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INTRODUCTION

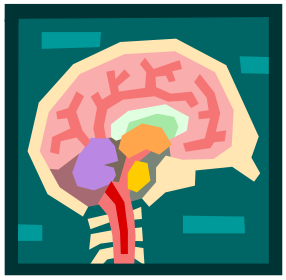
It is the holiday season, a time for food and festivity. It is also that time of the year when it becomes all too easy to pack on those pounds and join the growing ranks of the overweight and obese. This paper presents selected clinically tested dietary interventions which when combined with a healthy lifestyle, support a healthy body weight and composition.

Obesity is not a new problem – Paleolithic artists depicted obese figurines over 25,000 years ago! Obesity is however now described as a global epidemic, and overweight and obese individuals (Body Mass Index (BMI) of 25 and above) are at increased risk for chronic physical ailments. Some of the health problems caused by obesity include predisposing one to diabetes mellitus type 2, high blood pressure, high blood cholesterol and triglyceride levels, and atherosclerosis. Other diseases that are correlated with obesity include polycystic ovarian syndrome, menstrual disorders, infertility, colorectal cancer, breast cancer, uterine cancer, renal failure, osteoarthritis, and a number of other serious ailments (Esposito, et al.; 2004; Ejerblad, et al.; 2006; Whitmer, et al.; 2005). Certain psychological issues also arise in the obese person such as depression, low self esteem, body dysmorphic disorder, and social stigmatization.

Over the past 20 years, obesity has risen at a phenomenal rate in the United States, and the situation continues to worsen. The prevalence of overweight among children and adolescents and obesity among men increased significantly during the 6-year period from 1999 to 2004 (Ogden, et al.; 2006). According to the CDC's National Center for Chronic Disease Prevention and Health Promotion, one of the national health objectives for the year 2010 is to reduce the prevalence of obesity among adults to less than 15%.

From the global perspective, the costs involved in the management of obesity and its associated conditions have a significant economic impact on healthcare systems. Obesity in the population could also affect a country's economy by way of decreased productivity, restricted activity, absenteeism, sick days and increased premature mortality.

It is well established that dietary and lifestyle interventions can effectively be used to achieve a healthy body weight. Typically a patient is placed on a low calorie diet and an exercise program. However, weight loss maintenance is still an issue, attributable to the body's drive to maintain homeostasis, and difficulty on the individual's part to manage food cravings.



Recent scientific evidence highlights the neurobiological roots of energy balance in mammalian systems. Interacting feedback mechanisms function in the brain (hypothalamus, brain stem, higher brain centers), and in the peripherial organs (the stomach, gut, liver, thyroid and fat tissue) to control energy balance.

The hypothalamus is the principal regulator of energy metabolism sensing nutritional needs directly, as well as through hormonal signals. Interestingly, reward circuits that are activated by drugs of abuse are also activated by food, making eating a source of pleasure. Activation of the melanocortin system in the hypothalamus has an anorexigenic effect, while its inhibition stimulates appetite and body weight increase. The plasticity of the hypothalamic melanocortin system and the activation of its neurons by the hormone leptin generated in adipose tissue are key factors in regulating energy balance. Leptin has an anorexigenic effect when injected into mice, but obese people with elevated leptin levels are resistant to such anorexigenic effects (Markus, A, 2005).

MANAGING OBESITY

If diet and lifestyle measures are insufficient, drugs are sometimes prescribed to manage chronic obesity. Such drugs include the following:

- Orlistat (Xenical®) which reduces intestinal fat absorption by inhibiting pancreatic lipase. (approved as OTC in February 2007)
- Sibutramine (Reductil® or Meridia®) an anorectic or appetite suppressant
- Metformin (Glucophage®) useful in reducing body weight in Type 2 diabetics
- Byetta (Exenatide) is a long-acting analogue of the intestinal hormone GLP-1, which is secreted in response to the presence of food, delays gastric emptying and promotes a feeling of satiety.
- Symlin (Pramlintide) is an injectable synthetic analogue of the pancreatic hormone Amylin, which in secreted in response to the presence of food, delays gastric emptying and promotes a feeling of satiety.
- Rimonabant: A cannabinoid (CB1) receptor antagonist that not only causes weight loss, but prevents or reverses the metabolic effects of obesity
- Other drugs such as Redux®, Fen-Phen and phenylpropanolamine are related to amphetamine.

