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A Literature Review on Nutritional Supplements for the Treatment of Obesity

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***Abstract*—**The problem of obesity is one that continues to be faced in the United States health care system and across the developing world. Prescription medications are available, but are often very expensive with minimal insurance coverage. The over-the-counter diet aid industry is a robust one, selling billions of dollars in products every year. It is important for clinicians to understand the myriad of different nutritional supplements marketed for obesity, and to weigh the evidence behind these products. This manuscript outlines the most commonly used nutritional supplements currently marketed for weight loss, reviewing the evidence with a focus on the efficacy and safety of these products.

***Keywords*—**Obesity, weight loss, herbal products, nutritional supplements

I. Introduction

OBESITY and the complications that arise from it continue to be a challenge to the United States (U.S.) health care system, as well as developing countries throughout the world. Current estimates for the prevalence of obesity in the U.S. state that approximately 65% of the adult population is overweight or obese, and that childhood obesity in the country has tripled since the 1970s [1], [2]. Economically, the cost for treating obesity and its complications was estimated at $147 billion in 2008, accounting for 10% of all U.S. health care spending that year [3]. It is estimated that obese individuals spend 41.5% more on medical expenditures compared to their normal weight counterparts [3]. Obesity contributes to type 2 diabetes, heart disease, and cancer, all of which are among the top leading causes of death in the country [4].

Over 51% of adult Americans report wanting to lose weight, with over 108 million people dieting in the U.S. annually [5]; this translates to over $2.4 billion being spent in the country each year for weight loss [6]. Due to this robust industry, there are a number of over-the-counter agents that have been promoted for weight loss. This article reviews the current literature surrounding integrative health and medicine specifically used in obesity or to aid in weight loss.

II. Classification

Due to the large number of natural substances that have been evaluated for their effects on obesity, a classification system is necessary in order to help categorize the agents and provide guidance to clinicians regarding potential mechanisms in the body. Natural Medicines™ provides a good categorization system for weight loss supplements, and this system has been maintained for simplicity in this review [7]. Agents were identified by performing a literature search through PubMed, Google, and Google Scholar; searches included the terms obesity, weight, and weight loss, combined with the terms herbal, complementary medicine, plant sources, nutritional supplements, and over-the-counter agents. Reference lists from retrieved articles, as well as those from relevant review articles in this area were considered. Table I presents the various agents identified as potential anti-obesity agents by classification.

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III. Appetite Suppressants

Appetite suppressants are a category of agents that are associated with central activity in the body, affecting the brain's perceptions of hunger and satiety. This group of agents, also known as "anorexiants", affects various neurotransmitters or other brain signaling to reduce food intake. These agents are considered *stimulants* due to their ability to affect epinephrine and norepinephrine, neurotransmitters involved in the fight or flight response, which typically suppress appetite.

A. Hoodia Extract (Hoodia gordonii)

Hoodia refers to a group of over 20 different cacti succulent plants indigenous to Africa. Natives are known to chew hoodia during long hunts to provide energy and stave off hunger. The active ingredient, coined *P57*, has been evaluated for its efficacy in weight loss and appetite control. Animal studies, primarily conducted in rats, show decreased food intake and decreased overall body mass with hoodia use over short durations. There are limited human trials conducted on hoodia, and they show conflicting results. A small randomized placebo-controlled trial (RCT) with 103 subjects conducted over 40 days demonstrated a statistical change in body weight (-0.58 kg vs +0.2 kg in placebo, p=0.046) [8]. Other trials, including unpublished data, do not support these findings.

Hoodia appears to be safe across human trials, which is an important consideration, due to P57's low overall bioavailability. Subjects reported higher rates of nausea, vomiting, and skin sensation disturbances with treatment, but no severe adverse reactions have been identified. Adulteration is a common problem with Hoodia supplements, due to the slow-growing nature of the plant and limited number of

available plants.

B. Caralluma (Caralluma fimbriata)

The supplement caralluma is another edible cacti species used by natives for similar stamina and appetite suppressant benefits. The plant grows wild as a roadside shrub.

