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Effects of a Dietary Supplement Containing Salacia Extract, Citrus Bioflavonoids, and Trivalent Chromium on Markers of Glucose Control and Quality of Life: A Randomized, Placebo-Controlled, Double-Blind Study

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[#]Hector Lopez passed away prior to the submission of this paper. This is one of his last publications

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Abstract

The purpose of this investigation was to compare the efficacy of a combination of *Salacia chinensis* extract, citrus bioflavonoids, and trivalent chromium (SEC) on glucose and insulin control, psychobiological perceptions of hunger, and adverse events reported from 12 weeks of supplementation. Using a randomized, double-blind, placebo-controlled parallel group study design, subjects were randomized to consume SEC or a placebo (PLA). Participants completed two study visits (baseline and after 12 weeks of supplementation) where they were assessed for glucose and insulin changes after an oral sucrose tolerance test (OSTT), perceptual indicators of hunger and appetite, waist circumference, and clinical biomarkers of metabolic and physiological function associated with glucose and insulin control. Twelve weeks of SEC supplementation significantly reduced cravings for sweets, reduced insulin and glucose responses to an OSTT, and increased adiponectin levels. Improvements in BUN: creatinine ratio provides preliminary support for maintaining healthy kidney function. These results support the role of botanical supplements in improving outcomes associated with obesity, metabolic health and glucose intolerance.

Keywords: Obesity; Salacia chinensis; chromium; glycemia; glycemic control; metabolic syndrome; insulinemia; glucose intolerance; insulin sensitivity; supplementation

List of Abbreviations: SEC: *Salacia chinensis* extract; citrus bioflavonoids; and trivalent chromium; PLA: placebo; OSTT: oral sucrose tolerance test; BUN: blood urea nitrogen; CMP: comprehensive metabolic panel; CBC: complete blood count; VAS: visual analog scales; HS-CRP: high sensitivity C-reactive protein

Introduction

Obesity is associated with serious health risks with global prevalence rates presenting a startling picture in terms of future public health and associated health care costs [1-3]. Major factors influencing obesity are the increased availability of energy dense foods and a shift to a sedentary lifestyle resulting in an energy imbalance between calories consumed and calories expended. In conjunction with reductions in fitness and skeletal muscle health secondary to a more sedentary lifestyle, diets or eating patterns that result in increased carbohydrate and highly processed food intake further challenge various health outcomes, and may lead to a loss of eating control, which can go on to challenge blood glucose management, and negatively impact weight control [4]. Effective blood glucose management via a combination of a balanced diet and exercise is critical for improving long term health and reducing complications associated with hyperglycemia, including obesity, and should be the primary approach employed to reduce obesity [2].

In addition to primary efforts to modify diet and improve physical activity, the consumption of various dietary supplements, including botanicals and minerals, are commonly considered in conjunction with a healthy lifestyle to support weight management and a healthy metabolism. One such botanical, *Salacia chinensis*, a woody climber, belongs to the Celastraceae (spikethorn) family and is commonly found throughout South Asia (particularly India). The roots from *Salacia* species contain unique biologically active polyphenolic compounds, such as triterpenes, glycosides, salacinol, salaretin, mangiferin, and kotalanol, which have been previously reported to exhibit various medicinal properties [5,6]. Preclinical and clinical studies have examined the mechanistic considerations that extracts derived from Salacia roots exert on multiple targets which include the inhibition of pancreatic lipase, aldose reductase, and alpha glucosidase, all of which function to break down lipids and disaccharides into monosaccharides, respectively. Functionally, these actions should lead to reductions in glucose absorption into the blood, which has already been documented several times in the literature [7-10]. While preliminary evidence has grown, the need for human data using randomized, placebo-controlled study designs to further examine these outcomes are needed.

Chromium is another micronutrient that has a history of being used to manage weight loss and support healthy glucose metabolism [11-13] in various populations who struggle to maintain healthy glucose levels but has limited efficacy in healthy populations [14] and even less data in the millions of people who have begun to exhibit discordant patterns of glucose and insulin levels. One challenge associated with chromium use are the different valence states upon which it can exist, the auto-conversions that can happen between them, and the known safety hazards that can result (i.e., chromium VI). For these reasons, innovative approaches have been examined to minimize the known oxidation of chromium III to other more toxic forms of chromium. One such example is Crominex (Kerry Group, Naas, Ireland) where chromium (III) is complexed with antioxidant ligands, *Phyllanthus emblica* (amla) fruit extract and Shilajit. Due to its abundant composition of gallotannoids [15], the addition of amla fruit extract improves chromium bioavailability, reduces conversion to other chromium forms, and minimizes accumulation of chromium in tissues. Similarly, the addition of Shilajit also works to help improve chromium bioavailability [16]. Notably, this complex has been studied in patients with type 2 diabetes whereby glucose levels were reduced by 12.4 – 16.6%, which were greater than the observed changes in placebo (3.4 to 9.4% reduction) [17]. Additionally, greater improvements in C-reactive protein, LDL cholesterol, and other diabetic symptoms were observed in the patients who consumed the complex of chromium, amla extract, and Shilajit. Moreover, insulin signaling may depend to some degree on adequate levels of chromium to facilitate effective binding to insulin receptors, which instigates downstream signal transduction through the insulin receptor pathways and subsequently aids in the uptake of glucose into cells. Interestingly, chromium deficiency results in symptoms, including hyperglycemia and glycosuria, which further highlights its connection to glucose metabolism [3]. In consideration of these previous findings, a combination of citrus bioflavonoids and chromium has been shown to exhibit favorable improvements in several biomarkers associated with glucose and lipid levels as well as inflammation in individuals with type 2 diabetes [17] but limited research has explored its safety and efficacy in pre-diabetics or people who have begun to display elevated markers of glucose homeostasis. Finally, no research has examined the potential efficacy of the combination of *Salacia chi-*

nensis extract, citrus bioflavonoids, and chromium on weight loss. Thus, the primary objective of this study was to compare the effect of a formulation containing *Salacia chinensis* extract, citrus bioflavonoids and chromium (III) versus placebo on glycemic response, insulin resistance markers, standard biomarkers of liver and kidney function, and weight loss and body composition changes in individuals with slightly elevated fasting blood glucose and/or hemoglobin A1C levels.

Methods

Experimental Design

The study design employed for this protocol was a randomized, double-blind, placebo-controlled study with two parallel groups that spanned 12 weeks. Each participant completed four study visits (Table 1). The first visit was for screening purposes and consisted of signing an IRB-approved consent form, completing a medical history questionnaire, recording a 24-hr dietary recall, and assessing routine blood work (comprehensive metabolic panel [CMP], complete blood count [CBC], hemoglobin A1C, and lipid panel). During visit 2, participants were assessed for their body mass, hemodynamics, and had fasting blood samples collected. The baseline sample was analyzed for glucose (to confirm fasting), insulin, hemoglobin A1C, C-reactive protein, adiponectin, and ferritin. At this time, waist circumference, and questionnaires to assess physical activity (i.e. Framingham), quality of life (i.e. SF-12) and visual analog scales (VAS) for appetite, fullness, cravings, and sweet cravings were assessed. After baseline assessments were completed, participants ingested a 75-gram sucrose beverage (OSTT) and had subsequent blood samples collected at 30-, 60-, 90-, and 120 minutes post ingestion which were analyzed and assessed for changes in glucose and insulin. Sucrose was used as the carbohydrate challenge due to the anticipated inhibition of alpha-glucosidase activity by SEC. This enzyme blocks the breakdown of carbohydrate polymers but not monomers (glucose). After completion of visit 2 (baseline testing visit), participants were randomized in a double-blind, placebo-controlled fashion to ingest a daily dose of a glucose lowering agent that contained Salacia chinensis extract and chromium (identified herein as SEC) or a placebo (PLA). Participants ingested their assigned daily dose for 12 weeks and returned for the same OSTT assessment after 12 weeks of supplementation to evaluate the impact of supplementation on the intended outcomes. Prior to all study visits, participants were asked to replicate their previous dietary intake for the 24 hours prior to their visit, refrain from caffeine for 12 hours, fast for 10 hours, and abstain from exercise for 24 hours. Figure 1 provides a CONSORT flow diagram of the study.

