Evaluation of Clinical Studies of Dietary Supplements Used for Weight Loss

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Goal:

The goal of this article is to report study results and appraise the methods of the strongest evidence available describing some of the most commonly used dietary supplements intended for weight loss. The available evidence will be evaluated based on recommendations from the CONSORT Extension for Herbal Medicinal Interventions.

Learning Objectives:
Upon completion of this article the learner should be able to:

1. Define normal weight, overweight obese, and morbidly obese.
2. Describe the pharmacological basis supporting the use of caffeine, *Garcinia cambogia*, green coffee bean extract, and green tea for weight loss
3. Describe the efficacy and safety results of weight loss supplements from clinical trials.
4. Critically appraise the design of clinical trials for herbal supplements.

Introduction

An estimated two of every three adults in the United States are overweight or obese.[1] Adults who are overweight or obese are at a significantly increased risk for comorbidities, including hypertension, cardiovascular disease, type 2 diabetes mellitus, and cancer. Body mass index (BMI) is a commonly used calculation to determine level of excess weight. BMI is comprised of four categories: normal weight (BMI of 18.5 to 24.9 kg/m^2), overweight (25 to 29.9 kg/m^2), obese (30 to 39.9 kg/m^2), and morbidly obese (greater than 40 kg/m^2). Waist circumference (WC) is also a good method to approximate intra-abdominal fat, with greater than 40 inches in men and greater than 35 inches in women considered to be high-risk. These two measures can be used in combination to determine risk for type 2 diabetes mellitus, hypertension, and cardiovascular disease.

The American Heart Association/American College of Cardiology (AHA/ACC) developed clinical practice guidelines for the management of overweight and obese individuals. A weight loss of 5 to 10% of total body weight (an average up to 8 kg) should be attempted for 6 months, and can reduce the risk of obesity-

related diseases.[2,3] An energy deficit is required to lose weight. Generally, a deficit of at least 500 kcal/day compared to one's individual requirements will result in weight loss over time.[3]

Due to the high prevalence of obesity in the United States, options for helping obese and overweight people lose weight have increased beyond the basic behavioral modifications of eating less and exercising more to facilitate a calorie deficit. In patients who are unable to meet their weight loss goal, options include pharmacotherapy and weight loss surgery.[3] Pharmacological therapy could be initiated in combination with lifestyle therapy if BMI is greater or equal to 30 kg/m^2 or greater or equal to 27 kg/m^2 with obesity-related risk factors or diseases. Patients should be assessed during the acute weight loss period, 6 months, and 1-year follow-up visits. Orlistat (Alli®, Xenical®) is currently the only pharmacotherapy option identified in the AHA/ACC guidelines, but more recently FDA-approved medications for weight management include liraglutide (Saxenda®), lorcaserin (Belviq®), naltrexone/bupropion (Contrave®), and phentermine/topiramate (Qsymia®). Patients with a BMI greater than or equal to 40 kg/m^2 or greater than or equal to 35 kg/m^2 with a comorbidity may be candidates for bariatric surgery if they are unable to meet their weight loss goals through behavioral modifications.

A cross-sectional study of 1,444 US adults who have attempted to lose weight found that 33.9% report having tried a dietary supplement to help lose weight, with past use more common among women (44.9%), African-Americans (48.7%), Hispanics (41.6%), and lower income households (41.8%).[4] Although many dietary supplements are available and marketed to help promote weight loss, there is no supporting evidence or place of therapy for weight loss supplements in the ACC/AHA guidelines.[3] The goal of this article is to appraise the evidence for some of the more well-studied dietary supplements.

Learning Activity

How are normal, overweight, obese, and morbidly obese populations defined? [Learning Objective 1]

Clinical Studies

Supplements included in this article were selected based on popularity (determined by review of number of questions received by the Manchester University Drug Information Center), strength of supporting evidence, and availability of clinical trials. The supplements selected were caffeine, *Garcinia cambogia*, green coffee bean extract, and green tea. A systematic search via PubMed using the term "weight loss" and the name of the herbal supplement was conducted in order to identify clinical trials. Two clinical trials were selected for each supplement. Trials were selected based on quality of methods and sample size. Study results are summarized in Table 1.

