Supplements for Weight Loss

HOW TO RECEIVE CREDIT

- Read the enclosed course.
- Complete the questions at the end of the course.
- Return your completed Evaluation to NetCE by mail or fax, or complete online at www.NetCE.com. (If you are a physician or Florida nurse, please return the included Answer Sheet/Evaluation.) Your postmark or facsimile date will be used as your completion date.
- Receive your Certificate(s) of Completion by mail, fax, or email.

Faculty

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Faculty Disclosure

Contributing faculty, Chelsey McIntyre, PharmD, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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The division planners and director have disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Audience

This course is designed for healthcare professionals whose patients are taking or are interested in using supplements or natural therapies to facilitate weight loss.

Accreditations & Approvals

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INTERPROFESSIONAL CONTINUING EDUCATION

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This activity has been designated for 5 Lifelong Learning (Part II) credits for the American Board of Pathology Continuing Certification Program.

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NetCE designates this continuing education activity for 5 ANCC contact hours.

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NetCE designates this continuing education activity for 6 hours for Alabama nurses.

NetCE designates this continuing education activity for 5 pharmacotherapeutic/pharmacology contact hours.

AACN Synergy CERP Category A.

NetCE designates this activity for 5 hours ACPE credit(s). ACPE Universal Activity Numbers: JA4008164-0000-24-051-H04-P and JA4008164-0000-24-051-H04-T.

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Special Approvals

This activity is designed to comply with the requirements of California Assembly Bill 1195, Cultural and Linguistic Competency, and California Assembly Bill 241, Implicit Bias.

About the Sponsor

The purpose of NetCE is to provide challenging curricula to assist healthcare professionals to raise their levels of expertise while fulfilling their continuing education requirements, thereby improving the quality of healthcare.

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Disclosure Statement

It is the policy of NetCE not to accept commercial support. Furthermore, commercial interests are prohibited from distributing or providing access to this activity to learners.

Course Objective

The purpose of this course is to help healthcare professionals in all practice settings increase their understanding of supplements that are often used or are marketed for weight loss.

Learning Objectives

Upon completion of this course, you should be able to:

1. Review the most common classes of dietary supplement ingredients used for weight loss.
2. Compare and contrast the evidence for different fibers that are used to increase satiety.
3. Outline the use of various fruit supplements for potential weight loss.
4. Provide counseling points for the safe use of caffeine and caffeine-containing products.
5. Discuss the cardiovascular risks associated with most thermogenic agents.
6. List the dietary supplements with the greatest risk for drug interactions.

Pharmacy Technician Learning Objectives

Upon completion of this course, you should be able to:

1. Discuss supplements that patients may use as part of a weight loss effort.
2. Describe potential drug interactions with dietary supplements.

EVIDENCE-BASED PRACTICE RECOMMENDATION

Sections marked with this symbol include evidence-based practice recommendations. The level of evidence and/or strength of recommendation, as provided by the evidence-based source, are also included so you may determine the validity or relevance of the information. These sections may be used in conjunction with the course material for better application to your daily practice.

INTRODUCTION

Dieting has become so common in the United States that some people call it the national pastime. Each year, approximately 50% of adults younger than 50 years of age report following a diet, with the majority of people pursuing that diet in an effort to either lose weight or improve overall health.

Many adults who are trying to lose weight, or even maintain weight, also report using weight-loss supplements. In 2020, the global weight-loss market was valued at $33.4 billion, with a projected annual growth rate of 16.6% from 2021 to 2028 [1]. While this market value indicates a high rate of use, actual statistics on consumer use are limited. In one survey conducted in 2008, 65.8% of survey participants reporting making a serious weight-loss attempt. Of those respondents, one-third reported using a dietary supplement for weight loss [2].

Weight-loss supplements are often marketed as a method to reduce the amount of effort necessary to lose weight. Although the U.S. Food and Drug Administration (FDA) does not proactively review the safety or efficacy of these products, many consumers are under the false impression that dietary supplements have been approved as safe and effective. Additionally, many consumers believe that any relevant side effects caused by these products will be prominently displayed on the label, which is not the case. Thus, patients often turn to weight-loss supplements due to the incorrect belief that they are safe and potentially effective options for enhancing weight loss [2].

Unfortunately, many products which are marketed for weight loss have not been adequately studied to determine whether they are actually effective. Additionally, while some ingredients are generally safe, others can cause serious adverse effects and should be avoided. Finally, some natural products marketed for weight loss can cause serious interactions with drugs or medical conditions.

This course will cover the major classes of dietary supplements that are marketed for (and used for) weight loss, including digestion inhibitors, appetite suppressants, and thermogenic agents. The course will also cover some common dietary ingredients, such as fruits and fibers, that are also often promoted for weight loss.

APPETITE SUPPRESSANTS

Appetite suppressants have long been used for weight loss. Many of the prescription drugs that have traditionally been used for weight loss fall into this class. These products act on the central nervous system (CNS) to decrease appetite or cause a feeling of fullness or satiety.

One of the oldest prescription appetite suppressant medications—which is still available on the market today—is phentermine, which works by increasing norepinephrine levels. Another, more recent prescription appetite suppressant is bupropion-naltrexone. Sibutramine, which inhibits the reuptake of norepinephrine, serotonin, and dopamine to produce appetite suppression, was also approved as a prescription drug. However, due to serious safety concerns, it was removed from the U.S. market in 2010.