Table 1: Overview of Research Design

Procedure	Screening	Week 0	Week 12
Visit	1	2	3
Day (±5 days)	0	1	84
Informed consent, inclusion/exclusion	X		
Medical history, physical exam	X		
Height	X		
Body Mass	X	X	X
Body mass index	X		X
Hemodynamic assessment	X	X	X
Hemoglobin A1C	X	X	X
Insulin	X		
CMP, NMR Lipoprofile, CBC	X	X	X
OSTT		X	X

Glucose/insulin before and @ 0, 30, 60, 90, 120 min post		X	X
HS-CRP, Adiponectin, Ferritin		X	X
Waist circumference		X	X
Questionnaires (QOL/VAS, Framingham PA)		X	X
Weekly compliance checks		X	X
Adverse events monitoring		X	X

BMI = Body mass index; OSTT = Oral sucrose tolerance test; CMP = Comprehensive metabolic panel; CBC = Complete blood counts; NMR = Nuclear magnetic resonance; HS-CRP = High sensitivity C-reactive protein; QOL = Quality of Life; VAS = Visual analog scale; PA = Physical activity.

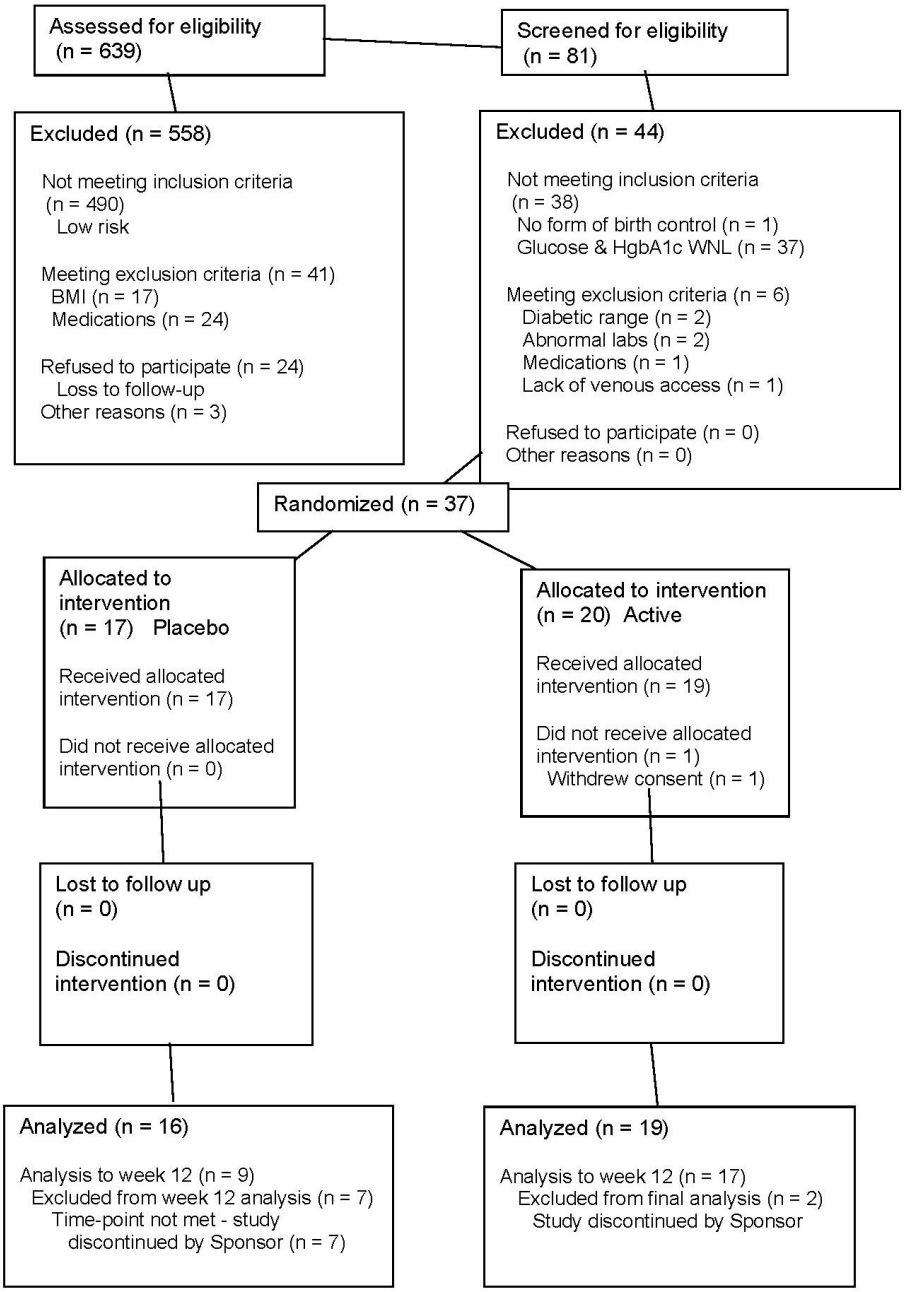

Figure 1: CONSORT Diagram

Study Participants

This study trial began during the COVID-19 pandemic and was terminated early due to recruitment difficulties. Due to a lower than expected a priori enrollment, 26 participants were randomized into the study protocol from a local suburban community in Ohio with nine people being assigned to PLA (48.9 ± 9.0 years, 176.4 ± 13.8 cm, 100.5 ± 23.6 kg, 31.7 ± 3.9 kg/m^2) and 17 people being assigned to SEC (51.8 ± 9.1 years, 172.0 ± 9.7 cm, 89.4 ± 16.8 kg, 30.1 ± 4.4 kg/m^2). Table 2 outlines baseline demographics characteristics recorded for the study cohort. All participants read and signed an IRB-approved informed consent form prior to participating in the study (Integreview, Austin, TX; Protocol # UPGRAID-001-2020, Approval date: November 19, 2020). Upon review of health/medical history documents and a physical exam, all study participants were determined to be in good health. Inclusion criteria were established that all participants were required to be between 21 – 65 years, have a minimum body mass of 120 pounds (54.5 kg), and body mass index between 18.5 – 34.99 kg/m^2. Participants were also required to be normotensive (<140 / <90 mm Hg) with a normal resting heart rate (<90 beats/min) and have fasting blood glucose levels between 100 – 125 mg/dL (5.6 – 6.9 mM) or hemoglobin A1c values of 5.7 – 6.4%. Further, females were excluded if they were determined to be pregnant, nursing, or trying to become pregnant. Alternatively, participants were excluded if they had a history of: unstable or new-onset cardiovascular or cardiorespiratory disease; diabetes, or other endocrine disorder; fasting blood glucose > 125 mg/dL (6.9 mM) or a HbA1 C > 6.4%; use of medications or dietary supplements known to affect glycemia or insulinemia; hyperparathyroidism or an untreated thyroid disease; malignancy in the previous five years except for non-melanoma skin cancer (basal cell cancer or squamous cell cancer of the skin); prior gastrointestinal bypass surgery (i.e., Lap band); other known gastrointestinal or metabolic diseases that might impact nutrient absorption or metabolism [e.g. short bowel syndrome, diarrheal illnesses, history of colon resection, gastroparesis, Inborn-Errors-of-Metabolism]; any chronic inflammatory condition or disease (e.g. rheumatoid arthritis, Crohn's disease, ulcerative colitis, Lupus, HIV/AIDS, etc.); known sensitivity to any ingredient in the test formulations as listed in the certificates of analysis. Additionally, participants were excluded if it was found they were currently participating in another research study with an investigational product or have been in another research study in the previous 30 days or they had any other diseases or conditions that, in the opinion of the medical staff, could confound the primary endpoints or place the subject at increased risk of harm if they were to participate.

