

CONTROL™

white paper provided by Archmore Botanical Research Group, LLC

*A Javita
International
product*



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Control™, an ActiveBlendz product

a Javita International product

- A technical overview outlining the safety and efficacy of Control™, a dietary supplement designed to support healthy weight management*
- This technical white paper will include:
 - Formulation breakdown
 - Synopsis of health benefits associated with the proprietary ingredients
 - Safety
 - In vitro and in vivo trials demonstrating the safety of ingredients in Control™ at recommended levels
 - A review of any adverse events associated with the ingestion of the proprietary ingredients
 - Efficacy
 - Cellular, animal, and human trials demonstrating weight management benefits
 - A review of any negative outcomes found in clinical trials using the proprietary ingredients
 - Potential secondary health benefits outside the scope of weight management
 - Recommended guidelines for use
 - Dosing recommendations for weight management
 - Potential adverse events and warnings

**These statements have not been evaluated by the Food and Drug Administration and are meant for research purposes only.*



Overview

It is unfortunate to see a rise in the statistics regarding the obesity epidemic. Billions of research dollars have been spent in this arena attempting to provide solutions to the growing weight problem throughout the civilized world. Although there is no one product that functions as a “cure-all” for this condition, there are several natural compounds that have shown great promise in recent medical and scientific literature. These findings were evaluated and utilized when formulating Control™, an ActiveBlendz product by Javita.

As there are many compounding factors contributing to weight gain and inhibiting weight loss, multiple pathways were targeted when designing Control™, including reducing appetite and cravings, burning more energy, and reducing inflammation oxidative stress. In addition, natural ingredients were included to assist in protecting against secondary ramification due to obesity, namely cardiovascular health, diabetes, memory, and blood pressure.

This white paper will review the available scientific evidence to support the formulation and use of Control™ as a weight management product. It will provide an overview of how the ingredients work both in vitro as well as in the body. For those wishing to pursue information further, a highly detailed review of the studies is also provided in this paper along with available citations for further reading. This paper is meant to assist in the education of consumers to determine the best weight management product for their needs. It is not meant to diagnose or treat, or be used in place of medical advice.



Formulation

Control™ was designed to be a convenient and great tasting supplemental beverage for use as part of a healthy weight management program. Control™ includes two powerful herbal ingredients to help reduce appetite and minimize the food cravings many dieters experience while trying to reduce weight. These ingredients are *Garcinia cambogia* and *Gymnema sylvestre*. In addition to the reduction in appetite and cravings, these herbs also help stimulate weight loss itself through definable mechanisms that work well in beverage form. It is formulated in a base of two additional fruits, Pomegranate and Concord grape, which provide additional benefits through their antioxidative actions. These benefits not only assist in weight management but also provide cellular defense from oxidative stress caused by obesity itself, possibly alleviating some of the secondary effects of this detrimental condition.

Formulation includes four key herbal ingredients for use as part of a comprehensive weight management program:

- *Garcinia cambogia* provides naturally occurring hydroxycitric acid (HCA)
 - HCA plays a role in inhibiting the conversion of carbohydrates to fat in the body
 - HCA contributes to an increase in available energy for calorie burning
 - HCA increases serotonin levels, assisting in the reduction of emotional overeating and craving reduction
- *Gymnema sylvestre*
 - Assists in suppressing appetite and sweet cravings
 - Assists in blood sugar regulation by reducing glucose absorption
- Pomegranate Fruit
 - Assists in regulating pathways that affect metabolic syndrome
 - Acts as an antioxidant to reduce stress and inflammation resulting from obesity
 - Protects and enhances nitric oxide
- Concord Grape Juice
 - Strong antioxidant that protects body systems from secondary ramifications of the metabolic syndrome
 - Alters gut microbiota to protect from diet-induced obesity and metabolic disease



Garcinia cambogia- overview

Garcinia cambogia, also known as Malabar tamarind, has been consumed by indigenous people throughout Southeast Asia for centuries. It is used as a food and flavor enhancer but has widespread anecdotal evidence of providing satiation to the consumer, a feeling of fullness after consumption. Because of this effect, researchers began studying the fruit to determine its usefulness in weight management. It was during this research that scientists determined that the naturally occurring chemical hydroxycitric acid (HCA) is the main active constituent providing weight loss potential.

HCA is a non-essential nutrient that is known for its ability to inhibit the enzyme ATP-dependent citrate lyase, which plays a role in the transformation of carbohydrates into fat in the body. It does this by competitively blocking the enzyme as it works to convert leftover glucose into adipocytes (fat cells), a storage mechanism utilized to supply energy at a later date. By blocking this conversion, excess glucose is no longer stored in fat cells and remains available for the body to use as energy. This is how *G. cambogia* provides an increase in energy levels without containing a “stimulant”, like natural caffeine. An increase in available energy may also assist in increased exercise potential and output, further assisting in weight management benefits.