In addition to these prescription options, various dietary supplements are also used as appetite suppressants. Some of these popular products can alter neurotransmitter levels and are thought to act through a similar mechanism of action as the prescription products, although evidence to support this hypothesis is generally lacking.

ST. JOHN'S WORT

St. John's wort (*Hypericum perforatum*) is a plant with yellow, star-shaped flowers that originally gained popularity as an antidepressant dietary supplement. The mild antidepressant properties of this plant appear to be due to the constituents hyperforin and adhyperforin, which partially inhibit the reuptake of serotonin, dopamine, and norepinephrine [3].

This same activity has led to interest in its use as an appetite suppressant. However, no clinical studies have evaluated St. John's wort for this purpose, and it is unclear if the plant or any of its constituents have clinically relevant activity for either appetite suppression or weight loss.

Patients considering St. John's wort as a weight-loss supplement should be aware of the risk for adverse events. Although the plant is considered generally safe for most adults, it has been associated with adverse effects similar to those that occur with selective serotonin reuptake inhibitors (SSRIs), including withdrawal. It has also been associated with photodermatitis. The photosensitivity that occurs with St. John's wort appears to be dose-dependent and occurs more often in women than men [4].

Patients taking other medications may need to steer clear of St. John's wort, which can induce multiple cytochrome P450 (CYP) enzymes, including 3A4, 1A2, 2C19, and 2C9. Together, these enzymes are responsible for metabolizing the majority of prescription drugs available on the market. Induction of these enzymes can increase the metabolism of a drug, reducing its effects. In fact, St. John's wort has been reported to cause life-threatening drug interactions in transplant patients taking immunosuppressants [5].

5-HTP

This chemical is naturally produced in the body from the essential amino acid L-trytophan; it is then converted to serotonin. The 5-HTP that is found in dietary supplement products, however, is typically obtained from the seeds of a plant called *Griffonia simplicifolia*.

Very small clinical studies suggest that 5-HTP can improve satiety, reduce caloric intake, and increase weight loss by increasing the levels of serotonin in the CNS. Two of these studies included adult females with obesity and evaluated 5-HTP 300 mg three times daily, taken 30 minutes prior to meals. On average, patients that did not reduce their calorie intake lost 1.7 kg over 6 weeks when compared with placebo. Patients who reduced their calorie intake to about 1,200 calories daily lost slightly more weight when taking 5-HTP, with an average of 3.3 kg lost when compared with placebo [6; 7]. Another study, which included moderately overweight adults with type 2 diabetes, evaluated 5-HTP 250 mg three times daily for 2 weeks. In this study, calorie intake was reduced by about 22% when compared to baseline and body weight decreased by 2 kg when compared to baseline. This study did not enroll a placebo or control group [8].

Unfortunately, these studies were very small and had multiple methodological issues. The efficacy of 5-HTP as an appetite suppressant remains unclear. Additionally, there have been multiple reports of gastrointestinal, psychiatric, and neurological adverse effects with the use of 5-HTP. In serious cases, serotonin syndrome could develop. In general, patients should use caution or avoid 5-HTP supplements for weight loss.

HOODIA

Hoodia (*Hoodia gordonii*) is a succulent plant that is found in the Kalahari Desert. It is purported to have been used by the San bushmen to stave off hunger during long hunts, which has led to interest in its use for weight loss and appetite suppression [9].

The chemicals in hoodia that may be responsible for any appetite suppressant effect are unclear. Some research has suggested that P57, an oxypregnane glycoside found in hoodia, is responsible for any appetite suppressant effects. This chemical is thought to act on the CNS to stimulate sensations of anxiety, although the exact mechanism of action is unknown [10]. Other research has suggested that gordonoside F, a steroid glycoside, is actually responsible for reducing appetite increasing insulin secretion [11].

Despite anecdotal reports of traditional use of hoodia for this purpose, very little clinical research has been conducted. One small study in overweight females shows that drinking a yogurt drink that contains hoodia purified extract 1,110 mg twice daily for 15 days does not reduce calorie intake or body weight when compared with placebo. This clinical study also found that some patients taking hoodia had increased blood pressure and heart rate, with increases of 4.6–11.5 mmHg and 4.8–12.4 beats per minute, respectively [12].

Considering the lack of any apparent benefit and the potential for cardiovascular adverse effects, patients should steer away from the use of hoodia for weight loss.

DIGESTION INHIBITORS

Digestion inhibitors are substances that can reduce the absorption of certain macronutrients, such as proteins, fats, or carbohydrates. Typically, these substances block the enzymes that break down the macronutrients protease, lipase, and amylase, respectively. Proponents of digestion inhibitors claim that blocking the breakdown of these macronutrients will reduce their absorption by the body and result in weight loss.

One example of a prescription digestion inhibitor is orlistat. This drug, which is a reversible lipase inhibitor, blocks the breakdown and absorption of dietary fats in the gastrointestinal tract, which reduces calorie intake. However, halting the breakdown of fats causes uncomfortable adverse effects, including oily stools, flatulence, and leakage. Thus, patients taking orlistat often either discontinue use or transition to a low-fat diet to limit the adverse effects.

There are also a handful of dietary supplement ingredients that are marketed as digestion inhibitors. These ingredients may either be sold as single-ingredient supplement products or added to a combination product for weight loss.

PHASEOLUS VULGARIS

Phaseolus vulgaris (the common bean) is a species of grain legume that is native to Central and South America. This species has multiple variants, which include black beans, green beans, kidney beans, pinto beans, and others, making it the most commonly consumed legume worldwide [13].

