is mixed (Onakpoya et al., 2011). One such supplement which is being promoted as a slimming aid is grapefruit.

The grapefruit, *Citrus paradisi* is a subtropical citrus tree first discovered in the 18th century (Carrington et al., 2003). The varieties of grapefruit vary in colour of their flesh between red/pink and white depending on the presence or absence of lycopene (Peterson et al., 2006). The fleshy part of the fruit is edible, and the seed extracts have been used as a food supplement and in the cosmetic industry (Ganzera et al., 2006). Phytochemically, grapefruit contains high amounts of polyphenols which are the bioactive compounds responsible for its pharmacologic properties (Benavente-Garcia et al., 2008; Shi et al., 2003).

Polyphenols are naturally occurring micronutrients which are abundant in plant-based diet (Li and Hagerman, 2013). Because they are reputed to possess antioxidant properties, it is thought that they might play a role in the prevention of various illness including cardiovascular and neurodegenerative diseases, as well as in cancers (Scalbert et al., 2005). The polyphenol molecules comprise of several hydroxyl groups on a phenol ring, and subclasses include the phenolic acids, flavonoids, lignans and stilbenes (Manach et al., 2005). The grapefruit flavonoid, naringin is responsible for its bitter taste (Ribeiro et al., 2008).

Grapefruit products are promoted as weight loss aids and there has been an increased research into its effects on body metabolism. Grapefruit has been reported to increase satiety due to its

high fibre content, as well as delay gastric emptying by increasing gastric acidity (Bolton et al., 1981; Blum et al., 1976; Chaw et al., 2001; Grundy et al., 1998). Animal studies have shown that the active flavonoids in grapefruits, naringin and hesperidin, appear to improve glycemic control by potentiating insulin secretion, enhancing the transport of blood glucose to peripheral tissues, or by inhibiting endogenous glucose production (Owira and Ojewole 2009; Ahmed et al 2012; Zunino 2009). Grapefruit has also been reported to stimulate AMP-activated protein kinase, with resulting enhancement of fatty acid oxidation and inhibition of cholesterol and triglyceride synthesis (Pu et al., 2012; Adeneye, 2008).

Evidence is also accumulating regarding the role of grapefruit as a dietary supplement for blood pressure reduction. *Invitro* and *invivo* models have demonstrated that grapefruit extracts decrease coronary vascular resistance and mean arterial pressure possibly by increasing nitric oxide (NO) synthesis, or potentiating the NO-cGMP pathway to induce vascular dilatation (Díaz-Juárez et al., 2009). Controlled human studies examining flow-mediated vasodilatation have also shown that grapefruit polyphenols could have cardioprotective effects on coronary heart disease by upregulating peripheral NO synthase (Barona et al., 2012a; Zern et al., 2005). However, many patients are told to avoid consuming grapefruit while on medication because it can potentiate the effects of drugs such as calcium channel blockers and HMG CoA reductase inhibitors which undergo hepatic first pass metabolism (Bailey et al., 1989; Lilja et al., 1998; Pirmohamed, 2013). Grapefruit products are widely consumed, and commonly available over-the-counter as dietary supplements. Therefore, the objective of this systematic review was to evaluate the effect of grapefruits on body weight and cardiovascular risk factors, using data from published clinical trials.

METHODS

We conducted electronic searches in the following databases: Medline, EMBASE, AMED, and the Cochrane Central Register of Controlled Clinical Trials. Each database was searched from inception to April, 2013. The search terms used included anti-obesity agent, overweight, obesity, weight loss, slimming, body weight, body fat, adiposity, BMI, blood pressure, vascular pressure, *Citrus paradisi*, grapefruit, chakotra, subtropical citrus, redblush, sweetie, oroblanco, marsh, and derivatives of these (comprehensive search strategy included as a supplement Figure 1S). We also searched the internet for relevant conference proceedings and hand searched relevant medical journals. The bibliographies of all located articles were also searched. No age, gender, or language restrictions were imposed.

Only randomized clinical trials (RCTs) were included in this review. To be considered for inclusion, RCTs had to test the effectiveness of orally administered grapefruits in any form for body weight reduction in overweight (BMI $\geq$ 25-29.9 kg/m^2) or obese (BMI $\geq$ 30kg/m^2) humans (World Health Organisation, 2013). In order to be included, studies had to report body weight, body composition and/or metabolic parameters as an outcome measure. Studies were also included irrespective of duration or lifestyle modification.

Two reviewers [IO and JOS] independently assessed the eligibility of studies. Data extracted by two reviewers [IO and JOS] included patient characteristics, type of grapefruit interventions, dose of naringin, outcomes and results. The reporting quality of all included studies was assessed by the use of a quality assessment checklist adapted from the Consolidated Standard of Reporting Trials (CONSORT) Statement (Schulz et al., 2010). The overall strength of the body

of evidence for each outcome was rated using the five-domain Grades of Recommendation, Assessment, Development and Evaluation (GRADE) criteria (Guyatt et al., 2008) namely: study design, risk of bias, inconsistency, imprecision, indirectness. Disagreements were resolved through discussion.