In addition, HCA has been shown to increase serotonin levels. Serotonin is a hormone naturally produced in the body which assists in regulating mood. Researches have determined that, in many cases, overeating is directly related to emotions and mood. In cases of depression and anxiety, serotonin levels are dramatically reduced. Thus, by increasing serotonin production, negative emotions are diminished, and emotional overeating is markedly reduced.



Gymnema sylvestre- overview

Gymnema sylvestre is an herb found throughout the tropical rain forests of southern and central India as well as parts of Sri Lanka. It is commonly referred to as *cowplant* or *gurmar*, which is translated from Hindi to be “sugar destroyer”. This is because for over two millennia, *Gymnema sylvestre* has been used in Ayurvedic medicine for balancing blood sugar levels and treating diabetes. Although this effect is mainly carried out inside the digestive system of the body, gymnema has an interesting side effect on sugary foods when they are eaten. Researchers noted that natives would chew this plant to help eliminate cravings for sweet foods, an effect that lasts for several hours. Scientists believe it is the herb’s ability to block sugar receptors that provides the benefit. They further discovered these same receptors in the gut; therefore, by taking gymnema in supplement form, this same craving suppression can be achieved.

Several compounds known as triterpenoid saponins found in this herb play a role in body systems dealing with blood sugar. Gymnema extracts have been shown to help balance blood sugar after food consumption by reducing the absorption of glucose in the intestine as well as reducing the production of glucose by the liver. This is beneficial not only for those individuals suffering from compromised blood sugar regularity, such as in type-2 diabetes mellitus, but also in those individuals looking to lose weight. By maintaining healthy blood sugar levels, excess blood sugar will be reduced and thus not converted and stored as fat.



Punica granatum (Pomegranate) Fruit- Overview

Pomegranate is a deciduous shrub native to Iran which has become an integral part of the diet in the Mediterranean area, the Middle East, and India. As its international popularity has grown, pomegranate is now cultivated throughout the Mediterranean region, as far norther as the Himalayas, in Southeast Asia, as well as California and Arizona in the United States. The fruit itself consists of an outer peel that is hard and inedible, a spongy interior membrane, and edible seeds that are surrounded by a water-laden pulp. Although these fruits range in size from that of a lemon to a grapefruit, they may contain anywhere from 200 to 1400 seeds each. Research has shown that all parts of the pomegranate contain beneficial compounds, making this a truly exotic “superfruit”.

Although delicious and unique in taste and texture, pomegranate has received much acclaim since ancient times for its use in treating a variety of ailments. The various parts of the fruit, including the seeds, peel, and fruit body, contain compounds that work alone as well as in harmony for treating many conditions. The fruit is rich in phenolic compounds, such as ellagitannins and anthocyanins, which have strong antioxidant activity. Over the past two decades, numerous studies have emerged measuring the benefits of these compounds for use in inflammation, anti-cancer treatments, cardiovascular disease, diabetes, bacterial infections, skin damage, infertility, Alzheimer’s disease, arthritis, obesity, and the metabolic syndrome.



Concord Grape Fruit Juice- Overview

Concord grape is a dark blue or purple grape that is used as a table or juice grape throughout much of the civilized world. Although it has been used to make some types of wines, mainly Kosher and sacramental wines, it is not well known for this, as it has a less desirable candied-strawberry flavor not conducive for wine. Therefore, much of its uses have been as a food product or in juices. It was originally developed in Concord, Massachusetts from where it gets its name, and continues to be most readily produced in the United States, with the majority cultivated in the New England region of the northeast. In 1854, it was introduced to the market by Dr. Thomas Welch as a juice, and has made history ever since in a variety of food and beverage products.

Over the years, Concord grape juice has been heralded as a powerful health product and has been studied extensively to determine the source of these benefits. Research has shown the grapes contain potent antioxidants that work particularly well in the cardiovascular system and the brain. Documented clinical data show that the incorporation of concord grapes into the diet would be a wise plan for those following a heart-healthy diet, a protocol that should be employed by those suffering from obesity. In addition, brain dysfunction has been shown to be induced by metabolic syndrome; Concord grape has been shown to play a protective role in the brain, helping to combat this negative outcome of obesity.



Safety

- Control™ was designed such that a single cup daily could produce results, but that multiples cups would maintain safety parameters.
- All safety studies outlined below are relevant to the dosages recommended for Control™
- Adverse safety and toxicity trials are also reviewed



Garcinia Cambogia- safety

Garcinia cambogia, also known as the Malabar tamarind from which HCA is extracted and supplied in Control™, has no known serious side effects, particularly at dosages commonly associated with supplements and beverages. *G. cambogia* has been consumed in high quantities as a food product for several decades in Southeast Asia, and thus is usually considered safe. However, when formulating with an extract of an herbal product, additional safety studies must be conducted before that ingredient can be considered safe for human consumption.

