SATIAL

CARB CONTROLLER

Resumen de Investigación Científica

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INVESTIGACIÓN CIENTIFICA

A continuación se detalla en un breve resumen, de estudios de investigación realizados sobre los inhibidores de amilasa en general, y sobre SATIAL® (Phase 2®) Phaseolamina en particular.

2013 -- A study was conducted in two phases to demonstrate the safety and efficacy of SATIAL (Phase 2) (IQP-PV-101) in weight management in obese and overweight Caucasian adults. The weight loss phase was a 12-week randomized, double-blind, placebo-controlled study where all subjects followed a strict diet plan; the second phase was the weight maintenance study over 24 weeks, where the subjects' energy intake was ad libitum. Results showed that those subjects taking Phase 2 lost significantly more weight than those on placebo after 12 weeks. In the weight management phase, 73.5% of participants successfully maintained their body weight after 24 weeks. ("Weight Reduction and Maintenance with IQP-PV-101: A 12-Week Randomized Controlled Study with a 24-Week Open Label Period," Barbara Grube, Wen-Fen Chong, Pee-Win Chong and Linda Riede, *Obesity*, published online 2013.)

2011 -- A review of over a dozen separate studies confirmed that SATIAL (Phase 2) Carb Controller™ demonstrated the ability to cause weight loss with doses of 500 to 3000 mg per day, in either a single dose, or in divided doses. The studies also showed that the ingredient has the ability to reduce the post-prandial spike in blood glucose levels. ("A Proprietary Alpha-Amylase Inhibitor from White Bean [Phaseolus Vulgaris]:
A Review of Clinical Studies on Weight Loss and Glycemic Control," Marilyn L. Barrett, Pharmacognosy Consulting, Jay K. Udani, MD, Medicus Research LLC, *Nutrition Journal*, March 2011.)

2010 -- A 30-day study of 50 overweight and obese subjects, of which 74% completed the study, revealed that 98% obtained positive results by reducing their body weight by 1.8 to 3.6 kg during the first 30 days with no special eating regimen and no additional exercise; no adverse reactions or gastrointestinal discomfort were reported. ("Random Multi-Center Evaluation to Test the Efficacy of Phaseolus Vulgaris [PreCarb/Phase 2] in Obese and Overweight Individuals," Lucila Velasso Osorio, Jorge Alberto Zavola Gamboa, 2010.)

2009 -- An open-label 6-arm crossover study was conducted with 13 randomized subjects. Standardized GI testing was performed on white bread with and without the addition of Phase 2 in capsule and powder form, each in dosages of 1500 mg, 2000 mg, and 3000 mg. Results indicated that, for the capsule formulation, the 1500 mg dose had no effect on the GI and the 2000 mg and 3000 mg capsule doses caused insignificant reductions in GI. For the powder, the 1500 mg and 2000 mg doses caused insignificant reductions in the GI, and the 3000 mg dose had a significant effect (-20.23 or 34.11%, p=0.023). Researchers concluded that Phase 2 white bean extract appears to be a novel and potentially effective method for reducing the GI of existing foods without modifying their ingredient profile. ("Lowering the Glycemic Index of White Bread Using a White Bean Extract," Jay K. Udani, Betsy B. Singh, Marilyn L. Barrett, Harry G. Preuss, *Nutrition Journal* 2009, 8:52.)

-- A review was developed of scientific studies on "diabesity" and the use of carb blockers to prevent and ameliorate the situation. ("Bean Amylase Inhibitor and other Carbohydrate Absorption Blockers: Effects on Diabesity and Health," Harry G. Preuss, MD, MACN, CNS, Georgetown University Medical Center, Departments of Physiology, Medicine and Pathology, Washington, D.C., August 2009.)

A review was written to provide a scientific perspective on the use of nutritional alpha-amylase inhibitors. It includes a brief review of carbohydrate digestion, the mechanism of digestion inhibition,

("Nutritional Carbohydrate Digestion Inhibitors, a Systematic Review of the Literature," Jay Udani, MD, assistant clinical professor, David Geffen UCLA School of Medicine; Mary Hardy, MD, Director, Integrative Medicine Group, Cedars-Sinai Medical Center, May 2009.)