The data were presented as means with standard deviations. Mean changes in body weight, percentage body fat, waist circumference, systolic and diastolic blood pressures, fasting blood sugar, total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol and triglycerides were used as primary endpoints to assess the differences between grapefruit interventions and controls. Using standard meta-analysis RevMan 5.0 software (Review Manager 2008), we computed mean differences (MD) and 95% confidence intervals (CI) for studies with sufficient data for statistical pooling. The fixed-effects model was used for meta-analyses (Deeks et al., 2011). Sensitivity analyses (analysing trials based on methodology) and subgroup analyses (analysing trials based on the type of grapefruit consumed) were used to investigate heterogeneity, using the I^2 statistic; values of 25%, 50%, and 75% indicated low, medium, and high statistical heterogeneity respectively. We used the correlation co-efficient to impute the standard deviation if this measure of dispersion was not reported (Higgins et al., 2011).

RESULTS

Our electronic searches identified 154 non-duplicate citations (Figure 1), out of which 4 eligible trials (Dallas et al., 2008; Dow et al., 2012; Fujioka et al., 2006; Silver et al., 2011) were identified. One RCT (Dallas et al., 2008) was excluded because the investigators combined

grapefruit with orange juice. Thus, three RCTs (Dow et al., 2012; Fujioka et al., 2006; Silver et al., 2011) including a total of 250 participants were included in the review. Key details of the RCTs are summarized in Tables 1 and 2. All the RCTs were of parallel design.

There were some variations in the methods and reporting characteristics of the included RCTs (Table 1). One RCT (Fujioka et al., 2006) used placebo controls and was reported as double-blinded; another (Silver et al., 2011) was described as an open-label, while the third (Dow et al., 2012) did not specify the blinding technique used. Two RCTs (Dow et al., 2012; Silver et al., 2011) reported adequate randomization techniques, and all RCTs performed adequate sample size calculations. The eligibility criteria for participants were similar across the RCTs, but one RCT (Dow et al., 2012) excluded postmenopausal women and used two separate cohorts for their study. One RCT (Silver et al., 2011) used intention-to-treat (ITT) analyses.

Body weight was measured using calibrated double ruler standing scale (Dow et al., 2012), an unspecified calibrated scale (Fujioka et al., 2006) and wall-mounted stadiometer (Silver et al., 2011) (Table 2). For body fat measurement, one RCT (Dow et al., 2012) used Omron Body Fat Analyzer, another (Silver et al., 2011) used bioelectric impedance (BIA), while the third (Fujioka et al., 2006) did not report body fat composition as an outcome. Waist circumference was measured with a Gulick II measuring tape in one RCT (Dow et al., 2012), another (Silver et al., 2011) used a flexible measuring tape placed above the right iliac crest, while the method used in the third RCT (Fujioka et al., 2006) was unspecified. For blood pressure measurement, one RCT used the Omron automated blood pressure cuff (Dow et al., 2012), another standard mercury sphygmomanometer (Fujioka et al., 2006), while the third RCT (Silver et al., 2011) did not specify the instrument used; two of these studies recorded the average of two blood pressure

measurements of participants for analysis in their study (Dow et al., 2012; Fujioka et al., 2006), while the type of recording used was not specified in the third RCT (Silver et al., 2011). Lipid profile was analysed in two studies using LDX Cholestech System (Dow et al., 2012) and selective enzymatic hydrolysis (Silver et al., 2011); one RCT did not specify the method used (Fujioka et al., 2006). Blood samples for biochemistry in all three RCTs were collected after an overnight fast by study participants at the beginning and at the end of the study.

All RCTs incorporated lifestyle modification into their trial regimen (Table 2). While subjects in one RCT (Dow et al., 2012) had a three-week wash-out, participants in another RCT (Silver et al., 2011) underwent a two-week run-in. One RCT (Fujioka et al., 2006) did not report any pre-trial regimen. Participants in two RCTs (Dow et al., 2012; Silver et al., 2011) had their diets restricted and analysed daily caloric intakes using the University of Minnesota Nutrition Data System for Research software; while those in the third RCT (Fujioka et al., 2006) continued their usual diet with no report on how caloric intake was analysed. All RCTs included exercise as part of their trial, and one RCT (Silver et al., 2011) measured the levels of activity of study participants using a pedometer. Two RCTs (Dow et al., 2012; Silver et al., 2011) monitored compliance by analysing submitted logs of study participants, of which one (Dow et al., 2012) reported a compliance rate of 93%, but the others(Fujioka et al., 2006; Silver et al., 2011) did not report the compliance rate.

Participants in all RCTs were obese adults, with mean BMI between 31.4 and 36.8 kg/m^2 (Table 2). The study duration was 6 weeks in one RCT (Dow et al., 2012), and 12 for the other two (Fujioka et al., 2006; Silver et al., 2011). The intervention formulations used included fresh grapefruit, grapefruit juice and capsules, and the daily dose of naringin in the grapefruit

formulations ranged from 81 to 142 mg; one RCT (Fujioka et al., 2006) did not report the dose of naringin. In one RCT (Fujioka et al., 2006) the grapefruit juice was reconstituted from frozen concentrate, while subjects in a second RCT (Silver et al., 2011) consumed juice produced by a commercial manufacturer (Ocean Spray). In the RCT which used capsules (Fujioka et al., 2006), the grapefruits used for preparing the capsules were reported to have been freeze-dried and compressed. In one RCT (Dow et al., 2012), participants were given a multivitamin/mineral supplement in addition to the interventions for the duration of the study. All RCTs reported no significant differences between grapefruit and control groups at baseline, and were all funded by public institutions.