In early research on *Garcinia cambogia*, and specifically the extract of HCA found in Control™, Preuss et al. determined that in a standard 90-day toxicity study, no remarkable toxicity results were detected. They then moved on to clinical trial using 60 human volunteers. They demonstrated that no adverse effects were reported, nor were any negative physical changes in the parameters measured.

Researchers concluded that HCA is safe and effective in this highly bioavailable form [1]. Marquez, et al. conducted a thorough examination in 2012 of the available published research to date for *Garcinia cambogia*, and more specifically extracts standardized to hydroxycitric acid (HCA), with regards to safety and efficacy in humans. They concluded that except in extremely rare cases, the research proved that *G. cambogia* does not increase mortality nor toxicity, and that no significant differences have been reported in terms of side effects or adverse events in humans treated with *G. cambogia* versus control [2]. Although still considered a food additive or herbal supplement and thus not granted GRAS status (Generally Recognized As Safe- a designation awarded by the FDA), it is assumed that *G. cambogia* is considered a relatively safe herbal product even at higher dosages than those found in Control™.

Further confirmation of these findings was reported in a separate review of available literature conducted by Li Oon Chuah and colleagues. Chuah concluded that even at levels up to 2800mg/day, *G. cambogia* did not show adverse events, suggesting its safety for use as a food ingredient or supplement [3].

More recently, HCA from *Garcinia* was tested for adverse effects in the liver. It was determined that HCA does not promote inflammation or hepatotoxicity but that it actually reduces markers of inflammation in the brain, intestines, kidney and serum [4].



Adverse Events in Clinical Trials: A Review of *Garcinia cambogia*

A controversial dose dependent animal trial was conducted in 2005 to determine the “no observed adverse effect level” (NOAEL) of *Garcinia cambogia* extract standardized to HCA content. Although the highest dosages of 154 mmol/kg showed a suppression of epididymal fat accumulation in developing obese male rats, a potent testicular atrophy and toxicity was observed. This same toxicity was not observed in diets containing a third of this dose HCA. There, a lower NOAEL was reported and is recommended when formulating with this ingredient [5].

However, K. Hayamizu, et al. conducted a more recent study to evaluate the specific effect of *Garcinia extract* on serum sex hormones in overweight human subjects. In Hayamizu's double blind placebo controlled trial, researchers conclusively determined that dosages of 1000mg of HCA per day over 12 weeks had no significant effect on serum testosterone, estrone, or estradiol levels. In addition, hematology, serum triacylglycerol and serum clinical pathology parameters did not reveal any significant adverse effects. Hayamizu concluded that as dosages commonly recommended for human consumption, *Garcinia cambogia* extract (HCA) does not affect serum sex hormone levels and blood parameters [6].

It must be noted that studies have not been conducted on pregnant or nursing women nor on children; thus care should be exercised when taking any herbal supplements if in these categories of individuals [7].



Gymnema sylvestre- safety

Gymnema has been used for centuries in Ayurvedic medicine, mainly for its ability to assist in blood sugar regulation and weight management. However, as modern medicine has adopted its use due to the positive outcomes in trials, toxicology research had to be completed to determine this herb's safety. In a detailed, prolonged toxicology study, *Gymnema sylvestre* was dosed daily over 52 weeks in both genders of Wistar rats, the standard for measuring toxicity in humans. Graded doses of extract ranging from 0.01, 0.10 and 1.00% of diet were used. General conditions were recorded daily. Body weights and food consumptions were recorded weekly. At 26 weeks an intermediate examination took place, and then again at 52 weeks, a final examination was conducted. During the trial period, no animals died. There were also no exposure-related changes in body-weight, in food consumption, in hematological examinations, or in serum biochemical examinations. Therefore researchers concluded that there are no toxic effects up to 1.00% of diet for 52 weeks. The no-observable-effect level from this study was 1.00%, which translates to 504mg/kg/day for male rats and 563mg/kg/day for female rats [8]. Translated into human figures, the no-observable effect doses would be between 5 and 5.5 grams per day of gymnema extract, a dose that far exceeds several cups of Control™.

In addition, in animal trials measuring the anti-obesity effect of gymnema, researchers noted histopathological studies of tissues showed no pathological changes [9].



Adverse Events in Clinical Trials: A Review of *Gymnema sylvestre*

In one animal study that evaluated different types of gymnema extract for hypoglycemic and antihyperglycemic potential, researchers administered extracts alone or in combination with a popular prescription drug, glimepiride, used to treat type-2 diabetes. The extracts alone showed safe and potent hypoglycemic and antihyperglycemic activities without creating severe hypoglycemia in normal rats. However, when the extract was administered at the highest dose of 200mg/kg body weight along with 10-20 mg/kg of glimepiride, lethal hypoglycemia was induced in normal rats. Translated to human dosages, this would be equivalent to almost 2 grams of gymnema in combination with 100-200mg of glimepiride [10]. Although it would be impossible to consume this much gymnema following the recommended doses of Control™, care should be exercised if an individual is taking glimepiride for type-2 diabetes. Individuals being treated with this prescription should consult their primary physician prior to consuming Control™.