Herbal supplement: Caffeine

Pharmacological rationale: Caffeine comes in many natural forms, including green tea, guarana (*Paullinia cupana*), kola nut (*Cola nitida*), and yerba mate (*Ilex paraguariensis*). Caffeine is a methylxanthine compound that stimulates the central nervous system and can lead to many effects in the body. Caffeine can stimulate gastric acid secretion, and can also increase resting energy expenditure, cellular thermogenesis, nonoxidative fatty acid turnover, and lipid oxidation.[5] These effects are postulated to contribute to weight loss effects.
Recommended dose: 200 mg three times a day[4]

A 2001 double-blind, placebo-controlled trial observed the effects of YGD®, a combination product containing yerba mate (1.0 to 1.5% caffeine), guarana (3 to 6% caffeine), and damiana (percentage caffeine not defined), in 47 overweight patients for 45 days.[6] Patients were

randomized to either 3 capsules of YGD (112 mg yerba mate, 95 mg guarana, 36 mg damiana/capsule) or placebo before main meals. The total caffeine dose for each capsule ranged from 3.97 mg to 7.38 mg. The primary endpoint was weight loss over 10 and 45 days.

Very few baseline characteristics were provided for this study.[6] Twenty-four patients were randomized to YGD treatment (fifteen women, nine men), and 23 patients were randomized to placebo (seventeen women, six men). The average BMI of the YGD treatment group was 25.1 to 29.5 kg/m², and the average age was 38.2 years. BMI of the placebo group was relatively similar to the treatment group, with an average BMI of 24.9 to 29.0 kg/m². The average age of the placebo group was 38.6 years. Patients were reported to be healthy, and were not on any medications or diet regimens prior to initiation of the study. Variability of baseline characteristics and other pertinent characteristics were not provided.

At 10 days, the mean decrease in body weight was 0.8 ± 0.05 kg for the treatment group and was 0.3 ± 0.03 kg for the placebo group.[6] After 45 days of treatment, patients showed a mean decrease of 5.1 ± 0.5 kg vs. 0.3 ± 0.08 kg in the placebo group. Statistical results were not provided for these values. The authors conclude that clinically significant weight loss was achieved with YGD.

There were many missing details regarding the patient population and design of this study that limit applicability to practice.[6] No information provided as to how patients were screened or how randomization occurred. The baseline characteristics provided were well balanced amongst the two groups; however, the only characteristics that were provided were mean BMI and average age. Similarly, no information provided regarding what population was used for data analysis (e.g., intention to treat, per protocol). It is unknown whether the decrease in weight in the YGD group was statistically significant. However, the mean weight loss might be considered clinically significant in practice since a mean weight loss of 5.1 kg in 45 days aligns with the recommendations in the AHA/ACC guidelines.[3] Patients were asked not to record dietary intake as a way to reduce the impact of diet on weight loss, but it is unknown whether patients were compliant. No information was provided in terms of adherence to the YGD treatment, or any adverse events that occurred.

A 2005 study in Netherlands randomized 76 patients in a double-blind, placebo-controlled study to receive a green tea-caffeine mixture (270 mg epigallocatechin gallate [EGCG, a component of green tea] and 150 mg caffeine a day) or placebo for 3 months following a run-in period.[7] The run-in period, which was 4 weeks in duration, consisted of a very low energy diet (2.1 MJ/day) in hopes of at least 4 kg weight loss in patients. Patients were then stratified into 2 groups according to gender, BMI, age, dietary restraint, resting energy expenditure, and caffeine consumers (low: <300 mg/day, high: >300 mg/day) during the maintenance period. There were no stated primary endpoints for this study, but the authors of this study evaluated the amount of weight loss during the run-in period, as well as the amount lost and/or the effect of the treatment in terms of weight maintenance during the maintenance period. Other results that were provided include waist circumference, BMI, respiratory quotient, and body fat.

Baseline characteristics were well distributed between the two groups.[7] Mean body weight for the green tea-caffeine mixture was 85.1 ± 9.5 kg (low caffeine) and 85.0 ± 8.5 kg (high caffeine) vs. 85.1 ± 9.6 (low caffeine) and 85.0 ± 8.3 (high caffeine) in the placebo group. Based on mean BMI, the patients in the groups were classified as being either overweight or obese. Patients who were initially screened ranged from 18 to 60 years of age, however the mean age for the treatment and placebo groups was not provided. Patients who were high caffeine consumers lost a statistically significant amount of weight compared to low caffeine consumers during the run-in period (6.7 ± 1.4 kg vs. 5.1 ± 1.2 kg, $p<0.01$). During the maintenance phase, the low caffeine active treatment group

continued to lose a mean percentage of 11.1 ± 24.3% of body weight, which was found to be statistically significant compared to the low caffeine placebo group who had a mean gain of 40.8 ± 28.9% ($p<0.01$) and the high caffeine active treatment group who had a mean gain of 24.4 ± 18.7% ($p<0.01$). Results were not provided for the high caffeine placebo group.