Effect of grapefruits on body weight and composition

A forest plot of three RCTs with 233 participants (Figure 2) showed a statistically non-significant difference in body weight between grapefruit and control arms, MD: -0.45 kg (95% CI: -1.06 to 0.16; I^2= 53%). Sensitivity analyses of participants in two RCTs with a trial run-in (n = 156; table 3) revealed a non-significant difference in body weight between grapefruits and controls, MD: -0.2kg (95% CI: -0.91 to 0.50; I^2= 59%); similar results were observed for the subgroup analyses by grapefruits subtype, MD: -0.37kg (95%CI: -0.97 to 0.23; I^2= 0%).

One RCT (Fujioka et al., 2006) reported a statistically non-significant difference in percentage body fat between participants allocated to grapefruit (actual values not reported, $p > 0.05$). Meta-analysis of the other two RCTs (n = 156; table 3) revealed a statistically significant decrease percentage body fat favouring grapefruits over controls, MD: -0.49% (-0.81 to -0.18; I^2= 22%; p = 0.002). A meta-analysis of waist circumference (Figure 3) also showed a statistically

significant reduction for grapefruits compared with controls, MD: -1.15cm (-1.45 to -0.85; I^2= 47%; p = <0.0001). Subgroup analysis of participants who consumed fresh grapefruit versus grapefruit juice revealed a significant reduction in waist circumference favouring grapefruits over controls, MD: -1.17cm (95%CI: -1.47 to -0.87; I^2=54.9%).

Effect of grapefruits on blood pressure

Meta-analysis of all RCTs (Figure 4) revealed a significant reduction in systolic blood pressure favouring grapefruits over controls, MD: -2.43 mmHg (-4.77 to -0.09; I^2= 0%). Meta-analysis of two RCTs which reported adequate randomization techniques revealed a non-significant difference in systolic blood pressure, MD: -2.32 mmHg (95%CI: -4.92 to 0.27; I^2=0%). However, meta-analysis of fresh grapefruit versus grapefruit juice showed a statistically significant reduction in favour of grapefruits compared with controls, MD: -2.48 mmHg; 95%CI: -4.44 to 0.52; I^2=16%.

Meta-analyses of all RCTs showed no statistically significant difference in diastolic blood pressure, MD: -1.65 mmHg (95%CI:-3.92 to 0.63; I^2= 0%; table 3). Subgroup analyses of participants who consumed fresh grapefruit versus grapefruit juice revealed similar results, MD: -2.18mmHg; 95%CI: -4.38 to 0.02; I^2=0%.

Effect of grapefruits on blood glucose and lipid profile

Meta-analysis of two RCTs revealed no significant differences in fasting blood glucose, MD: 0.10 mg/dL (95%CI: -0.04 to 0.24; I^2= 0%). Meta-analysis of two RCTs (table 3) revealed a non-significant difference in total cholesterol, MD: -3.02 mg/dL (95%CI: -7.01 to 0.97; I^2= 0%) and

LDL cholesterol, MD: -0.71 mg/dL (95%CI: -3.69 to 2.28; I^2= 68%). Meta-analysis of all RCTs (table 3) showed a significant increase in HDL cholesterol in the grapefruits group compared with controls, MD: 3.21 mg/dL (95%CI: 0.77, 5.65; I^2= 73%). Sensitivity analyses of two RCTs which reported adequate randomization techniques also showed similar results, MD: 4.6 mg/dL (95%CI: 1.85 to 7.26; I^2=63%). Subgroup analyses of fresh grapefruit versus grapefruit juice revealed a significant increase in HDL cholesterol favouring grapefruit compared with controls, MD: 3.56 mg/dL (95%CI: 1.62, 5.50; I^2=71.9%; table 3). Meta-analysis of all RCTs revealed a non-significant difference in triglycerides between grapefruits and controls, MD: -1.76 mg/dL (-8.26 to 4.75; I^2= 0%).

Adverse events and attrition

One RCT (Fujioka et al., 2006) reported constipation and diarrhea as adverse events (Table 2). Drop-out rates in the RCTs (Dow et al., 2012; Fujioka et al., 2006; Silver et al., 2011) were 3, 14 and 17 respectively. There were no significant differences in drop-out rates between grapefruits and control groups in all RCTs.

Strength of the evidence

Using the GRADE criteria (Guyatt et al., 2008), the overall body of evidence from the RCTs for each outcome could be rated as moderate, i.e., further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate (Table 3); the exceptions being LDL and HDL cholesterol which were rated downwards to low quality because of high heterogeneity in addition to high risk of bias.

DISCUSSION:

Main findings

Based on the results of our meta-analysis of three RCTs including 233 participants, grapefruit supplementation does not lead to statistically significant reductions in body weight in obese adults. However, grapefruit intake does lead to small but significant reductions in systolic blood pressure and waist circumference in overweight and obese adults. Our results should be interpreted with caution because of some variation the design of the included RCTs and the short duration of the interventions. To our knowledge, this is the first systematic review which synthesizes the evidence from RCTs examining the effects of grapefruits on body metabolic parameters.