Pomegranate Fruit and Concord Grape Fruit- Safety

Both pomegranate fruit and Concord grapes are widely consumed foods throughout the world. As they are included in Control™ in their whole fruit or juice form and are not extracts, they fall under the FDA's classification of GRAS, or Generally Recognized As Safe. However, because numerous clinical studies have been conducted to evaluate the efficacy of these products for use in health management, additional safety evaluations have been conducted. This is particularly true with respect to pomegranate. In a trial to assess the efficacy of both pomegranate juice and extract for use in patients undergoing hemodialysis, pomegranate was shown to be safe and well tolerated by study participants. In addition, no changes were seen in lipid profiles, plasma C-reactive protein, interleukin 6, nor in systolic or diastolic blood pressure. They concluded that pomegranate juice and extract are safe and well tolerated by patients undergoing hemodialysis (11).

In another human trial on overweight individuals with increased waist size, pomegranate juice was shown to be safe and well tolerated. Even at relatively high doses, pomegranate juice had no adverse events reported by any subjects. Complete blood count, chemistry and urinalysis also showed no negative outcomes from juice supplementation (12)

When an animal toxicity study was attempted using pomegranate, no toxicity was observed even at doses ten times higher than what would normally be used in a human clinical trials, further confirming its status as GRAS (13).



Adverse Events in Clinical Trials: A Review of Pomegranate

Some trials have shown a potential interaction between pomegranate preparations and synthetic drug metabolism, specifically warfarin. Researchers believe this may be caused by the activation of liver enzymes sometimes seen with specific preparations of pomegranate (14). Because these results are only seen sporadically, researchers have encouraged those taking warfarin to discuss the potential for this fruit-drug interaction with their clinician (15).



Formulation Efficacy

Control™ contains four powerful herbal ingredients that work in multiple ways to reduce weight. Outlined below are the mechanisms of action conclusively defined in the available published literature. In some cases, mechanisms of action outside the scope of weight management were discovered. For the purposes of this paper, these mechanisms will only be briefly discussed. Should any potentially negative outcomes in clinical trials be discovered, they are presented here as well, and rationale for these outcomes are discussed.

- *Garcinia cambogia*
 - Competitively inhibits citrate lyase to prevent the formation of fat cells
 - Increases energy
 - Increases serotonin levels to reduce emotional overeating
- *Gymnema sylvestre*
 - Maintains blood sugar homeostasis through glucose suppression
 - Suppresses sweet receptors to reduce the perceived sensation of sweet
- Pomegranate Fruit
 - Suppresses or activates compounds known to play a role in metabolic syndrome, including resistin secretion, PPAR gamma, and corticosteroid.
 - Promotes mitochondrial function, eliminating oxidative stress and inflammation
 - Protects and enhances nitric oxide (NO)
- Concord Grape Fruit Juice
 - Provides antioxidant protection to assist with secondary outcomes stemming from obesity and metabolic syndrome
 - Alters gut microbiota to protect from diet-induced obesity and metabolic disease



Garcinia cambogia- efficacy

Mechanism of Action: Competitively inhibits citrate lyase to prevent excess fat cell formation

Garcinia cambogia extract standardized for HCA content has been extensively studied for its use in weight management. This is primarily due to the mechanism of action of the HCA itself, namely competitively inhibiting the enzyme that converts excess carbohydrates into fat in the body [16]. In the metabolic processes of the body, a particular enzyme called ATP-dependent citrate lyase is necessary to catalyze the cleavage of citrate to oxaloacetate and acetyl-CoA. This cleavage, or separation, is necessary for lipogenesis, or the formation of fat cells. If the enzyme is inhibited, lipogenesis is also inhibited. Therefore, it has been hypothesized and later shown in cellular and animal trials that *G. cambogia*/HCA can in fact competitively inhibit extra-mitochondrial citrate lyase and reduce the formation of fat cells [17].

Another study by Roy et al., utilized female human subcutaneous preadipocytes collected from obese women which were then differentiated to adipocytes (fat cells) for 2 weeks in culture. This allowed researchers to test the effect of HCA on lipid metabolism as well as study the genetics involved in this process. It was determined that HCA significantly down regulated (or reduced) the expression of fat- and obesity-related genes, supporting the antilipolytic and antiadipogenic effects of HCA from *G. cambogia*. In other words, HCA was shown to prevent the expression of obesity-related genes as well as the formation of fat cells, reducing weight and improving long term health [18].