There are limited data in humans regarding the safety and efficacy of caralluma. A small trial conducted over 60 days showed significant reductions in waist circumference and hunger levels, with BMI reductions that trended towards significance [9]. Another small trial over 12 weeks demonstrated significant total body weight and BMI reductions with the active group using 1 gram of caralluma [10]. The supplement was well tolerated in both trials, with the most prevalent side effects reported being gastrointestinal symptoms. The total population studied across these studies was only 93 subjects, highlighting the need for further research on this supplement.

TABLE I
COMMONLY USED NUTRITIONAL SUPPLEMENTS FOR OBESITY

Class	Common Name	*Genus*	Evidence
Appetite suppressants	Hoodia	*Hoodia gordonii*	Limited data
	Caralluma	*Caralluma fimbriata*	↓waist circumference
	5-HTP	*N/A*	Modest (1.7kg) loss
Digestion Inhibitors	Barley	*Hordeum vulgare*	Increased satiety
	Bean pod	*Phaseolus vulgaris*	Modest (1.9kg) loss
	Blonde psyllium	*Plantago ovata*	Modest (2.0kg) loss
	Fenugreek	*Trigonella foenum-graecum*	Increased satiety
	Glucomannan	*Amorphophallus konjac*	Slight (0.22kg) loss
	Guar Gum	*Cyamopsis tetragonoloba*	No benefit
	Chitosan	*N/A*	Moderate (3.3kg) loss
Thermogenic Agents	Ephedra	*Ephedra sinica*	Safety concerns
	Bitter orange	*Citrus aurantium*	Modest (1.5kg) loss
	Capsaicin	*Capsicum genus*	↓ Adipose tissue
Miscellaneous	Aristolochia	*Aristolochia auricularia*	Renal toxicity
	Cha de bugre	*Cordia ecalyculata*	Lacks evidence
	Forskolin	*Coleus forskohlii*	Increased satiety
	Garcinia	*Garcinia cambogia*	Modest (1.4kg) loss
	Usnea	*Usnea barbata*	Liver toxicity
	Irvingia	*Irvingia gabonensis*	Moderate (5%) loss
	Green tea	*Camellia sinensis*	Modest (0.9kg) loss
	7-keto DHEA	*N/A*	Lacks evidence
	Chromium	*N/A*	Conflicting data
	CLA	*N/A*	↓Adipose tissue
	Pyruvate	*N/A*	Modest (0.7kg) loss
	Raspberry Ketone	*N/A*	↓ Adipose tissue

C. 5-Hydroxytryptophan

The substance 5-hydroxytryptophan, or 5-HTP, is produced naturally by the body as a precursor to serotonin. While its main use is for the treatment of depression, it has been evaluated for weight loss benefits. Studies have shown a benefit of weight loss of approximately 1.7 kg over six weeks, an effect that is augmented with caloric restriction to 3.3 kg over the same time interval [11]. Another trial evaluated the effects of 5-HTP on overweight patients with type 2 diabetes, and demonstrated a 2 kg body weight reduction, as well as decreased caloric intake [12]. All of these trials used the supplement three times a day before meals.

In regards to safety, 5-HTP was generally well tolerated in human trials. Due to the formation of serotonin from the supplement, concurrent use of 5-HTP with other antidepressants or other serotonergic drugs should be avoided due to risk of serotonin syndrome. Further evidence is needed to clarify 5-HTP's role in obesity.

IV. DIGESTION INHIBITORS

Evaluating digestion inhibitors for their weight loss effects stemmed from the success seen with the lipase inhibitor orlistat, available both by prescription and over-the-counter in the U.S. Clinicians began to use various fibers to minimize the side effects of orlistat, and theorized that these fibers, themselves, may have clinical benefit in weight management.