Grapefruits are a rich source of naringin. Aside potentiating insulin secretion, this polyphenol appears to attenuate insulin resistance by up-regulating peroxisome proliferator-activated receptor gamma (PPAR-γ) and a variety of proteins (Cho et al., 2011; Sharma et al., 2011). The ability of grapefruit extracts to delay gastric emptying is also demonstrated by the increased bioavailability of certain drugs when consumed together with grapefruits (Odou et al., 2005). However, the results of our review do not convincingly show that these mechanistic properties of grapefruit translate to significant reductions in body weight. A lack of statistically significant effect in energy expenditure observed in one RCT (Silver et al., 2011) also lends credence to the fact that grapefruit may not have beneficial effects on body weight. The effect sizes observed for the reductions in percentage body fat and waist circumferences are also small and the clinical

relevance of these is uncertain; whether these results, if true, suggest that grapefruit may be beneficial for reducing central adiposity warrants further research.

Results from small randomized controlled studies have appeared to show an effect of grapefruit in reducing blood pressure in patients with stage I hypertension as well as metabolic syndrome (Reshef et al., 2005; Barona et al., 2012b), and grapefruit products have reportedly been used in management of hypertension (Lans, 2006). Our results confirmed significant reductions in systolic blood pressure. Though the size of the effect was small, such reduction could be clinically relevant particularly for longer term management of hypertension. However, the trueness of this effect is debatable. Indeed only one RCT (Fujioka et al., 2006) included participants whose blood pressure was ‘’being controlled’’, while the others (Dow et al., 2012; Silver et al., 2011) excluded patients with cardiovascular diseases. Whether grapefruits could be used as adjuncts to conventional drugs for the management of hypertension is at best conjectural.

Results from the meta-analyses did not show a consistently beneficial effect of grapefruits on the blood lipid profile. Though we observed a significant effect on HDL cholesterol, there was a high heterogeneity, and the effect was largely due to one RCT (Silver et al., 2011). As earlier stated, the active flavonoids in grapefruit have been reported to possess lipolytic properties (Pu et al., 2012; Adeneye, 2008). Other authors have also suggested that naringin lowers plasma lipids in patients with hypercholesterolemia (Cerda et al., 1998; Jung et al., 2003), but this has been contradicted by other investigators (Demonty et al., 2010). Because the RCTs in this review are few in number, and excluded subjects with hypercholesterolemia, the effect of grapefruits on lipid profile is not clear and requires further research.

There is no established minimum effective dose at which grapefruits can generate its reported effects; and because of the small number of included studies, we could not also plot dose-effect correlation curves for naringin. However, we noted slight variations in the daily doses of naringin across the two RCTs which reported concentration levels (Dow et al., 2012; Silver et al., 2011). Though data on bioavailability is sparse, pharmacokinetic analyses in healthy subjects has demonstrated that hesperetin and naringenin are rapidly absorbed in their conjugated forms after oral administration, reaching peak plasma concentrations in 3.5 and 4.0 hours respectively with urinary excretion rates of 3 to 6% (Kanaza et al., 2007). While it is unclear if the processing of fresh grapefruits into grapefruit juice influenced the level of activity and/or bioavailability of its constituent polyphenols or flavonoids, the results of subgroup analyses (except for fasting blood sugar) did not suggest that processing of raw grapefruit caused any significant changes in the directions or sizes of effects.

Adverse effects of grapefruit were poorly reported in the included trials, one RCT (Fujioka et al., 2006) reported adverse events which included diarrhea and constipation. Perhaps more worrying for clinicians is the lack of evidence on effects on concurrent medications. Grapefruit contains furanocoumarins which have been shown to irreversibly inhibit the cytochrome P450 enzyme, CYP3A4 (Bailey et al., 1991; Ho and Saville, 2001). *Invitro* studies have also indicated that naringin specifically inhibits CYP1A2 activity (Bailey et al., 1998). Added to the fact that grapefruit inherently possesses blood pressure-lowering and gastric emptying delay properties, the synergistic action of grapefruit with this group of drugs has led to several cautions about the potential dangers of such food-drug interactions (Odou et al., 2005; Adigun and Mudasiru, 2002; Nakagawa and Goto, 2010).

Strengths and limitations

We employed a robust search strategy, and the three trials included in this review were of moderate reporting quality; this is corroborated by the low heterogeneity observed for majority of the meta-analyses. We also used the GRADE criteria to rate the strength of the overall body of evidence. Most of our sensitivity and subgroup analyses were also consistent with our overall analyses. However, we recognise several important limitations in this review. Firstly, we identified only a small number of included trials and due to variations in their design, and short durations of interventions, our ability to make firm conclusions on effectiveness is limited. Secondly, the RCTs used different formulations of grapefruit, and in different quantities. Using sensitivity analyses we did note some effect of formulation on outcome, which may be supported by the variation in naringin concentrations in grapefruit products across the RCTs. Thirdly, the participants in all three trials underwent different modifications to lifestyles (e.g. behavior, diet and physical activity). While these were similar in control and active arms, they may have influenced the overall effect sizes. We could not also perform subgroup analyses based on baseline demographic characteristics participants in the individual RCTs. In addition, the blinding methods across individual RCTs differed; this may be of particularly importance in community based dietary interventions where total blinding of participants, care providers, outcome assessors may be impossible. Finally, although we used robust search methods, we may not have identified all RCTs involving the use of grapefruit especially unpublished studies.

