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REVIEW

The safety and effectiveness of commonly-marketed natural supplements for weight loss in populations with obesity: A critical review of the literature from 2006 to 2016

Sean Wharton[a,b], Revi Bonder[b], Aaron Jeffery[a], and Rebecca A. G. Christensen[a]

[a]The Wharton Medical Clinic, Toronto, Ontario, Canada; [b]School of Kinesiology and Health Science, York University, Toronto, Ontario, Canada

ABSTRACT

Objective: To evaluate the evidence published from 2006 to 2016 on the effectiveness and safety of commonly used natural supplements for weight loss in individuals with obesity.
Methods: Amazon and Google were searched for names of mono-agent natural supplements marketed for weight loss and a list of the 10 supplements was created. Google Scholar, Pubmed, Science Direct, and the Cochrane Library were searched for articles that met inclusion.
Results: At least one article was published on the effectiveness or safety of bitter orange, capsinoid, carnitine, chromium picolinate, *Coleus forskohlii*, conjugated linoleic acid, glucomannan, green tea and psyllium for weight loss in populations with obesity from 2006 to 2016. There was insufficient evidence to suggest that the natural supplements examined contribute to significant weight loss, with the exception of perhaps glucomannan in the form of PGX. In general, the majority of side-effects reported were minor to moderate, and gastrointestinal-related. However, in some cases extreme side-effects such as liver and kidney failure were observed.
Conclusion: Contrary to popular belief, results of this review suggest that the use of natural supplements for weight loss are unlikely to contribute to meaningful weight loss and in some cases may contribute to harm.

KEYWORDS
Overweight and obesity; dietary supplements; adverse events; efficacy; weight management

Introduction

Currently, overweight or obesity affects about 603 million adults worldwide and contributes to 4 million deaths annually (Global Burden of Disease 2015 Obesity Collaborators et al. 2017). Obesity is also associated with an array of chronic diseases, such as cancer, diabetes, kidney disease, and cardiovascular disease (Global Burden of Disease 2015 Obesity Collaborators et al. 2017). In order to alleviate these symptoms, individuals are often prescribed weight loss.

Lifestyle interventions (i.e. diet and physical activity) are the cornerstone of weight management strategies, however, results are often discouraging with individuals regaining lost weight (Curioni and Lourenço 2005). Accordingly, pharmaceuticals are sometimes prescribed to assist the weight loss process, albeit health care practitioners are often resistant to prescribing these medications, due to a variety of factors such as lack of specialized training and fear of side-effects (Wharton, Lee, and Christensen 2017). Consequently, natural supplement[1] use for weight loss has become increasingly popular, with some believing there are no associated health risks (Health Canada 2010). Accordingly, more than 70% of adults in Canada report consuming a natural health product at some point in their life, and three-quarters of these individuals believe natural supplements are better at treating medical conditions than pharmaceuticals (Health Canada 2010).

The recent popularization of natural supplement use has brought to light a rising concern over the lack of regulation in the dietary supplement industry. In Canada, health claims must be federally approved before appearing on natural health products. However, evidence supporting these claims can be quite lenient – for example, from a "reputable textbook", or approval from another regulatory agency (Health Canada 2012) – compared to the evidence needed for weight loss medications. In addition, purported health benefits of natural supplements often require the use of terminology that is vague such as "could" or "likely" (Health Canada 2012), which is concerning since more than half of Canadians taking natural supplements disagree that the claims made by these products are unproven (Health Canada 2010). This is not dissimilar to legislation for natural supplements in Europe and the United States. For example, while there is clear legislation in the European Union (EU) regarding functional claims on natural weight loss products, the exact rigor of the required evidence is unclear (e.g. "requires generally accepted scientific evidence" (The European Parliament, and The Council of the European Union 2006)). In the United States, natural supplements are not required to receive Federal Drug Administration (FDA) approval to be marketed, and the

CONTACT Rebecca A. G. Christensen r.christensen@mail.utoronto.ca 402 – 658 Danforth Avenue, Toronto, Ontario M4J 5B9, Canada.

responsibility to ensure the safety of the product lies with the company (Food and Drug Agency 2015).

Given the lack of clear regulations regarding natural supplements, their popularity, and trust from consumers, there is a need to evaluate the existing literature on the safety and efficacy of natural supplements for consumers and clinicians. Therefore, the objective of this literature review is to provide a critical update on commonly-used weight-loss natural supplement research conducted from 2006 to 2016 in populations with obesity. The top nine most commonly advertised supplements on Google and Amazon Canada were reviewed.

Methods

One author (AJ) searched google.ca and amazon.ca for natural weight loss supplements, and a list of the 10 most advertised products was created. Ephedra was excluded *a-priori* due to its ban in several countries (Davis Cockey 2004; European Food Safety Authority (EFSA) 2013). Articles were sourced by two authors (RAGC and AJ) using Google Scholar, PubMed, Science Direct, and The Cochrane Library search engines. For Good Scholar, search terms entered included "CLA or conjugated linoleic acid OR green tea OR green tea extract OR glucomannan OR konjac OR l-carnitine OR coleus forskohlii OR synephrine OR bitter orange OR gacinia cambogia OR chromium picolinate OR psyllium OR capsaicin OR safety OR effectiveness OR efficacy AND weight loss AND adults. The final search of databases occurred in January 2018.

Articles were included if they: (1) had information on weight loss or the safety of the weight loss supplement; (2) examined a population with obesity (mean BMI $\geq$30 kg/m^2); (3) were an original research article; and (4) were published from January 2006 to December 2016. Articles were excluded if they: (1) were not in English; (2) examined a multi-agent supplement; or (3) were not peer reviewed. In certain cases, multiple journal articles were published using a single dataset with similar aims. When this occurred, only the most rigorous article in terms of sample size and completeness of outcome measure(s) was included. When disagreement on articles occurred, a third author (RB) reviewed the article to ensure it satisfied inclusion criteria. Reference lists for chosen articles were examined for additional articles. One supplement was excluded due to there not being any published research that met inclusion, leaving 9 supplements for review. One article was removed after initial article exclusion (Holmes and Tavee 2008) due to subsequent information made available on the supplement, which established that there are other active ingredients present in the supplement, making it a multi-agent supplement.

Quality of the research articles was quantitatively assessed by two authors (AJ and RAGC) using the Quality Assessment Tools for Quantitative Studies by the Effective Public Health Practice Project (Thomas, Ciliska, M Dobbins, and Micucci 2004; Effective Public Health Practice Project 1998). If there was a discrepancy in the scoring, authors were asked to review the criteria on that specific criteria (e.g. selection bias, confounders), and then rate that section again. This resulted in concordant ratings for all literature included in this review. See Table 1 for the global rating quality of each article.

Table 1. Assessment of research quality.

Supplement	Author	Rating
BitO	Burke et al. (2007)	Weak
BitO	Kaats et al. (2013)	Strong
Capsinoid	Lee et al. (2010)	Strong
Capsinoid	Snitker et al. (2009)	Moderate
Carn	Elmslie et al. (2006)	Weak
CLA	Adams et al. (2006)	Strong
CLA	Carvalho, Uehara, and Rosa (2012)	Moderate
CLA	Gaullier et al. (2007)	Moderate
CLA	Joseph et al. (2011)	Strong
CLA	Laso et al. (2007)	Moderate
CLA	Mądry et al. (2016)	Weak
CLA	Norris et al. (2009)	Moderate
CLA	Sahin, Uyanik, and Inanc (2008)	Weak
CLA	Steck et al. (2007)	Strong
CLA	Syvertsen et al. (2007)	Moderate
CLA	Taylor et al. (2006)	Strong
Colf	Loftus et al. (2015)	Strong
CrP	Anton et al. (2008)	Moderate
CrP	Brownley et al. (2013)	Moderate
CrP	Cefalu et al. (2010)	Moderate
CrP	Iqbal et al. (2009)	Moderate
CrP	Kleefstra et al. (2006)	Moderate
CrP	Tian et al. (2013)	Weak
CrP	Yazaki et al. (2010)	Weak
GM	Keithley et al. (2013)	Moderate
GM	Kraemer et al. (2007)	Weak
GM	Lyon and Reichert (2010)	Weak
GM	Onakpoya, Posadzki, and Ernst (2014)	Weak
GM	Pal et al. (2016)	Moderate
GM	Zalewski, Chmielewska, and Szajewska (2015)	Weak
GTE	Basu et al. (2010)	Moderate
GTE	Belcaro et al. (2013)	Weak
GTE	Brown et al. (2011)	Moderate
GTE	Cardoso et al. (2013)	Weak
GTE	Chan et al. (2006)	Strong
GTE	Chen et al. (2016)	Strong
GTE	Hill et al. (2007)	Weak
GTE	Hsu et al. (2008)	Moderate
GTE	Hursel, Viechtbauer, and Westerterp-Plantenga (2009)	Weak
GTE	Maki et al. (2009)	Moderate
GTE	Molinari et al. (2006)	Weak
GTE	Suliburska et al. (2012)	Weak
GTE	Vieira Senger et al. (2012)	Weak
GTE	Zhang et al. (2012)	Moderate
GTE	Zhong et al. (2015)	Weak
Psyllium	Kazmi et al. (2009)	Weak
Psyllium	Pal et al. (2011)	Moderate
Psyllium	Pal et al. (2016)	Moderate

BitO, Bitter Orange; Carn, Carnitine; CLA, Conjugated Linoleic Acid; Colf, *Coleus forskohlii*; CrP, Chromium Picolinate; GM, Glucomannan; GTE, Green Tea Extract.

