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Clinical Trial**

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# **Efficacy of Novel Biologically Active Food Supplement in Type 2 Diabetes Mellitus: A Patient Blinded Prospective Clinical Trial**

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**PURPOSE:** Despite significant achievements in prevention and management of diabetes, its prevalence has risen exponentially creating a paramount need for alternative therapies. Since

diabetes has a multi-factorial origin, balanced modulation of several targets can provide superior therapeutic outcome with decreased side effects. The purpose of the study is to investigate the safety and efficacy of a novel biologically active food supplement (Fenugreek, Fennel, Sage, Olive, and Cinnamon) in decreasing blood glucose level (BGL) in type 2 diabetes mellitus (T2DM).

**DESIGN AND METHODS:** Between *June 2008* and *July 2009*, 154 patients were screened for T2DM and inadequate glycemic control. 51 subjects meeting inclusion/exclusion criteria were enrolled in a prospective clinical study. All patients (*n=51*) were studied for 24 weeks (6 months) with first 3 weeks of placebo phase, followed by 14 weeks of active supplement use and observation for 3 weeks. Patients returned to active supplement use for an additional 3 weeks. All participants were tested for fasting BGL once every week during a 22-week period. The glucose-lowering effect was measured by comparing BGL tested at baseline, during placebo phase (Weeks 1-3), treatment with supplement (Weeks 4-17) and during no treatment period (Weeks 18-20). No other glucose-lowering medication was allowed except study medication during the course of the study.

**RESULTS:** Average age of the subjects was 52.6 years (23M: 28F) and average reference blood glucose level (on day 1) was 265.7mg/dL. During the first 3-week placebo period, patients showed no detectable change in the BGL. At Week 10 (after 7 weeks of supplement use) the BGL was reduced by 47% compared to baseline; (mean±SD, day1 vs. week10, 265.7+86.2 vs. 131.6+31.7; paired t-test = -11.8,  $p<0.001$ ) and at Week 17, BGL decreased by 59% ( $p<0.001$ ). Between Week 18-20, during which no participant received placebo nor supplement, BGL did not decrease. Glucose lowering effect of the supplement was stable and prolonged to maintain BGL at a constant level. Patients reported satisfaction on Likert scale and no side effects during the course of the study.

**CONCLUSIONS:** The current study indicates that the new biologically active food supplement was effective in decreasing blood glucose level in T2DM patients with no side effects and has a therapeutic promise in regulating blood glucose levels.

## **INTRODUCTION**

The growing prevalence of obesity and sedentary lifestyle are the key underlying causes for type 2 diabetes mellitus (T2DM) to become a global public health problem, imposing a high financial burden

on health care costs.<sup>1-4</sup> The rising epidemic of T2DM reflects the profound changes in society and in behavioral patterns of the population over recent decades. While genetic make-up is important in determining a person's susceptibility to diabetes, societal changes and worldwide high caloric nutrition transition are driving the diabetes epidemic. Although new research in medications is leading the way towards better therapies and can be an important part of the treatment plan, common drugs as anti-diabetics like sulfonylureas, meglitinides, biguanides, thiazolidinediones, alpha-glucosidase inhibitors and GLP-1 agonists and DPP4 inhibitors are limited by drug interactions, associated side effects with long term complications and high cost of prescription drugs.<sup>5</sup>

Balanced modulation of several targets in the treatment of diabetes can provide superior therapeutic outcome with decreased side effects compared to the action of a single selective ligand.<sup>6</sup> In order to hit the multiple targets implicated in complex clinical disorders such as diabetes, two strategies have been proposed. The first attempts to employ a single compound to hit multiple targets. The second methodology is the use of multiple active ingredients in one preparation.<sup>6-8</sup> Although this premise has become a common feature in the drug development process, its principle applicability in developing nutritional supplements is still primitive. A unique novel combination of *Trigonella foenum-graecum* (Fenugreek), *Foeniculum vulgare* (Fennel), *Salvia Officinalis* (Sage), *Olea europea* (Olive), Cinnamon and *Silybum marianum* and other ingredients with high insulinotropic properties holds great promise in this direction influencing multiple biological activities with significant physiological effects. 4-hydroxyisoleucine (4-OH-Ile), an amino acid extracted and purified from fenugreek seeds which is the main component of such preparation has been found to display an insulinotropic activity in vitro because its stimulating effect is clearly related to the augmentation of glucose concentration.<sup>9</sup> Such a glucose dependency is not shared by sulfonylureas,<sup>10</sup> the only insulinotropic drug currently used to treat type II diabetes, and as a consequence, hypoglycemia remains a frequent undesirable side effect of sulfonylurea management.<sup>11,12</sup> Consequently, 4-OH-Ile, which is only found in plants, due to its particular insulinotropic action<sup>9</sup> may be considered as a novel secretagogue triggering insulin release. This action brings immense value in the treatment of type II diabetes, a condition characterized by defective insulin secretion associated with various degrees of insulin resistance<sup>13-16</sup>

However, current studies offer limited clinical evidence about the role of these biologically active compounds in glucose homeostasis and insulin sensitivity. The purpose of the study is to clinically examine the effect of these biologically active food supplements (*Sugar Crush, Naturera LLC. Israel*) by

investigating the efficacy in decreasing blood glucose level (BGL) in patients with type 2 diabetes mellitus.