Research Implications

Well conducted clinical trials with longer durations of intervention evaluating the effects of grapefruits on body weight and metabolic parameters are warranted. Because of the effects seen on systolic blood pressure, clinical trials which are adequately powered to detect such effects are required. There also needs to be an established effective minimum dosage at which grapefruits can generate the reported reductions in blood pressure. Furthermore, future investigators should adhere strictly to standardized reporting guidelines so as to minimise the risk of bias in their studies.

Clinical Implications

Increasing intake of fruit is widely recommended for healthy lifestyles, and consuming grapefruits can form part of a well-balanced diet. However, for obese individuals there does not seem to be convincing evidence to recommend grapefruits as a slimming aid. Grapefruit could potentially lead to a reduction in blood pressure with regular use, but it should not be recommended as a substitute for current hypertensive management at present. Consumption of grapefruits in individuals taking medications which are metabolized by the cytochrome P450 enzymes could lead to the potentiation of the actions of such drugs.

CONCLUSION

The available evidence from RCTs does not indicate that grapefruit supplementation generates significant reductions on body weight. Grapefruits could cause significant reductions in systolic blood pressure. Variations in the design, a dearth in the number of RCTs, short duration of interventions, and the lack of an established minimum effective dose limit the conclusions that

can be drawn about its effects on body composition and metabolic parameters. Further clinical trials evaluating the effects of grapefruits are warranted.

Conflicts of interest

None.

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Table 1: Reporting quality of RCTs of grapefruit supplements*

Study Year Country	Study design	Randomization appropriate?	Allocation concealed?	Sample size determined?	Groups similar at baseline?	Care provider blinded?	Patients blinded?	Outcome assessor blinded?	Attrition bias?	ITT analysis?
Dow et al 2012 USA	Parallel	Unclear	Unclear	Yes	Yes	Unclear	Unclear	No	No	Unclear
Fujioka et al 2006 USA	Parallel	Yes	Unclear	Yes	Yes	Unclear	Unclear	Unclear	No	Unclear
Silver et al 2011 USA	Parallel	Yes	No	Yes	Yes	No	No	Yes	No	Yes

*The checklist for the reporting quality has been adapted from the CONSORT Statement (Schulz et al., 2011)

Abbreviation: ITT: intention-to-treat analysis

Table 2: Study characteristics and main results RCTs of grapefruit supplements*

Study Year	Main outcome	Type of subjects	Sex M/F	Intervention (s)	Control	Body weight at baseline (kg)	Study duration	Adverse events	Lifestyle adjustment	Source of funding
Dow et al 2012	BW, %BF, WC, BP, blood lipids	Obese adults	17/57	½ Rio-Red GF three times daily; estimated naringenin intake 142 mg daily	Diet restricted in bioactive-rich fruits and vegetables	FGF: 92.4±14.9 CT: 90.8±12.8	6 weeks	Not reported	Diet restricted in bioactive-rich foods	Public institution
Fujioka et al 2006***	BW, %BF, WC, BP, blood lipids	Obese adults	17/74	½ GF, 207 ml GFJ or 500mg GFC three times daily; naringin intake not reported	Placebo capsules	FGF: 103±19.3 GFJ: 99.9±20.3 GFC: 99.2±18.9	12 weeks	Constipation, diarrhea	Exercise	Public institution

Silver et al 2011**	BW, %BF, WC, BP, blood lipids	Obese adults	64/21	½ GF or 127g GFJ three times daily; estimated naringin intake 81 &119 mg respectively	127g bottled water three times daily	FGF: 99.8±13.8 GFJ: 95.9±11.5 WA: 99.5±13.5	12 weeks	Not reported	12.5% caloric restriction	Public institution

*Unless otherwise stated, all values have been reported as means with standard deviations

**Two grapefruit intervention groups have been compared with controls

***Three grapefruit intervention groups have been compared with controls

Abbreviations: BW: Body weight; % BF: Percentage body fat; WC: Waist circumference; FGF: Fresh grapefruit; GFJ: Grapefruit juice; CT: Control; PLA: Placebo; WA: Bottled water