Weight estimates in this review were extracted as presented in the articles, except in the case where only baseline and follow-up weight estimates were present, then mean difference (MD) was calculated. Weight change estimates may be reported in absolute (kg), or percent weight change (%), changes in body mass index (kg/m^2), or MD between treatment and placebo groups.

Supplements

Bitter orange (BitO)

Bitter orange (BitO) extract is produced from the peels of the bitter orange (*Citrus aurantium*). BitO gained popularity

Table 2. Bitter orange.

Author	Sample	Design	Intervention	Results
Burke et al. (2007)	1 M BMI: 31 kg/m^2 Age: 22 years	Case study	Amount NR Intervention NR for 3 months	Effectiveness: NR Safety: Sickle cell, fatigue, lightheadedness, myalgias, elevated liver functioning and creatine phosphokinase, hypovolemic shock, respiratory failure, acute renal failure, hypercalcemia, disseminated intravascular coagulation, compartment syndrome in lower-extremities, severe skeletal muscle ischemia and necrosis.
Kaats et al. (2013)	75 M/F BMI: 30.8 kg/m^2 Age: 51.3 years	3-armed RCT	49 mg BID Maintain routine for 60 days	Effectiveness: NR Safety: No AEs reported by any groups.

M, Male; F, Female; BMI, Body Mass Index; NR, Not reported; AE, Adverse Events/Side-effects; RCT, randomized control trial.

as a weight loss supplement after the ban of ephedra (Haaz et al. 2006). The main active ingredient in BitO extract is synephrine, which has similar stimulant properties to ephedra (Kaats et al. 2013).

Effectiveness for weight loss

No studies published from 2006 to 2016 examined the efficacy or effectiveness of BitO for weight loss in patients with obesity.

Safety

Two articles (Burke et al. 2007; Kaats et al. 2013) were published between 2006 and 2016 examining the safety of BitO as a weight loss supplement (Table 2). Burke and colleagues (2007) presented a single-patient case study and while the exact dose was not reported, it was stated that the patient consumed the BitO supplement twice a day (Burke et al. 2007). This sparsity of information in part contributed to the weak rating this article received. The patient reported to the emergency room with renal and respiratory failure (Burke et al. 2007). Following cessation of the supplement, the patient had improved kidney function but sustained residual motor neurological impairments in both legs (Burke et al. 2007). The other article was a three-armed RCT which assessed the safety of BitO supplementation in 67 men and women with obesity over 60 days (Kaats et al. 2013), and received a strong rating of research quality. While the case study (Burke et al. 2007) reported rather severe adverse events (AEs), the safety study observed no AEs, or clinically significant changes in other safety markers such as blood pressure (Kaats et al. 2013). Various factors could have contributed to the discrepancy in these findings, such as the case study patient altered their dietary and physical activity regiment while taking the supplement (Burke et al. 2007), and the RCT instructed participants to maintain their current routine (Kaats et al. 2013). Nonetheless, owing to the severity of the adverse events reported in the case study, caution is recommended regarding the use of BitO for weight loss. Future case studies should strive to include key factors, such as dose and duration, to allow for comparison of findings to intervention studies. There is a need for more research of longer duration to evaluate the safety of BitO supplementation. Lastly, owing to the dearth of recent studies regarding the efficacy and effectiveness of BitO for weight loss, no assessment regarding the weight change potential of this supplement can be made.

Capsinoid

Capsinoid and capsaicin are compounds found in chili peppers. Both of these compounds are structurally similar, except for the substitution of an ester bond for an amide bond (De Lourdes Reyes-Escogido, Gonzalez-Mondragon, and Vazquez-Tzompantzi 2011). This slight structural difference is why capsaicin is spicy while capsinoids are sweeter (Sutoh et al. 2006).

Effectiveness for weight loss

Two studies (Lee et al. 2010; Snitker et al. 2009) of moderate to strong research quality were published between 2006 and 2016 examining the use of capsinoid for weight loss and met inclusion (Table 3). Both were RCTs; one RCT was 12 weeks (Snitker et al. 2009) and the other 4 weeks in duration (Lee et al. 2010). There were also differences in the dose and caloric restriction, with one prescribing a 300–600 kcal/day deficit with 6 mg/day of capsinoid (Snitker et al. 2009), and the other prescribing an 800 kcal/day deficit with 3 mg or 9 mg of capsinoid daily (Lee et al. 2010). After 12 weeks of supplementation, neither the placebo nor capsinoid supplement group lost weight (Snitker et al. 2009). Conversely, significant decreases in body weight were observed (range: 4.7–5.3 kg) in the 4 week study (Lee et al. 2010). These differences in the amount of weight loss achieved may be due to variations in caloric prescription, with the intervention that prescribed the more severe caloric prescription losing more weight (Lee et al. 2010). Nonetheless, neither study reports the supplement group losing more weight than those consuming the placebo.

Safety

With regard to the safety of the supplement, both studies provided AEs information. Lee et al. (2010) stated that no participants withdrew because of AEs related to the supplement, yet provided no further information regarding specifics of the AEs. Snitker et al. (2009) reported similar rates of AEs between those taking the supplement and placebo. However, there were certain types of AEs that were more prevalent in the capsinoid group, specifically gastrointestinal

Table 3. Capsinoid.

Author	Sample	Design	Intervention	Results
Lee et al. (2010)	46 M/F Postmenopausal BMI: 27–35 kg/m^2 Age: 30–65 years	3-armed RCT	Capsinoid1: 1 mg TID, Capsinoid2: 3 mg TID 800 kcal/day for 4 weeks	Effectiveness: Capsinoid1: −5.3 kg, Capsinoid2: −5.2 kg, and placebo: −4.7 kg; $P < 0.05$ for all. Safety: No patients withdrew due to AE. No other AE reported by author.
Snitker et al. (2009)	75 M/F BMI: 25–35 kg/m^2 Age: 30–60 years	RCT	3 mg BID. 300 to 600 kcal/day deficit for 12 weeks	Effectiveness: Capsinoid: −0.9 kg versus placebo: −0.5 kg; $P > 0.05$. Safety: 17 treatment related AEs for capsinoid, and 26 for placebo. AEs identified as related to agent: dyspepsia (2 capsinoid), bowel irregularities (1 capsinoid), diarrhea (1 capsinoid), and skin rash (1 capsinoid).

M, Male; F, Female; BMI, Body Mass Index; AE, Adverse Events/Side effects; RCT, randomized control trial; NR, Not reported.

and skin related AEs (e.g. diarrhea, skin rash). AEs in both studies were not considered serious by the authors, and it was reported that capsinoid supplementation was well tolerated by participants overall (Lee et al. 2010; Snitker et al. 2009).

Limited available evidence suggests that there are low rates of minor side effects with capsinoid, which may suggest that it is a relatively safe natural supplement. However, due to similar weight losses between capsinoid and placebo groups, supplementation does not result in superior weight loss outcomes. Thus, it appears as though capsinoid does not increase weight loss beyond what can be achieved from lifestyle intervention alone and should not be recommended to support weight loss.

Chromium picolinate

Chromium is an essential mineral to the human body (Cefalu and Hu 2004) and is found in many foods, such as grains, and meats (Anderson, Bryden, and Polansky 1992). Chromium has been shown to be necessary for proper insulin action in the human body and has been studied since the 1970s as a supplement to help control blood sugars in patients with diabetes (Cefalu and Hu 2004). More recently, chromium picolinate (CrP), a more absorbable form of chromium (Anderson et al. 1997), has been studied for weight loss.

Effectiveness for weight loss

Seven articles (Brownley et al. 2013; Yazaki et al. 2010; Anton et al. 2008; Iqbal et al. 2009; Kleefstra et al. 2006; Cefalu et al. 2010; Tian et al. 2013) of weak to moderate research quality examined the weight effects of CrP supplementation and met inclusion (Table 4). Five of the studies concluded CrP supplementation does not result in statistically significant weight loss (Iqbal et al. 2009; Kleefstra et al. 2006; Cefalu et al. 2010; Anton et al. 2008; Yazaki et al. 2010). Considerable similarities were found among these studies: all were RCTs and prescribed 1,000 µg/day (Iqbal et al. 2009; Kleefstra et al. 2006; Cefalu et al. 2010; Anton et al. 2008; Yazaki et al. 2010), and the majority instructed patients to consume their regular diet (Iqbal et al. 2009; Kleefstra et al. 2006; Cefalu et al. 2010; Anton et al. 2008). Studies differed in duration (range: 8 weeks to 6 months), population (e.g. excess weight without complications, T2D), and weight assessment variable. These differences did not appear to impact the results of the studies. Studies shorter in duration (i.e. <6 months) (Anton et al. 2008; Iqbal et al. 2009) reported similar non-significant changes in weight (−0.1 kg to −0.5 kg) to the longer-term (+0.8 kg, +0.1–0.3 kg/m^2) studies (Yazaki et al. 2010; Kleefstra et al. 2006; Cefalu et al. 2010).

Two studies of weak to moderate research quality – one RCT (Brownley et al. 2013) and one meta-analysis (Tian et al. 2013) – observed that CrP supplementation resulted in statistically but not clinically significant weight loss. Brownley and colleagues (Brownley et al. 2013) randomized patients with binge eating disorder to one of three treatment groups: (1) moderate-dose CrP (600 µg/day), (2) high-dose CrP (1000 µg/day), or (3) placebo for 6 months. Initially, there was no significant difference in the weight changes for those in the moderate-dose CrP (−0.1 kg/month), high-dose CrP (+0.2 kg/month), or placebo (+0.6 kg/month) groups. However, after exclusion of one participant from the high-dose group, slightly greater weight loss occurred for the moderate- and high-dose CrP groups compared to placebo ($p < 0.02$). Tian and colleagues (Tian et al. 2013) examined the use of CrP in patients with overweight and obesity, and observed a significant decrease of 1.1 (0.4 to 1.7kg) after 12–16 weeks of CrP supplementation. Interestingly, only the sub-analyses of 400 µg/day CrP analysis was associated with a significant weight loss (1.1 kg) which was similar to the overall pooled results, when higher doses (e.g. ≥500 µg) were not. Further, four (Yazaki et al. 2010; Anton et al. 2008; Iqbal et al. 2009; Kleefstra et al. 2006) of the nine studies included in the meta-analysis are also in this review and all concluded that CrP supplementation was not associated with significant changes in weight. However, three of these studies were excluded from the pooled analysis.