These beans contain enzymes that inhibit alpha-amylase, which is responsible for breaking down carbohydrates in the small intestine. Carbohydrates which aren't broken down in the small intestine are instead fermented by bacteria in the large intestine [14]. This has led to interest in using an extract of the common bean as a digestion inhibitor. Additionally, some small clinical studies have suggested that the bean may suppress appetite by suppressing ghrelin [15].

A meta-analysis of the available clinical research shows that taking an extract of *Phaseolus vulgaris* daily for one to three months reduces body weight by about 1.6% when compared with placebo [16]. Additionally, some small studies show that taking a specific extract of white kidney bean 800–1,000 mg three times daily for 5 to 12 weeks reduces body weight by about 1.5–4 kg when compared with either placebo or a control group. It also seems to reduce body mass index (BMI) and waist circumference [17].

Although these studies do suggest that these bean extracts can increase weight loss, any effect appears to be modest at best. For patients who are interested in using these extracts, they seem to be generally safe, with reports of mild adverse effects such as nausea, vomiting, diarrhea, flatulence, constipation, and abdominal discomfort.

CHITOSAN

Chitosan is a derivative of chitin, which is found in the exoskeletons of arthropods such as insects, spiders, and crustaceans. It is also found in some types of fungi. There are a number of commercial uses for chitosan, including as a pharmaceutical carrier and excipient and as a component in tissue engineering and wound healing materials [18].

Chitosan is commonly sold as a dietary supplement and promoted as a fat blocker. It is thought to work by binding to the negatively charged dietary fats and bile acids found in the intestine. This would be expected to reduce their absorption and increase the excretion of fat; however, studies in overweight adults have not found an increase in fat excretion with the use of chitosan [19].

Clinical research in overweight and obese adults shows that taking 1–3 grams of chitosan daily for up to a year may modestly increase weight loss when compared with placebo. However, the average additional weight lost in these trials was only 1 kg [20; 21]. Some of the small clinical studies that have been conducted to date suggest that chitosan is only beneficial when combined with a reduced calorie diet; when patients take chitosan without reducing calorie intake, no benefit is seen.

The very small increase in weight loss that has been seen with chitosan in clinical studies is not likely to result in clinically relevant improvements for patients. However, if patients are interested in taking chitosan supplements, it is considered to be a generally safe option. Some patients have reported mild gastrointestinal adverse effects, including abdominal discomfort, constipation, flatulence, diarrhea, and nausea.

LAXATIVES

It is not unusual for some fad diets to recommend the use of laxatives to assist in weight loss. The general thinking behind this recommendation is that the use of certain types of laxatives—particularly stimulant laxatives—can reduce the absorption of macronutrients from the gastrointestinal tract.

In most cases, fad diets incorporate laxatives that are sold over-the-counter (OTC) as drugs. However, there are also many dietary supplement products that have laxative effects. In fact, natural laxatives are often found in "natural" weight loss products.

One of the most common natural laxatives is senna. Senna, which is the pod or leaf of the plant *Senna alexandria*, contains sennosides which act as stimulant laxatives. This product is available both as a dietary supplement and as an OTC drug. The OTC drug is an FDA-approved stimulant laxative that contains a standardized quantity of sennosides. Supplements, on the other hand, contain variable amounts of the senna leaf, which contains variable amounts of sennosides [22]. The senna leaf is a relatively common ingredient in weight-loss supplement products and "cleansing" products.

Another common natural laxative is castor oil. This oil is derived from castor beans and acts as a stimulant laxative. It has long been used in traditional Indian systems of medicine, including Ayurveda and Unani [23].

Safety

Although these products may be marketed as safe and natural alternatives to OTC laxative options, stimulant laxatives can cause both minor and serious adverse effects. With normal use, these laxatives can cause abdominal pain, discomfort, bloating, cramping, diarrhea, and flatulence. When taken in high doses for long periods of time, they can cause serious fluid loss and electrolyte imbalance [24].

The long-term use of laxatives, particularly stimulant laxatives, can also cause a form of dependence, as well as tolerance. In the case of dependence, patients may begin to require the use of a laxative in order to maintain adequate bowel frequency. As for tolerance, patients may require increasing doses of stimulant laxatives in order to continue achieving the desired effect [24].

FIBER

Fiber is commonly mentioned as a "natural" supplement that can assist with weight loss. The most commonly cited explanation for taking fiber for weight loss—particularly fibers that become very thick or gel-like in the gastrointestinal tract—is that it can increase feelings of fullness, resulting in reduced appetite and overall food intake.

Fiber is an important component of the diet. It is recommended that all adults consume a minimum amount of fiber every day, with recommendations differing depending on age and biological sex. Adult women 19 to 30 years of age should consume at least 28 grams daily; those 31 to 50 years of age should consume 25 grams daily; those 51 or older should consume 22 grams daily. Recommended intake for men is higher, at 34 grams daily for those 19 to 30 years of age, 31 grams daily for those 31 to 50 years of age, and 28 grams daily for those 51 years of age and older [25].

The FDA has an established definition for what can be referred to as a dietary fiber on a product label. This definition essentially states that the fiber must be a naturally occurring, nondigestible carbohydrate that is obtained from plants and has beneficial effects in the body. Fiber can be either water-soluble or water-insoluble. Water-soluble fibers, such as oats, beta-glucans, and barley, help to lower both blood glucose and cholesterol levels. Water-insoluble fibers, such as wheat bran and rice bran, help the body digest food and improve bowel health [26].