A. Fiber Products (Bean Pod, Barley, Psyllium, Fenugreek, Glucomannan and Guar Gum)

There appears to be a consistent, modest weight loss effect with the use of various soluble and insoluble fibers. A review examining various fibers classified wheat bran and oatmeal as having the best weight loss effects, followed by psyllium, with guar gum not showing benefit [13]. A meta-analysis performed in 2009 quantified fiber's effects at approximately 4.9% reduction of body weight at 8 weeks, compared to 2.9% reduction in placebo [14]. Two prospective cohort studies evaluated the effects of dietary fiber consumption and weight gain. The first, following over 74,000 women, showed that those with the highest quintile of fiber consumption had 49% lower risk of major weight gain compared with the lowest quintile [15]. The second, a European study with over 900,000 subjects, associated increased fiber consumption with reduced

waist circumference and lower weight [16].

B. Chitosan

Chitosan is derived from the shells of crustaceans, and has been studied for potential weight loss by blocking the absorption of fat. There are a number of smaller studies evaluating the metabolic effects of chitosan, with conflicting results. A meta-analysis performed in 1998 showed an overall weight loss effect of approximately 3.3 kg between chitosan and placebo groups [17]. Some of these trials, however, were criticized for their design and methodological flaws. A second meta-analysis including only larger, higher quality studies, found the weight loss effect to be much more modest, around 0.5 kg, when taken for 1-6 months [18]. Across trials, chitosan was well tolerated, with only transient or mild side effects reported.

V. Thermogenic Agents

The thermogenic agent classification refers to supplements that affect the body's metabolic rate, increasing the rate of calorie consumption. These agents often influence neurotransmitters that affect physiologic arousal, such as epinephrine and norepinephrine.

A. Ephedrine (Ephedra sinica)

The most well known thermogenic agent is ephedrine, also known as *ma huang* in Chinese medicine, a supplement widely studied and marketed for weight loss in the late part of the 20th century. There are a number of studies documenting successful weight loss with ephedrine, used alone or in combination with other supplements. A 24-week randomized, placebo-controlled trial evaluated ephedrine and caffeine with or without leptin in 90 patients [19]. The trial demonstrated significant weight reductions in both ephedrine arms, with or without leptin, compared to leptin therapy alone. A meta-analysis published in 2003 evaluated the safety and efficacy of ephedrine across 22 trials [20]. These trials were all of short duration (< 6 months), but collectively demonstrated a weight loss benefit of approximately 0.6-1 kg per month of treatment compared to the placebo group.

There are well-documented safety concerns with ephedrine use, which led to the supplement's removal from the U.S. market in 2004. The same meta-analysis estimated a 2.2-3.6 fold increase in risk for adverse events, including psychiatric symptoms, gastrointestinal distress, and heart palpitations [20]. This article further cited another case-control study where ephedrine doses over 32 mg/day were associated with increased risk of hemorrhagic stroke. These safety concerns far outweighed any benefits shown with the supplement.

B. Bitter Orange (Citrus aurantium)

Bitter orange is a supplement structurally similar to ephedrine, which has fallen under similar criticism for safety concerns due to these structural similarities. The active ingredient is the alkaloid synephrine, which has been shown to increase metabolism and possibly induce lipolysis. Efficacy studies have shown varying effects of weight loss, but are difficult to attribute directly to synephrine because many studies use combination products that also contain caffeine and other supplements. A review article evaluating over 20 human trials concluded that synephrine increased metabolic rate and energy expenditure, and that in the short term (~12 weeks) produced a modest weight loss effect, estimated between 1-2 kg [21].

In regards to safety, the specific enantiomer p-synephrine has been studied in some depth. The same review evaluated various safety parameters of p-synephrine, with a particular focus on cardiovascular parameters and blood chemistry. The authors found no significant adverse events across these trials, and hypothesized that previously identified cardiovascular adverse events were due to other isomers of synephrine, which may cross the blood-brain barrier more readily or bind more efficiently to catecholamine neurotransmitters. Another review and a study focused specifically on p-synephrine's safety profile demonstrated similar findings, where there was little or no negative cardiovascular effect [22], [23]. These data suggest that utilizing the proper p-synephrine source can safely produce modest weight loss over a short term, but longer-term trials are needed.