Frequency and intensity of adverse events during the study were recorded; however the authors of the study stated that none occurred.[7] It is also unknown how many patients discontinued the study during the run-in period and/or the maintenance phase, as well as the reasons for discontinuation. This information would help determine whether patients might be candidates for the supplement. The authors concluded that active treatment intake led to greater weight loss compared to low caffeine intake. There was no monitoring plan, so it is unknown whether the authors were ensuring the patients were continuing their outside consumption of caffeine during the study duration.

Herbal supplement: *Garcinia cambogia*

Pharmacological rationale: Hydroxycitric acid, found in garcinia fruit rind extract, is thought to interfere with lipogensis and competitively inhibit ATP-citrate-lyase, which is responsible for conversion of citrate into acetyl Co-A, preventing the conversion of carbohydrate to fat. Other studies have shown evidence that hydroxycitric acid inhibits the supply of fatty acids and the accumulation of lipid droplets in fat cells.[8]
Recommended dose: 1000 mg three times daily of extract (containing 50% hydroxycitric acid), or hydroxycitric acid 500 mg four times daily[8]

A randomized, double-blind, placebo-controlled trial evaluated the efficacy of *Garcinia cambogia* 3000 mg (1500 mg hydroxycitric acid, the active ingredient) daily for weight loss and reduction in percentage of body fat in 135 overweight human subjects.[9] Patients received two 500 mg capsules three times daily 30 minutes before meals or matching placebo. The placebo group consisted of 69 subjects while the treatment group was comprised of 66 subjects. The primary endpoints were change in body weight and change in total percentage body fat mass at 12 weeks. Reported adverse events were also assessed.

Baseline characteristics between the treatment and placebo groups were overall well distributed. Both groups were mainly women (92% vs. 80%).[9] The mean age in both groups was similar (38.6 vs 39.4 years). The mean weight was 83.8 ± 10.1 kg in the treatment group and 88.2 ± 13.0 kg in the placebo group. The mean BMI was 31.2 ± 2.8 kg/m^2 in the treatment group and 31.9 ± 3.1 kg/m^2 in the placebo group. Men in the treatment group had a lower body fat percentage (28.4 ± 2.6%) than men in the placebo group (36.6 ± 5.9%).

In the treatment group, mean weight loss at 12 weeks was 3.2 ± 3.3 kg.[9] Mean weight loss at 12 weeks in the placebo group was 4.1 ± 3.9 kg. Weight loss in each group was significant from baseline ($p<0.001$), but was not different between the groups ($p=0.14$). No differences were found between groups in terms of secondary endpoints (Table 1). No patients withdrew from the study due to treatment-related adverse events, and the number of reported adverse events did not differ between the groups. Commonly reported events in the placebo and treatment groups included headache (12 vs. 9), upper respiratory tract symptoms (13 vs. 16), and gastrointestinal tract symptoms (6 vs. 13). Patients with missing data were included in the analysis using the last observation carried forward. The results of this study do not support the use of *G. cambogia* for weight loss in overweight subjects.

The 12-week duration of the study allowed for an appropriate amount of time to determine effect on weight loss of the product, especially when compared to previous trials of *G. cambogia*.[9] Also, the intention-to-treat population was an appropriate population for analysis since it included all patients who were randomized including patients who might have

dropped out, which is common in weight loss studies. A possible limitation of this study includes calorie restriction. With a calorie restriction of 1200 kcal/day included in the protocol, weight loss would be expected over a 12-week period due to the creation of a calorie deficit. It is likely that the weight loss observed in both groups is a result of the strict calorie restriction as opposed to the use of *G. cambogia* or placebo effect. Also, patients often turn to weight loss supplements when they have failed or are unwilling to commit to dietary modifications, so patients taking *G. cambogia* in the general population are not likely to be maintaining a 1200 kcal/day diet. The weight loss seen in this study might be misleading to readers who overlook the strict calorie restriction that played a large role in generating the results.