Safety

Six articles examined reported on AEs (Brownley et al. 2013; Yazaki et al. 2010; Anton et al. 2008; Iqbal et al. 2009; Kleefstra et al. 2006; Tian et al. 2013), some of which were also examined in the meta-analysis but will be reported for the original article here. Two studies (Anton et al. 2008; Iqbal et al. 2009) stated that no serious AEs were reported, but did not specify if minor to moderate AEs occurred. None of the studies tested whether rates of AEs differed

Table 4. Chromium picolinate.

Author	Population	Design	Intervention	Results
Anton et al. (2008)	42 F BMI: 31.3 kg/m^2 Age: 33.2 years	RCT	1000μg CrP QD NR for 8 weeks	Effectiveness: CrP: −0.5kg versus placebo +0.5 kg; $P > 0.05$. Safety: One participant dropped out in placebo group due to emotional reaction to treatment.
Brownley et al. (2013)	24 M/F Binge Eating Disorder BMI: 34.2 kg/m^2 Age: 36.6 years	3 armed RCT	600 μg CrP (moderate dose), 1000μg CrP (high dose) QD NR for 6 months	Effectiveness: High dose: −0.2 kg/month, low dose: −0.1 kg/month, and placebo: +0.55 kg/month; $P > 0.05$ for all. Safety: Headache report pretreatment (2 high, 4 moderate, 3 placebo), and end-of-treatment (1 high, 2 moderate, 4 placebo)
Cefalu et al. (2010)	137 M/F Type 2 diabetes BMI: 25–40 kg/m^2 Age: 30–70 years	RCT	500μg CrP BID Weight maintenance diet for 24 weeks	Effectiveness: CrP: +0.8 kg and placebo: +0.7 kg; $P > 0.05$ for both. Safety: NR
Iqbal et al. (2009)	66 M/F BMI CrP: 37.8, placebo: 35.2 kg/m^2 Age: 18–75 years	RCT	500μg CrP BID NR for 16 weeks	Effectiveness: CrP: −0.1 kg and placebo: +0.7 kg; $P>0.05$ for both. Safety: No AEs in either group.
Kleefstra et al. (2006)	46 M/F Type 2 diabetes BMI: 34 kg/m^2 Age: 18 to < 75 years	3-armed RCT	250μg CrP (low dose), or 500μg CrP (high dose) BID Maintain diet for 6 months	Effectiveness: High dose: +0.2 kg/m^2, low dose: +0.2 kg/m^2, and placebo +0.0 kg/m^2; $P>0.05$ for all. Safety: AE reported include watery stools, weakness, dizziness, nausea headaches, vertigo, vomiting. 2 high dose CrP discontinued intervention due to AEs.
Tian et al. (2013)	9[α] M/F BMI: ≥25 kg/m^2 Age: ≥18 years	Meta-analysis	200–1000μg Variable intervention for 8–24 weeks	Effectiveness: GTE versus placebo MD: −1.1 kg; $P<0.05$. Safety: AEs were reported in three of the 9 articles examined.
Yazaki et al. (2010)	80 M/F BMI: >25.0 kg/m^2 Age: 25–75 years	RCT	500μg CrP BID Nutrition education program for 6 months	Effectiveness: CrP: +0.1 kg/m^2 and placebo: 0.0kg/m^2; $P>0.05$ for both. Safety: Urticaria (1 CrP).

M, Male; F, Female; BMI, Body Mass Index; Chromium picolinate, CrP; AE, Adverse Events; RCT, randomized control trial; NR, Not reported; MD, mean difference/placebo-subtracted difference.

between placebo and CrP groups, making it difficult to determine which AEs presented a unique association with CrP use. Nevertheless, two studies (Yazaki et al. 2010; Kleefstra et al. 2006) cited a total of three patients halting CrP supplementation due to AEs, which included urticaria, vertigo, nausea and vomiting, and resolved when they cessed supplementation. All six studies prescribed 1000 μg/day, but half did not observe dropouts related to AEs (Brownley et al. 2013; Anton et al. 2008; Iqbal et al. 2009). Other AEs reported were minor to moderate and included tiredness, abdominal cramps, and bloating. However, there may be issues relating to transparency in reporting of AEs as one study (Brownley et al. 2013) reported several side-effects without identifying whether it occurred in the CrP or placebo group.

There appears to be insufficient evidence to suggest that CrP supplementation is associated with greater weight loss than could be expected with lifestyle interventions alone. While two studies did suggest minor decreases in weight, five other articles suggest that negligible changes in weight occur with CrP use. In general, the majority of AEs reported were minor to moderate, but some patients withdrew due to severe side-effects. Thus, careful monitoring is still recommended should a patient choose to initiate CrP supplementation.

Conjugated linoleic acid

Conjugated Linoleic Acid (CLA) is a fatty acid that is found naturally in beef and dairy products (Chin et al. 1994). While there are many different forms of CLA, the two most common isomers used in health supplements appear to be c9, t11 and t10, c12.

Effectiveness for weight loss

Eleven articles examining the weight loss effects of CLA supplementation met inclusion (Table 5). All of the studies used CLA that was approximately equal parts c9, t11 and t10, c12 isomers, so the impact of different structural forms of CLA on weight loss was not evaluated. Two studies – one crossover (Norris et al. 2009) and one observational (Sahin, Uyanik, and Inanc 2008) – observed a significant effect on weight (range: −0.1 to −3.2 kg) due to CLA supplementation. Participants were instructed not to alter their diet or physical activity and consume 3–8 capsules for a total of 1.8–8g/day of CLA or placebo equivalent. These studies were short in duration (8–16 weeks), exclusively examined females, and were of weak to moderate research quality.

The majority of studies ($n = 9$) (Taylor et al. 2006; Syvertsen et al. 2007; Adams et al. 2006; Laso et al. 2007; Joseph et al. 2011; Mądry et al. 2016; Carvalho, Uehara, and Rosa 2012; Gaullier et al. 2007; Steck et al. 2007) did not observe a significant association between CLA and weight loss. These studies were arguably of a higher rigor, being primarily RCTs (Taylor et al. 2006; Syvertsen et al. 2007; Adams et al. 2006; Laso et al. 2007; Mądry et al. 2016; Carvalho, Uehara, and Rosa 2012; Gaullier et al. 2007; Steck et al. 2007), and included several articles rate as strong research quality. CLA doses (range: 2.8–6.4g/day) and weight loss (range: +0.3 to −1.9 kg) were similar to studies that observed a significant effect of supplementation. However,

Table 5. Conjugated linoleic acid.