C. Capsaicin (Capsicum genus)

Capsaicin originates from the cayenne pepper, and has been prepared topically, orally, and through various cooking recipes for a variety of medicinal uses. It is thought to activate brown fat thermogenesis, leading to fat burning and weight loss. Two large epidemiological studies associated the consumption of dietary chili peppers with decreased body mass, leading to interest in capsaicin [24], [25]. A small, 13-week study demonstrated that subjects using a capsaicin extract formulation put into capsules had a greater reduction in abdominal adiposity, but no overall weight difference when compared to a control [26].

Capsaicin has been well established as having a good safety profile with use. Topical preparations are associated with burning and skin irritation, due to the pepper qualities of the supplement. It has been shown safe both as a food additive, as well as with oral supplementation. Capsaicin holds *Generally Recognized as Safe* (GRAS) status with the U.S. Food and Drug Administration (FDA).

VI. Miscellaneous Agents

A. Aristolochia (Aristolochia auricularia)

Aristolochia, or aristolochic acid, is a traditional botanical medicine used in many Chinese medicine preparations. The genus comprises over 800 similar species of plants that grow wild in a variety of temperate and tropical regions. Aristolochia contains a variety of alkaloids and flavonoids that are responsible for its pharmacologic actions.

There is limited evidence regarding Aristolochia's efficacy in weight loss. This herb was included in a variety of commercial weight loss products, but was removed after some serious safety concerns emerged. Case reports of serious nephrotoxicity emerged associated with the supplement, with

concerns about its carcinogenic properties emerging soon after. The increased number of adverse events associated with Aristolochia prompted the FDA to issue a consumer warning in 2001 to avoid any products that may contain the supplement [27]. Any therapeutic benefit it may hold is overshadowed by these serious toxicities.

B. Cha de bugre (Cordia ecalyculata)

The supplement Cha de bugre originates from a Brazilian plant historically known to produce energy and suppress the appetite. It has been called "Brazilian coffee", or "coffee of the woods". There are a variety of commercial products, marketed as Brazilian diet aids, containing this compound.

There is limited evidence currently evaluating claims around the efficacy of Cha de bugre in helping with appetite suppression or weight loss. While there exists rich cultural beliefs around this plant, there are very few scientific studies evaluating any medicinal properties. More research needs to be performed to establish both the safety of the supplement as well as any efficacy seen with its use.

C. Forskolin (Coleus forskohlii)

Coleus forskohlii is a mint plant native to India that has been evaluated for its medicinal properties. The active ingredient stems from the root of the plant, which have activity on adenylate cyclase, leading to increasing levels of cyclic AMP (cAMP), resulting in increased lipolysis and subsequent weight loss. There have been a few small studies evaluating Forskolin's effects on weight in humans. A study following 23 women over 12 weeks showed that Forskolin use was associated with less fatigue and hunger, and more satiety, but failed to demonstrate any significant body weight changes or caloric intake [28]. Another study conducted in 30 overweight or obese men did establish a statistically significant decrease in total body fat percentage compared to the placebo (-4.14 +/- 4.47% compared with -0.96 +/- 1.66%, $p<0.05$) at twelve weeks [29]. In regards to safety, the supplement was well tolerated with no adverse effects occurring at higher rates than the placebo. These small studies suggest a potential role for Forskolin, but larger population sizes are needed to confirm its safety and potential effectiveness.

D. Garcinia (Garcinia cambogia)

The dried rind of the Southeast Asian plant produces Garcinia, an herb studied for weight loss, joint pain, and as an anti-parasitic. The active ingredient from the rind is hydroxycitric acid, or HCA. HCA is thought to decrease the synthesis of fatty acids by the inhibition of ATP-citrate lyase enzyme.

Garcinia has been associated with a modest, approximately 1.4 kg weight loss when compared to placebo over short intervals of 8-12 weeks in two studies, conducted in 50 women and 200 subjects, respectively [30], [31]. The product was well-tolerated, with no serious adverse effects reported. Another study with 135 subjects showed significant weight loss in both the Garcinia and the placebo group at 12 weeks, but there were no differences between the two groups in either body weight or fat mass loss [31]. These trials suggest a modest benefit with short-term use of Garcinia.