Table 2: Baseline Characteristics

	Placebo(n=9)	SEC(n=17)
Age(years)	48.9 ± 9.0	51.8 ± 9.1
Height(cm)	176.4 ± 13.8	172.0 ± 9.7
Weight(kg)	100.5 ± 23.6	89.4 ± 16.8
Body Mass Index(kg/m^2)	31.7 ± 3.9	30.1 ± 4.4
Systolic Blood Pressure (mm Hg)	127.8 ± 10.5	131.4 ± 9.1
Diastolic Blood Pressure (mm Hg)	77.6 ± 7.7	80.4 ± 7.3
Resting Heart Rate(beats/min)	71.4 ± 11.7	66.9 ± 7.4
HOMA-IR[1]	3.6 ± 1.9	3.6 ± 2.5
QUICKI[2]	.33 ± .03	.33 ± .03
Diabetes Risk Score[3]	4.7 ± 1.9	4.5 ± 1.3
Fasting Blood Glucose	96.7 ± 7.9	99.2 ± 8.7
Hemoglobin A1c	5.71 ± 0.15	5.63 ± 0.43

Data are presented as mean ± SD. [1]Calculated as: fasting insulin (μIU/mL) x fasting glucose (mg/dL)/405. [2]Calculated as: 1 / [Log (fasting insulin) + Log (fasting glucose)]. [3]Calculated as: Based off the 7 question ADA Prediabetes Risk Test.

Procedures

Height, Body Mass, Heart Rate, Blood Pressure

Standing height was determined using a wall-mounted stadiometer with each study participant in socks with heels together. Body mass was measured using a Seca 767™ Medical Scale. Resting heart rate and blood pressure was measured using an automated blood pressure cuff (Omron HEM-780) after participants had remained sitting for a minimum of five minutes.

Waist Circumference

Waist circumference was assessed by a trained investigator using a flexible tape measure with an attached tensiometer to ensure consistent application of tension before (week 0) and after 12 weeks of supplementation. Three measurements were taken at each site with the two closest measurements being averaged. For each measurement, care was taken to ensure the tape measure stayed level laterally and anteriorly/posteriorly. Waist circumference was determined to be the narrowest portion of the torso around the level of umbilicus [18].

Visual Analog Scales (VAS) and Questionnaires

VAS were completed by each study participant before and after 12 weeks of supplementation for ratings of appetite, satiety, food cravings, and sweet food cravings. All VAS were constructed similarly with a 100-mm line anchored by "Lowest Possible" and "Highest Possible". The validity and reliability of VAS to assess fatigue and energy have been previously established [19] and these methods have been published previously by our laboratory [20,21]**.** The Framingham physical activity questionnaire was administered before and after 12 weeks of supplementation to assess physical activity habits throughout the study protocol and to ensure participants were complying with their instructions to maintain their physical activity habits. The SF-12 Health Survey was administered before and after 12 weeks of supplementation to assess quality-of-life. This questionnaire has been used in previous intervention and population-based investigations as an assessment of quality-of-life status and provides a physical and mental function score [22-24].

Venous Blood Collection

A time course of venous blood samples was collected before and after 12 weeks of supplementation. Using standard aseptic phlebotomy techniques, an indwelling catheter was inserted into a forearm vein to sample venous blood before (0 minutes) and 30, 60, 90, and 120 minutes after ingestion of their assigned supplement. Whole blood samples were collected into K_2-EDTA treated Vacutainer™ tubes and upon collection were slowly inverted ten consecutive times prior to immediate refrigeration. Serum samples were collected in serum separation tubes and allowed to clot for 30 minutes at room temperature prior to being centrifuged (652E Centrifuge, Drucker Diagnostics, Port Matilda, PA) for 10 minutes at 3,200 rpm.

Biochemical Analysis

Venous blood samples were analyzed for a comprehensive metabolic panel to assess fasting blood glucose, electrolyte and fluid balance, kidney, and liver function before and after 12 weeks of supplementation. All analyses from the same day were completed using automated clinical chemistry analyzers (LabCorp, Ohio) and were batch analyzed with test-retest reliabilities commonly reported using internal quality control data from clinical laboratories and associated automated analyzers within a range of 3 – 5% [25] . In addition, hemoglobin A1C, NMR Lipoprofile, high-sensitivity C-reactive protein (HS-CRP), adiponectin, and ferritin were analyzed before and after 12 weeks of supplementation (LabCorp, Ohio). All blood samples collected as part of the

OSTTs were analyzed for changes in glucose and insulin by a commercial diagnostic laboratory (LabCorp, Ohio).

Diet and Physical Activity Control

Throughout the 12-week study protocol, participants were instructed to maintain their current physical activity and dietary intake patterns, while refraining from strenuous physical activity 24 hours prior, and arrive at least 10 hours fasted to each laboratory visit. During the initial screening visit, participants were asked to complete a 24-hour dietary recall to assess their dietary composition. Upon the initial dietary recall, the research staff met with each subject to explain and instruct the proper procedures for recording dietary intake on future three-day records. To facilitate replication of baseline conditions, copies of their 24-hour food recall from their initial screening visit were made and provided to each study participant to allow them to standardize their dietary and fluid intake for 24 hours prior to each laboratory visit. Before (week 0) and after 12 weeks of the supplementation protocol, three-day dietary records (including 2 weekdays and one weekend day) were completed to assess general compliance to the protocol and further to assess if dietary changes occurred. Dietary records were analyzed for average daily energy and macronutrient intake by the MyFitnessPal (MyFitnessPal, Inc. Francisco Partners, San Francisco, CA).

Supplementation

All participants were randomly assigned to receive either SEC or PLA. Subjects were instructed to consume their respective supplement daily for 12 weeks, approximately 15 – 30 minutes prior to their evening meal. All supplements were prepared in identical, coded generic tablets and bottles for double-blind administration. Supplements were blinded by the sponsor prior to initiation of any research activities. All research activities, including statistical analyses, were completed while blinded. Compliance to the supplementation regimen was monitored by daily logs and weekly phone calls to the participants. SEC is marketed as Control Glucose (MEND Labs, Inc.) and is comprised of: 400 mcg chromium (delivered as Crominex® 3+, a blend of chromium, Capros® Amla Extract (Fruit), PrimaVie® Shilajit), and 325 mg of MetaviveTM complex (*Salacia Chinensis* Extract (Fruit) and a Citrus Bioflavonoid Complex) (Figure 2). The PLA consisted of a maltodextrin tablet. Third-party verification of all active ingredients was completed and outlined in certificates of analysis by an independent laboratory.