Table 3: Results of Meta-analyses of RCTs of grapefruit supplements*

Outcome	Overall analyses** Mean difference (95% CI)	Sensitivity analyses Mean difference (95% CI)	Subgroup analyses Mean difference (95% CI)
Bodyweight (3RCTs; n = 233)	-0.45kg (-1.06 to 0.16); I^2= 53%	2 RCTs with adequate randomization (n = 162): -0.37kg (-1.33 to 0.58); I^2 =77% 2 RCTs with trial run-in (n = 156): -0.2kg (-0.91 to 0.50); I^2=59%	Fresh grapefruits *versus* cont 40% Grapefruit juice *versus* contr 53% Fresh grapefruit versus grape 0.23); I^2= 0%; p = 0.58
Percentage body fat*** (2 RCTs; n = 156)	-0.49% (-0.81 to -0.18); I^2= 22%		
Waist circumference (3 RCTs; n = 233)	-1.15cm (-1.45 to -0.85); I^2= 47%	2 RCTs with adequate randomization (n = 162): -0.10cm (-1.31 to 1.11); I^2=0% 2 RCTs with trial run-in (n = 156): -1.18cm (-1.49 to -0.88); I^2= 64%	Fresh grapefruits *versus* cont I^2= 67% Grapefruit juice *versus* contr 0% Fresh grapefruit versus grape 0.87); I^2=54.9%; p = 0.14
Systolic blood pressure (3 RCTs; n = 233)	-2.43mmHg (-4.77 to -0.09); I^2= 0%	2 RCTs with adequate randomization (n = 162): -2.32mmHg (-4.92 to 0.27); I^2=0% 2 RCTs with trial run-in (n = 156): -1.91mmHg (-4.58 to 0.75); I^2=0%	Fresh grapefruit *versus* contr 0.83); I^2= 49% Grapefruit juice *versus* contr 0% Fresh grapefruit versus grape to -0.52); I^2=16%; p = 0.28
Diastolic blood pressure (3 RCTs; n = 233)	-1.65 mmHg (-3.92 to 0.63); I^2= 0%	2 RCTs with adequate randomization (n = 162): -2.66mmHg (-5.51 to 0.19); I^2=0% 2 RCTs with trial run-in (n = 156): -1.05mmHg (-3.71 to 1.61); I^2=0%	Fresh grapefruit *versus* contr I^2= 0% Grapefruit juice *versus* contr I^2= 0% Fresh grapefruit versus grape to 0.02); I^2=0%; p = 0.28
Fasting blood sugar*** (2 RCTs; n = 162)	0.10mg/dL (-0.04 to 0.24); I^2= 0%		Fresh grapefruit *versus* contr 82% Grapefruit juice *versus* contr I^2= 67% Fresh grapefruit versus grape 0.24); I^2=81.8%; p = 0.02
Total cholesterol*** (2 RCTs; n = 154)	-3.02mg/dL (-7.01 to 0.97); I^2= 0%		
LDL cholesterol*** (2 RCTs; n = 154)	-0.71mg/dL (-3.69 to 2.3); I^2= 68%		

HDL cholesterol (3 RCTs; n = 231)	3.21mg/dL (0.77 to 5.65); I^2= 71%	2 RCTs with adequate randomization (n = 162): 4.6mg/dL (1.85 to 7.26); I^2=63% 2 RCTs with trial run-in (n = 154): 4.3mg/dL (1.49 to 7.03); I^2=78%	Fresh grapefruit *versus* contr I^2= 78% Grapefruit juice *versus* contr 0% Fresh grapefruit versus grape 5.50); I^2=71.9%; p = 0.06
Triglycerides (3 RCTs; n = 231)	-1.76mg/dL (-8.26 to 4.75); I^2= 0%	2 RCTs with adequate randomization (n = 162): 1.34mg/dL (-7.90 to 10.57); I^2=0% 2 RCTs with trial run-in (n = 154): -4.49mg/dL (-12.1 to 3.12); I^2=0%	Fresh grapefruit *versus* contr 2.85); I^2= 0% Grapefruit juice *versus* contr I^2= 40% Fresh grapefruit versus grape 3.31); I^2=0%; p = 0.43

* The results for the overall analyses include participants who were administered grapefruit capsules in one RCT (Fujioka et al., 2006). The p values for subgroup analyses represent the test for between-group subgroup differences

** The GRADE criteria (Guyatt et al., 2008) was used to rate the body of evidence. **Study design**: Not serious; **Risk of bias**: Serious; **Inconsistency**: Not serious; **Indirectness:** Not serious. The overall strength of the body of evidence from the RCTs for each outcome could be rated as moderate, i.e., further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate (with the exception of LDL and HDL cholesterol which were rated downwards to low quality due to high heterogeneity)

***Because only two RCTs reported this outcome, the results of the sensitivity analyses are same as for overall analyses

†Both RCTs had interventions of fresh grapefruit and grapefruit juice, thereby allowing for subgroup analysis

Abbreviations: LDL cholesterol: Low-density lipoprotein cholesterol; HDL cholesterol: High-density lipoprotein cholesterol; MD: Mean difference; 95%CI: 95% Confidence Interval