E. Usnea (Usnea barbata)

Usnea originates from moss or lichen that grows on a variety of different tree species. It has been included in a variety of commercial diet aids, thought to increase metabolism and burn fat. There is little standardization or human studies evaluating Usnea's efficacy in weight loss, likely due to safety concerns.

Shortly after the inclusion of Usnea in over-the-counter diet products, a series of case reports came out citing severe liver toxicity with the supplement's use. A number of *in vitro* laboratory studies and animal studies demonstrated clear detrimental effects of Usnea on the liver, elevating liver enzymes and damaging liver cells, with one study showing effects similar to a known hepatotoxic compound, carbon tetrachloride [32]. Due to these safety concerns, Usnea should be avoided.

F. Irvingia (Irvingia gabonensis)

The African bush mango, Irvingia gabonensis, has medicinal properties attributed to its fruits and seeds. It is thought to inhibit adipogenesis, and may have some effects on gut hormone secretion, promoting fullness and weight loss. A review article published in 2013 evaluated the different trials associated with Irvingia, but was limited by poor study designs and methodology, leading to inclusion of only three trials out of the original 431 identified [33]. These three studies did demonstrate significant weight loss with Irvingia use compared with placebo (12.8 kg vs. 0.7 kg, $p<0.01$) [34], (4.1 kg vs. 0.1 kg, $p<0.01$) [35], and (11.9 kg vs. 2.1 kg, $p<0.001$) [36]. The review article authors identified a 10-week time point to compare these three studies, which showed a 5% or greater weight loss from baseline with Irvingia use compared to placebo, which is clinically relevant and comparable to existing prescription medications. Waist circumference was also reduced in these trials.

In regards to safety, the supplement was well tolerated across these trials, which is notable, because the second trial used approximately 10-fold higher amounts of Irvingia then the other two studies and still showed low incidence of adverse events. These data suggests that there could be a substantial role for Irvingia for weight loss and obesity treatment.

G. Green Tea (Camellia sinensis)

The dried leaves of the Camellia sinensis tree are used in a variety of tea preparations, and are well-known for anti-oxidant and medicinal effects. The active ingredient for green tea is epigallocatechin-3-gallate, or EGCG. Doses around 500-1000 mg daily have been evaluated for weight loss properties. Overall, the data are mixed regarding green tea's ability to promote weight loss. A number of different mechanisms have been proposed utilizing animal models, with effects on the peroxisome proliferator-activated receptors, and regulation of metabolism-related genes and transcription factor expression [37], [38]. In humans, the data are also mixed, with some trials

demonstrating significant weight loss, and others showing no effects. A Cochrane review in 2012 performed a meta-analysis across 14 studies using green tea for weight loss, and concluded that overall green tea produced a modest, non-significant reduction in weight with short-term use. The authors acknowledged limitations based on a fair amount of heterogeneity across these trials.

Looking at the safety of green tea, it is generally well tolerated both in tea form and in extracts made into capsules. Stimulant effects, possibly due to the caffeine content, have been reported, but without serious consequences. Due to the conflicting data, more evidence is needed to clarify green tea's role, if any, in the treatment of obesity.

H. 7-Keto Dehydroepiandrosterone (7-Keto DHEA)

7-keto DHEA is a by-product of the body's natural steroid, dehydroepiandrosterone. It has been used to increase metabolism and thermogenesis, possibly leading to weight loss. While the potential benefits of weight loss and increased metabolism are highly promoted commercially through health food stores, there is currently no data available on the efficacy of this product on weight management in humans. More studies need to be performed to clarify the efficacy and the safety of this product before it can be recommended.

İ. Chromium

Chromium is one of the trace minerals present in the human body, and has been studied for its supplementation for a variety of different health conditions, including weight loss. It has been studied at doses up to 1000 mcg per day and has been established as safe, with few adverse events reported.