Dietary surveys suggest that most adults are not obtaining enough fiber from the diet, so for most adults, increasing fiber intake will be a healthy and beneficial lifestyle modification. Most people can adequately increase fiber intake simply by increasing their intake of certain healthy foods, such as oatmeal, whole wheat cereals, and grains.

Patients who are interested in consuming fiber for the purpose of weight loss may also be interested in taking fiber supplements. Most of the popular fiber supplements on the market contain blond psyllium (*Plantago ovata*), which is a water-soluble fiber that has shown benefits for constipation, coronary heart disease, hyperlipidemia, and diabetes. However, psyllium has not shown benefit for increasing satiety or for improving weight loss [27]. In fact, a systematic review of various dietary fibers found that many fibers do not increase satiety or reduce food intake. The fibers that did not show any benefits included psyllium, corn bran, wheat bran, guar gum, and inulin [28].

There are some fibers that appear to modestly reduce food intake and increase satiety in clinical studies. These fibers include beta-glucans (derived from oats or barley), whole grain barley, lupin, and rye bran [28]. It is important to clarify, however, that these fibers have not always been shown to increase weight loss, regardless of their effects on satiety. For example, beta-glucans has been evaluated in multiple small studies, which have shown that it may improve weight loss by only about 0.8 kg when compared with not consuming beta-glucans; it does not seem to affect waist circumference [29]. Other fibers, such as lupin, appear to reduce satiety but, when evaluated specifically for weight loss, do not seem to be beneficial [30].

Finally, there are some fibers that have shown benefit for both increasing satiety and increasing weight loss when combined with other lifestyle changes.

Flaxseed

This common food contains both fiber and oil. The fiber is found in the seed coat gum, whereas the oil is found within the seed itself. Flaxseed powder typically contains fiber, mucilage, lignan, and oil.

A meta-analysis of clinical studies in overweight and obese adults shows that consuming flaxseed can modestly reduce body weight by an average of 1.8 kg when compared with not consuming flaxseed. It also reduces BMI by an average of 0.6 kg/m^2 and waist circumference by 1.2 cm. These results occurred in people consuming at least 30 grams daily for at least a few months [31; 32].

Some research has also evaluated whether either the isolated flaxseed fiber or the isolated flaxseed oil is beneficial for weight loss. The isolated fiber, or mucilage, may modestly reduce body weight, waist circumference, and BMI when 1,280–2,560 mg is taken daily for 4 months [33]. The oil, on the other hand, does not improve weight loss or other anthropometric measures. However, flaxseed oil is high in omega-3 fatty acids and is considered a healthy component of the diet, regardless of its effects on weight loss [32].

Glucomannan

In clinical studies, glucomannan has both increased satiety and modestly increased weight loss. Glucomannan is an indigestible soluble fiber that is typically obtained from the roots of the konjac plant (*Amorphophallus konjac*). Small clinical studies have shown that it can reduce body weight by about 5 kg when taken in combination with a calorie-restricted diet. It may also modestly reduce BMI, fat mass, and waist circumference. These studies used doses of 3–4 grams daily, divided into two to three doses throughout the day [34; 35].

Inulin

This nondigestible fiber is fermented by the bacteria that naturally reside in the colon. It is found in various plant roots and tubers and is commonly used as a food additive (for bulk). Inulin can also be found in prebiotic and other dietary supplement products.

Some research in overweight and obese females shows that taking inulin 10 grams daily for two months reduces body weight by 2.6 kg when compared with placebo. In studies in which patients increased their levels of physical activity, taking inulin 16 grams daily also reduced BMI [36].

Safety

If patients choose to take a fiber supplement, encourage them to drink plenty of fluids, both for safety and full effect. In order for these fibers to swell up and increase satiety, they must mix with adequate water, typically 500 mL. It is also important for patients to consume enough water to ensure that the fiber supplement reaches the stomach. There have been reports of choking and esophageal obstruction when fiber products are taken without adequate liquids [37].

FRUITS AND FRUIT EXTRACTS

It is not uncommon to hear of certain fruits or fruit extracts being recommended as adjuncts for weight loss. In some cases, this may be due to the belief that the fruit will increase metabolism; in other cases, it may be due to the desire to replace unhealthy calories with healthy calories. In yet other cases, certain fruits are recommended due to their status as "superfoods." This term usually implies that a food yields many nutritional benefits but contains only minimal calories.

For example, acai (*Euterpe oleracea*) is often marketed as a superfood due to its high vitamin and antioxidant content, which is paired with a relatively low sugar content. Similarly, strawberries (*Fragaria vesca*), which are also high in vitamins and antioxidants, tend to be touted as superfoods. However, acai has not been studied for weight loss, and strawberry, which has been evaluated for obesity in multiple clinical studies, has not shown benefits for weight loss [38; 39].

Fruit is a healthy component of the diet. Regardless of whether a specific fruit can actually increase weight loss, substituting other, less healthy food choices with fruit is considered a healthy and beneficial lifestyle change that can improve many measures of cardiovascular health [25].

APPLE

There has been extensive interest in the health benefits of apples, which has led to clinical studies evaluating whole apples as well as apple derivatives, including apple polyphenols and apple cider vinegar.