A randomized, double-blind, placebo-controlled study evaluated the efficacy of IQP-GC-101, a patented blend of extracts of *Garcinia cambogia*, *Camellia sinensis*, unroasted *Coffea arabica*, and *Lagerstroemia speciosa*, in reducing body weight and body fat mass in overweight subjects over 14 weeks.[10] Subjects were randomized to placebo or treatment with IQP-GC-101. Each 850 mg tablet of IQP-GC-101 was comprised of 650 mg *Garcinia cambogia* extract, standardized to at least 60% hydroxycitric acid; 100 mg *C. sinensis* extract, at least 15% epigallocatechin-3-gallate and 11% caffeine; 75 mg unroasted *C. arabica* extract, at least 25% chlorogenic acid and 5% caffeine; and 25 mg *L. speciosa*, at least 5% corosolic acid. The placebo was identical in appearance and was replaced with inert ingredients. Subjects took three tablets 30 minutes before breakfast and lunch. Subjects also received diet counseling and a diet plan. The diet plan implemented a 500 kcal/day deficit based on the calculated energy needs of each subject. The primary endpoints were differences between the treatment and placebo groups in mean loss of body weight (kg) and body fat mass (kg) after 12 weeks.

Forty-six subjects were randomized to each group.[10] Baseline characteristics were similar between groups. Males comprised of 26.2% (n=12) of the treatment group and 37.8% (n=17) of the placebo group. The mean age of both groups was approximately 43 ± 11 years. The mean body weight was 82.3 ± 12.3 kg in the treatment group and 83.3 ± 9.6 in the placebo group. The mean weight loss at week 12 was 2.26 ± 2.37 kg in the treatment group and 0.56 ± 2.34 kg in the placebo group. The difference between the groups was statistically significant (p=0.002). In the treatment group, the mean loss of body fat at 12 weeks was 1.12 ± 1.84 kg. The placebo group lost body fat at week 4 but regained it at weeks 8 and 12. The placebo group had a mean gain in final fat mass of 0.37 ± 2.14 kg. The mean fat loss in the treatment group was statistically significant compared to placebo (p=0.001). No serious adverse events were reported. In the treatment group, 9 adverse events were reported including toothache, diarrhea, and upper respiratory tract infection. In the placebo group, 4 adverse events were reported including gastrointestinal infection, bronchitis and upper respiratory tract infection. All of the adverse events were considered mild or moderate and unrelated to the study products. The authors conclude that IQP-GC-101 reduced body weight and fat mass when used with a slightly hypocaloric diet. They also concluded that IQP-GC-101 has a favorable safety profile.

The study length of 12 weeks was appropriate to assess possible weight loss benefits, and was a strength compared to other studies identified in this review. Use of intention-to-treat principle increased external validity of the study. A possible limitation of this study is the use of a combination product. A combination product containing multiple supplements with weight loss claims makes it difficult to ascertain which compounds were related to weight loss.

Herbal supplement: Green coffee bean extract

Pharmacological rationale: The chlorogenic acid component of coffee is thought to have an effect on weight. Animal and human studies have shown that chlorogenic acid inhibits fat accumulation and reduces weight.[11] It is

hypothesized that the weight loss effects of green coffee beans may also be due to presence of caffeine, particularly in liquid formulation. Green coffee beans have a higher level of chlorogenic acid because they have not be roasted.
Recommended dose: Varies by brand – Svetol, Naturex: 80-200 mg daily; GCA, Applied Food Sciences: 700 or 1050 mg daily[11]

A 2006 randomized, placebo-controlled study evaluated the use of Svetol®, green coffee extract rich in chlorogenic acids, for weight loss in overweight subjects with a BMI > 25 kg/m^2.[12] The active compound consisted of 200 mg Svetol®. Patients took the capsule or placebo with each main meal, twice a day for 60 days. Thirty subjects were randomized to the treatment group while 20 subjects were randomized to the placebo group. The efficacy endpoints included change in weight, BMI, and muscle mass/fat mass (MM/FM) ratio from baseline to day 60. A low calorie diet was also required of the subjects in both groups.