Mechanism of Action: Increases energy

The second known mechanism of action for *Garcinia cambogia* (HCA) may be directly related to its ability to inhibit citrate lyase, as outlined above. The outcome of this action is the reduced formation of fat storage cells from glucose. Therefore, excess glucose remains available in the body to be used as an energy source. Having excess glucose readily available in the body should produce a rise in energy, allowing for the opportunity to burn excess calories. Researchers were able to scientifically demonstrate this property by showing that HCA is capable of activating hypoxia inducible factor (HIF). This is a transcription factor involved in energy metabolism and, when activated, increases the burning of energy [19].



Energy is also available for use due to *G. cambogia's* ability to assist in fat oxidation. In human clinical trials, urinary fat metabolites significantly increased in subjects taking HCA over an 8 week trial period. Urinary fat metabolites are a biomarker of fat oxidation. If fat is being oxidized, it is being released from its dormant state to be used as energy in the body. Thus weight reduction is achieved through increased energy expenditure as fat is oxidized [20].

A pleasant side effect of HCA is the decrease in oxidative stress, inflammation, and insulin resistance associated with obesity [21].

Mechanism of Action: Increases serotonin to diminish emotional overeating

With obesity being a global health epidemic, billions of dollars and countless hours of research have been spent to determine the cause. One of the main causes of obesity and overweight is overeating due to emotional stressors, such as depression and anxiety. Although a highly complex relationship, researchers have shown that various moods can enhance or diminish eating primarily due to a subject's unique response to pleasure and gratification. For example, eating a particular food may stimulate the production of dopamine, a special excitatory neurotransmitter that helps with depression and focus. Dopamine activates the pleasure center of the brain and enlists the subject to continue to consume this food to experience the positive feeling of gratification that dopamine provides. This repetitive behavior is extremely strong and can override other signals, such as satiety and hunger. Thus a gratification habit may be formed leading to overeating and obesity. The effect of the individual's mood can also play a role in the gratification. If the individual is stressed, anxious, or depressed, they may seek gratification by eating foods known to previously stimulate their pleasure centers, thus providing relief from the stressor, albeit for a short period of time. This is known as "stress- or emotional- overeating" [22].

Serotonin is an inhibitory neurotransmitter, which means that it does not directly stimulate the brain. Adequate amounts are necessary for stabilizing mood and balancing the excitatory neurotransmitters, such as dopamine, that are firing in the brain. As emotional-overeating has been linked to a desire for dopamine release, it was hypothesized that an increase in serotonin production should help assuage this desire for pleasure and gratification from eating. This was tested in animals by measuring body weight and abdominal fat gene expression profile after consuming *G. cambogia* extract (HCA). By conducting genetic assays on fat leptin expression as well as physical measurements on body weight, researchers



were able to show that HCA is effective in restricting body weight gain, and that it does so through the upregulation of genes encoding serotonin receptors [23].

Furthermore, these same researchers went on to publish data postulating that this mechanism also contributed to a feeling of satiety (fullness) as a direct result of HCA supplementation [24]. This two prong approach shows the neurological benefits of HCA for managing weight through the reduction of emotion overeating and increasing satiety [25].



Garcinia cambogia: a review of negative outcomes from clinical trials

Although the majority of the published cellular, animal, and human studies show *Garcinia cambogia* (HCA) to be highly effective for weight management, there has been a human trial published in the highly reputable Journal of the American Medical Association that attempts to show the opposite. In this randomized controlled trial, 135 subjects received HCA or placebo for twelve-weeks. Following the trial, there were no significant differences estimated between the two groups in terms of body fat mass loss [26].

There have been over sixteen years' worth of additional clinical testing on *Garcinia cambogia* since this study was published, the majority of which have found significant improvements in body weight and fat loss, as outlined earlier in this white paper. However one particular study cited the JAMA article, noting that there was a flaw in the study design that eliminated the positive results other have seen. They claim that because researchers administered a high-fiber, low-energy diet, HCA absorption was impaired and thus did not have a significant effect in the body [27]. Although the precise reason remains unknown, researchers have shown that administering HCA on an empty stomach or prior to feeding, achieved optimal reduction in hepatic lipid synthesis [28].



Gymnema sylvestre-efficacy

Mechanism of Action: Maintains blood sugar homeostasis through glucose suppression

Homeostatis is a condition of balance, and *Gymnema sylvestre* has the ability to balance blood sugar in the body [29]. It does this through two means- decreasing glucose absorption in the intestine and reducing glucose production in the liver. Through various trials, researchers have determined that gymnema is able to suppress glucose uptake in the intestine. In one such trial, researchers examined several different plant fractions containing triterpenoid saponins, known as gymnemic acids, and how they affected glucose transport through the muscles of the intestine. By observing lower levels of blood glucose after administration of these fractions, researchers determined gymnemic acid inhibits glucose uptake by the intestine [30]. This mechanism was duplicated in another study showing the inhibitory affect gymnemic acid also has on oleic acids in the intestine as well, another beneficial therapy for diabetes and obesity [31].