Supplement Facts		
Serving Size: 1 Tablet		
Servings Per Container: 30		
	Amount Per Serving	**% Daily Value**
Calcium (as Aquamin™ mineralized red algae)	100mg	8%
Magnesium (as Aquamin™ MG marine magnesium)	50mg	12%
Chromium [as Crominex® 3+ chromium with Capros® amla extract (fruit) and PrimaVie® Shilajit]	400mcg	1,143%
Proprietary Blend: MetaVive® *Salacia chinensis* (root) and citrus bioflavonoid complex	325mg	*
*Daily value not established		
Other ingredients: Microcrystalline cellulose, vegetable stearic acid, coating (polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc), croscarmellose sodium, and silica.		

Figure 2: Supplement Facts Panel

Adverse Events

During weekly phone calls, the frequency and intensity of local and systemic non-serious and serious adverse events (AEs) were recorded by study team members. All reported events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) while the intensity of recorded adverse events was graded using Common Terminology Criteria for Adverse Events (CTCAE) criteria.

Statistical Analysis

Based on previous studies and input from the sponsor, a sample size of 60 was chosen to detect statistically significant changes between treatments. These calculations were completed assuming an alpha of 0.05, beta of 0.80, and effect sizes ranging from 0.20 to 0.35 on the changes in glucose from baseline. Using these parameters, a sample size of 46-74 was calculated. However, due to slower than expected enrollment, an analysis was conducted at approximately 43% of our target sample size (26/60 finishers). Primary outcomes from this investigation were changes observed in glucose and insulin kinetics, secondary outcomes were hemodynamic, metabolic, inflammatory, and iron biomarkers while tertiary outcomes were all hematology and metabolic safety markers. It was hypothesized that the changes observed in SEC supplementation would be different than PLA supplementation across the 12-week protocol. All data were entered into two separate Microsoft Excel (Microsoft Corp., Seattle, WA USA) spreadsheets (i.e., manual double-key data entry) and compared to assure data quality prior to analysis. IBM Statistical Package for the Social Sciences (SPSS, v23, Chicago, IL USA) and GraphPad Prism (La Jolla, CA USA) were used for figure construction. Area under the curve (AUC) calculations from the OSTT (glucose and insulin) were computed using the trapezoidal rule using a pre-formatted Microsoft Excel sheet.

Normality assumptions were checked on all variables using a one-sample Shapiro-Wilk test. Independent t-tests were used to assess baseline differences. The primary statistical approach employed were mixed factorial ANOVA with repeated measures on time. When baseline values were different, ANCOVA was employed with the baseline value for each condition serving as the only covariate. Change scores from baseline were computed and separate independent t-tests were completed to assess between-group differences at each timepoint. Chi square testing was used for AE data. Significance was set *a priori* at $p < 0.05$ and trends defined as $0.051 < p < 0.10$.

Results

Glycemic Control and Hemodynamics

Prior to the OSTT at baseline on visit 2, no differences were identified between groups for fasting blood glucose (95% CI: -2.89, 8.01, p = 0.34) or insulin (95% CI: -6.58, 9.08, p = 0.74) (Table 3). Separate 2 x 2 (group x time [week 0 and week 12]) mixed factorial ANOVAs with repeated measures on time for each timepoint of the OSTT were computed using the raw data from week 0 and week 12. Significant group x time interactions occurred for the glucose (p = 0.032) and insulin (p = 0.006) concentrations 60 minutes after the OSTT was initiated. To decompose the interaction, changes from baseline were then computed for each group and analyzed using an independent t-test. Using this approach, insulin levels in PLA were significantly different than what was observed in SEC (Mean difference: 46.9 ± 15.5 μIU/mL, 95% CI: 14.9, 78.9 μIU/mL; p = 0.006). A similar pattern of change was observed for the changes in glucose after initiation of the OSTT with PLA levels experiencing a greater increase than what was observed in SEC (Mean difference: 24.9 ± 10.9 mg/dL; 95% CI: 2.35, 47.51 mg/dL, p = 0.032). No significant differences in glucose AUC (p = 0.99) or insulin AUC (p = 0.96) were identified between groups at baseline testing (week 0). Glucose AUC revealed no main effect for time (p = 0.15) or group x time interaction ($p = 0.17$). Similarly, no main effect for time (p = 0.68) or group x time interaction ($p = 0.40$) was present for insulin AUC.

Systolic blood pressure in SEC was greater than PLA (-12.1 ± 5.4 mm Hg; 95% CI: -23.2, -0.89 mm Hg, p = 0.036) at the baseline visit (week 0) but was no longer different between groups after 12 weeks (p = 0.53). No other significant differences between groups at all measured time points were identified at baseline or week 12 for systolic blood pressure, diastolic blood pressure or resting heart rate. Using a mixed factorial ANOVA, a significant group x time interaction was observed (p = 0.03) for systolic blood pressure values 60 minutes after the OSTT showing that SEC was lower at week 12 from baseline while PLA was higher at week 12 from baseline. No other group x time interactions were observed for any hemodynamic variables. All recorded values remained within clinically accepted normative values.

Table 3: Glycemic Control and Hemodynamics.

		PLA		**SEC**			
	Time	Week 0	Week 12	Week 0	Week 12	*Time (p)*	*G x T (p)*
Glucose(mg/dL)	0	101.4 ± 5.8	100.9 ± 10.6	98.9 ± 6.7	98.4 ± 7.6	0.71	0.99
	30	152.6 ± 25.1	161.7 ± 25.9	149.3 ± 29.3	141.1 ± 30.6	0.93	0.10
	60	128.2 ± 39.1	154.4 ± 34.5*	133.1 ± 45.2	134.4 ± 47.2	0.02	0.03
	90	110.8 ± 39.7	115.6 ± 38.9	115.1 ± 48.1	116.4 ± 31.7	0.69	0.81
	120	92.0 ± 29.4	88.0 ± 24.0	89.7 ± 20.4	97.6 ± 21.9	0.60	0.12
		Week 0	Week 12	Week 0	Week 12	*Time (p)*	*G x T (p)*
Insulin(μIU/mL)	0	16.5 ± 9.1	19.0 ± 9.9	15.3 ± 9.2	14.7 ± 7.6	0.42	0.18
	30	89.9 ± 53.5	81.3 ± 22.1	98.6 ± 68.2	83.9 ± 50.9	0.22	0.74
	60	74.2 ± 42.9	110.0 ± 49.5*‡	81.5 ± 49.4	70.4 ± 41.8	0.12	0.006
	90	50.3 ± 35.4	63.7 ± 38.6	46.4 ± 20.7	53.3 ± 38.8	0.21	0.69
	120	23.8 ± 18.7	28.1 ± 14.3	32.7 ± 28.8	37.4 ± 32.2	0.16	0.95
		Week 0	Week 12	Week 0	Week 12	*Time (p)*	*G x T (p)*
Systolic BloodPressure(mm Hg)	0	119.1 ± 12.5	122.1 ± 20.4	131.2 ± 13.4‡	126.5 ± 14.3	0.72	0.11
	30	120.1 ± 20.0	123.0 ± 19.7	124.5 ± 17.0	121.7 ± 15.9	0.98	0.16
	60	117.7 ± 16.8	121.1 ± 14.3‡	122.8 ± 15.8	116.8 ± 13.6*	0.56	0.03
	90	117.0 ± 13.3	119.0 ± 16.1	119.3 ± 17.7	117.4 ± 17.2	0.99	0.38
	120	120.1 ± 13.6	120.9 ± 15.5	124.6 ± 16.3	121.5 ± 13.3	0.66	0.47
		Week 0	Week 12	Week 0	Week 12	*Time (p)*	*G x T (p)*
Diastolic Blood Pressure(mm Hg)	0	78.2 ± 5.8	78.8 ± 8.6	83.7 ± 7.8	81.5 ± 10.0	0.59	0.38
	30	73.6 ± 5.1	74.7 ± 9.6	78.1 ± 9.7	77.9 ± 12.6	0.79	0.72
	60	72.6 ± 12.1	75.1 ± 11.3	76.8 ± 7.3	72.5 ± 9.4	0.65	0.09
	90	74.8 ± 8.6	75.0 ± 7.9	76.9 ± 10.8	73.8 ± 11.0	0.44	0.37
	120	76.7 ± 6.1	76.2 ± 10.8	79.1 ± 7.6	79.2 ± 10.2	0.92	0.90
		Week 0	Week 12	Week 0	Week 12	*Time (p)*	*G x T (p)*