Author	Sample	Design	Intervention	Results
Adams et al. (2006)	30 M BMI: >25 kg/m^2 Age: 35–55 years	RCT	3.2g QD 50% c9, t11 and 50% t10, c12 Maintain diet and add resistance training for 4 weeks	Effectiveness: CLA: −0.2 kg and 0.0 kg/m^2 and placebo: 0.1 kg and 0.0 kg/m^2; P>0.05 for all. Safety: NR
Carvalho, Uehara, and Rosa (2012)	14 F BMI: 30.0 to <35.0kg/m^2 Age: 30–50 years	RCT	3g/day of jam with 50% c9, t11 and 50% t10, c12 CLA infused. Hypocaloric diet and maintenance of PA for 12 weeks	Effectiveness: CLA: −1.9 kg and −0.7 kg/m^2 versus placebo: −2.5 kg and −1.0 kg/m^2; P>0.05 for both. Safety: Epigastric pain in 1 CLA participant, no AEs reported by placebo group. AEs were not associated with supplement.
Syvertsen et al. (2007)	105 M/F BMI: 28–32 kg/m^2 Age: 18–65 years	RCT	1.13g TID 37.5% c9, t11 and 38% t10, c12. No changes to diet or PA required but information provided on patient request for 6 months	Effectiveness: CLA: -0.9kg and -0.3kg/m^2 versus placebo: 0.0kg and 0.1kg/m^2; P>0.05 for both. Safety: *Serious AEs:* breast cancer and myocardial infarction in CLA group. *Other AEs:* mild to moderate and gastrointestinal or musculoskeletal related.
Joseph et al. (2011)	36 M BMI: >25 kg/m^2 Age: 18–60 years	Crossover	CLA1: 2.8 g 50% c9, t11 or 37–50% t10, c12 CLA2: 2.7g 100% c9, t11 QD Maintain routine for 8 weeks with 4 weeks washout period	Effectiveness: CLA1: 0.1 kg and 0.0 kg/m^2, CLA2: 0.3 kg and 0.1 kg/m^2, and placebo: 0.7 kg and 0.2 kg/m^2; P>0.05 for all. Safety: NR
Laso et al. (2007)	23 F/M Metabolic Syndrome BMI: 25–35 kg/m^2 Age: 35–65 years	RCT	3g QD 50% c9, t11 and 50% t10, c12 Maintain routine for 12 weeks	Effectiveness: CLA: −0.3 kg/m^2, and placebo: 0.0 kg/m^2; P>0.05 for both. Safety: NR
Mądry et al. (2016)	74 F BMI: 28–42 kg/m^2 Age: >18 years	RCT	1 g TID 50% c9, t11 and 50% t10, c12. Maintain current routine for 12 weeks	Effectiveness: CLA: −0.4 kg and −0.2 kg/m^2 versus placebo: 0.2 kg and 0.0 kg/m^2; P>0.05 for both. Safety: Nausea (2 placebo, 1 CLA) and rash (1 placebo).
Norris et al. (2009)	55 F Postmenopausal T2D BMI: >30 kg/m^2 Age: ≤70 y of age	Crossover	2 g QID 41.6% c9, t11 and 40.4% t10, c12 Maintain routine for 16 weeks active period, 4 weeks washout	Effectiveness: *Period 1:* CLA −1.3 kg and −0.5 kg/m^2 versus placebo: −0.1 kg and 0.1 kg/m^2. *Period 2:* CLA: −0.9 kg and −0.4 kg/m^2 versus placebo: 0.9 kg and 0.5 kg/m^2; P=0.03 and P<0.001, respectively. Safety: AEs recorded but NR. Rate of AE did not differ based on treatment.
Sahin, Uyanik, and Inanc (2008)	20 F BMI: 30.4 kg/m^2 Age: 22–48 years	1-armed	0.6g TID 37-42% c9, t11 and 37-42% t10, c12 Maintain routine for 8 weeks	Effectiveness: weight: −3.2 kg (P<0.05) and BMI: −1.4 kg/m^2 (P<0.05). Safety: NR
Steck et al. (2007)	48 M/F BMI: 30–35 kg/m^2 Age: 18–50 years	3-armed RCT	CLA-low: 3.2 g QD, CLA-high: 6.4 g QD 50% c9, t11 and 50% t10, c12. Maintain routine for 12 weeks	Effectiveness: CLA-high: 0.4kg and 0.1kg/m^2, and CLA-low: 0.4kg and 0.1kg/m^2 versus placebo: 0.4kg and 0.0kg/m^2; P>0.05 for all. Safety: 13 patients reported AE (2 CLA-low, 7 CLA-high, and 4 placebo). AEs include: gas, bloating, face itching, indigestion, diarrhea, and heartburn (*P-value* NR).
Syvertsen et al. (2007)	41 M/F BMI: 28–32 kg/m^2 Age: 47.6 years	RCT	3.4g/day 37.5% c9, t11 and 38% t10, c12 Maintain current routine for 6 months	Effectiveness: CLA: 0.2kg and -0.1kg/m^2 versus placebo 0.0kgand 0.0kg/m^2; P>0.05 for both. Safety: NR
Taylor et al. (2006)	40 M BMI: >27 kg/m^2 Age: 35–60 years	RCT	4.5g/day 35% c9, t11 and 36% t10, c12 Maintain current routine for 12 weeks	Effectiveness: CLA: −0.2 kg and −0.1 kg/m^2 versus placebo: 0.9 kg and 0.3 kg/m^2; P>0.05 for both. Safety: NR

CLA, Conjugated linoleic acid; F, Female; M, Male; BMI, Body Mass Index; AE, Adverse Events; NR, Not reported; PA, Physical Activity; RCT, randomized control trial.

these studies were longer in duration (range: 4 weeks to 6 months), and used a variety of delivery methods for CLA supplementation (e.g. infused in jam or oils). Two studies (Carvalho, Uehara, and Rosa 2012; Adams et al. 2006) instructed participants to alter their diet or physical activity, which was associated with greater changes in weight (−1.2 to −1.9 kg) than those who maintained their current routine (0.4 to −0.4 kg) (Taylor et al. 2006; Syvertsen et al. 2007; Laso et al. 2007; Joseph et al. 2011; Mądry et al. 2016; Gaullier et al. 2007; Steck et al. 2007). Nevertheless, all nine of the studies concluded there was no significant difference in weight changes between CLA supplementation and placebo groups (Taylor et al. 2006; Syvertsen et al. 2007; Adams et al. 2006; Laso et al. 2007; Joseph et al. 2011; Mądry et al. 2016; Carvalho, Uehara, and Rosa 2012; Gaullier et al. 2007; Steck et al. 2007).

Safety

AEs were reported in five studies (Steck et al. 2007; Gaullier et al. 2007; Carvalho, Uehara, and Rosa 2012; Mądry et al. 2016; Norris et al. 2009). All studies included

gastrointestinal AEs (e.g. bloating, indigestion) and where comparisons were made, reported simiar rates of AE between CLA and placebo groups. One study (Steck et al. 2007) compared two doses of CLA (3.2 g, 6.4 g) to placebo, and a slightly higher rate of AEs was observed in the high dose group (7 AEs) compared to placebo (4 AEs) and low dose (2 AEs) groups, but the authors did not report if rates of AEs were significantly different. Unfortunately, the study which prescribed the highest CLA (L. E. Norris et al. 2009) did not report which AEs were reported by CLA or placebo group, therefore further research is necessary to confirm whether higher doses are associated with more frequent AEs. Four of the five studies (Steck et al. 2007; Gaullier et al. 2007; Mądry et al. 2016; Norris et al. 2009) reporting on AEs provided participants CLA capsules, while one provided CLA infused jam (Carvalho, Uehara, and Rosa 2012). Interestingly, the jam-infused CLA study (Carvalho, Uehara, and Rosa 2012) reported only one AE – epigastric pain – which was found to not be associated with supplementation as it was a preexisting condition. While this may imply that infusing CLA into food products may lessen side-effects, more research is still necessary to confirm this hypothesis. In another study (Gaullier et al. 2007), one serious AE – an acute myocardial infarction – was reported. It was determined to not be related to CLA and the participant was able to continue taking the supplement without issue.

In general, supplementation with CLA does not appear to pose a major risk to health, with AEs occurring at a similar rate among those taking CLA as those taking placebo. Nevertheless, the majority of evidence, which was also of higher research quality, suggest CLA does not improve weight loss outcomes. Indeed, very few studies have demonstrated a significant weight loss with CLA, and the changes in weight tend to be small and likely not clinically significant (0.4 to −3.2 kg). Future research is still necessary to evaluate AEs associatred with higher doses of CLA or CLA infused food products.

Glucomannan

Dietary fiber is thought to assist in weight loss through various mechanisms, including slowing of gastric emptying which leads to satiety, and binding to foods causing caloric excretion (Howarth, Saltzman, and Roberts 2009). Glucomannan (GM), or konjac glucomannan, is a specific fiber isolated from the konjac tuber plant (*Amorphophallus konjac*) (Zhang, Xie, and Gan 2005). PGX is a type of GM with greater viscosity and water-holding capacity (Lyon and Reichert 2010) and is sold as a weight loss supplement. Six articles were published on the use of GM supplementation and met inclusion (Table 6).

Effectiveness for weight loss

An RCT conducted by Keithley and colleagues (2013) observed non-significant changes in weight in both GM (−0.4 kg) and placebo (−0.4 kg) groups. Conversely, three studies – one RCT (Kraemer et al. 2007) and two meta-analyses (Onakpoya, Posadzki, and Ernst 2014; Zalewski, Chmielewska, and Szajewska 2015) – observed small but significant decreases in weight with GM supplementation. The RCT, conducted by Kraemer et al. (2007), did not use a placebo control group, but instead randomized patients taking GM to either remain sedentary or participate in an exercise intervention (Kraemer et al. 2007). Thus, while they did observe statistically significant decreases in weight (range: 0.8 to 1.3kg), these changes in weight could be attributed to the healthy diet subjects were consuming rather than GM supplementation. Both meta-analyses exclusively examined RCTs, but the RCTs varied in duration, use of adjunctive interventions, and dose (Zalewski, Chmielewska, and Szajewska 2015; Onakpoya, Posadzki, and Ernst 2014). Onakpoya, Posadzki, and Ernst (2014) conducted a pooled analysis that found non-significant decreases in weight (MD: 0.2 kg) with GM supplementation. However, due to a moderate heterogeneity score ($I^2 = 65\%$), several sensitivity analyses were conducted. While four of the six sensitivity analyses suggested no significant changes in weight with GM supplementation (−0.4 to −1.0kg), results excluding crossover RCTs and those in populations without comorbidities reported significant reductions in weight (1.1 kg and 1.0 kg, respectively). Zalewski and colleagues (2015) reevaluated changes in weight from five GM supplementation RCTs as placebo-subtracted means at different time points without pooling results. In the five studies, changes in weight were found to be significant at 4 time-points (MD range: −0.2 to −3.2kg) and not significant at 5 time-points. It is important to note that while the meta-analysis by Onakpoya did not contain any articles examined in this review, there was one article in the meta-analysis by Zalewski that is also included in this review – the RCT by Keithley et al. (2013). Non-significant changes in weight (GM group: −0.4 kg) were initially reported by Keithley et al. (2013), but Zalewski and colleagues (2015) recalculated weight change as the MD in weight change between treatment and placebo groups, and found significant changes in weight (MD: −3.2 kg (1.3–5.1 kg)). Nevertheless, owing to the variability of the results, both meta-analyses (Onakpoya, Posadzki, and Ernst 2014; Zalewski, Chmielewska, and Szajewska 2015) concluded there is insufficient evidence to suggest GM supplementation contributes to meaningful weight loss.