The other side to this equation is the reduction of glucose production. In multiple studies involving diabetic rats, gymnema extract was administered for a prolonged period of time. Not only were several parameters reduced that normally lead to obesity, glucose itself was significantly reduced. This is one of the leading causes of overweight and obesity. Researchers concluded in all studies that gymnema extract could be a very useful intervention for the treatment of obesity as well as type-2 diabetes mellitus through the suppression of glucose production. The other improvements were seen in visceral fat pad, mean arterial pressure, heart rate, serum leptin, and apolipoprotein B, to name a few. [32, 33, 34].

Another study took these results a step further to determine a precise mechanism for this glucose reduction. By administering various levels of gymnema extract against glucose load, they were able to measure Dipeptidyl peptidase-4 (DPP-4) inhibitors; these inhibitors are the emerging class of anti-diabetic agents currently used in modern medicine. They found that at all gymnema doses administered, DPP-4 was inhibited through an increase in plasma active glucagon-like peptide-1 (GLP-1), a potent antihyperglycemic hormone that induces glucose-dependent stimulation of insulin secretion while suppressing glucagon secretion. Following a complex biochemical pathway, GLP-1 also contributes to a satiating effect [35].



Researchers then determined that gymnema also has a protective effect prior to the glucose load. By administering gymnema extract 30 minutes before an intraperitoneal glucose load, they were able to significantly improve their glucose tolerance. These promising results demonstrate the use of gymnema as a potential therapy for hyperglycemia associated with obesity-related type-2 diabetes mellitus [36]. Therefore, gymnema may be used as both a weight gain preventative to keep the weight off in addition to enhancing the weight loss itself.

Although mechanism of action is demonstrated internally in these studies, other studies investigated the more visible external results with regards to weight management. One study showed a significant reduction in food and water intake along with a reduction in body weight by animals supplemented with gymnema extract. The researchers felt it was gymnema's ability to reduce hyperlipidemia that led to this significant weight loss. They also saw no withdrawal rebound effect once gymnema was removed from the diet, meaning these were maintainable results that were achieved [37]. Similar results were seen in a separate independent study, where animals were supplemented with gymnema for a period of eight weeks. Body weight was significantly decreased as was food consumption itself. Also reduced were levels of triglycerides, total cholesterol, low-density lipoproteins, while levels of high-density lipoproteins were increased [38].

Mechanism of Action: Suppresses sweet receptors to perceive sensation of sweet

Sweet cravings generally drive consumers to over-indulge in foods that are not going to contribute positively to weight loss. In fact, many sweet foods will convert rapidly into fat in the body, thus causing over-weight and obesity. Gymnema contains many compounds that actually help to suppress the sensation of sweet. These compounds include gymnemic acids, gymnemasaponins, and the polypeptide gurmarin [39]. Many native peoples will chew gymnema leaves to help alleviate cravings during the day, an effect that lasts up to about 2 hours [40].

However it is not simply the taste buds that drive sweet cravings. These same taste receptors are also expressed in the gut where they are involved in intestinal absorption, metabolic regulation, and glucose homeostasis. Therefore, by suppressing the sweet taste receptors on the tongue and in the gut, gymnema has the ability to reduce those cravings for sweet foods, helping with weight management [41].



In animal studies, nerve responses to various taste substances before and after treatment with gymnema extracts have shown the selective suppression of responses to sucrose without affecting responses to NaCl (salt), HCO, and quinine; thus, only sweet response was suppressed, and this response was found to be reversible; therefore, no permanent taste changes were seen [42].



Gymnema sylvestre: a review of negative outcomes from clinical trials

An interesting meta-analysis was conducted on all publications through the end of 2012 that used acceptable human clinical trials to analyze natural supplements used to suppress appetite for obesity control and management. Of the thousands of available studies, only 14 were found to meet the strict inclusion criteria these particular researchers set for their analysis- among these were randomized, double blind, placebo controlled design, sample size greater than twenty, and measurable outcomes on appetite or food intake. The research revealed that while most contained inconclusive evidence that plant extracts are effective in reducing body weight through appetite suppression, only the unique combination of *Garcinia cambogia* and *Gymnema sylvestre* showed weight loss directly linked to appetite suppression [43]. This limited, although positive result, could be due to the strict inclusion criteria the researchers randomly assigned for their analysis or from the subjective measurement of appetite suppression. While food intake itself is often indicative of appetite suppression, in human subjects this may not always be the case. Availability of food, time management, and forgetfulness are also factors that may lead to a reduction in calories consumed during the day, not just appetite suppression. Therefore, lifestyle and daily events need to also be considered when determining appetite suppression. In regards to Control™, however, this study is actually a positive one, as it conclusively demonstrates that the unique combination of *Garcinia cambogia* and *Gymnema* do indeed suppress appetite for weight management.