Small clinical studies evaluating the apple fruit have shown no clear benefit for weight loss. One small study found that people consuming three apples per day lost 1.2 kg, whereas people consuming

oat cookies lost 0.9 kg—a negligible difference in weight loss [40]. Similarly, a small study in females with overweight or obesity found that consuming a juice containing blueberry, apple, chokeberry, and cranberry every day does not improve weight loss or any other anthropometric measures when compared to the patient's baseline weight [41].

Apple cider vinegar is another popular product that is sometimes promoted for weight loss. It is made by fermenting apple juice and contains pectin, vitamins, minerals, acetic acid, and citric acid. One small clinical study shows that drinking 15 mL twice daily for three months, along with a calorie-restricted diet, can modestly increase weight loss when compared with the calorie-restricted diet alone [42]. Some people have suggested that apple cider vinegar may improve weight loss by increasing satiety. However, research shows that drinking 30 mL daily for four days does not alter food intake [43].

AVOCADO

The avocado is another popular "superfood" due to its unique texture and flavor and the higher content of protein, fiber, and monounsaturated fats that it offers in comparison to other fruits. It is also rich in potassium, beta-sitosterol, and various micronutrients while being relatively low in sugar.

Although avocado is a popular component of many diets, it is unclear whether it is beneficial for weight loss. In overweight and obese adults, eating half of an avocado with lunch every day increased satisfaction and reduced the desire to eat when compared with not eating an avocado [44]. However, a large observational study has found that habitual consumption of avocado over five years is not associated with lower body weight when compared with no avocado consumption. Similarly, it does not seem to reduce the odds of becoming overweight or obese over that time period [45].

GRAPEFRUIT

Although grapefruits themselves are often recommended as a component of many fad diets, the whole fruit has not been evaluated for this purpose in clinical research. Rather, clinical studies have focused on grapefruit extract supplement products.

Grapefruit extracts are sometimes marketed as "fat burners" due to laboratory studies that suggest that the flavonoids found in grapefruit can cause lipolysis. Three small clinical studies evaluating one specific product, which contains extracts of orange and grapefruit, suggest that taking the extract daily for 12 weeks can reduce body weight and body fat percentage in healthy overweight adults when compared with placebo. Due to the small size of these studies, any outcomes should be interpreted with caution.

POMEGRANATE

This pomegranate fruit, which has gained widespread attention due to a popular juice product, is also often touted as a superfood due to its high antioxidant content. This has led to the use of pomegranate fruit and fruit juice for various purposes, including high blood pressure, diabetes, weight loss, and even improved athletic performance.

Clinical studies of pomegranate have evaluated the extract, juice, and concentrate. A meta-analysis of the available research shows that none of these products improve weight loss when compared with either placebo or a control. However, many of these studies included adults with normal body weight and were not intended to evaluate weight loss as a primary outcome [46]. One small study that focused on weight maintenance suggests that drinking 120 mL of pomegranate juice daily for one month is beneficial for weight maintenance when compared with placebo [47]. Weight loss was not evaluated in this study.

DRUG INTERACTIONS

Certain fruit juices can alter the absorption or metabolism of many medications. Depending on the juice, this can be due to the inhibition or induction of enzymes that metabolize these medications, such as the CYP enzymes. This can also be due to the inhibition or induction of transporters that carry medications into cells, including the organic anion-transporting polypeptides (OATP).

Grapefruit is an especially significant culprit and can cause major drug interactions with a wide range of medications. Whole grapefruit, grapefruit juice, and grapefruit extracts have been shown to inhibit CYP3A4, which is responsible for the metabolism of a large number of prescription drugs. A sample list of affected drugs includes clopidogrel, amiodarone, atorvastatin, carvedilol, estrogen, and losartan; CYP3A4 is responsible for the metabolism of hundreds of drugs. The effects of grapefruit on CYP3A4 can last for at least 48 hours, so simply separating the consumption of grapefruit from medications will not prevent an interaction. Generally, patients who are taking medications that can interact with grapefruit should avoid grapefruit products altogether.

Apple is a lesser-known cause of drug interactions. Apple juice can inhibit OATP, which can reduce the availability of many oral drugs, including fexofenadine, atenolol, and aliskiren. For example, clinical research shows that taking fexofenadine along with apple juice can decrease the bioavailability of fexofenadine by 78%. However, unlike with grapefruit, the effects of apple are short-lived. Thus, separating drug administration from consumption of apple juice by at least 4 hours may reduce the risk of an interaction.

THERMOGENIC AGENTS

Thermogenic agents, often referred to as "fat burning" drugs, increase energy expenditure. In the US, there are currently no prescription drugs that are classified as thermogenic agents. However, there are a handful of dietary supplement products that are marketed and used for this purpose.

CAFFEINE

Perhaps the most popular and well-known thermogenic agent is caffeine. Most people consume caffeine to improve mental alertness via a range of beverages, including coffee, tea, and energy drinks. However, caffeine is also available in dietary supplements, and these products may be marketed for multiple purposes, such as increasing energy levels and enhancing weight loss.

Although caffeine has never been directly evaluated for weight loss, research has established that caffeine intake increases resting energy expenditure, resting metabolic rate, and cellular thermogenesis [48]. Additionally, some clinical research has shown that a single large dose of caffeine can modestly increase fat oxidation during exercise [49]. Proponents of caffeine theorize that these mechanisms of action can contribute to additional weight loss in people who are actively trying to lose weight.

Safety

When used in moderation, caffeine is generally safe. The available clinical research indicates that consuming up to 400 mg of caffeine daily is not associated with an increased risk of major chronic conditions [50]. This quantity of caffeine can be obtained from approximately 4 cups of coffee or 8 cups of green tea.