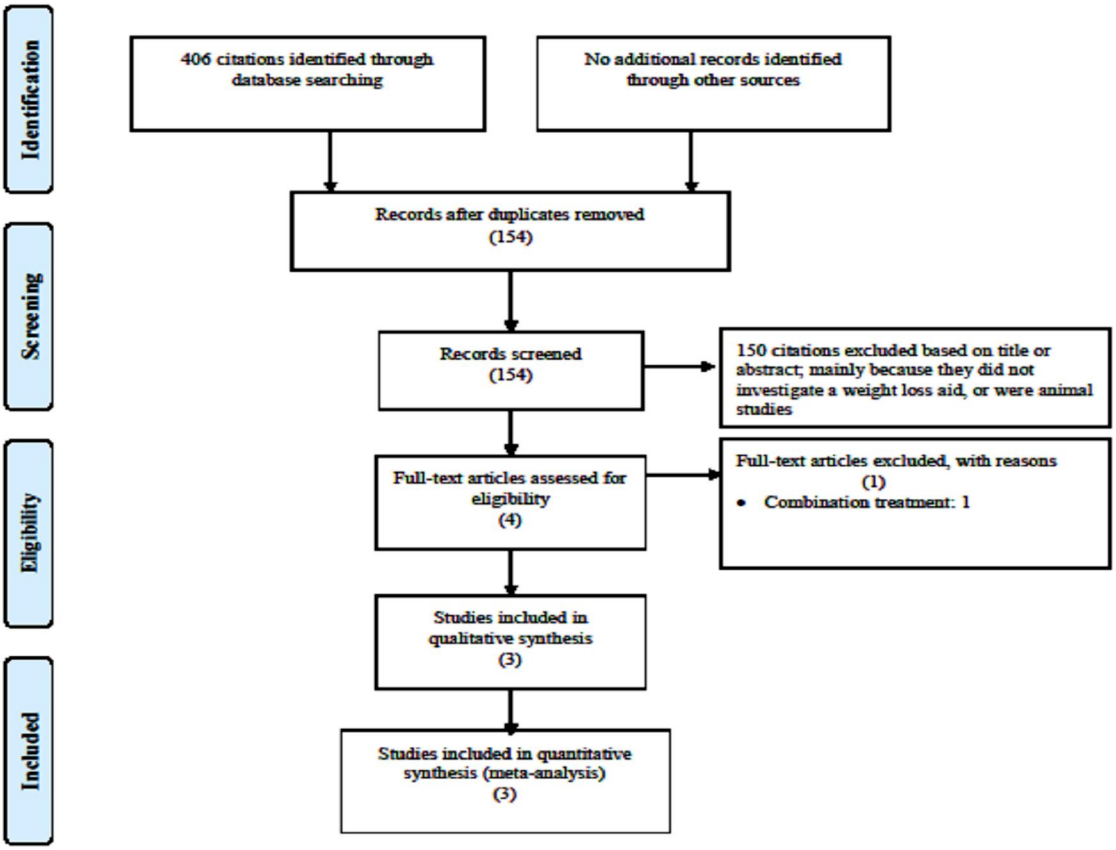

Figure 1: Flow Diagram showing process for inclusion of grapefruit RCTs[1]

[1]The Flow Diagram has been adapted from the online version of the PRISMA statement, 2009. Available from: http:// www.prisma-statement.org/statement.htm

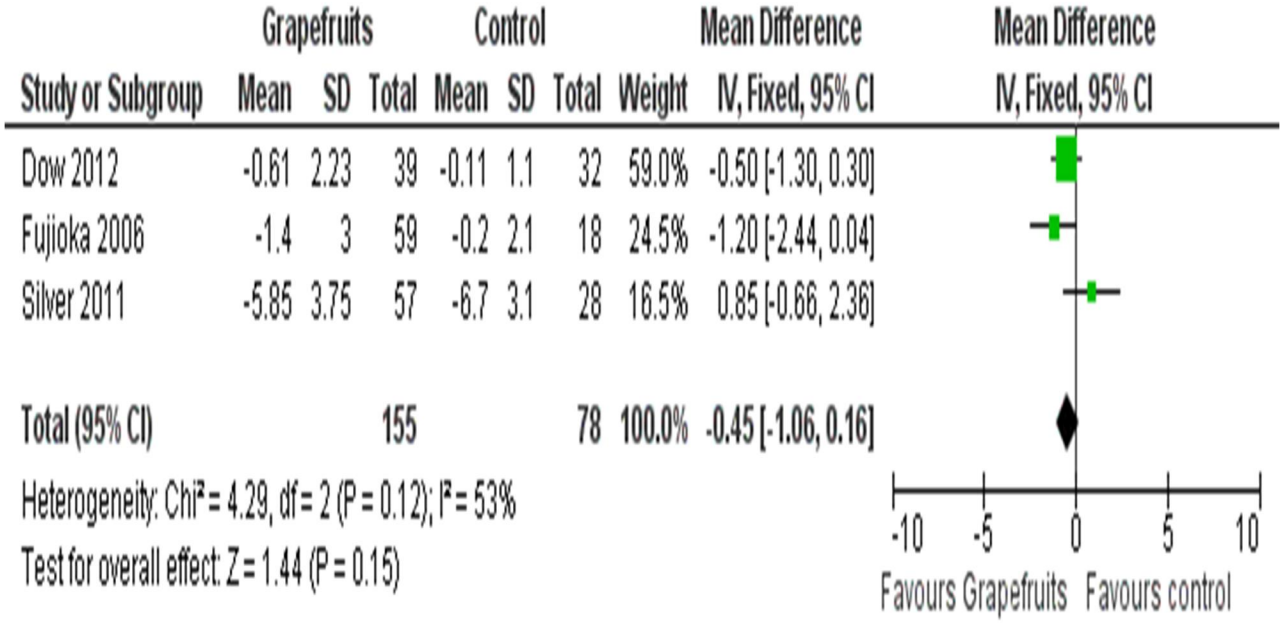

Figure 2: Effect of grapefruits on body weight (kg).