Resting Heart Rate(beats/min)	0	70.9 ± 10.5	71.8 ± 9.9	66.9 ± 6.8	68.6 ± 8.5	0.26	0.72
	30	72.1 ± 12.3	70.1 ± 12.1	65.6 ± 7.4	67.3 ± 8.2	0.91	0.24
	60	73.8 ± 11.6	73.2 ± 12.1	67.7 ± 7.5	69.5 ± 11.3	0.70	0.47
	90	74.1 ± 14.9	76.1 ± 12.8	68.8 ± 8.6	70.7 ± 12.0	0.24	0.99
	120	69.6 ± 12.1	72.4 ± 12.9	67.4 ± 8.0	69.3 ± 10.3	0.08	0.71

Data are presented as means ± SD. G x T = Group x time interaction effect. * = Different than week 0 ($p < 0.05$); ‡ = Value in PLA different than value in SEC at corresponding timepoint ($p < 0.05$).

Metabolic, Inflammatory, and Iron Biomarkers

Adiponectin levels at baseline were not different between groups (p = 0.70). Changes in adiponectin were different between groups (PL: -1.0 ± 1.7 vs. SEC: 0.35 ± 1.5 μg/mL) across the 12-week study period ($p = 0.044$, d = -0.89). No significant main effect for time ($p > 0.05$) or group x time interaction ($p > 0.05$) were identified for HS-CRP, ferritin, and hemoglobin A1c (See Table 4). Ferritin levels at baseline (week 0) were significantly greater in SEC than PLA (95% CI: 7.7, 213.7, $p = 0.036$). ANCOVA was performed using the week 0 values as the covariate, and no differences were found between groups, visits, or time.

Table 4: Metabolic, Inflammatory, and Iron Biomarkers.

Variable	**N**	**Week 0**	**Week 12**	**Within *(p)***	***p***	
Adiponectin (μg/mL)						
PLASEC	917	6.52 ± 3.995.88 ± 3.91	5.48 ± 3.236.23 ± 3.80	0.100.37	TimeG x T	0.300.04
CRP (mg/L)						
PLASEC	917	1.98 ± 2.302.02 ± 1.89	1.49 ± 0.991.98 ± 1.74	0.490.69	TimeG x T	0.310.40
Ferritin (ng/mL)						
PLASEC	917	238 ± 147§127 ± 102	205 ± 152112 ± 99	0.090.06	TimeG x T	0.0070.31
Hemoglobin A1c (%)						
PLASEC	917	5.64 ± 0.185.59 ± 0.48	5.68 ± 0.245.65 ± 0.43	0.400.25	TimeG x T	0.210.77
Glucose AUC						
PLASEC	917	488.3 ± 96.2489.1 ± 113.3	526.1 ± 93.7490.0 ± 113.0	0.080.96	TimeG x T	0.150.17
Insulin AUC						
PLASEC	917	250.1 ± 111.0247.7 ± 102.6	269.9 ± 96.7240.9 ± 128.0	0.530.62	TimeG x T	0.680.40

Data are presented as means ± SD. Within (p) = Change within each supplementation group from week 0 to week 12. G x T = Group x time interaction effect.§ = Different than SEC at designated timepoint ($p < 0.05$). CRP = High sensitivity C-reactive protein, AUC = Area under the curve.

Whole Blood Cell, Hematology, and Metabolic Markers

No differences between groups ($p > 0.05$) were identified for any of the complete blood count or comprehensive metabolic components (Table 5). Significant group x time interactions were observed for blood urea nitrogen (BUN): creatinine ratio (95% CI: 0.53, 6.26, $p = 0.022$), sodium (95% CI: 0.28, 3.13, $p = 0.021$), and chloride (95% CI: 0.59, 5.17, $p = 0.022$). A significant

main effect for time (p = 0.044) was identified for creatinine. No other main effects for time or group x time interactions (p > 0.05) were identified for any of the components of the complete blood count or comprehensive metabolic panel.

Table 5: Whole Blood Cell, Hematology, and Metabolic Markers

Variable	N	Week 0	Week 12	Within (p)		P
White blood cell count (cells/mm^3)						
PLASEC	917	6.17 ± 1.055.86 ± 1.37	5.83 ± 1.105.78 ± 1.44	0.090.80	TimeG x T	0.350.55
Red blood cell count (cells/mm^3)						
PLASEC	917	4.97 ± 0.333.87 ± 0.37	4.94 ± 0.264.75 ± 0.37	0.560.03	TimeG x T	0.070.25
Hemoglobin (grams/dL)						
PLASEC	917	14.78 ± 1.2014.38 ± 1.61	14.73 ± 1.0213.97 ± 1.59	0.830.04	TimeG x T	0.120.18
Hematocrit (%)						
PLASEC	917	43.4 ± 3.442.5 ± 3.9	43.0 ± 2.741.4 ± 3.8	0.480.05	TimeG x T	0.080.37
Blood Urea Nitrogen (BUN) (mg/dL)						
PLASEC	917	15.0 ± 4.714.5 ± 3.0	15.9 ± 4.913.4 ± 3.2	0.230.13	TimeG x T	0.840.08
Creatinine (mg/dL)						
PLASEC	917	0.87 ± 0.180.88 ± 0.19	0.81 ± 0.160.86 ± 0.15	0.070.41	TimeG x T	0.040.29
Blood Urea Nitrogen (BUN): Creatinine Ratio						
PLASEC	917	17.4 ± 4.616.8 ± 4.2	19.7 ± 5.5‡15.7 ± 3.7	0.050.20	TimeG x T	0.460.02
Sodium (mEq/mL)						
PLASEC	917	139.7 ± 2.2139.8 ± 1.6	140.7 ± 1.9‡139.1 ± 1.9	0.110.10	TimeG x T	0.670.02
Potassium (mEq/mL)						
PLASEC	917	4.30 ± 0.194.31 ± 0.18	4.31 ± 0.184.25 ± 0.18	0.870.19	TimeG x T	0.510.35
Chloride (mEq/mL)						
PLASEC	917	102.4 ± 2.5103.5 ± 2.3	104.7 ± 1.9‡102.8 ± 3.1	0.030.28	TimeG x T	0.240.02
Carbon Dioxide (mEq/mL)						
PLASEC	917	22.67 ± 1.1223.00 ± 1.66	22.00 ± 1.2322.29 ± 1.90	0.140.18	TimeG x T	0.080.96
Calcium (mg/dL)						
PLASEC	917	9.39 ± 0.249.48 ± 0.33	9.27 ± 0.259.48 ± 0.29	0.140.99	TimeG x T	0.380.38
Total Protein (mg/dL)						
PLASEC	917	7.04 ± 0.367.04 ± 0.30	6.98 ± 0.296.90 ± 0.30	0.370.11	TimeG x T	0.110.56
Albumin (mg/dL)						
PLASEC	917	4.50 ± 0.254.48 ± 0.25	4.46 ± 0.204.41 ± 0.29	0.450.37	TimeG x T	0.310.85
Globulin (mg/dL)						
PLASEC	917	2.54 ± 0.322.57 ± 0.29	2.52 ± 0.292.49 ± 0.30	0.560.25	TimeG x T	0.300.57
Albumin: Globulin Ratio						
PLASEC	917	1.81 ± 0.281.77 ± 0.23	1.78 ± 0.251.80 ± 0.30	0.500.54	TimeG x T	0.980.43