Higher daily doses of caffeine can increase the risk of adverse effects, including palpitations, anxiety, restlessness, and diarrhea. Also, chronic use of caffeine can result in tolerance and habituation, which can lead to symptoms of withdrawal when caffeine is not consumed [50]. Patients should be counseled on the importance of limiting daily caffeine intake to no more than 400 mg.

Keep in mind that only the amount of added caffeine must be stated on product labels. The amount of caffeine from caffeine-containing natural ingredients such as coffee or green tea does not need to be provided. In other words, a beverage that contains coffee with additional caffeine may only state the amount of added caffeine in the beverage; the caffeine that is naturally found in the coffee does not need to be listed on the label. This can make it difficult to determine the total amount of caffeine in a given product.

It is also important to remember that, despite its prevalent use, caffeine can cause a number of drug interactions. Caffeine is metabolized by CYP1A2—drugs that can inhibit this enzyme can increase levels of caffeine in the body, which may increase the risk for caffeine-related adverse effects. There have also been multiple reports of caffeine decreasing the levels of other drugs in the body, which can alter the effects of those medications [51].

Very high doses—about 10–14 grams of caffeine—can be fatal. Although this dose would be difficult to obtain from a caffeinated beverage, it can be accidentally obtained from highly concentrated or purified formulations of caffeine. Concentrated liquid caffeine can contain about 2 grams of caffeine in one-half of a cup. Powdered pure caffeine can contain about 3.2 grams of caffeine in a single teaspoon. This means that powdered pure caffeine can be fatal when taken in a quantity of only 2 tablespoons [52].

Due to the risks associated with pure formulations of caffeine and the multiple reports of death due to accidental overdose, the FDA has deemed these products to be unlawful when sold to consumers in bulk quantities. However, these products can still be purchased online [53].

GREEN TEA

Many weight-loss supplements contain green tea extract. Although it might be assumed that green tea extract is popular for weight loss due to its caffeine content, caffeine is only one component of green tea extract that is thought to promote weight loss. Another substance, called epigallocatechin gallate (EGCG), has been shown to increase the metabolism of calories and fat in early research. The caffeine in green tea is thought to enhance and contribute to this effect [54].

Clinical research evaluating green tea extract for weight loss is conflicting, however. Many clinical studies in adults with overweight and obesity show that taking green tea extract containing about 70–200 mg caffeine and 576–886 of catechins (primarily EGCG) modestly improves weight loss when compared with a control group. The average additional weight loss appears to be only about 1.8 kg, and some clinical studies have shown no additional weight loss with the use of green tea extract [55]. It is possible that some of these studies used decaffeinated green tea products or products with lower quantities of EGCG, which may have reduced any weight-loss effects.

Safety

Green tea (as a beverage) and green tea extract (taken orally) are both generally safe when used in moderation. Some patients have reported bloating, constipation, diarrhea, dyspepsia, flatulence, and nausea with use.

There is some concern that certain green tea extracts may cause hepatotoxicity. There have been numerous case reports of hepatotoxicity with green tea extracts; however, the actual rate of occurrence is estimated to be about 1 in 2.7 million patients. It is unclear whether certain factors can increase the risk of liver damage, although there is some indication that higher doses of EGCG, and higher peak plasma concentrations of EGCG, may be associated with an elevated risk [56].

To reduce the risk of hepatotoxicity, patients with existing liver dysfunction should avoid use. The United States Pharmacopeia (USP) requires all green tea products that are USP-verified to include the following text on the label: "Do not take on an empty stomach. Take with food. Do not use if you have a liver problem and discontinue use and consult a healthcare practitioner if you develop symptoms of liver trouble, such as abdominal pain, dark urine, or jaundice (yellowing of the skin or eyes)" [57].

EPHEDRA

Ephedra, also known as *ma huang*, used to be a common ingredient in weight-loss supplements. The ephedra plant naturally contains ephedrine, pseudoephedrine, and phenylpropanolamine and has been shown to promote weight loss. However, ephedra has also been associated with serious adverse effects [58].

Ephedra has been linked to numerous cases of heart attack, arrhythmia, stroke, psychosis, seizures, and death. In 2004, after several years of legal wrangling, the FDA banned ephedra products in the United States due to safety concerns [59]. Prior to the ban, ephedra products accounted for 1% of herbal product sales but were responsible for 64% of herbal adverse reaction reports to poison control centers [58].

BITTER ORANGE

Bitter orange (*Citrus aurantium*), which should not be confused with the commonly consumed sweet orange, is a fruit that is considered too sour to eat raw. Instead, the fruit, as well as its peel and essential oils, are used for flavoring and aroma. Certain substances found in the peel of the bitter orange are also included in weight-loss supplements. In fact, when ephedra was removed from the market, many manufacturers replaced the ephedra in their weight loss products with bitter orange extracts.

For the purposes of weight-loss supplements, the most important chemical in the bitter orange peel is synephrine. This chemical can increase resting energy expenditure, metabolic rate, and fat breakdown. In healthy humans, a single dose of synephrine has been shown to increase fat oxidation during exercise [60]. However, clinical research has shown that taking 6–214 mg of synephrine daily for 8 weeks does not reduce body weight or fat mass when compared with placebo [61].