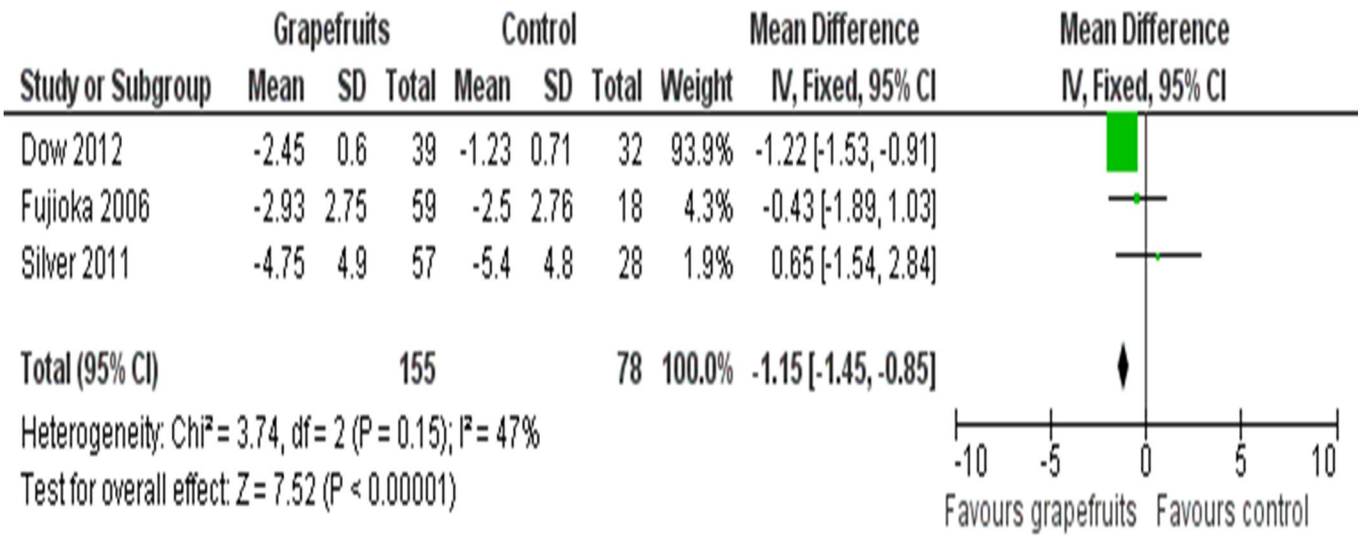

Figure 3: Effect of grapefruits on waist circumference (cm).

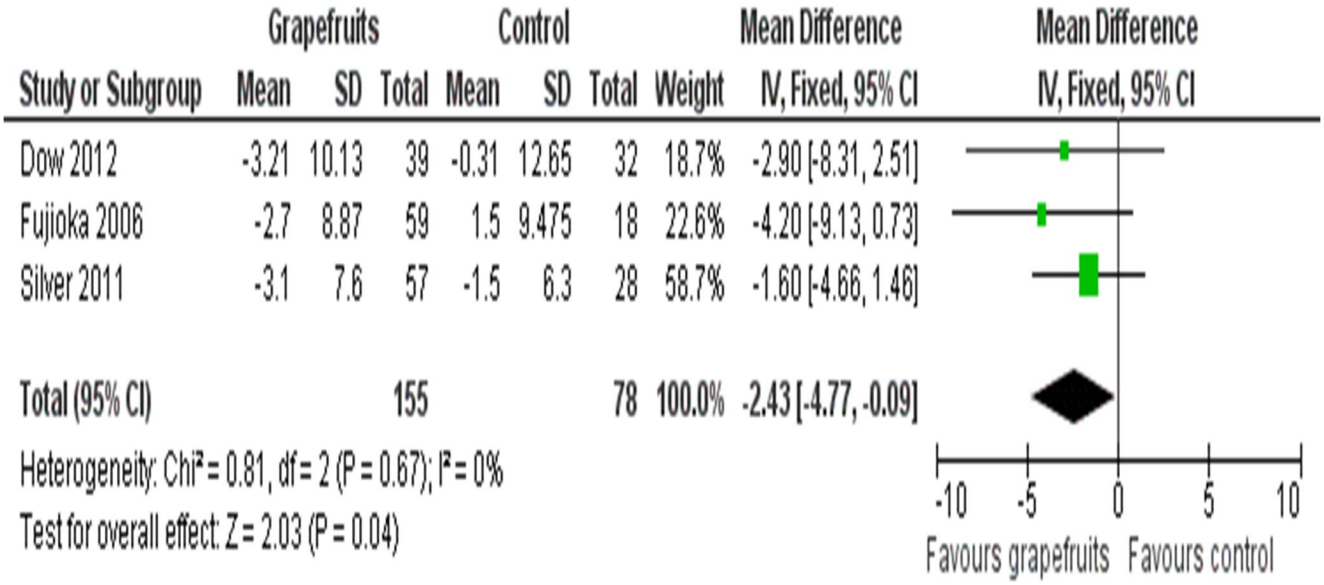

Figure 4: Effect of grapefruits on systolic blood pressure (mmHg).