In contrast to the above findings, two studies – one RCT (Pal et al. 2016) and one observational study (Lyon and Reichert 2010) – reported statistically and potentially clinically significant decreases in weight. Both of these studies were longer in duration (14 (Lyon and Reichert 2010) to 52 weeks (Pal et al. 2016)) and prescribed a considerably higher dose (10 (Lyon and Reichert 2010) to 15g/day (Pal et al. 2016; Lyon and Reichert 2010)) than most of the other GM studies examined (range: 2–12 weeks, 1.2–4.0 g/day) with the exception of one RCT included in a meta-analysis (Onakpoya, Posadzki, and Ernst 2014) which prescribed 10 g/day. Perhaps most importantly, these were the only two studies which prescribed PGX. Specifically, Pal and colleagues (2016) conducted a three-armed RCT comparing the

Table 6. Glucomannan.

Author	Population	Design	Intervention	Results
Keithley et al. (2013)	47 M/F BMI 25–35 kg/m^2 Age: 40.6 years	RCT	1.3g TID Maintain routine for 8 weeks	Effectiveness: GM: −0.4 kg and −0.1 kg/m^2, and placebo: −0.4 kg and −0.3 kg/m^2; $P>0.05$ for all. Safety: AE reported include belching (13.4% versus 4.1%), bloating (12.7% versus 3.7%), and stomach fullness (11.9% versus 2.4%) which occurred more frequently in participants in GM than placebo group ($p < 0.05$).
Kraemer et al. (2007)	42 M/F BMI: >25 kg/m^2 Age: 18–57 years	Matched RCT	1.5g BID GM-Ex: 2 hours 3times/week of aerobic and resistance PA Dietary education for 8 weeks	Effectiveness: GM M: −2.7kg and -0.8kg/m^2 and F: −3.0kg and -0.9kg/m^2, and GM-Ex M: −2.2kg and -0.9kg/m^2 and F: −3.3kg and -1.3kg/m^2; $P<0.05$ for all. Safety: NR.
Lyon and Reichert (2010)	29 M/F BMI: 33.8 kg/m^2 Age: 20–65 years	Observational study	5 g PGX TID Dietary and exercise education for 14 weeks	Effectiveness: −5.8 kg, $P < 0.05$. Safety: 68% of subjects reported AEs such as bloating, constipation, loose stool that resolved within 3 weeks. 32% of participants experienced GI side-effects for the duration of the study but did not discontinue use.
Onakpoya, Posadzki, and Ernst (2014)	9[α] M/F BMI: >25 kg/m^2 Age: All	Meta-analysis	1.0–3.9g/day Variable intervention for 3 to 12 weeks	Weight loss: GM versus placebo MD: −0.22 kg, $P > 0.05$. Sensitivity analysis excluding crossover trials, and the analysis excluding patients with comorbidities MD: −1.1 kg and −1.0 kg ($P<0.05$ for both), respectively. Safety: AE included diarrhea, constipation, abdominal discomfort, and mild meteorism. One RCT showed significant increase in adverse events in GM group.
Pal et al. (2016)	159 M/F BMI: 25–47 kg/m^2 Age: 19–68 years	3-armed RCT	5g PGX or psyllium TID Maintain routine for 52 weeks	Effectiveness: PGX versus placebo MD at 3 months: −1.6 kg ($P < 0.05$), 6 months: −2.6 kg ($P < 0.05$), and 12 months: −2.7 kg ($P < 0.05$). Safety: Minor AE such as flatulence and diarrhea in both groups. Rates of AE not compared.
Zalewski, Chmielewska, and Szajewska (2015)	6[α] M/F BMI: overweight or greater (threshold NR). Age: All	Meta-analysis	1.2 to 3.9g/day GM Variable intervention for 4 to 12 weeks	Effectiveness: One study observed a significant weight loss at week 2 (0.2 kg, $p < 0.05$), but non-significant by end of study (i.e. week 8). One study observed a significant weight loss at week 5 (1.30 kg, $p < 0.05$). One study observed a significant weight loss at 8 weeks (3.17 kg, $p < 0.05$). Three studies had non-significant weight change at all time points (−2.0, 0.0, +0.1kg). Safety: One RCT reported more frequent belching, bloating, stomach fullness in GM group compared to placebo group but did not report significance. One RCT reported significant increase in diarrhea in GM group compared to placebo group.

GM, Glucomannan; F, Female; M, Male; BMI, Body Mass Index; AE, Adverse Events; NR, Not reported; PA, Physical Activity; RCT, randomized control trial; MD, Mean Difference.

effects of PGX, psyllium (another fiber supplement), or placebo on weight loss. Patients taking PGX lost significantly more weight than the placebo groups at 3 (MD: 1.6 kg, $p = 0.003$), 6 (MD: 2.6 kg, $p = 0.001$), and 12 months (MD: 2.6 kg, $p = 0.0012$), but no comparison was made between the PGX and psyllium groups. Lyon and colleagues (2010) retrospectively analyzed patients who attended a biweekly lifestyle intervention and took PGX over 14 weeks. Participants had a statistically and clinically significant decrease in weight (5.8 kg). Unfortunately, without a control group, it is unclear whether these reductions in weight are due to the supplement or lifestyle intervention.

Safety

Five studies (Lyon and Reichert 2010; Pal et al. 2016; Keithley et al. 2013; Zalewski, Chmielewska, and Szajewska 2015; Onakpoya, Posadzki, and Ernst 2014) reported on AEs and included AEs that were GI-related such as belching, bloating, and diarrhea. Of the studies reported in the meta-analysis by Zalewski, Chmielewska, and Szajewska (2015), the only study which observed AEs was the RCT by Keithley et al. (2013) included in this review. No statistical analysis was undertaken to compare the rates of AEs among groups, but Zalewski and colleagues (2015) noted that rates are approximately 3-times greater in GM than in placebo groups. Of the three RCTs in the meta-analysis by Onakopya and colleagues (2014), there was considerable variability in the rate of AEs with one study reporting none, one reporting similar rates between GM and control, and one reporting greater AEs in GM group. AEs in the two studies which prescribed PGX (Pal et al. 2016; Lyon and Reichert 2010) appeared to be more significant with two participants discontinuing due to GI-related AE in one of the studies (Pal et al. 2016), and all participants experiencing GI symptoms in the other (Lyon and Reichert 2010). While this may suggest that PGX is associated with a worse AE profile than GM, it may also be attributable to the higher dosage prescribed in these studies. Nevertheless, in all five of the studies, there were no severe AEs reported.

None of the GM studies received a strong rating for research quality. The majority of studies reported non-

Table 7. Green tea extract.

Author	Sample	Design	Intervention	Results
Basu et al. (2010)	35 M/F Metabolic Syndrome BMI: 36.1 kg/m^2 Age: 42.5 years	3-armed RCT	GTE-caps: 4.4g GTE and 1.8mg caffeine BID, GTE-tea: 4.7g GTE and 4.5mg caffeine BID Maintain routine for 8 weeks	Effectiveness: GTE-tea versus placebo MD: −2.5 kg and −0.9 kg/m^2; $P<0.05$ for both. GTE-cap versus placebo MD: −1.9 kg and −0.7 kg/m^2; $P < 0.05$ for both. Safety: NR
Belcaro et al. (2013)	98 M/F Borderline metabolic syndrome BMI GTE: 31.0, Placebo: 30.9 kg/m^2 Age: 45–55 years	RCT	1.5g BID Caloric deficit (750 F, 1000 M), and 210 minutes of PA weekly 24 weeks	Effectiveness: GTE: −11.8 kg and −4.3 kg/m^2 versus placebo: -5.9 kg and −2.0 kg/m^2, $P < 0.05$ for both. Safety: NR
Brown et al. (2011)	71 M BMI: 28–38kg/m^2 Age: 40–69 years	Crossover	4g decaffeinated GTE BID Maintain routine 6 weeks	Effectiveness: *Period 1:* GTE: -0.6kg versus placebo +0.5kg; P=0.025. *Period 2:* Similar decreases in weight among GTE: -0.3kg versus placebo: -0.6kg; P>0.05. Overall, no significant effect of GTE on body weight. Safety: NR
Cardoso et al. (2013)	36 F BMI: 25–35 kg/m^2 Age: 20–40 years	4-armed RCT	10g GTE and 20mg caffeine BID 1200 caloric. PA groups participated in resistance training which increased at the discretion of the participants for 4-week diet run-in, and 8-week with supplementation	Effectiveness: GTE: −5.7 kg and −2.6 kg/m^2 versus, placebo: −0.3 kg and −0.2 kg/m^2, GTE + PA: 1.4 kg and 1.2kg/m^2, and placebo + PA: 0.4 kg and 0.3 kg/m^2; P<0.05 for all comparisons. Only decreases in BMI were significant and in the GTE only group. Safety: NR
Chan et al. (2006)	34 F PCOS BMI: >28.0 kg/m^2 Age: 34.8 years	RCT	1.8g GTE TID Maintain routine for 3 months	Effectiveness: NR Safety: Gastrointestinal upset (1 placebo), no other AEs reported
Chen et al. (2016)	102 F BMI: > 27.0kg/m^2 Age: 20–60 years	RCT	2.9g GTE TID Maintain routine for 12 weeks	Effectiveness: GTE: -1.1kg and -0.4kg/m^2 versus placebo: -2.0kg and -0.9kg/m^2; P>0.05 for both. Safety: NR
Hill et al. (2007)	38 F Post-menopausal BMI: 25–39.9 kg/m^2 Age: 45–70 years	RCT	1.5g BID Maintain diet and 45 minutes of PA 3 times/week for 12 weeks	Effectiveness: GTE: +0.1 kg and 0.0 kg/m^2 versus and placebo: −0.5 kg and −0.2 kg/m^2; $P > 0.05$ for both. Safety: NR
Hsu et al. (2008)	100 F BMI: >27 kg/m^2 Age: 16–60 years	RCT	4g GTE TID Maintain routine for 12 weeks	Effectiveness: GTE: −0.2 kg and −0.1 kg/m^2 versus placebo: 0.0 kg and 0.0 kg/m^2; $P > 0.05$ for both. Safety: Mild constipation (3 GTE, 2 placebo), abdominal discomfort (2 GTE, 1 placebo). No dropout due to AE.
Hursel, Viechtbauer, and Westerterp-Plantenga (2009)	11α M/F BMI: 18.5–35 kg/m^2 Age: 18–65 years	Meta-analysis	1.4 to 7.1 g/day GTE NR for 12 weeks	Effectiveness: GTE vs. placebo MD: 1.3 kg; P<0.001. Safety: NR
Maki et al. (2009)	128 M/F BMI: 25 to <40 kg/m^2 Age: 21–65 years	RCT	6.3g GTE and 39mg caffeine QD Maintain diet and increase PA to ≥ 180min/week for 12 weeks	Effectiveness: GTE: −2.2 kg versus placebo −1.0 kg, P=0.079. Safety: Similar rate of AE between groups ($P = 0.57$). *Minor to Moderate AE:* Joint pain (6 GTE, 9 placebo), rhinitis (5 GTE, 5 placebo) sinusitis (8 GTE, 2 placebo), dyspepsia (1 GTE), hypertension (3 GTE), elevated liver enzymes (1 GTE)*Severe AE:* Hospitalization for high blood pressure (1 GTE), tooth disorder (1 GTE), tachycardia (1 placebo)
Molinari et al. (2006)	1 F BMI: 35kg/m^2 Age: 44 years	Case study	7.2g/day GTE Increased PA for 6 months	Effectiveness: NR Safety: Progressive malaise, right quadrant upper abdominal pain, jaundice, encephalopathy, and acute liver failure (>50% hepatocellular necrosis) with eventual transplant.
Suliburska et al. (2012)	46 M/F BMI: > 30 kg/m^2 Age: 30–60 years	RCT	3.8 g GTE and 2.1g EGCG QD Maintain routine for 3 months	Effectiveness: GTE: −0.4 kg/m^2 versus placebo: +0.1 kg/m^2; $P < 0.03$. Safety: NR
Vieira Senger et al. (2012)	45 M/F Metabolic syndrome BMI GTE: 30.5, placebo: 30.4 kg/m^2 Age: >60 years	RCT	1g TID Maintain routine for 60 days	Effectiveness: GTE: −1.2 kg and −0.5 kg/m^2 versus placebo: −0.5 kg and −0.2 kg/m^2; P<0.001 for both. Safety: NR
Zhang et al. (2012)	118 M/F BMI: 24 to <40kg/m^2 Age: 20–65 years	RCT	6.1g GTE and 0.7g caffeine QD. Maintain routine for 12 weeks	Effectiveness: GTE: −1.0 kg and −0.7 kg/m^2 versus placebo: −0.4 kg and −0.2 kg/m^2; P>0.05 for both. Safety: AEs reported: change in stool, abdominal discomfort (4 GTE; 2 placebo), appetite changes (7 GTE, 6 placebo), insomnia (2 GTE, 3 placebo), tiredness (2 GTE, 2 placebo), and dizziness (1 GTE, 2 placebo) at similar rates between groups (P=0.538).