Some bitter orange supplements also contain a chemical called octopamine. Although this chemical does occur naturally in the peel of the fruit, it is only present in quantities of less than 0.03%. Thus, it is likely that the octopamine found in bitter orange dietary supplements is actually synthetic and has been added in addition to the bitter orange itself [62]. Although animal research has found that octopamine stimulates lipolysis, octopamine appears to have only minimal activity in human fat cells [63].

Safety

Unfortunately, synephrine can cause many of the same adverse effects as ephedra, including elevated blood pressure and heart rate [61]. It has also been associated with heart attack, seizure, stroke, and serious arrhythmias [64]. Although clinical research on octopamine is lacking, it is chemically similar to synephrine and may be associated with many of the same safety concerns [65].

Many weight loss products that contain bitter orange also contain caffeine. The combination of synephrine and caffeine can increase the risk of cardiovascular adverse effects, including QT interval prolongation [66].

MISCELLANEOUS AGENTS

There are many dietary supplement ingredients that are marketed for weight loss and yet do not fit into any specific classification. Some of these ingredients are mainstays in the weight-loss market, whereas others come and go as fads and trends change.

BERBERINE

This ingredient has seen a relatively recent surge in popularity, obtaining the Internet nickname of "nature's Ozempic." Berberine is a yellow-colored alkaloid that is found in the roots and stem bark of multiple plants, including European barberry, Oregon grape, phellodendron, and tree turmeric.

Its reputation as a natural alternative to semaglutide, a prescription GLP-1 agonist, has not been earned. Thus far, clinical research suggests that taking berberine 300–3,000 mg daily for 1 to 24 months may modestly reduce body weight by an additional 3 kg when compared to baseline (no placebo control was used) [67]. Most of these studies have been small and have had major methodological issues, limiting any interpretation.

Berberine has the potential to interact with a number of drugs by inhibiting CYP3A4, 2C9 and 2D6. It has been shown to increase blood levels of important medications like cyclosporine, tacrolimus, and midazolam [68; 69; 70]. Considering its apparent limited benefits for weight loss, patients taking medications should steer clear of berberine.

COLLAGEN PEPTIDES

Collagen is another product that has gained recent popularity for weight loss. This hard, insoluble protein occurs naturally in the human body and is found in the muscles, skin, tendons, ligaments, and connective tissues, including cartilage and bone. There are many different types of collagen; however, types I, II, and III are thought to make up 80% to 90% of all collagen in the human body [71].71

Collagen peptides (hydrolyzed collagen) are the form of collagen typically being promoted for weight loss. Collagen peptides are created by enzymatic degradation of collagen via the use of specific proteinases. This produces shorter peptides with an average size of 3.3 kilodaltons [71].

Although there are many proposed theories as to why collagen peptides may promote weight loss, none of these theories have been validated in research. Similarly, there is limited clinical research evaluating the effects of these supplements for actual weight loss. That being said, for patients still interested in trying them, collagen peptides are generally safe for use and do not have any known drug interactions [72].

CONJUGATED LINOLEIC ACID (CLA)

Conjugated linoleic acid (CLA) is a fatty acid that is found in a typical diet, with sources such as milk products, beef, soybean oil, and safflower oil. Some laboratory research suggests that this fatty acid can promote lipolysis, which has led to interest in its use for weight loss.

Clinical research shows that taking CLA 3.4 grams daily can decrease total body fat mass, increase lean body mass, and reduce waist circumference. Interestingly, however, CLA does not seem to decrease overall body weight or BMI. Doses of greater than 3.4 grams daily do not seem to provide any additional benefit over lower doses [73].

Some patients have reported diarrhea, dyspepsia, flatulence, and nausea with the use of CLA supplements, but CLA is otherwise considered to be generally well tolerated.

GARCINIA

One supplement that has seen fluctuating popularity over the past decade is garcinia (*Garcinia gummigutta*). Garcinia extract contains hydroxycitric acid (HCA), which is thought to reduce the production of fatty acids in the body. However, clinical research on the use of garcinia for weight loss is conflicting, with one meta-analysis suggesting that taking this product for two to three months may increase weight loss by about 1.3 kg when compared with a control group [74].

Although garcinia appears to be generally well tolerated, there is some concern that the HCA found in this ingredient may cause liver damage in some patients. Several cases of liver toxicity have been reported in patients taking garcinia supplements, but it is not clear whether garcinia was the cause of these adverse events. Many patients were taking combination products, including products that contained green tea extract [75].

Garcinia also has serotonergic effects and has been linked to several cases of mania. Its serotonergic activity may also increase the risk of serotonergic side effects, including serotonin syndrome, when used with drugs that have serotonergic activity. In one case report, a patient taking garcinia extract in conjunction with an SSRI experienced serotonin syndrome [76].

GYMNEMA

This plant (*Gymnema sylvestre)* has gained popularity for weight loss due to a very unique mechanism of action—altering the sense of taste. Certain chemicals found in gymnema can inhibit the ability to taste either bitter or sweet flavors. In some small clinical studies, taking gymnema reduced the consumption of sweet foods when compared with taking placebo, suggesting that this supplement may help with weight loss [77; 78].

However, the clinical studies conducted to date have been small and have shown no clear benefit. These studies used a dose of 300 mg twice daily for 3 months. Although one study found a reduction in body weight, that study did not have a placebo comparator group [79]. Another study that did have a placebo comparator group did not find a reduction in body weight [80].

That being said, gymnema does seem to be generally well tolerated with minimal reported adverse effects. Patients who are interested in altering their taste perceptions as a way to reduce overall food intake could consider taking a gymnema supplement.