A meta-analysis of chromium trials suggests that chromium picolinate given orally produces a slight decrease in overall body weight of between 0.4 kg-1.1 kg [39]. There are several other studies, however, which did not demonstrate any significant difference from placebo. A study in overweight military personnel showed no changes in metabolic rate or body composition after 12 weeks [40]. These conflicting data suggest that any benefit seen from the supplement is modest at best.

J. Conjugated Linoleic Acid (CLA)

The family of conjugated linoleic acids refers to a group of approximately 30 isomers of linoleic acid found in meat and dairy products. CLA was found to have anti-proliferative effects in the early 1980s and has been studied since that time for various medicinal benefits. There have been a number of proposed mechanisms that CLA has that would help with weight loss, including effects on PPAR gamma, direct increased lipid peroxidation, and effects on various gut hormones, such as leptin. There is some evidence that CLA improves human body composition, decreasing fat mass and increasing lean body mass [41]. A study performed in overweight children showed decreased body fat and abdominal fat percentages after seven months of treatment [42]. The evidence suggests that CLA does not affect total BMI or total body weight, working instead to remodel the body and decrease adipose percentage. CLA has been shown to be safe as a dietary additive and as an oral supplement with doses up to 0.45 g/day.

K. Pyruvate

Pyruvate is a natural substance in the body, produced during the glycolysis process, when the body is breaking down carbohydrates. It has been researched as a supplement for various medicinal purposes, including weight loss.

The evidence with this supplement is also mixed. Used in large amounts as a replacement to dietary carbohydrates, pyruvate appears to aid in weight loss and decrease body fat. A meta-analysis identified nine trials evaluating pyruvate for weight loss, and included six within their analysis, although they identified that all had methodological weaknesses [43]. They reported a decrease in body weight of approximately 0.72 kg from baseline with pyruvate use, compared to the placebo.

In regards to adverse events, GI side effects were reported most frequently, including bloating, flatulence, and diarrhea. Pyruvate has been used in high concentrations, ranging from 6-44 grams, without any serious adverse effects. These data suggest that the supplement may provide some benefit as a meal-replacement additive.

L. Raspberry Ketone

This supplement originates from a variety of different fruits, including cranberries and blackberries, but is generally synthesized due to the overall low yield occurring naturally from fruit. It is a common additive used in the flavoring of foods and drinks. Medicinally, it has been evaluated topically for treating alopecia and orally for weight loss. Animal models suggest an effect on lipolysis mediated through norepinephrine, resulting in decreased fat mast.

There is little human data on the effectiveness of raspberry ketone. A small uncontrolled clinical trial suggested modest weight loss and decreased body fat when combined with vitamin C over four weeks [44]. A second study examined raspberry ketone as part of a proprietary blend, where subjects had improved waist circumference, decreased fat mass, and lower weight compared to diet alone [45]. In regards to safety, it is observed that raspberry ketone is structurally similar to synephrine and capsaicin. There is one case report where the person experienced tachycardia and shakiness with use, but this was not routinely reported in previous studies. More evidence is needed to clarify both the safety profile and the efficacy of this product.

VII. Conclusion

The problem of obesity is one that continues to pose a tremendous impact on the U.S. healthcare system, as well as throughout the developing world. Clinicians now recognize obesity as a disease, and need options to help manage this challenging condition. The cause of obesity is multifactorial, and as such, requires a multifactorial approach to management in order to be successful. There are now several prescription medication options available for use, but these tend to be very expensive and are rarely covered by insurance. This inevitably

leads consumers to explore alternative options for weight loss.

It is important for clinicians to recognize the vast market of anti-obesity supplements available over-the-counter, and to help patients with decisions regarding these products, specifically helping to make sure the supplement will not be harmful or detrimental to the patient. While there is much more research needed to better clarify the role of the products discussed in this review, studies are now being conducted to help either substantiate or refute claims made by manufacturers. Building the knowledge about common supplements marketed to consumers will help practitioners be able to answer and guide their patients in decision-making, and hopefully avoid toxic combinations of supplements.

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