Currently available drugs for obesity management are often associated with side effects related to their mechanisms of action in the body. For example, side effects associated with appetite suppressants include raised blood pressure, elevated heart rate, restlessness, nervousness, difficulty sleeping, and dry mouth. Besides the health risks, appetite suppressant weight loss drugs are not a permanent solution to controlling weight and are generally prescribed for short-term treatment. Amphetamine like drugs are known to be associated with dangerous cardiovascular side effects. Orlistat, blocks absorption of dietary fats, and as a result may cause gastrointestinal side effects.

Another type of treatment is bariatric surgery. This involves an adjustable gastric band placed around the stomach to decrease the amount of food one can eat in a sitting.

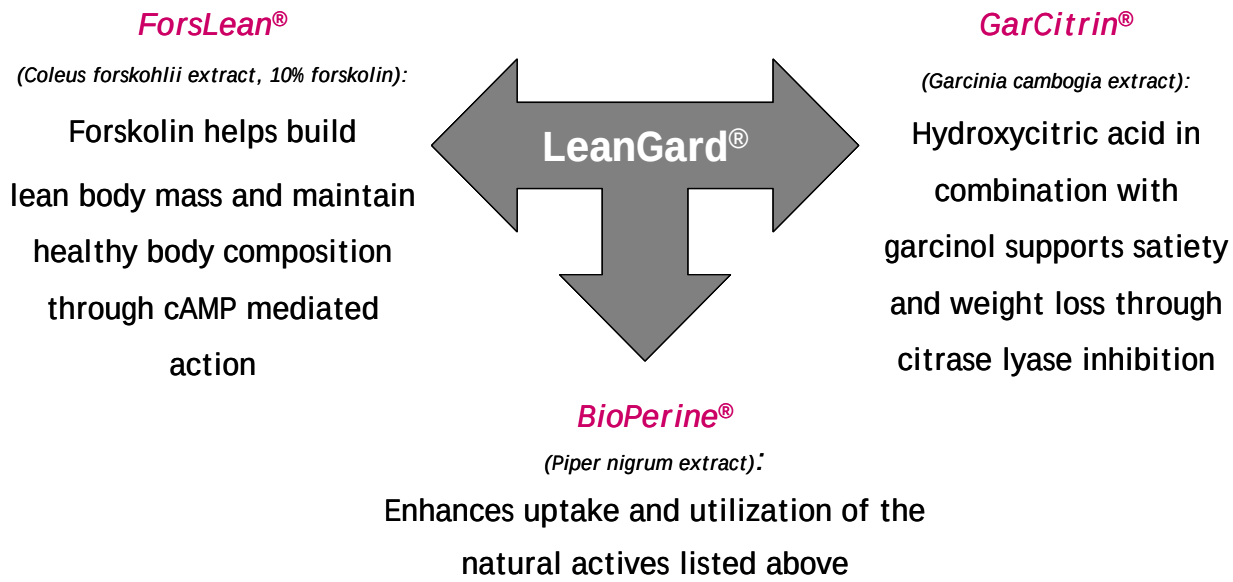
A “diet, exercise, and lifestyle regimen only” approach may sometimes be insufficient to significantly lower body weight. The drug route resorted to in such cases, may produce side effects such as diarrhea, increased blood pressure, and metabolic dysfunction. The bariatric surgery method is expensive, invasive, and may deplete macro and micro nutrients due to inadequate food consumption.

PHYTONUTRIENTS FOR COMPREHENSIVE WEIGHT MANAGEMENT SUPPORT

A number of phytonutrients have shown promise in supporting a healthy body weight and composition, with no untoward side effects. Their modes of action as evidenced by *in vitro*, preclinical and clinical data involve effects on carbohydrate and fat absorption and metabolism, and the neurobiology of appetite regulation, with a resultant beneficial shift in body composition towards increased lean body mass.