PYRUVATE

A specific form of pyruvate—calcium pyruvate—has seen recurring popularity as a weight-loss supplement. Pyruvate is an organic acid that is naturally formed from glucose in the body. Laboratory research suggests that calcium pyruvate increases fat oxidation and reduces weight gain in animals [81].

Several small clinical studies in adults with obesity or hyperlipidemia show that taking pyruvate 6–44 mg daily for up to six weeks, in combination with a low-calorie diet, can increase weight loss by an additional 0.7 kg when compared with various diet and exercise strategies without calcium pyruvate [82; 83]. It isn't clear whether calcium pyruvate has any benefits in people who are not on a reduced calorie diet.

Calcium pyruvate is generally well-tolerated, with some patients reporting bloating, diarrhea, and flatulence. Unlike many of the other dietary supplement ingredients used for weight loss, there are no known drug interactions with this product.

GENERAL SAFETY CONSIDERATIONS

INHERENT RISKS WITH COMBINATION SUPPLEMENTS

Many weight-loss supplement products contain a large number of ingredients. Any time that multiple ingredients are added to a product, there is an increased risk for adverse effects and interactions. In some cases, these products may also contain "proprietary blends" of ingredients. Proprietary blends are not required to list the actual quantity of each ingredient on the product label. Thus, it can be difficult to determine from the supplement label whether a product with a proprietary blend contains a small or large quantity of a given ingredient.

MISLEADING SUPPLEMENT LABELS

Many ingredients found in dietary supplements can be listed under a number of different names. For instance, *Phaseolus vulgaris* can be listed under its scientific name, or under "kidney bean extract," or even under "common bean extract." In some cases, these names may be even more difficult to parse. For example, bitter orange is also called *Citrus aurantiam* but may also be listed on a product label as neroli oil or orange peel extract. Caffeine can also be hidden on a dietary supplement product label. Some products that contain caffeine may only list the name of a natural ingredient that contains caffeine, such as guarana, cola nut, mate, and/or tea extract. This can make it difficult to determine whether a product contains an ingredient that is likely to introduce a higher risk for adverse effects.

Similarly, while some products may list the amount of the active ingredient on the product label (e.g., in the case of St. John's wort, a product may list its hyperforin content), others will list only the total quantity of the plant. This may be true for a wide range of ingredient types, including fiber, which may only list the quantity of psyllium and not the amount of fiber provided, and apple cider vinegar products, which often do not list the amount of acetic acid present.

PRODUCT QUALITY AND CONTAMINATION CONCERNS

It is very important to recognize that, as a class, dietary supplements for weight loss are at an increased risk for adulteration. This means that many of these products have been found to contain ingredients that are not listed on the label. In fact, the prevalence of adulterated (contaminated) weight loss products is so high that the FDA has launched a targeted initiative related to these products. To answer consumer and healthcare professional questions about the risks associated with these products, the FDA now hosts a Q&A page on the topic [84].

In the vast majority of cases, weight-loss supplements are adulterated with sibutramine, a prescription drugs that was removed from the U.S. market in 2010 due to serious safety concerns. These concerns included heart attack, stroke, and arrhythmia. This drug can also interact with a number of medications and is more likely to cause serious issues in patients with certain conditions, such as hypertension, cardiovascular disease, liver dysfunction, and more.

Third-Party Quality Verification

To ensure that a patient is selecting a high-quality dietary supplement product, it is generally best to look for third-party quality certification stamps, such as those from USP or NSF. Unfortunately, most dietary supplements that are marketed for weight loss do not carry these stamps, increasing the likelihood for quality and contamination issues. When a certified product cannot be identified, it may be best to counsel patients on foregoing use.

CONCLUSION

Despite the exceptional amount of hype surrounding many weight-loss supplements, the majority of these products have not been adequately evaluated for either safety or efficacy. Of the ingredients that have been studied, most have shown either no efficacy or only minimal benefits for weight loss. And some of these ingredients are known to increase the risk for serious adverse effects, including cardiovascular and hepatic adverse effects. Additionally, a number of ingredients that are found in weight-loss supplements can cause serious drug interactions by inducing or inhibiting important drug metabolizing enzymes.

Understanding the reasons that these products are used, as well as their actual risks and benefits, will allow healthcare professionals to help patients sift through the hype, avoid dangerous products, and save money on products that are unlikely to work.

Implicit Bias in Health Care

The role of implicit biases on healthcare outcomes has become a concern, as there is some evidence that implicit biases contribute to health disparities, professionals' attitudes toward and interactions with patients, quality of care, diagnoses, and treatment decisions. This may produce differences in help-seeking, diagnoses, and ultimately treatments and interventions. Implicit biases may also unwittingly produce professional behaviors, attitudes, and interactions that reduce patients' trust and comfort with their provider, leading to earlier termination of visits and/or reduced adherence and follow-up. Disadvantaged groups are marginalized in the healthcare system and vulnerable on multiple levels; health professionals' implicit biases can further exacerbate these existing disadvantages.

Interventions or strategies designed to reduce implicit bias may be categorized as change-based or control-based. Change-based interventions focus on reducing or changing cognitive associations underlying implicit biases. These interventions might include challenging stereotypes. Conversely, control-based interventions involve reducing the effects of the implicit bias on the individual's behaviors. These strategies include increasing awareness of biased thoughts and responses. The two types of interventions are not mutually exclusive and may be used synergistically.

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