(*continued*)

Table 7. Continued.

Author	Sample	Design	Intervention	Results
Zhong et al. (2015)	5α M/F Metabolic Syndrome BMI: overweight and obese (threshold NR) Age: adults (years NR)	Meta-analysis	3.0 to 10g/day GTE Maintain current routine and some education for 2 to 6 months	Effectiveness: Overall pooled analysis for green tea or GTE versus placebo MD: −1.3 kg ($P = 0.14$), and −0.7 kg/m^2 ($P = 0.02$). Safety: Diarrhea (1 GTE) caused dropout

GTE, Green Tea Extract; F, Female; M, Male; BMI, Body Mass Index; AE, Adverse Events; NR, Not reported; PA, Physical activity; RCT, randomized control trial; MD, Mean Difference.
[α]Sample size refers to articles, not participants.

significant or small statistically significant decreases in weight with the use of GM. GI side-effects appear common with GM (and in PGX) and can last for the entire supplementation duration. GM appears generally safe, but there is insufficient evidence to suggest its efficacy in weight loss. GM in the form of PGX may be an exception but further studies looking at dosing and comparing different forms of GM head-to-head are needed.

Green tea extract (GTE)

Green tea has been used for medicinal purposes for thousands of years (Sato and Miyata 2000). In its natural form, green tea contains caffeine (Mitchell et al. 2014), but decaffeinated versions are also available. Fifteen articles (Suliburska et al. 2012; Hursel, Viechtbauer, and Westerterp-Plantenga 2009; Vieira Senger et al. 2012; Basu et al. 2010; Cardoso et al. 2013; Belcaro et al. 2013; Zhang et al. 2012; Zhong et al. 2015; Chan et al. 2006; Hsu et al. 2008; Chen et al. 2016; Hill et al. 2007; Maki et al. 2009; Brown et al. 2011; Molinari et al. 2006) published on the use of GTE met inclusion (Table 7).

Effectiveness for weight loss

Six studies (Suliburska et al. 2012; Hursel, Viechtbauer, and Westerterp-Plantenga 2009; Vieira Senger et al. 2012; Basu et al. 2010; Cardoso et al. 2013; Belcaro et al. 2013) rated as weak to moderate quality suggest greater weight loss for patients taking GTE compared to placebo. While the majority of these studies used caffeinated-GTE ($n = 5$) (Suliburska et al. 2012; Hursel, Viechtbauer, and Westerterp-Plantenga 2009; Vieira Senger et al. 2012; Basu et al. 2010; Cardoso et al. 2013), there was variability in the type of intervention (i.e. maintain or change current dietary and physical activity routine), duration (i.e. 8–24 weeks) and dose (i.e. 1.4–20.0 g/day). For example, two studies (Cardoso et al. 2013; Belcaro et al. 2013) reported considerably higher weight loss outcomes (5.7 kg and 11.8 kg, respectively) for GTE supplementation groups than the other four studies (range: 1.2–2.5 kg) (Basu et al. 2010; Hursel, Viechtbauer, and Westerterp-Plantenga 2009; Suliburska et al. 2012; Vieira Senger et al. 2012). However, both of these studies provided patients with a caloric prescription (Cardoso et al. 2013; Belcaro et al. 2013), and the other four instructed patients to maintain their current dietary habits (Basu et al. 2010; Hursel, Viechtbauer, and Westerterp-Plantenga 2009; Suliburska et al. 2012; Vieira Senger et al. 2012). While one of these studies prescribed the highest dose of the GTE studies examined (i.e. 20 g/day) (Cardoso et al. 2013), the other study prescribed a more moderate dose of 3g/day (Belcaro et al. 2013) which was similar to other studies reporting negligible amounts of weight loss (Hursel, Viechtbauer, and Westerterp-Plantenga 2009; Suliburska et al. 2012; Vieira Senger et al. 2012). Both studies (Cardoso et al. 2013; Belcaro et al. 2013) were similar in length to the other GTE studies, further strengthening the notion that caloric rather than GTE supplementation resulted in the greater weight loss. Nevertheless, the studies (Suliburska et al. 2012; Hursel, Viechtbauer, and Westerterp-Plantenga 2009; Vieira Senger et al. 2012; Basu et al. 2010; Cardoso et al. 2013; Belcaro et al. 2013) observing a significant weight loss in GTE groups tended to report on study completers rather than the intention-to-treat population, which can introduce considerable bias into the results.

Six RCTs (Zhang et al. 2012; Chan et al. 2006; Hsu et al. 2008; Chen et al. 2016; Hill et al. 2007; Maki et al. 2009), one crossover (Brown et al. 2011), and one meta-analysis (Zhong et al. 2015) reported similar changes in weight among GTE and placebo groups. These studies were arguably of greater research quality than those reporting significant decreases in weight with GTE, with two studies receiving a rating of strong research quality. There was considerable variability in the duration (6 weeks to 6 months), and dose (3–12 g/day) of GTE. Regardless, the amount of weight loss reported with GTE supplementation was minimal (range: −2.2 to +0.2 kg) and not significantly greater than placebo. Similarly to the aforementioned six studies, the majority ($n = 5$) of the eight studies used caffeinated-GTE (Zhang et al. 2012; Hsu et al. 2008; Chen et al. 2016; Hill et al. 2007; Maki et al. 2009). Further, changes in weight were similar among caffeinated- (range: −1.8 to +0.2 kg) and decaffeinated-GTE (range: −1.1 to −0.3 kg) studies that had participants maintain their current diet and physical activity routine. Thus, caffeinated- and decaffeinated-GTE may have similar weight change properties.

Safety

Seven studies (Zhang et al. 2012; Zhong et al. 2015; Chan et al. 2006; Hsu et al. 2008; Chen et al. 2016; Maki et al. 2009; Molinari et al. 2006) reported on AEs associated with GTE. None of these studies observed a significant effect of GTE on weight. Furthermore, studies with the lowest (1.4–3.8 g) (Hursel, Viechtbauer, and Westerterp-Plantenga 2009; Hill et al. 2007; Vieira Senger et al. 2012; Suliburska

Table 8. Psyllium.