Bilirubin (mg/dL)						
PLASEC	917	0.57 ± 0.260.50 ± 0.26	0.58 ± 0.290.49 ± 0.22	0.760.91	TimeG x T	0.940.82
Alkaline Phosphatase (U/L)						
PLASEC	917	75.1 ± 16.875.9 ± 15.5	77.0 ± 17.276.6 ± 16.4	0.160.61	TimeG x T	0.210.55
Aspartate Aminotransferase (U/L)						
PLASEC	917	21.6 ± 6.922.5 ± 7.2	21.9 ± 6.723.1 ± 6.1	0.840.59	TimeG x T	0.640.87
Alanine Aminotransferase (U/L)						
PLASEC	917	26.1 ± 11.926.0 ± 11.8	26.3 ± 14.325.9 ± 14.1	0.940.98	TimeG x T	0.960.94

Data are presented as means ± SD. Within (p) = Change within each supplementation group from week to week 12. G x T = Group x time interaction effect. ‡ = Changes in PLA different than changes in SEC ($p < 0.05$).

Cholesterol Components and Particle Size

No differences between groups ($p > 0.05$) were identified for any of the lipid panel markers (Supplementary Data Table 1). The group x time interaction for LDL cholesterol (95% CI: -27.7, 0.24, p = 0.054) approached significance and the change score in PLA decreased by -7.9±14.9 mg/dL (Week 0: 135.1 ± 38.9 vs. week 12: 127.2 ± 26.2 mg/dL) while values in SEC increased by 5.8±17.1 mg/dL (week 0: 128.0 ± 26.1 vs. week 12: 133.8 ± 27.5 mg/dL). No other group x time interactions ($p > 0.05$) were identified for any of the lipid panel markers.

Supplementary Data Table 1: Cholesterol Components and Particle Size.

Variable	**N**	**Week 0**	**Week 12**	**Within (*p*)**		***p***
Waist Circumference (cm)						
PLASEC	917	109.6 ± 14.3101.5 ± 11.2	109.3 ± 14.6101.0 ± 12.2	0.560.55	TimeG x T	0.520.84
Body Mass (kg)						
PLA	9	100.7 ± 24.1	100.8 ± 24.0	0.87	Time	0.44
SEC	17	89.7 ± 16.9	89.1 ± 16.8	0.04	G x T	0.25
VAS Appetite						
PLASEC	917	5.1 ± 1.85.2 ± 1.9	5.9 ± 1.35.6 ± 1.0	0.340.38	TimeG x T	0.190.76
VAS Fullness						
PLASEC	917	5.8 ± 1.26.3 ± 1.5	6.1 ± 0.75.8 ± 1.1	0.530.21	TimeG x T	0.810.21
VAS Cravings						
PLASEC	917	5.1 ± 1.75.0 ± 1.6	6.1 ± 1.44.8 ± 1.3	0.210.56	TimeG x T	0.420.15
VAS Sweet Cravings						
PLASEC	917	4.9 ± 1.65.3 ± 1.9	6.3 ± 2.1*4.3 ± 1.8*	0.040.02	TimeG x T	0.620.002
SF-12 Physical Function						
PLASEC	917	54.6 ± 1.553.9 ± 3.4	55.1 ± 1.653.9 ± 2.1	0.130.93	TimeG x T	0.530.63
SF-12 Mental Function						
PLASEC	917	55.7 ± 4.257.2 ± 3.7	56.6 ± 3.157.9 ± 4.3	0.400.27	TimeG x T	0.170.88

Waist Circumference and Body Mass

No differences between groups ($p > 0.05$) were identified for waist circumference or body mass (Table 6). No group x time interaction (p = 0.84) or main effect of time (p = 0.52) for waist circumference was identified. Similarly, no group x time interaction (p = 0.25) or main effect of time (p = 0.44) was identified for body mass.

Table 6: Waist Circumference, Body Mass, and Perceived Indicators of Hunger Control.

Variable	N	Week 0	Week 12	Within (*p*)		*p*
LDL Particle Number						
PLASEC	917	1647 ± 4431503 ± 376	1650 ± 3941594 ± 402	0.960.13	TimeG x T	0.320.35
LDL Cholesterol (mg/dL)						
PLASEC	917	135.1 ± 38.9128.0 ± 26.1	127.2 ± 26.2133.8 ± 27.5	0.510.18	TimeG x T	0.760.05
HDL Cholesterol (mg/dL)						
PLASEC	917	44.4 ± 11.049.2 ± 15.1	47.2 ± 10.949.4 ± 13.9	0.120.87	TimeG x T	0.210.29
Triglycerides (mg/dL)						
PLASEC	917	135.3 ± 47.1137.0 ± 52.1	158.9 ± 68.1146.6 ± 58.9	0.110.43	TimeG x T	0.090.45
Total Cholesterol (mg/dL)						
PLASEC	917	204.0 ± 39.4210.5 ± 33.9	202.6 ± 28.8214.7 ± 34.0	0.790.34	TimeG x T	0.700.43
HDL Particle Size (μmol/L)						
PLASEC	917	30.9 ± 5.533.0 ± 7.5	31.2 ± 6.833.9 ± 6.9	0.890.17	TimeG x T	0.430.64
Small LDL Particle Size (nM/L)						
PLASEC	917	765 ± 376720 ± 349	821 ± 415730 ± 355	0.160.86	TimeG x T	0.440.60
LDL Particle Size (nm)						
PLASEC	917	20.71 ± 0.6120.73 ± 0.64	20.73 ± 0.6620.83 ± 0.55	0.770.32	TimeG x T	0.410.60
LPIR Score						
PLASEC	917	59.8 ± 16.053.9 ± 19.9	59.8 ± 19.155.1 ± 18.0	0.990.71	TimeG x T	0.800.80
Total Cholesterol: HDL Ratio						
PLASEC	917	4.86 ± 1.544.57 ± 1.46	4.45 ± 1.054.53 ± 1.11	0.110.79	TimeG x T	0.120.21

Data are presented as means ± SD. Within (p) = Change within each supplementation group from week to week 12. G x T = Group x time interaction effect. *Different than respective week 0 ($p < 0.05$).