According to the authors, baseline characteristics including weight and BMI between the treatment and placebo groups were similar; however, data were not provided.[12] The age range was 19-75 years. The mean weight loss after 60 days of treatment was 4.97 kg (SEM=0.32 kg) in the treatment group and a loss of 2.45 kg (SEM=0.37) with placebo. The authors concluded that Svetol® is able to aid weight and fat mass loss when used with a low caloric diet in overweight subjects.

The small sample size and brief study duration makes generalizing results difficult. The short duration of the study prevents assessment of the long-term effects of Svetol® and whether the weight loss is maintainable beyond 60 days. Additionally, the level of blinding is unclear. The lack of explanation of blinding prevents one from knowing the risk of bias. Values for baseline characteristics are not presented making it difficult to understand the study population, and which patients could be potential candidates for this intervention.

Another study aimed to determine the effects of chlorogenic acid enriched coffee on body mass in overweight subjects.[13] The study was a randomized, placebo-controlled study that randomized thirty slightly to moderately overweight (BMI 27.5 to 32.0 kg/m^2) non-smokers to drink 5 cups/day (11 g coffee/day containing 1 g green coffee) of Coffee Slender®, a freeze dried coffee containing Svetol, or to normal Nescafe® Gold Norwegian blend instant coffee (11 g coffee/day containing 330 to 440 mg chlorogenic acid) in a 1:1 allocation. The subjects were told not to engage in any other weight loss programs and to stay consistent with their usual lifestyle. Endpoints included weight reduction and body fat percentage reduction.

Mean baseline characteristics were balanced between the groups.[13] The Coffee Slender® group, consisting of 8 females and 7 males, had a baseline mean weight of 85.2 ± 4.5 kg and a mean BMI of 29.2 ± 2.5 kg/m^2. The Nescafe group, consisting of 10 females and 5 males, had a baseline mean weight of 84.3 ± 4.3 kg and a mean BMI of 29.9 ± 2.4 kg/m^2. Mean weight reduction from baseline to week 12 was 5.4 ± 0.6 kg in the Coffee Slender group and 1.7 ± 0.9 kg in the Nescafe group. The difference in weight loss between the groups was statistically significant ($p<0.05$). The weight loss in the Coffee Slender group from baseline to week 12 was statistically significant ($p<0.05$). The Coffee Slender group had a statistically significant reduction in percentage of body fat of 3.6 ± 0.3% from baseline to week 12 ($p<0.05$). The difference in body fat between the groups (3.6 ± 0.3% in the Coffee Slender group vs. 0.7 ± 0.4% in the instant coffee group) was statistically significant ($p<0.05$). All 30 participants completed the study according to protocol and the interventions were well-tolerated with no side effects reported that could be related to the interventions. The authors suggest that prolonged use of chlorogenic enriched coffee reduced body weight compared to normal instant coffee.

Herbal supplement: Green tea

Pharmacological rationale: Polyphenols such as favanols, flavandiols, flavonoids, and phenolic acids are abundant in green tea.[14] Flavanols such as epigallocatechin gallate (EGCG), epicatechin gallate (ECG), and epicatechin (EC), also known as catechins, are thought to be responsible for many of the potential benefits of green tea. Evidence shows that the EGCG can increase calorie and fat metabolism, with other catechins, caffeine, and theanine components possibly contributing. There is also evidence that EGCG may suppress appetite and inhibit adipocyte proliferation and differentiation *in vitro*. Additionally, caffeinated green tea products may have additional potential to promote weight loss as previously described.
Recommended dose: 240 to 320 mg polyphenols, 576 to 870 mg catechins, or 1500 mg green coffee extract[14]

A randomized, double-blind, placebo-controlled study that took place in Taiwan evaluated the effect of green tea extract on obese women for 12 weeks. The study randomized 100 women with a BMI greater than 27 kg/m² 1:1 to receive green tea extract 400 mg three times daily (total daily dose 491 mg catechins containing 302 mg EGCG or placebo.[15] The primary endpoints were percent reduction in body weight (BW), body mass index (BMI), and waist circumference (WC).Concentrations of hormone peptides leptin, adiponectin, and ghrelin were also analyzed at baseline and after 12 weeks of treatment.