Reference	Sample	Design	Intervention	Results
Kazmi et al. (2009)	120 M/F adults BMI: 36.9 kg/m^2 Age: ≥18 years	Non-randomized, Non-blinded, parallel group	2 tablespoons psyllium TID, 120 mg orlistat TID, or 15mg sibutramine QD. NR for 150 days	Effectiveness: Psyllium: −4.6 kg, orlistat: −7.8 kg, and sibutramine: −13.4 kg; *P-value* NR. Safety: Abdominal distention and fullness, increase frequency of defecation in psyllium group.
Pal et al. (2011)	72 M/F BMI: 25–40 kg/m^2 Age: 18–65 years	4-armed RCT	12g TID Healthy eating according to the Dietary Guidelines for Australian Adults for 12 weeks	Effectiveness: Both the psyllium only, and the psyllium-healthy eating groups weighed significantly less than the placebo only group at follow-up ($P = 0.007$ and $P < 0.001$, respectively). Safety: Minor bloating
Pal et al. (2016)	159 M/F adults BMI: 25 to 47kg/m^2 Age: 19–68 years	RCT	5g of psyllium or PGX TID Maintain routine for 52 weeks	Effectiveness: Psyllium versus placebo MD at 3 months: −1.1kg ($P < 0.05$), 6 months: −2.4 kg ($P < 0.05$), and 12 months ($P > 0.05$). Safety: NR

BMI: body mass index, RCT: randomized control trial, PA: physical activity, NR: not reported; MD, Mean Difference.

et al. 2012; Belcaro et al. 2013) and highest (20 g) (Cardoso et al. 2013) GTE doses did not report AEs, making it difficult to draw conclusions on the impact of dose on AE profiles. Nonetheless, at moderate doses (5–12 g/day) AEs appeared to be primarily GI, regardless of caffeine content, and include abdominal discomfort and diarrhea (Zhang et al. 2012; Zhong et al. 2015; Chan et al. 2006; Hsu et al. 2008; Chen et al. 2016; Maki et al. 2009; Molinari et al. 2006). Two studies (Maki et al. 2009; Molinari et al. 2006) reported severe side-effects associated with GTE supplementation which resulted in hospitalization. Molinari et al. (2006) reported on one female who took GTE for 6 months and developed acute liver failure, eventually required a transplant. Maki et al. (2009) reported that one patient taking GTE in a RCT was hospitalized for high blood pressure, and others experienced severe side-effects such as hypertension and elevated liver enzymes. Interestingly, these were two of the four studies that prescribed increased physical activity in addition to GTE supplementation, however the other articles (Hill et al. 2007; Belcaro et al. 2013) did not report on AEs. While this may suggest increased physical activity can worsen AEs when taking GTE, further research is necessary to examine this association.

Considerable evidence has been published on the use of GTE for weight loss in populations with obesity. Similar amounts of studies report GTE supplementation is associated with weight loss (Suliburska et al. 2012; Hursel, Viechtbauer, and Westerterp-Plantenga 2009; Vieira Senger et al. 2012; Basu et al. 2010; Cardoso et al. 2013; Belcaro et al. 2013) as those that do not (Zhang et al. 2012; Zhong et al. 2015; Chan et al. 2006; Hsu et al. 2008; Chen et al. 2016; Hill et al. 2007; Maki et al. 2009; Brown et al. 2011). However, the studies which report non-significant weight loss received higher ratings of research quality. While two studies (Cardoso et al. 2013; Belcaro et al. 2013) report weight loss of a magnitude typically observed with weight loss pharmaceuticals use (>5 kg), the majority of the papers report losses that are unlikely to have a clinical effect (<2 kg) (Suliburska et al. 2012; Hursel, Viechtbauer, and Westerterp-Plantenga 2009; Vieira Senger et al. 2012; Basu et al. 2010; Zhong et al. 2015; Chan et al. 2006; Hsu et al. 2008; Chen et al. 2016; Zhang et al. 2012). Furthermore, less than half of the studies reported on AEs. While AEs were primarily GI, some were severe (e.g. liver failure). The lack of surveillance and/or reporting of AEs in GTE studies is concerning as some studies did observe AEs that required medical intervention. Thus, the effects of GTE for weight are suspect, and greater surveillance and transparency is needed in future studies to evaluate the safety of GTE supplementation.

Psyllium

Fiber is a naturally-occurring plant-based substance mainly known to medicinally alleviate bowel-movement-related symptomology (Blackwood et al. 2000). Two subtypes of fiber exist – water soluble and water insoluble – with psyllium, or rather, ispaghula husk, being a gel-forming fiber belonging to the former (Blackwood et al. 2000). Extracted psyllium has been used as a dietary fiber supplement in those who do not receive adequate recommended amounts of fiber in their daily diet (Blackwood et al. 2000) and is sold under a variety of different trade names, including *Metamucil*. Three studies examining psyllium were included in this review, two of which were RCTs (Pal et al. 2011, 2016), and the third a non-randomized, non-blinded parallel group study (Kazmi et al. 2009). Key details are summarized in Table 8.

Effectiveness for weight loss

Compared to controls, both RCT studies (Pal et al. 2011, 2016) reported significant reductions in weight for patients taking psyllium. More specifically, Pal et al. (2011) employed a parallel-group control trial consisting of four groups: (1) placebo and usual-diet; (2) psyllium-eating and usual-diet; (3) psyllium- and 'healthy'-eating diet; and (4) 'healthy'-eating diet. Body weight was significantly reduced in the psyllium-eating, psyllium- and 'healthy'-eating, and 'healthy'-eating groups, compared to placebo and usual-diet at 12 weeks. Analyses between psyllium-eating and 'healthy'-eating groups were not reported, neither were exact measurements of weight lost. In the other RCT study (Pal et al. 2016), participants were randomized into one of three groups: (1) placebo; (2) psyllium supplement; or (3) PGX supplement. Weight was significantly lower in the psyllium

Table 9. Carnitine.

Reference	Sample	Design	Intervention	Results
Elmslie et al. (2006)	60 M/F Bipolar BMI: >25 kg/m^2 Age: 42 years	RCT	1.5g/kg of body weight/day Low fat diet with 500 kcal/day deficit and ≥ 30 min of PA ≥5days/week for 26 weeks	Effectiveness: Carn: −1.9 and −0.6 kg/m^2 versus placebo: −0.9 kg and −0.4 kg/m^2; P=0.38 and P=0.47, respectively. Safety: NR

Carn, Carnitine; F, Female; M, Male; BMI, Body Mass Index; AE, Adverse Events/Side effects; NR, Not reported.

Table 10. Coleus forskohlii.

Reference	Sample	Design	Intervention	Results
Loftus et al. (2015)	30 M/F Metabolic Syndrome BMI: >25.0 kg/m^2 Age: 20–65 years	RCT	2.5g BID 500 kcal/day deficit for 12 weeks	Effectiveness: Colf: −1.5 kg and −1.4 kg/m^2 versus placebo: −1.4kg and −0.6 kg/m^2; P>0.05. Safety: Increased bowel motions (1 Colf) and loose stools (1 Colf) which resolved by week 4.

Colf, Coleus forskohlii; F, Female; M, Male; BMI, Body Mass Index; AE, Adverse Events/Side effects.

group compared to placebo at 3 (−1.1 kg) and 6 (−2.4 kg) months, but not at 12 months.

In the non-randomized, non-blinded parallel group study, participants were intentionally placed in one of three groups: (1) psyllium, (2) orlistat, and (c) sibutramine (Kazmi et al. 2009). Clinically significant weight loss was reported for all groups, with the sibutramine group having the greatest weight loss (13.5 kg, 14.1%), followed by the orlistat (7.9 kg, 8.0%) and psyllium (4.6 kg, 5.1%) groups. Importantly, compared to the other two studies reviewed, Kazmi et al. (2009) administered the highest dosage of psyllium to participants (6 tablespoons/day). In addition, while there was no mention of the use of additional interventions in the study itself, the abstract of the study briefly mentioned a "diet chart" and "lifestyle modification" (Kazmi et al. 2009), which may have contributed to the significant weight loss observed in all groups.

Safety

Two of the three studies reported on AEs (Pal et al. 2011; Kazmi et al. 2009). One of the RCT studies reported minor bloating, yet lacked mention of which group this AE was found in (Pal et al. 2011). Psyllium patients of the Kazmi et al. (2009) study mentioned AEs of abdominal distension, fullness, and increased frequency of defecation in the psyllium group. However, more AEs were reported in the weight loss pharmaceutical than psyllium group, with orlistat participants reporting flatulence with discharge, oily stool, increased defecation, fullness, and constipation, and the sibutramine group showing slight increase in systolic blood pressure and diastolic blood pressure, increase in pulse rate, insomnia, dry mouth, chest pain, and constipation (Kazmi et al. 2009).

It remains unclear whether psyllium is an effective weight loss supplement that can lead to clinically significant results. More specifically, while the Pal et al. (2016) study did report statistically significant weight loss at 3 and 6 months, the amounts of weight loss were minor and, no longer significant at the end of the study. In addition, while the Kazmi et al. (2009) study reported clinically significant results, it is unclear whether the study included lifestyle interventions as well and lacked a placebo group as a control. Due to the fact that these changes in weight may simply be attributed to the change in lifestyle, further work is needed to establish whether psyllium on its own can lead to clinically significant weight loss. Irrespective, psyllium displays minimal to any AEs on individuals, making it a seemingly safe substance.

Miscellaneous supplements

Carnitine (carn) is a naturally occurring compound that can be found in nearly every cell in the human body (National Institutes of Health Office of Dietary Supplements 2017). In the body, carn transports long-chain fatty acids so they can be transformed into energy, and helps transport toxic compounds outside of the cell (National Institutes of Health Office of Dietary Supplements 2017). While there are several forms of carn, L-carnitine appears to be the isomer used for weight loss.

Effectiveness for weight loss

There was only one article that met inclusion; it examined the use of carn as an adjunct to a lifestyle intervention for individuals with bipolar disorder (Elmslie et al. 2006) (Table 9) and received a weak rating for research quality. Participants were randomized to receive 1.5g/kg/day of carn or placebo for 26 weeks. Both groups had similar non-significant decreases in weight by the end of the intervention, and the authors did not report on AEs.