-- A concentrated northern kidney bean extract was tested in two single dose human studies. Eleven fasting subjects were given 4 slices of white bread and 42 g of margarine with or without 1.5 g of bean extract. Absorption as measured by the area under the plasma glucose-time curve was inhibited 66%. A full meal study with 7 subjects and 0.75 g of extract caused a non-significant 28-41% reduction in absorption. There was a dose-response decrease in glucose absorption by the extract. The bean extract has in vivo efficacy for inhibition of starch absorption and researchers concluded it may prove beneficial in weight reduction in individuals consuming large amounts of starch. It also may inhibit starch-induced hyperglycemia in normal and diabetic subjects. ("Investigation of an Amylase Inhibitor on Human Glucose Absorption after Starch Consumption," Joe A. Vinson, Hassan Al Kharrat, and Donna Shuta, Department of Chemistry, Loyola Hall, University of Scranton, Scranton, PA, USA, *The Open Nutraceuticals Journal*, 2009; 2: 88-91.)

-- A randomized, double-blind, placebo-controlled study was conducted in China on 101 volunteers with a BMI between 25-40. The volunteers were divided into two groups that received either placebo or the active substance. A single capsule containing Phaseolus vulgaris extract (1,000 mg) or placebo was taken three times per day (just before each meal) for 60 consecutive days. After 30 days, 51 subjects receiving Phaseolus vulgaris extract compared to a placebo group of 50 subjects had clinical and statistically significant greater average reduction of body weight [-1.9Kg vs. -0.4Kg, ($p<0.001$)] and waist circumference [-1.9cm vs. -0.4cm, ($p<0.001$)], but no difference in the changes of average hip circumference [-0.3cm vs. -0.3cm, ($p=0.84$)]. ("Enhanced weight loss from a Dietary Supplement Containing Standardized Phaseolus Vulgaris Extract in Overweight Men and Women," Duo Li, Jianguo Shen, Xiaofeng Xu, Harry Preuss, et.al., 2009.)

2008 -- This review article assesses the potential of the Phaseolus vulgaris a-amylase inhibitor isoform 1 (a-AI1) starch blockers as a widely used remedy against obesity and diabetes. Research developments in the distribution and biosynthesis of the a-amylase inhibitor, relevant physico-chemical properties, the molecular starch-blocking mechanism, anti-obesity and anti-diabetes effects, safety of extracts and the need for research into their potential anti-colorectal cancer effect are discussed. Authors concluded that, although obesity and diabetes are on the increase worldwide, based on research developments discussed, the common bean (P. vulgarius) alpha-amylase inhibitor has potential to serve as a widely used remedy against these conditions. ("The Nutraceutical Role of Phaseolus Vulgaris Alpha-Amylase Inhibitor," Wokadala Cuthbert Obiro, Tao Zhang, Bo Jiang. *British Journal of Nutrition*, 2008, 100, 1-12.)

-- In this 2-year trial, researchers randomly assigned 322 moderately obese subjects to one of three diets: low-fat, restricted-calorie; Mediterranean, restricted-calorie; or low-carbohydrate, non-restricted-calorie. The mean weight loss was 2.9 kg for the low-fat group, 4.4 kg for the Mediterranean-diet group, and 4.7 kg for the low-carbohydrate group ($P<0.001$ for the interaction between diet group and time); among the 272 participants who completed the intervention, the mean weight losses were 3.3 kg, 4.6 kg, and 5.5 kg, respectively. The relative reduction in the ratio of total cholesterol to high-density lipoprotein cholesterol was 20% in the low-carbohydrate group and 12% in the low-fat group ($P = 0.01$). Among the 36 subjects with diabetes, changes in fasting plasma glucose and insulin levels were more favorable among those assigned to the Mediterranean diet than among those assigned to the low-fat diet ($P<0.001$ for the interaction among diabetes and Mediterranean diet and time with respect to fasting glucose levels). Researchers concluded that Mediterranean and low-carbohydrate diets may be effective alternatives to low-fat diets. ("Weight Loss with a Low-Carbohydrate, Mediterranean, or Low-Fat Diet," Iris Shai, Dan Schwarzfuchs, Yaakov Henkin, et al. *The New England Journal of Medicine*, July 2008; Vol. 359, No. 3, 229-41.)