Baseline characteristics of the two treatment groups were well balanced, with the average weight being 78.5 ± 10.3 kg and 76.3 ± 14.5 kg in the green tea extract and placebo groups, respectively.[15] Patients in both categories fit the classification of obese, with a mean BMI of 31.2 ± 3.5 kg/m² in the green tea extract group and 30.5 ± 4.6 kg/m² in the placebo group. Other relevant baseline characteristics for this patient population included WC, which was 94.7 ± 7.7 cm in the green tea extract group and 93.0 ± 12.6 cm in the placebo group, and age (43.0 ± 11.1 vs. 43.9 ± 12.6 years). The mean weight loss in the green tea extract group was 0.15 ± 2.0 kg and 0.03 ± 1.9 kg in the placebo group (p=0.67). There was a mean decrease of 0.06 ± 2.8 kg/m² in terms of BMI in the green tea extract group, versus a mean decrease in BMI of 0.006 ± 0.8 kg/m² in the placebo group (p=0.72). Results for other primary endpoints are presented in Table 1.

Adverse effects were minor in this study.[15] Five patients in the green tea extract group experienced adverse effects (three with mild constipation and two with abdominal discomfort, 2). One patient in the placebo group experienced abdominal discomfort. All adverse effects were reported in the first week of treatment, but did not account for withdrawal from the study. No other major adverse effects were reported.

Baseline characteristics were also well distributed amongst the two groups, reducing impact of confounding variables such as weight, BMI, and waist circumference.[15] The total daily dose of green tea extract (491 mg catechins containing 302 mg EGCG) was also well tolerated in the treatment group for the duration of the study. However, it was found that serum EGCG was found in only 5 of 41 samples, suggesting that the total daily dose was not enough to exert effects in the subjects. Further studies would need to be conducted to determine the optimal dose of green tea extract. Results of this study were lacking in terms of detail. Due to the nature of the treatment, safety endpoints and more rigorous monitoring of adverse events would have provided a better understanding as to the safety of green tea extract. Applicability of the study will be reduced since minor changes in endpoints such as weight, LDL-C, and HDL-C were not statistically significant.

A randomized, controlled trial assessed the safety and efficacy of a green tea meal replacement formula in 120 overweight or obese patients.[16] Patients were randomized 1:1 to either green tea meal replacement formula or normal diet. Patients in both groups received dietary counseling and a pamphlet encouraging weight loss. Green tea meal replacement

formulas were meant to be taken 5 times a day, and composed mainly of green tea, chitosan, and selenium yeast. The authors did not state primary or secondary endpoints, but it can be inferred that the primary endpoint was weight loss from baseline to week 12. Other endpoints included change in body fat percentage and fat mass, blood pressure, cholesterol, and waist circumference.

The mean age for the treatment group was 42.0 ± 1.1 years versus 44.3 ± 1.2 years in the control group.[16] A majority of the patients in both groups were of female gender, with 50 women and 10 men comprising of the treatment group and 53 women and 7 men comprising of the control group. The average weight of both groups was well balanced, with the treatment group having an average weight of 81.3 ± 11.8 kg versus 79.4 ± 11.3 kg in the control group. Based on the mean BMI of both groups, a majority of the patients in both categories were considered to be obese (treatment vs. control, 33.1 ± 0.5 kg/m² vs. 31.6 ± 0.2 kg/m², respectively).

There was a statistically significant difference found in terms of weight loss from baseline to week 12, with the treatment group losing a mean of 6.5 kg (95% CI 6.3 to 6.8) vs. the control group loss of 2.4 kg (95% CI 1.8 to 3.0, p<0.0001).[16] There were no statistically significant differences in terms of fat mass and blood pressure. The decrease in waist circumference was significantly lower in the treatment group when compared to the control, with the treatment group having a mean waist circumference of 90.6 ± 5.6 cm vs. 98.7 ± 6.4 cm (p=0.0056).

There were no stated safety endpoints, but the authors stated that the green tea meal replacement was found to be well tolerated.[16] Discontinuation in the treatment group was most commonly due to minor events of gas/indigestion and other gastrointestinal reactions. Although the results for mean weight loss and secondary endpoints were found to be statistically significance, there were many variables that could have influenced the results of this study. There was no information provided regarding recruitment of patients into the study, and whether they and/or the investigators were blinded for the duration of the study. Patients had a follow-up visit every 6 weeks to check for compliance in the treatment group and receive enough meal replacement formula until the next visit. However, there was no information provided regarding compliance to the formula, as well as the diet in the control group. Power calculations for this study were also limited, and it was unknown which population were used in the analysis. The authors stated that 10% of the patients did not complete the trial, but the reasons were unknown. Although the degree of weight loss achieved with green tea was clinically relevant considering study duration, application of these results are limited due to the lack of a direct comparator.