Coleus forskohlii (colf) is a member of the mint family Indian (Schaneberg and Khan 2003). Colf has been used medicinally for centuries, and it is the root of the plant that is commonly used in health supplements (Schaneberg and Khan 2003).

Effectiveness for weight loss

There was one article published on colf that met inclusion which examined the efficacy of colf supplementation for weight loss in 30 adults with metabolic syndrome, but it received a strong rating of research quality (Table 10). Participants were randomized to take 5g/day colf or placebo

in addition to a 500 kcal/day deficit for 12 weeks. Both colf supplementation and placebo groups had similar and non-significant weight loss (1.5 vs. 1.4 kg, respectively) and decreases in BMI (1.4 vs. 0.6 kg/m^2, respectively).

Safety

AEs were only reported for the colf group, with two participants reporting increased or loose stools, however, these AEs were categorized as minor and subsided after the third week.

Limited research was published from 2006 to 2016 on carn and colf supplementation for weight loss in adults with obesity. Both of the studies (Elmslie et al. 2006; Loftus et al. 2015) were short in duration, had a small sample size and reported similar reductions in weight to placebo. Importantly, while no major AEs were reported, it still cannot be insinuated that supplementation with these products are safe, due to the above limitations. Further research in necessary to assess the efficacy and safety of these products for weight loss in adults with obesity.

Discussion

Natural supplements are currently marketed as safe and efficacious alternatives to pharmaceutical to support weight reduction efforts. However, results of the current review suggest that commonly used weight loss supplements (i.e. psyllium, GM, CLA, CrP, green tea, carn, colf, capsinoid, and bitO) do not meet the weight loss requirements emplaced on pharmaceutical agents, and in some cases may cause harm.

Health Canada guidelines for the approval of weight loss pharmaceuticals are unclear, but current FDA, and to a lesser extent, the European Medicines Agency (EMA) guidelines contain well-established weight-related efficacy thresholds for the approval of weight loss pharmaceuticals. More specifically, the FDA requires a weight loss agent to meet 1 of 2 requirements following one year of treatment: (1) a statistically significant difference of 5% or more weight loss favoring the active agent; or (2) at least 35% of the active-agent group achieving $\geq$ 5% weight loss, which must also be at least double the proportion of participants in the placebo who achieve $\geq$ 5% weight loss and be significantly different (Kennett and Clifton 2010). Similarly, the EMA requires evidence of a 5% placebo-substracted decrease in weight for a medication to be approved, and recommend reporting 5% and 10% weight loss, but unlike with the FDA, no specific thresholds regarding categorical weight loss are identified (European Medicines Agency 2016). When considering these guidelines, none of the supplements examined in this review reached these clinical thresholds to be marketed as a weight loss pharmaceutical. Other reviews which examined natural supplements included in this review have reached analogous conclusions (Allison et al. 2001; Saper, Eisenberg, and Phillips 2004). Given this, commonly marketed natural supplements do not appear to offer any clinically significant weight loss benefits, and thus, should not be recommended as an adjunct to weight loss treatment, particularly when some research has shown that weight loss can be achieved by lifestyle intervention alone (Franz et al. 2007; Norris et al. 2004).

Pharmaceuticals are currently being used as an adjunct to lifestyle weight management intervention, with three weight management pharmaceuticals available in Canada – orlistat, liraglutide 3.0, and a naltrexone/bupropion combination medication (Contrave®). While these medications have been approved for weight management due to their weight-reduction effects (Drent and van der Veen 1993; Verhaegen and Van Gaal 2017; Greenway, Plodkowski, and Greenway 2010), they are not without potential side-effects. For example, increased nausea and indigestion is a prevalent side-effect for all three weight management medications (Roche 2015; Novo Nordisk 2016; Valeant 2018). Similarly, the majority of natural supplements examined in this review resulted in moderate GI side-effects (Zhong et al. 2015; Steck et al. 2007; Snitker et al. 2009; Onakpoya, Posadzki, and Ernst 2014; Zalewski, Chmielewska, and Szajewska 2015; Pal et al. 2016; Kleefstra et al. 2006; Hsu et al. 2008) such as constipation, diarrhea and vomiting. Importantly, most of these AEs were reported after relatively short-term monitoring, and therefore, do not account for harm that may occur after long-term use.

Long-term surveillance is vital in appropriately evaluating the consummatory safety of any agent, whether man-made or from nature. This has been evident in the case of sibutramine, a weight management pharmaceutical initially approved for use in 1997 (National Institutes of Health 2018). Results of the phase III clinical trials suggested clear efficacy of this agent, with 4.1kg more weight loss compared to placebo, and fairly well tolerated AEs at a similar rate to those in the placebo group (Wirth and Krause 2001). However, case studies of prolonged use – which surfaced soon-after, reported serious cardiac events following sibutramine use (Wooltorton 2002; Bosello et al. 2002); by 2002 some countries started suspending sibutramine use (Committee for proprietary medicinal products 2002), and it was finally pulled from the market in 2010 (Center for Drug Evaluation and Research 2018). The tale of sibutramine is quite similar to that of the natural supplement ephedra. Initially, when used with caffeine, ephedra was found to be as efficacious as FDA and EMA approved weight loss pharmaceutical. It was later determined that the concomitant use of ephedra and caffeine was responsible for 50% of natural-supplement related poison reports, despite only accounting for 1% of herbal medicine sales (Bent et al. 2003). Ultimately, ephedra was banned by the FDA in 2004 (National Advisory Council for Complementary and Alternative Medicine 2003) and the EU in 2015 (European Parliament and The Council of The European Union 2015) due to concerns of an increased risk of serious cardiac events and death with its use. This is shockingly similar to the long-term studies and case reports included in this review, which reported complete liver failure (Molinari et al. 2006) and renal transplant (Burke et al. 2007) in green tea and bitter orange extract users, respectively. It is therefore

necessary to emphasize that natural supplements are not devoid of potential consequences, and, while they are often heralded as a safe alternative to pharmaceuticals, should still be regarded as medicines that can potentially have severe detrimental effects on health over time. This is especially pertinent due to lax natural-supplement regulatory approval and monitoring by key health.

There are several strengths and limitations in this review that warrant mentioning. A strength of this review includes the use of multiple reviewers to assess each article for inclusion, which limited the potential impact of personal biases on article selection. Due to the number of natural supplements available worldwide for weight loss, it is not possible to examine the efficacy and tolerability of every agent. As such, this review focused on contemporary natural weight management supplements which are widely-marketed through online retailers (e.g. Amazon), allowing us to examine those supplements which are most relevant to current clinical practice. Articles examined in this review were restricted to those which examined individuals with obesity. To be prescribed a weight management pharmaceutical, an individual must have a BMI $\geq 30\,kg/m^2$ or BMI $\geq 27\,kg/m^2$ with a comorbidity (e.g. diabetes, heart disease, hypertension (National Institutes of Health 2000; Lau et al. 2007)). Thus, this review was restricted to a similar population (i.e. those with obesity), to better reflect those who would be prescribed adjunctive therapies for weight loss. Further, having obesity is associated with greater pharmaceutical use and risk of health complications, which could impact the efficacy and tolerability of natural supplements. Nonetheless, there was considerable heterogeneity within each supplement in the studies examined in terms of dosing and type of intervention, making it difficult to draw conclusions regarding their use. There were also concerns regarding the rigor and lack of transparency in the studies' reporting. In essence, reviews are only able to comment on the literature available, and in the case of the natural weight management pharmaceuticals examined, there was an inadequate amount of studies with negligible references to safety. We selected a research quality assessment tool that can be used to evaluate any quantitative study. While this allowed us to have a measure to compare each study direct, this assessment tool also had some limitations. Specifically, studies are rated as high or moderate quality primarily because of the design (i.e. randomized control trial), and they likely would not have been rated so well using a quality assessment tool specific to that type of study. For example, insufficient information regarding randomization would have likely resulted in considerable deductions in an RCT specific assessment tool, but there were no deductions for this lack of clarity. In addition, while meta-analyses are often viewed as high-quality research, this tool prevented the scoring of meta-analyses higher than of moderate quality. Lastly, weight loss is one of many outcomes associated with weight management. Other important clinical indicators of health, such as blood glucose or cholesterol levels, are also important determinants of successful weight management and were not examined in this review. Therefore, while the natural supplements reviewed do not appear to result in clinically significant reductions in weight, it is possible that they could provide additional benefits in regards to health and weight management.

The commonplace use of natural supplements is likely here to stay, mainly owing to the marketing of these products as an efficacious and safe alternative to pharmaceuticals. Conversely, results of this review suggest that some of the most commonly advertised natural weight loss supplements do not have sufficient evidence to be recommended as an adjunctive weight loss therapy and in extreme cases may cause irreparable harm. Larger and more rigorous RCTs, and stricter regulatory guidelines regarding standardization for dosing and delivery are needed to concretely establish the efficacy of these natural supplements. Greater transparency and reporting of AEs are also necessary, especially over long-term use. In the interim, natural weight loss supplements should be used with caution, and like pharmaceuticals, require medical monitoring.

Note

1. Health Canada defines "natural health products" as vitamins, minerals, herbal remedies, probiotics, and amino acids and fatty acids (Health Canada 2012). In this review, "natural supplements" refers to anything derived from nature (e.g. vitamins, minerals, herbs), and excludes anything chemically manufactured (e.g. pharmaceuticals).

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ORCID

Revi Bonder https://orcid.org/0000-0002-9711-851X
Rebecca A. G. Christensen http://orcid.org/0000-0001-5212-8688

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