-- Researchers studied the effect of carbohydrate restriction on the origin of gluconeogenic precursors (GNG from glycerol [GNGglycerol] and GNG from lactate/amino acids [GNGphosphoenolpyruvate {PEP}]) or its consequence to hepatic energy homeostasis, in a group of overweight/obese subjects undergoing weight-loss via dietary restriction. Researchers used 2H and 13C tracers and nuclear magnetic resonance spectroscopy to measure the sources of hepatic glucose and tricarboxylic acid (TCA) cycle flux in weight-stable subjects (n_7) and subjects following carbohydrate restriction (n_7) or calorie restriction (n_7). The majority of hepatic glucose production in carbohydrate restricted subjects came from GNGPEP. The contribution of glycerol to GNG was similar in all groups despite evidence of increased fat oxidation in carbohydrate restricted subjects. A strong correlation between TCA cycle flux and GNGPEP was found, though the reliance on TCA cycle energy production for GNG was attenuated in subjects undergoing carbohydrate restriction. Together, these data imply that the TCA cycle is the energetic patron of GNG. However, the relationship between these two pathways is modified by carbohydrate restriction, suggesting an increased reliance of the hepatocyte on energy generated outside of the TCA cycle when GNGPEP is maximal. Carbohydrate restriction modifies hepatic GNG by increasing reliance on substrates like lactate or amino acids but not glycerol. This modification is associated with a reorganization of hepatic energy metabolism suggestive of enhanced hepatic ß-oxidation. ("Alterations in Hepatic Glucose and Energy Metabolism as a Result of Calorie and Carbohydrate Restriction," Jeffrey D. Browning, Brian Weis, Jeannie Davis, et al. *Hepatology*, November 2008.)

2007 -- A scientific study was conducted to determine the stability of Phase 2 in processed foods and develop a method for monitoring its alpha-amylase inhibiting activity. The study showed that the alpha-amylase inhibiting action of Phase 2 was not affected during preparation of instant mashed potatoes. It also showed that exposure of alpha-amylase to Phase 2 for 30 minutes resulted in significant inhibition. (Yesu Das, Ph.D., ISSI Laboratories, Inc., Piscataway, NJ, 2007.)

-- A study was conduced to assess the efficacy of Phase 2 in inhibiting the human salivary alpha amylase in chewing gum. The study showed that alpha amylase was significantly inhibited by Phase 2 and the inhibiting action of Phase 2 was not affect by the processing/ manufacturing of the chewing gum. (Yesu Das, Ph.D., ISSI Laboratories, Inc., Piscataway, NJ, 2007.)

-- Studies were conducted on Super Bows Diet Type B, a supplement in the Japanese marketplace that contains Phase 2, to evaluate its effect on body weight, body fat and blood glucose levels. In an 8-week open test on 47 human subjects who took Super Bows Diet Type B, there was a significant decrease in the body weight and body fat percentage of test subjects after 8 weeks. In a double-blind cross-over test of 13 human subjects, those who took Super Bows Diet Type B had blood glucose and insulin levels 30 minutes after intake that were significantly lower than those on placebo. ("Effects of Combination of Functional Food Materials on Body Weight, Body Fat Percentage, Serum Triglycerides and Blood Glucose," Yamada Jun, Yamamoto Tetsuro, Yamaguchi Hideyo, 2007.)

-- An open-label 6-arm crossover study with 13 randomized subjects using standardized GI testing showed that the GI of Wonder Brand White Bread was significantly reduced by the addition of 3000mg of the Phase 2/StarchLite white bean extract in powder form with other dosages and formulations trending toward significance. ("A Novel Method of Lowering the Glycemic Index of White Bread Using a Proprietary White Bean Extract," Jay Udani, Mary Hardy, Sudeep Shrestha, 2007.)