One such agent, trademarked LeanGard®*, contains a proprietary synergistic combination of two patented, standardized natural extracts formulated with a natural bioavailability enhancer – ForsLean®* a *Coleus forskohlii* root extract containing 10% forskolin[§], and a patented natural composition GarCitrin®* from *Garcinia cambogia* (Malabar tamarind) containing hydroxycitric acid and garcinol[€], in combination with BioPerine®*, a patented standardized extract from black pepper fruit containing 95% piperine (a bioavailability enhancer)[±]. The two phytonutrient extracts, work in synergy to support lean body mass, and healthy body composition, promote satiety, and provide antioxidant support, with the third extract of piperine functioning as a bioavailability enhancer.

Synergistic Weight Management Formula



[§] U.S. Patent # 5,804,596, EP0977564 and International patents
[€] US Patent # 7,063,861, EP1254209, and International patents
[±] US Patent # 5,536,506 and others, EP0810868 and International patents
* Trademarks of Sabinsa Corporation

ForsLean is an extract of *Coleus forskohlii* root, standardized to contain 10 percent forskolin. This unique extract has shown promising results in enhancing lean body mass. The roots are traditionally pickled for culinary use in India, and the plant is the only known species producing forskolin (Shah, 1985).

Lean body mass is constituted by the muscles, vital organs, bone and bone marrow, connective tissue and body water. The percentage of lean body mass to fat not only determines the body's aesthetic appearance, but more importantly, it is also an index of physical fitness, health status, susceptibility to disease, and premature mortality. Recent studies further suggest that at the molecular level, the regulation of bone remodeling by an adipocyte- derived hormone implies that bone may exert a feedback control of energy homeostasis (Lee, et al.; 2007).

Forskolin is valued as an adenylate cyclase activator. Adenylate cyclase is the enzyme involved in the production of Cyclic Adenosine Monophosphate (cAMP), (a significant biochemical agent in metabolic processes) from the high energy molecule, ATP (Adenosine triphosphate). Nicknamed in literature as a "second messenger," cyclic AMP facilitates the action of “primary messengers" or various hormonal and bioactive substances in the body. The role of cyclic AMP is indispensable to many body functions. It induces a chain of biochemical events that trigger the metabolic processes and diet induced thermogenesis (Palou, 1998), thereby providing the means to maintain a healthy body composition and lean body mass levels. The root material is the commercial source for forskolin. Research carried out over the last few decades has revealed the multi-faceted pharmacological effects of forskolin (deSouza et al, 1983; Dohadwalla, 1985). Most of these effects have been linked to the role of forskolin as an activator of adenylate cyclase (Seamon, 1985; Ammon, et al. 1985. Normally, cAMP is formed when a stimulatory hormone (e.g., epinephrine) binds to a receptor site on the cell membrane and triggers the activation of adenylate cyclase. The receptors in each cell are specific to the activating hormone. Forskolin appears to bypass the hormone-receptor interactions and activates adenylate cyclase. Adenylate cyclase activation induces a rise in intracellular cAMP levels (Murray, 1995).

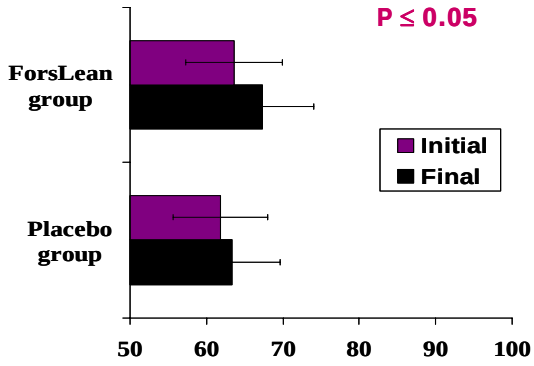
Forskolin helps build lean body mass and maintain healthy body composition through cAMP mediated action. Furthermore, the patented forskolin composition is well tolerated and without adverse side effects, as was evidenced by a number of clinical studies. (www.forslean.com). More importantly,

although efficacy was the primary purpose of these trials, those parameters related to safety were also monitored.