Learning Activity

Make a table illustrating, for each dietary supplement, the proposed active component(s) and theoretical mechanism of action for weight loss. [Learning Objective 2]

Add a column to your table that indicates approximately how much weight a patient could expect to lose on each study drug, as well as any potential safety issues that were noted in studies. [Learning Objective 3]

Literature Appraisal

Most published studies examining weight loss supplements that were reviewed found that use of caffeine, *G. cambogia*, green coffee bean extract, and green tea was inconsistently associated with a statistically significant weight reduction.[6,7,9,10,12,13,15,16] the observed differences compared to placebo were highly variable, ranging from approximately 1 kg (*G. cambogia*) to 6 kg (green tea). These results suggest that the

examined dietary supplements would not provide sufficient weight loss efficacy for most patients to reach weight loss goals consistent with clinical practice guideline recommends of 5 to 10% of total body weight, decreasing clinical significance.[3] Additionally, weight loss studies should assess impact of the intervention on other metabolic endpoints (e.g., fat loss, BMI, waist circumference, blood pressure, fasting blood glucose). [6,7,9,10,12,13,15,16] Most identified studies did not thoroughly assess these related endpoints, and the changes observed were generally marginal. Finally, little information regarding safety of these products can be determine due to lack of reported results and short study duration. See Table 1 for an overview of efficacy results.

While study authors should be applauded for their objective of assessing dietary supplements for weight loss in clinical trials, the design and methods of most of the studies were flawed. In its Extension for Reporting Herbal Medicinal Interventions, the Consolidated Standards of Reporting Trials group (CONSORT) provides recommendation for the reporting of dietary supplement clinical trials.[17] Table 2 provides an assessment of the included studies using this tool. The lack of completeness in reporting of these trials makes the efficacy and safety of these supplements unclear.

Of the eight studies evaluated, all provided an adequate statement of reasoning and objectives for the study.[17] Six out of eight studies stated eligibility criteria for inclusion in their study, which allows for a better understanding of the patient population. While only four gave a precise description of dosage and duration of administration, all eight provided a description of the contents per dosage unit form of their product. This information allows for an appropriate assessment of adequate dosing. Only two out of eight studies clearly defined primary and secondary objectives. Defined objectives give the study transparency and a clear purpose. The number of subjects included in analysis was unclear in five of the eight studies, preventing a clear understanding of generalizability; similarly, a sample size calculation was only provided for one study. A summary of results for each group including precision was given in six out of eight studies. This information helps determine clinical significance. Six studies included adverse events in their study. Knowing common adverse events associated with herbal supplements is beneficial, as the FDA does not regulate the supplements. All eight of the studies gave an interpretation of their results while only four related their results to trials of other available products.

An optimal study design would be a randomized, double-blinded, and placebo-controlled (since there are no clear first line pharmacological options for weight loss).[3] An optimal study length should be at least twelve weeks, if not six months, to determine the effect of the supplement on weight loss over time, as well as better describing supplement safety and tolerability.[2,3] Studies should be designed to detect a difference in weight loss of 5 to 10% of total body weight (an average up to 8 kg) in order to position the product to not only reduce weight, but also obesity-related conditions.[2,3] The study should include lifestyle modifications such as diet and exercise for all treatment groups. Results for all endpoints should be clearly stated and the potential impact including limitations of the study should be described.

Learning Activity

Review Table 2. In your own words, identify three CONSORT extension domains where the assessed studies performed well, and three domains where they did not. [Learning Objective 4]

Conclusion

Of the four supplements evaluated, each demonstrated statistically significant weight loss compared to placebo in at least one study. Two displayed clinically significant weight loss: caffeine and green coffee bean extract. However, the study design for these trials was

not ideal for establishing a clear causal relationship. When approached by a patient about the use of these supplements, pharmacists should take the following factors into consideration when determining their recommendation: type of study, subject eligibility, dose of the supplements, and lifestyle modifications included in the study. An explanation to patients giving a generalization about these factors could guide patients in making their own decisions about herbal supplements.