-- A double-blind, human pilot study found that those who ate the most carbohydrates and took a supplement containing Phase 2 Starch Neutralizer®, lost significantly more weight and inches from their waist than the placebo group. When stratified by total carbohydrate intake, the Phase 2 group lost an average of 8.7 lbs and 3.3 inches off their waists, while the placebo group lost an average of 1.7 lbs and 1.3 inches. The results were statistically significant. ("Blocking Carbohydrate Absorption and Weight Loss: A Clinical Trial Using a

Proprietary Fractionated White Bean Extract" Jay Udani, MD, Medical Director, Integrative Medicine Program, Northridge Hospital Medical Center, Northridge, CA; Betsy Singh, Ph.D., Dean of Research, Southern California University of Health Sciences. *Alternative Therapies in Health and Medicine*, Jul/Aug 2007, Vol. 13, No.4.)

-- After critical independent evaluation of the available safety and clinical information, the undersigned experts conferred and, anticipating imminent publication of the 28-day rodent study manuscript, concluded that Phase 2 may be Generally Recognized as Safe (GRAS) by scientific procedures providing an upper limit of aggregate intake of 6 g of Phase 2 per day from supplement and qualified food use applications. ("Evaluation of the Generally Recognized as Safe (GRAS) Status of Phase 2 White Bean (Phaseolus Vulgaris) Extract," Robert Nicolosi, Ph.D., Donald Hughes, Ph.D., and David Bechtel, Ph.D., 2007.)

-- A double-blind, placebo-controlled study of 60 human subjects who took Phase 2 lost an average of 6.45 lbs. in 30 days, compared to those on placebo, who lost less than 1 lb., on average. Those participants on Phase 2 also lost, on average, over 10% of body fat mass, and more than 3% in waist circumference. There was no loss of lean body mass. ("A Dietary Supplement Containing Standardized Phaseolus Vulgaris Extract Influences Body Composition of Overweight Men and Women," Leonardo Celleno, Maria Tolaini, Alessandra D'Amore, Nicholas Perricone, Harry Preuss. *Int. J. Med. Sci.,* 2007; 4:45-52.)

2005 -- An 8-week trial of 10 overweight subjects showed that those who took Phaseolamin™ 1600 diet reduced body weight, body fat ratio, body fat, abdomen fat ratio, BMI, waist-hip size and triglycerides in the blood serum at a statistically significant level. In addition, the basal metabolism quantity per weight (kg.) was increased at a statistically significant level. ("The Anti-Obesity Effect and the Safety of Taking Phaseolamin™ 1600 Diet," Takashi Koike, Yoshimitsu Koizumi, Liang Tang, Kyouko Takahara, Yasuhiro Saitou; *J. New Rem & Clin*, Vol. 54, No. 7; 2005.)

-- A series of baked goods, including breads, pizza, muffins and coffee cake, was developed containing Phase 2/StarchLite at the David Geffen Center for Human Nutrition, UCLA. The products were then subjected to a series of consumer taste tests comparing the Phase 2-containing (Test) baked goods to traditional baked goods (control). In all cases, the Phase 2 products were liked similarly to the control products suggesting the products are interchangeable. In addition, researchers concluded that Phase 2/StarchLite does not affect the taste or texture of foods. ("The Mighty Bean: Dr. Kanak Udani Described the Results of the Incorporation of the Phase 2 Fractionated White Bean Extract in Baked Goods and its Impact on Consumers," Kanak Udani, Ph.D., *European Baker*, December 2005.)

2004 -- A randomized, double-blind, placebo-controlled, cross-over study of 54 overweight and obese subjects showed minor weight loss and favorable alterations of BMI in some of the stratified groups; several statistically significant favorable changes in blood pressure in the single arm prospective study; and statistically significant improvement in total cholesterol levels in all stratified groups. ("The Effect of TheraSlim [with Phase 2] on Weight, Body Composition, and Select Laboratory Parameters in Adults with Overweight and Mild-Moderate Obesity," Stuart I. Erner, M.D., 2004.)