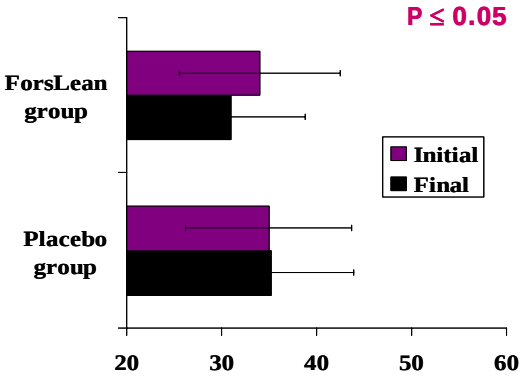
Open field studies 8 to 12 weeks in length have reported significant decreases in mean body weight and body fat with no significant adverse effects in overweight men and women who consumed 125 to 250 mg ForsLean twice daily (providing 25 to 50 mg forskolin/day) (Tsuguyoshi, 2001 ; Badmaev et al, 2002).significantly increased compared to baseline values. The regimen did not adversely affect the systolic/diastolic blood pressure nor the pulse rate. Indeed, a trend towards lower systolic/diastolic pressure was observed during the course of treatment.

Similarly, double blind, randomized, placebo-controlled trials ranging in length from 8 to 12 weeks have demonstrated no significant adverse effects in subjects who consumed 250 mg ForsLean twice daily (50 mg forskolin/day) (Agena; Kamath et al., Bhagwat et al, 2004; Godard et al., 2005; Henderson et al, 2005). Measurements of systolic and diastolic blood pressure and pulse rate in each of the studies also revealed no significant effects as a result of ForsLean consumption. In addition, Henderson et al, 2005 reported no clinically significant effects in metabolic markers, blood lipids, muscle and liver enzymes, electrolytes, red blood cells, white blood cells, hormones (insulin and thyroid hormones), heart rate, blood pressure, or other side effects. Bhagwat et al. (2004) and Kamath et al, (unpublished) also reported no significant changes in liver and kidney function, thyroid function, as measured by triiodothyronine (T3), thyroxine (T4), and thyroid stimulating hormone (TSH) levels, nor any significant changes in blood lipid profile, with the exception of a significant increase in high-density lipoprotein (HDL) cholesterol and a significant decrease in total cholesterol/HDL ratio reported by Bhagwat et al. (2004). A twice daily dose of 250mg *Coleus forskohlii* extract significantly increased lean body mass and decreased body fat in obese male subjects (Godard, et al.; 2005). The subjects also showed increased bone mass and a significant increase in serum free testosterone levels.

Randomized, double-blind, placebo-controlled; 30 overweight/obese male subjects; 12 weeks, Active therapy: 250 mg ForsLean® twice daily



Lean Body Mass (kg)
(significant increase in treated group)



Body Fat %
(significant decrease in treated group)

Bone mass also increased significantly in the treated group

(Godard et al.; 2005)

The second extract is a patented natural composition from *Garcinia cambogia* (Malabar tamarind), trademarked GarCitrin®, containing hydroxycitric acid (HCA) and garcinol. Its primary purpose is for weight management support. The patented natural composition of bioactives from *Garcinia cambogia* is clinically proven to enhance lean body mass and support health body composition (Badmaev, et al; 2004). HCA is a well researched compound, clinically proven to support weight management.

(Garcinia cambogia fruit)

Garcinol "amplifies" the biological action of HCA and contributes antioxidant activity to the formulation. The combination of calcium salt HCA and Garcinol reduces fatty acid and lipid synthesis and improves lean body mass much more effectively than HCA alone. The patented extract is much more effective than HCA in reducing total body weight and body mass index, reducing body fat, increasing lean body mass and content of body water, and in beneficially influencing satiety. Moreover, the treatment did not produce subjective or objective side effects.

The combination consisting of 500 mg of calcium salt of HCA and 25 mg of Garcinol (NC) was evaluated in a double-blind 12 weeks clinical study against the formula containing 500 mg of calcium

salt HCA(C). The study was carried on 46 overweight female volunteers (BMI greater than 25). Participants were instructed to take one capsule of either active or placebo formula three times a day, half an hour before a meal. Each participant was asked to maintain her previous daily physical exercise and eating habits.

During the 12 week trial, the mean values in group NC for body weight and fat content significantly decreased, whereas lean body mass and total body water significantly increased compared to the baseline values and C group values. Appetite levels were significantly reduced in the NC group as compared to the C group, whereas energy levels increased equally in both study groups, as compared to the baseline. No subjective or objective adverse effects were reported in the course of this study. The pulse rate, systolic and diastolic blood pressure were maintained at the same level throughout the study.