At this time, given the lack of rigorously conducted studies, marginal results, and lack of evaluation of safety data, dietary supplements should not be recommended as weight loss aids. Rather, lifestyle modifications, including diet, calorie reduction, and exercise, should be the foundation of weight management. Patients interested in using dietary supplements should be educated regarding topics such as potential adverse effects and other safety concerns, lack of consistent efficacy compared to appropriate control, and lack of FDA-approval of these products.

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Table 1. Efficacy endpoints from clinical trials

		Weight loss kg (SD)		Weight change (% from baseline)		Change in fat mass kg (SD)		Fat loss (%)		BMI loss kg/m²		Waist circumference loss (cm)		Hip circumference loss (cm)	
		I	C	I	C	I	C	I	C	I	C	I	C	I	C
Caffeine[6,7]	2001*	5.1 (0.5)	0.3 (0.08)												
	2005+			-11.1 (24.3), +24.4 (18.7)	+ 40.8 (28.9)										
Garcinia cambogia[9,10]	1990	3.2 (3.3)	4.1 (3.9)					1.44 (2.15)	2.16 (2.06)						
	2014	2.26 (2.37)	0.56 (2.34)			-1.12 (1.84)	+0.37 (2.14)			0.78 (0.81)	0.22 (0.80)	2.00 (2.44)	0.69 (2.24)	1.54 (1.76)	0.64 (1.91)
Green coffee bean extract[12,13]	2006*	4.97 (0.32)	2.45 (0.37)	-5.7 (0.3)	-2.9 (0.4)					1.9 (0.1)	0.9 (0.1)				
	2007	5.4 (0.6)	1.7 (0.9)					3.6 (0.3)	0.7 (0.4)						
Green tea[15,16]	2008	0.15 (2.0)	0.03 (1.9)	-0.31 (2.6)	-0.05 (2.6)					0.06 (2.8)	0.006 (0.8)	1.7 (4.1)	1.3 (5.8)	1.2 (2.7)	2.2 (3.5)
	2009^	6.8	0.8			-3.9	+0.6	7.6	0.5			7.6	0.8		

	Caffeine[6,7]		*Garcinia cambogia*[9,10]		Green coffee bean extract[12,13]		Green tea[15,16]	
	2001	2005	1990	2014	2006	2007	2008	2009
1. Title & Abstract								
Description of how patients were allocated to interventions		X	X	X	X	X	X	X
Latin binomial name	X		X	X				
Part of the plant used	X							
2. Introduction								
Statement of reasoning behind trial with reference to specific herbal product being tested	X	X	X	X	X	X	X	X
3. Methods								
Eligibility criteria for participants		X	X	X		X	X	X
Setting and location where data were collected	X		X	X			X	
4. Interventions								
Latin binomial name and common name	X		X	X		X		X
Part of plant used	X						X	
Dosage and duration of administration	X		X		X		X	
Explanation of how the dose was determined								
Content of all herbal products per dosage unit form	X	X	X	X	X	X	X	X
Rationale for type of control or placebo								
5. Objectives								
Specific objectives & hypotheses	X	X	X	X	X	X	X	X
6. Outcomes								
Clearly defined primary & secondary outcomes				X			X	
7. Sample size								
How sample size was determined								X
8. Randomization								
Methods used for randomization			X	X			X	
9. Blinding								
Description of who is blinded	X	X	X	X		X	X	
10. Statistical methods								
Description of statistical methods used for analysis	X	X		X	X	X	X	X
11. Results								
Flow of participants through each stage			X	X			X	
12. Recruitment								

Dates of period of recruitment and follow-up				X			X
13. Numbers analyzed							
mber of subjects in each group included in the analysis			X	X			
14. Outcomes							
Summary of results for each group with precision			X	X	X	X	X
15. Ancillary analyses							
Report of any other analyses performed indicating prespecified and exploratory		X	X				
16. Adverse events							
All important adverse events or side effects in each group		X	X	X		X	X
17. Discussion							
Interpretation of results taking study hypotheses into account	X	X	X	X	X	X	X
Sources of potential bias or imprecision	X	X	X	X			X
18. Generalizability							
External validity of trial results			X	X			
19. Overall evidence							
General interpretation of the results in the context of current evidence	X	X	X	X	X	X	X
Discussion of trial results in relation to trials of other available products			X	X			X

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