Pomegranate Fruit- Efficacy

Mechanism of Action: Suppresses or activates compounds known to play a role in metabolic syndrome

Pomegranate naturally contains several compounds that have been demonstrated to activate or suppress pathways or genes involved in the metabolic syndrome. Ellagic acid is one compound found in pomegranate that has such a benefit. This polyphenol not only has potent free radical scavenging capabilities, but it can also suppress resistin secretion. Resistin is an adipocytokine, a cell signaling protein secreted by fatty tissues, and is considered the link between obesity and type-2 diabetes. In an animal study, researchers proved the potential for resistin suppression, suggesting the possibility for improving obesity-induced dyslipidemia, or abnormal amounts of lipids in the blood (44). In a trial conducted on human volunteers, pomegranate juice was shown to reduce both systolic and diastolic blood pressure through the inhibition of 11 β -hydroxysteroid dehydrogenase type 1 enzyme activity. This enzyme, sometimes referred to as a corticosteroid, catalyzes the conversion of inert 11 keto-products, or cortisone, to active cortisol, and vice versa. (45). Inhibition of this enzyme was shown through the reduction in the cortisol/cortisone ratio, which was measured in both the urine and saliva. Researchers concluded that by inhibiting this compound's activity, pomegranate juice may have therapeutic benefits for those with non-insulin dependent diabetes, obesity, and the metabolic syndrome (46).

Another compound found to be impacted by pomegranate supplementation is PPAR gamma (peroxisome proliferator-activated receptor gamma). PPAR gamma is the molecular target for specific antidiabetic agents. By activating PPAR gamma, antidiabetic agents can ameliorate glucose homeostasis and obesity-related inflammation. In an in vitro trial, researchers found that pomegranate, and specifically punicalic acid from pomegranate, functions as an antidiabetic agent, effectively by activating PPAR gamma. They concluded that pomegranate can be an effective mediator for ameliorating some of the effects of diabetes and obesity-related inflammation (47).

Mechanism of Action: Promotes mitochondrial function, eliminating oxidative stress and inflammation

One of the main compounds in pomegranate that affects triglyceride and cholesterol content, is punicalic acid. The mechanism by which this compound functions was evaluated in animals. Punicalic acid from pomegranate was found to inhibit high-fat-induced hyperlipidemia and hepatic lipid decomposition through the suppression of mitochondrial protein oxidation, thereby improving mitochondrial complex



activity in the liver. This targeted antioxidation in the mitochondria helps to eliminate oxidative stress and inflammation associated with obesity (48). Similar oxidative protection was demonstrated in humans where researchers evaluated the efficacy of pomegranate for use in overweight individuals with increased waist size. After supplementing with a pomegranate preparation, antioxidant activity was measured by TBARS (thiobarbituric acid reactive substances) in the plasma, which are formed as a byproduct of lipid peroxidation. There was a significant decrease in TBARS through this supplementation. This reduction has been linked with reduced cardiovascular disease risk, demonstrating the powerful antioxidant potential of pomegranate (49).

Mechanism of Action: Protects and Enhances Nitric Oxide (NO)

Nitric oxide (NO) is a colorless gas under standard conditions, yet is a valuable signaling molecule in the body. It plays a fundamental role in neuroscience, physiology and immunology and is a key vertebrate biological messenger. It is a vasodilator and is more present in the blood of individuals living at high altitudes than those at sea level. Because it contributes to vessel homeostasis by inhibiting vascular smooth muscle contraction and growth, platelet aggregation, and leukocyte adhesion to the endothelium, those individuals with atherosclerosis, diabetes, or hypertension often show impaired NO pathways (50). Unfortunately, nitric oxide can be destroyed through oxidation by superoxide anions. However, research has shown that pomegranate juice, with its rich source of potent flavonoid antioxidants, can protect from this degradation. They further discovered that pomegranate can also augment the proliferative action of nitric oxide on vascular smooth muscle cells. Thus it was concluded that pomegranate can not only protect nitric oxide through antioxidation but can additionally increase the benefits of this compound (51). These results were confirmed in live animals showing that pomegranate juice significantly decreased the expression of vascular inflammation markers while increasing endothelial NO synthase expression (52).



Pomegranate : a review of negative outcomes from clinical trials

It is interesting to note that although pomegranate impacts the expression of many different compounds or genes involved in the metabolic syndrome, it was not shown to affect insulin secretion or sensitivity directly in one particular trial. In this human clinical trial using 20 obese adult volunteers, researchers found no modification to insulin secretion and sensitivity after pomegranate juice supplementation. They did note, however, that weight gain and adiposity were both halted by the administration of pomegranate juice, suggesting a different mechanism of action. (53). To counterbalance these findings, other trials have been conducted that do indeed show an effect on insulin or blood glucose levels. At high doses, pomegranate juice was shown to significantly lower blood glucose levels in animals (54). These same results have been recreated in human trials, where administration of the juice increased serum insulin levels while simultaneously decreasing body weight gain, food consumption, and serum levels of lipid, leptin, and glucose (55). It may be the design of the study itself or perhaps a variation in measurements taken, but these differing results, in light of the immense evidence supporting its applications for the metabolic syndrome, suggest that pomegranate does indeed play a role, even indirectly, in regulating insulin levels in vivo.