Weight loss effects have been demonstrated *in vivo* following oral, intravenous or intraperitoneal administration of (-) hydroxycitrate to experimental animals (Sullivan 1972, 1973). This mechanism of energy expenditure, decreased lipogenesis, and the reduction in food intake in the (-) HCA receiving animals contributes to weight and total body fat content loss in experimental animals (Sullivan, 1973, Vasselli, et al.; 1998). Clinical studies further established the beneficial role of (-) HCA in energy metabolism and weight management in human subjects (Badmaev, et al.; 1995, Conte; 1993, 1994; Thom, 1996; Katts, 1995). Some studies did not show significant effects, (Heymsfield, 1998), attributable to the administration of a high fiber diet in conjunction with (-) HCA (Badmaev, 1999).

Water soluble salt forms of (-) HCA such as Citrin®* K[ℑ] (GRAS affirmed), which additionally contains the essential mineral nutrient potassium, are convenient forms for use in beverage applications including sports nutrition products.

The third component of the synergistic combination is a standardized piperine extract obtained from the fruits of the *Piper nigrum L.* (black pepper) and/or *Piper longum L.* (long pepper) plants that are cultivated in the damp, nutrient-rich soil regions of southern India. It has been clinically tested in the United States and shown to significantly enhance the bioavailability of supplemented nutrients through increased absorption (www.bioperine.com).

[ℑ] Trademark of Sabinsa Corporation, US Patent Nos 5,783,603, 6,770,782.
* A trademark of Sabinsa Corporation

Green tea catechins are reported to enhance energy expenditure and help in weight management (Chantre, 2002). Green tea extract may play a role in the control of body composition via sympathetic activation of thermogenesis, fat oxidation, or both (Duloo, 1999). Caffeine in the tea may act synergistically, by promoting lipolysis. According to researchers, green tea extract, via its catechins and caffeine, is effective in stimulating thermogenesis by relieving inhibition at different control points along the noradrenaline-cAMP axis (Duloo, 2000).

Excess carbohydrates in the diet are ultimately converted to fats and stored in the body. In both plants and animals, starch is broken down by amylases and maltase to yield glucose. Plants break down starch during seed germination or tuber sprouting to supply the energy and carbon skeletons. Animals and fungi break down plant starch to obtain glucose for their own metabolism. The enzymes that catalyze the conversion of starch (a polysaccharide) into sugar molecules (monosaccharides) are called amylases. Surprisingly, plants usually contain amylase inhibitory compounds in the same organs (seeds and tubers) where the starch is stored, to ward off bacterial, fungal and animal predators. No parallels exist in mammalian systems.

An alpha-amylase inhibitor inhibits the digestion of starch thereby potentially improving postprandial carbohydrate tolerance in people with low glucose tolerance. As excess dietary carbohydrate is metabolized to fat, inhibition of carbohydrate digestion may help in weight management as well. A partially purified white bean amylase inhibitor was found to reduce starch digestion and inactivate intraduodenal amylase in humans by 94 to 99.9% (Layer 1985). The inhibitor also inactivated intraileal and salivary amylase in vitro studies. Additionally, the specific activity of the inhibitor was not affected by exposure to gastric juice and was only minimally affected by exposure to duodenal juice. In studies in normal subjects and in patients with diabetes mellitus, a purified amylase inhibitor from beans was found to exert a “starch blockade” effect (Layer 1986). In comparison with the placebo, ingestion of this inhibitor with 50 g starch substantially reduced post-prandial increases in plasma concentrations of glucose and insulin in both normal subjects and those with diabetes.

Fabenol®* is an alpha-amylase inhibitory natural extract obtained from *Phaseolus vulgaris* (common bean, kidney bean) that blocks the digestion of dietary starch, thereby offering potential benefits in the maintenance of healthy blood sugar levels and optimal body composition.

* A trademark of Sabinsa Corporation

CONCLUSIONS

Phytonutrients and nutritional interventions, along with a sensible diet, lifestyle and exercise, can help a person who is borderline obese from actually becoming obese. Such measures also support lean body mass, healthy body composition, satiety, general energy levels and well being. Contact Sabinsa Corporation for further information on the healthful ingredients discussed in this paper, as well as details on other natural options for weight management support.

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