Questionnaires and Perceptual Indicators of Hunger Control

As seen in table 6, no differences between groups ($p > 0.05$) at baseline were identified between groups for the SF-12 physical or mental function as well as several perceptual indicators of hunger control on the VAS. This included self-reported levels of appetite, feeling of gastric fullness, and food cravings. A significant difference was observed for the changes in sweet cravings (95% CI: 0.96, 3.71; p = 0.002, d = 1.45) showing that self-reported levels were significantly reduced in SEC but increased in PLA at week 12 compared to baseline (week 0) (See Figure 3). No other group x time interactions or main effects for time were observed for any other perceptual indicators of hunger control or for physical or mental functions (p > 0.05).

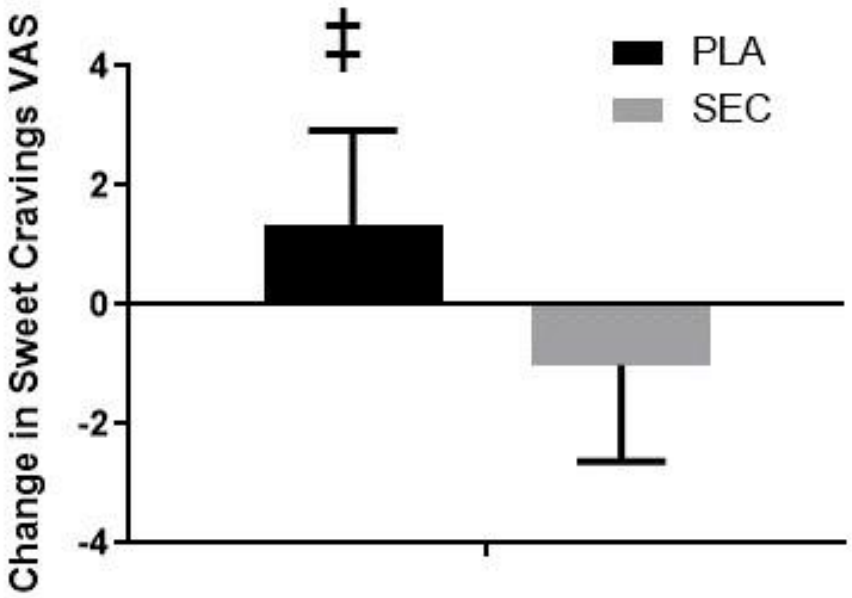

Figure 3: Changes in Sweet Cravings VAS

Changes in self-reported levels at week 12 compared to baseline.

‡ = Different than SEC ($p < 0.05$)

Physical Activity and Dietary Intake

Framingham physical activity scores revealed no significant main effect for time ($p = 0.46$) or group x time interaction ($p = 0.14$). However, the change in Framingham scores (delta) indicated a significant difference between groups ($p = 0.024$, $d = -0.54$). The active group showed a greater positive change in physical activity (PL: -.41±1.2 vs. Active: 1.2±2.8 au). Similarly, no significant main effect for time ($p > 0.05$) or group x time interaction effects were identified for any of the dietary variables. (Supplementary Data Table 2).

Supplementary Data Table 2: Physical Activity and Dietary Intake

	n	Week 0	Week 12	Within (*p*)		*p*
Framingham Physical Activity						
PLASEC	917	35.4 ± 5.033.0 ± 3.5	35.0 ± 4.734.2 ± 5.0	0.360.10	TimeG x T	0.460.14
Energy (kcals/day)						
PLASEC	816	1636 ± 4301496 ± 378	1649 ± 489*1540 ± 497	0.930.56	TimeG x T	0.700.83
Fat (grams/day)						
PLASEC	816	79.5 ± 29.768.8 ± 29.5	74.9 ± 39.670.2 ± 25.6	0.890.94	TimeG x T	0.770.60
Carbohydrate (grams/day)						
PLASEC	816	145 ± 64156 ± 38	147 ± 72155 ± 54	0.730.79	TimeG x T	0.950.87
Protein (grams/day)						

PLASEC	816	74.6 ± 22.864.3 ± 21.2	73.9 ± 24.0*65.9 ± 20.3	0.900.72	TimeG x T	0.910.75
Relative Energy (kcals/kg/day)						
PLASEC	816	15.8 ± 5.117.3 ± 4.2	15.7 ± 5.0*17.8 ± 5.4	0.980.62	TimeG x T	0.790.76
Relative Fat (g/kg/day)						
PLASEC	816	0.77 ± 0.360.76 ± 0.26	0.72 ± 0.410.79 ± 0.27	0.630.61	TimeG x T	0.800.45
Relative Carbohydrate (g/kg/day)						
PLASEC	816	1.35 ± 0.611.83 ± 0.54	1.38 ± 0.681.81 ± 0.63	0.870.91	TimeG x T	0.980.86
Relative Protein (g/kg/day)						
PLASEC	816	0.71 ± 0.230.75 ± 0.24	0.69 ± 0.19*0.76 ± 0.23	0.760.71	TimeG x T	0.990.65

Data are presented as means ± SD. Within (p) = Change within each supplementation group from week to week 12. G x T = Group x time interaction effect.

Adverse Events

A total of 13 adverse events were reported across the entire study protocol. In this respect, nine of the reported adverse events were in the SEC group while four of the reported adverse events were in the PLA group. The nine reported events in the SEC group were made by seven (37%) of the 19 participants assigned to that group. All these adverse events (n=9) were mild in severity and were considered to not be related to the study treatment. Three of the adverse events were bloating and six were related to flatulence. The four reported events in the PLA group were made by four (24%) of the 17 participants assigned to that group. All these adverse events (n=4) were mild in severity and were considered to not be related to the study treatment. Specifically, one adverse event was for bloating, two for fatigue, and one was for pruritus.

Discussion

The purpose of this investigation was to compare the impact of a combination of *Salacia chinensis* extract and chromium on its ability to impact glycemic control, markers of insulin sensitivity, perceptual indicators of hunger control, and indicators of kidney and liver function. The primary outcomes for this project centered upon the impact SEC supplementation would have on glycemic control. Secondary outcomes involved changes in perceptual indicators of hunger control, biomarkers associated with inflammation, insulin sensitivity, and iron metabolism, and components of blood counts and metabolic panels in addition to reported adverse events. The primary findings indicated that SEC supplementation reduced food cravings for sweets, blunted insulin and glucose responses an hour after an OSTT and increased fasting adiponectin concentrations. Previous research involving chromium has highlighted the positive potential for chromium to aid in weight loss and improvements in glucose and insulin metabolism. Additionally, a study by Brownley et al. [26] highlighted chromium's potential to reduce glucose and modulate associated psychopathology associated with eating control in people with a binge eating disorder. Results from the present study align with previous findings that suggest chromium supplementation exerts little influence towards weight loss [27], while the observed changes in sweet cravings require more research. Possibly, chromium may offer support for low energy levels, which are commonly associated with low blood sugar, dysregulated energy metabolism and elevated insulin in people who

are challenged to maintain a euglycemic status.