-- A double-blind, placebo-controlled study of 27 subjects showed that those taking Phase 2 lost nearly a half pound per week (3.8 lbs. over eight weeks), on average, or 129% more than those on placebo. Those on placebo lost 1.65 lbs. Patients on the starch neutralizer also lost 1.47 inches around their waists, on average, or 36% more than those on placebo. Those on placebo lost 1.07 inches. ("Blocking Carbohydrate Absorption and Weight Loss: A Clinical Trial Using Phase 2 Brand Proprietary Fractionated Bean Extract," Jay Udani, MD, Mary Hardy, MD, and Damian C. Madsen, B.A., *Alternative Medicine Review*, 2004; 9:1, 63-69.)

2003 -- A double-blind, placebo-controlled study involving 60 overweight subjects showed that those taking StarchAway (Phase 2 chews) experienced significantly more weight loss than their placebo counterparts. Overall the StarchAway group lost nearly 7 lbs. compared with a gain of almost 1 lb. in the Placebo group after 12 weeks. ("Reduction in Body Weight with a Starch Blocking Diet Aid: StarchAway Comparison with Placebo," Dana Rothacker, Ph.D., Leiner Health Products; 2003.)

2000 -- A double-blind, placebo-controlled study of 40 overweight human subjects showed that those who took a supplement containing Phase 2 several times a day for 12 weeks experienced statistically significant weight loss and BMI reduction. The Phase 2 supplement had a significantly greater effect on body weight than did the placebo (weight loss of 3.5 kg vs. 1.2 kg). In addition, body mass analyses show that the weight loss in the active group consisted mainly of fat loss as >85% of the weight loss was accounted for by fat. ("A Randomized, Double-Blind, Placebo-Controlled Trial of a New Weight-Reducing Agent of Natural Origin," Dr. E. Thom. *Journal of Int'l Medical Research* 2000; 28: 229-233.)

1984-88 -- The Mayo Clinic begins a series of studies on white bean extracts as amylase inhibitors. These are included in this dossier as studies 25 through 30. Major findings include:

"Commercial amylase inhibitors failed to decrease starch digestion in vivo mainly because they have insufficient anti-amylase activity.

"Partially purified inhibitor, prepared by simple extraction of crude bean powder, has much more specific anti-amylase and less agglutinating activity compared with commercial preparations.

"[Partially purified inhibitor] causes dose-dependent intraluminal amylase inactivation in the human intestine, and decreases in vitro digestion of both cooked and raw dietary solid starches."

Orígenes

1982 -- Food and Drug Administration suspends sale of crude bean amylase inhibitors (marketed as starch blockers) based on clinical studies showing that the products failed to influence fecal calorie excretion; postprandial concentrations of plasma glucose or breath hydrogen; and metabolism of C-labeled starch.

1980 -- First crude bean amylase inhibitor preparations are commercially advertised and sold as weight control remedies.

1974 -- J. John Marshall and Carmen M. Lauda purify a proteinaceous inhibitor of alpha-amylase from kidney beans (Phaseolus vulgaris), which they name Phaseolamin.

The researchers perform the first in-vitro research on phaseolamin and conclude it is a specific alpha-amylase inhibitor.

1940's -- Specific inhibitors of animal alpha-amylases were found in plants, particularly wheat and beans.

SATIAL CARB CONTROLLER - RESUMEN

La materia prima bajo patente presente en SATIAL CARB CONTROLLER ha sido objeto de más de una docena de estudios clínicos desde 2001, que han demostrado su seguridad y eficacia.
En 2006, la Administración de Alimentos y Fármacos de Estados Unidos (FDA) llevó a cabo una extensa revisión de los datos clínicos e información, confirmando su eficacia y aprobando los claims de uso y seguridad:

- "Ayuda a controlar el peso cuando se utiliza junto con una dieta y un programa de ejercicio"
- "Reduce la digestión enzimática de almidón presente en los alimentos."

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