Concord Grape Fruit Juice- Efficacy

Mechanism of Action: Provides antioxidant protection to assist with secondary outcomes stemming from obesity and metabolic syndrome

The high concentration of flavonoids found in Concord grapes are strong antioxidants in the body. Oxidative stress is a contributing factor involved in the metabolic syndrome. It not only plays a role with the weight gain itself, but is responsible for a number of the ramifications associated with the syndrome. These included cardiovascular risk, diabetes, and even brain dysfunction (56). By treating with Concord grape juice, many of these body systems may be protected from the adverse effects of obesity. In both animal and human trials, Concord grape juice was found to decrease latent learning impairment that occurs naturally with oxidative stress (57). This was determined to be due to the juice's activation of anterior and posterior regions of the right hemisphere of the brain, as observed with functional magnetic resonance imaging (58). An enhancement of overall cognitive function was also seen in older adults without dementia following Concord grape juice supplementation, demonstrated by a significant improvement in verbal learning (59). As cognitive decline is often a result from obesity and its corresponding complications, these results demonstrate the importance of including Concord grape in a product targeting the effects of the metabolic syndrome.

Another human clinical trial attributed its similar results to the decrease in stress signals induced by oxidative and inflammatory stressors (60). This same antioxidant potential has contributed to a decrease in the development of atheroma and to significantly lower total serum cholesterol and blood pressure levels. (61). These findings have been repeated in two separate human clinical trials demonstrating the antioxidant potential of Concord grape juice to reduce systolic and diastolic blood pressure, and to reduce LDL oxidation rate, respectively (62, 63). These are all biomarkers associated with the metabolic syndrome.



Mechanism of Action: Alters gut microbiota to protect from diet-induced obesity and metabolic disease

Although secondary to the main mechanism by which Concord grape works in the body, altering gut microbiota seems to be an upcoming area of research for this botanical. In a recent publication, researchers noted that there may be reduced gastrointestinal absorption of many polyphenols, thus diminishing some of their efficacy for protecting from the metabolic syndrome. In an animal trial, they tested Concord grape polyphenols for their ability to alter gut microbiota and then carried it a step further to determine their biological effects for weight management. They found Concord grape did indeed change the microbial community structure, and it attenuated several effects of a high fat diet. These included reducing weight gain, adiposity, serum inflammatory markers, and glucose intolerance. Researchers determined that by altering gut microbiota, Concord grape juice supplementation allowed for better absorption of its own polyphenols, resulting in more pronounced weight management benefits. (64).

Concord grape: a review of negative outcomes from clinical trials

In 2009, in a human clinical trial involving seventy-six men and women with obesity, researchers tested the effects Concord grape juice or a grape flavored beverage had on body composition. After 12 weeks, they found no significant changes in body weight or composition following administration of the Concord grape juice, while the grape flavored beverage actually contributed to weight gain. They attributed the lack of weight gain for the Concord grape group to thermogenesis and oxidative protection of the substrate (65). These are actually positive results, considering that Concord grape juice is not itself meant to be a weight loss product, but rather a supplementary ingredient meant to augment the effects of more targeted weight management ingredients.



Usage Guidelines

As there are varying degrees of weight loss desired by consumers, a personalized weight management program should be designed on a case by case basis. However, for the purposes of Control™, it is advised to consume 1-3 cups per day to achieve results. This is based on the available research and proven efficacy of the active ingredients at these recommended dosages. This should be combined with a healthy diet and exercise routine to achieve optimal results.

By taking this product in combination with diet and exercise, a reduction in weight should be experienced by most individuals, along with a reduction in cravings and appetite. Once optimal weight is achieved, Control™ may continue to be consumed to help manage the weight and minimize cravings.

As noted in this white paper, safety studies were conducted using doses of the herbal ingredients much higher than those provided in Control™, even when multiple cups are consumed per day. Therefore, consuming even 1-3 cups of this beverage should yield health benefits without negative safety concerns. However, should you be under the care of a physician for any ailment, but specifically for type-2 diabetes or taking any synthetic drugs such as warfarin, consult your physician before consuming Control™ to insure there will not be any detrimental interactions.

If possible, this beverage may be consumed on an empty stomach, thus increasing the benefits of HCA; however, these are still present even when consumed after a meal.

As always, pregnant and nursing women as well as children should consult their health care professional before beginning any supplement program.

Should adverse effects be felt when consuming any new supplement, discontinue use and contact your healthcare professional immediately.



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