Supplementation with SEC resulted in improvements in glucose and insulin response one hour after ingestion of a carbohydrate load. These results are in accordance with other published studies assessing the benefits of *Salacia chinensis* extract for metabolic and glycemic responses [7-10]. In single dose clinical protocols [8, 9], *Salacia chinensis* extract showed significant dose-dependent reductions of postprandial blood glucose and insulin levels in overweight or prediabetic individuals. In multi--dose studies up to 12 weeks, [7, 9], *Salacia chinensis* significantly improved several blood glucose and metabolic related parameters, including post prandial glucose and insulin levels, HgA1c, GI peptides/hormones as well as positively impacted appetite and satiety.

In addition, other Salacia plant species have also shown efficacy in lowering blood glucose levels as well as optimizing other critical metabolic processes. A recent review [10] summarized data from well controlled studies testing *Salacia oblonga*, *Salacia chinensis*, or *Salacia reticulata*. The active ingredients responsible for inhibiting blood glucose include salacinol, kotalanol, and kotalagenin 16-acetate. These extracted ingredients strongly inhibited a-glucosidase activity, which is the main mechanism by which Salacia works to lower blood glucose levels.

Previous research has highlighted that elevated baseline adiponectin levels or increases in adiponectin correlate with a lower risk of type 2 diabetes [28]. Mechanistic data in multiple experimental models have demonstrated that adiponectin influences key signaling pathways that promote enhanced glucose uptake, fatty acid oxidation, anti-inflammatory, anti-atherogenic effects across broad tissue/cell types such as macrophages, hepatocytes, adipose tissue, skeletal muscle, and vascular endothelium [29]. Furthermore, plasma levels of adiponectin have been found to be lower in obese subjects when compared to lean participants [30], which provides valuable independent lines of evidence supporting attempts to stimulate increases in adiponectin. Results from the present study indicate that SEC supplementation over 12 weeks and when compared to placebo led to favorable increases in adiponectin levels. Towards this end, previous research [30] has highlighted inverse correlations between adiponectin and body mass index, a relationship that was also identified in the present study (r = -0.60, p = 0.002) . In addition, a six-month lifestyle modification regimen increased adiponectin levels by 8%, improved insulin resistance and resulted in an 8.7% weight loss [31]. This suggests that even modest improvements in adiponectin levels may be associated with beneficial effects on metabolic health. Considering the above references, the improvement in adiponectin levels by SEC could be considered clinically significant, however no changes in body mass or waist circumference were realized in the present study. Future research involving defined exercise and diet interventions should examine further the impact of SEC supplementation on weight loss, metabolic health and body composition changes.

Over a 12-week study period, weekly supplementation monitoring was completed to evaluate any changes that may have occurred in terms of health, safety, and adverse events. Three variables in the blood counts and metabolic panel (BUN: creatinine, sodium, and chloride) were changed after supplementation. While more work is needed, changes in the BUN: creatinine ratio is a well-established indicator of kidney function where decreased levels suggest an improvement in kidney function and renal perfusion [32]. The clinical relevance of this finding in terms of renal health and disease remain to be fully established.

The supplementation appeared to be well-tolerated within the confines of the study design and dosing employed. In this respect, LDL cholesterol levels were found to increase slightly in the SEC group when compared to the PLA group. This was an unexpected finding since previous data has indicated that chromium aids in glucose and insulin metabolism and improves cardiometabolic risk [11,12]. This outcome also conflicts with the previous findings of Akhtar et al. [33] who randomized healthy and type 2 diabetes patients to 1, 2, or 3 grams of Emblica officianlis for 21 days to examine its ability to manage glucose and lipids. While the dosages of amla fruit used were much higher than that used in the present study, these authors did report improvements in glucose control and lipid levels (increases in HDL cholesterol and reductions in LDL cholesterol). Further, no

other cholesterol markers changed in response to supplementation. While limited research has examined these outcomes, all changes remained within clinically acceptable values and need to be examined further using larger randomized controlled trials, powered for lipoprotein changes with an evaluation of lipoprotein particle size and number.

Strengths of this protocol involve the randomized, double-blind, placebo-controlled study design in addition to the stringent inclusion criteria to ensure that the participants did not classify as having type II diabetes yet exhibited distinct signs of insulin resistance and/or dysregulation of glucose homeostasis. As highlighted throughout, limited research to date has examined the potential of a combination of *Salacia chinensis* extract and chromium and our data represent some of this research for this specific metabolic population. Limitations of our project first and foremost relate to the sample size and disproportionate distribution of participants into each supplement condition (n=9 for PLA vs. n=17 for SEC). For this reason, the reader should consider these outcomes to be that of an underpowered, pilot investigation that warrants a larger, deeper investigation. Further, we employed a 'per protocol' approach to analyzing the data, which led to us having a smaller sample size than other statistical approaches. As indicated in the methods earlier in the paper, the original plan was to recruit for and conduct a fully powered clinical investigation, but local and state governmental regulations and restrictions led to difficulty in enrollment due to the COVID pandemic. Consequently, the study was terminated early due to a failure to make continued recruiting progress.

A smaller sample size reduces statistical power, leading to a higher risk of Type II errors, where true effects may go undetected. This reduction in power necessitates larger effect sizes to achieve statistical significance, often missing clinically relevant smaller effects and resulting in wider confidence intervals, indicating less precision. Smaller sample sizes are also more susceptible to selection bias, potentially yielding unrepresentative samples that do not capture the diversity of the target population, thereby limiting generalizability. Reliance on p-values becomes problematic, with an elevated risk of false positives and negatives, emphasizing the need to focus on effect sizes and confidence intervals. To mitigate these issues, future studies should aim to increase sample sizes and validate these findings.

Other limitations involve the single dose used for this preliminary investigation and future work should explore the efficacy of other dosages in addition to increasing the duration of time of the supplementation regimen for all doses used in this study. Finally, the absence of any other associated interventions (e.g., diet or exercise) that may work synergistically to promote improvements in health and glucose metabolism associated with the supplementation protocol were not included in this initial protocol and should be explored in future randomized controlled trials. In consideration of these strength and limitations, future research should involve larger placebo-controlled investigations with relevant dietary controls to see how the SEC complex augments body composition and other health outcomes. Further, researchers are strongly advised to consider combining SEC supplementation with a regular, structured exercise program to see if any potential benefit from SEC supplementation is additive to known health-promoting benefits of regular exercise.

In conclusion, results from this investigation indicate that 12 weeks of supplementing with a combination of *Salacia chinensis* extract and chromium in healthy men and women led to an attenuation of changes in food cravings for sweets observed in PLA. Moreover, the observed glucose and insulin levels were significantly different between groups at the 60-minute time point after 12 weeks of ingestion. Follow-up analysis revealed that the SEC group reported lower glucose and insulin levels at this timepoint than what was observed in PLA. Further, a significant group x time interaction was identified for adiponectin, whereby SEC values increased, and PLA values decreased over the 12-week study period. Finally, the reductions in BUN: Creatinine ratio may indicate a potential lead for future positive implications on kidney function, hydration, and renal perfusion. Supplementation appears to be safe and well tolerated with no clinically significant changes in hemodynamics and components of blood counts and metabolic panels associated with supplementation. Future research should first examine larger cohorts to reinforce the preliminary findings outlined herein using well-controlled randomized study protocols. Additionally, the lack of any other concomitant intervention while valuable from an ecological validity perspective does create many scenarios that

should be examined first, namely the impact of combining SEC supplementation with various hypo energetic feeding plans, as well as the potential interaction of SEC supplementation with various types of exercise.

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