## **MATERIALS AND METHODS**

### **Plant materials and preparation of extract**

A proprietary liquid formulation containing six active key ingredients (a) *Trigonella foenum graecum*(35%), (b) *Foeniculum Vulgare*(10%), (c) *Salvia Officinalis*(18%), (d) *Olea europea*(9%), (e) *Cinnamon*(9%), and (f) *Silybum marianum*(9%) with minor quantities of secondary elements was developed in the laboratory and then adapted for production in a commercial manufacturing facility. The formula was carefully constructed with standard quality control measures applied throughout the preparation process. All ingredients required for the preparation were obtained from a certified local commercial source in Israel. Samples of the ingredients are sent to the lab for testing prior to release for production. All solid forms were grounded to a fine powder in a mixer under chilled conditions, suspended and filtered. Each ingredient is placed in a drum for 21 days for extracting purposes, during which period the ingredient is mixed with organic alcohol and purified water. Weighed amounts of individual ingredients were distilled in separate containers and later mixed in proportions with required amounts of water and surface sterilization. Water is added under stirring with constantly maintaining pH adjustments. At the end of 21 days the extract is checked and mixed with the rest of the ingredients under proprietary formulation achieving accurate proportions. A dispersing agent was added to the concentrated active ingredient extract to prevent clumping and aggregation of individual components. The dialysed extract was aliquoted and stored at predetermined temperatures. Advanced manufacturing process for in-situ conversion and incorporation of the concentrated compounds into a sustained release therapeutic liquid dosage form were established. The process was carefully tested to provide an efficient and reproducible method to manufacture liquid supplement with active ingredients. The entire process facilitates a sustained release of the biologically active food supplement over prolonged intervals of time, thereby improving efficacy and patient satisfaction. Caution was executed to obtain a homogenous preparation that did not separate on standing. Final product was packaged in sterilized bottles measuring 125 mL each for the study purpose. No refrigeration was required for storage of the bottled preparation at any time.

### **Patients**

Between June 2008 and July 2009, 154 patients were screened for Type 2 diabetes and a history of poor glycemic control. Only patients meeting inclusion/exclusion criteria as discussed below were enrolled in the prospective clinical study. Fifty-one (23 males and 28 females) subjects under a diet-treatment only, diagnosed with T2DM and between the ages of 18 and 70 years who were not pregnant or nursing a child formed the study sample. Subjects with consistent glucose levels documented by previous medical test records on diet-treatment only were selected for study. Other exclusion criteria were (a) patients taking medications such as systemic glucocorticoids that can affect blood sugar levels, (b) any chronic medications that did not have a stable dose for at least 3 months prior to entering the study, (c) severe hypoglycemia (less than 50 mg%), and (d) any hypoglycemic event requiring intravenous glucose infusion. Approximately 70% of the patients were responders to the advertisement of the newsletter from the investigator and the rest were referred by community physicians. The study was closed for participation in July 2009. *Figure 1 demonstrates the participant flow.* Bio-Medical Research Design Board (Ness Ziona, Israel) approved the protocol for the study, and written informed consent was obtained from each patient before the initiation of the study.

Patients were sequentially enrolled and assigned a randomized number by the investigator if they met the inclusion criteria. All participants had an initial screening visit where they completed a generic health questionnaire, and medical history was reviewed by the study investigator (MW) prior to enrollment. Concurrent lipid-lowering, anti-hypertensive medications were allowed for the study purposes. The study was conducted in four phases during a total of 24-week period (6 months). (See *Figure 1*). All patients received a placebo for the first 3 weeks of the study (placebo phase) followed by an active dosage of the investigational supplement up until week 17 (supplement phase). Between weeks 18 through week 20 no study supplement was given, followed again by an active dosage of the supplement until week 23. The last week of the study was utilized to follow-up on patient data. All active supplement and placebo were supplied by the manufacturer in a liquid form in pre-labeled bottled containers. The study participants were blinded to the study treatment during the entire 24-week period until after the completion of the study and final data review, except in case of an emergency.

### **Measurements and Assessment**

Five mL fasting blood samples were collected from all patients and serum was analyzed for glucose by spectrophotometric assays on automated clinical chemistry analyzer Dimension RxL (Dade Behring, Newark, NJ). Fresh, clear, unhemolyzed serum was collected as the specimen with the patient

fasting for 12 hours prior to specimen collection. All lab collection was performed using a standard venipuncture tube to draw patient sample by a trained lab technician. Subject weights and fasting blood glucose level (BGL) was measured on the first day of the study and every week thereafter. Fasting was defined as no caloric intake for at least 8 hours before testing. Subjects were scheduled on a Monday, Wednesday or Friday, measured between 9.00 am and 11.00am after meals to maintain constant and reliable measurement interval.

The glucose-lowering effect of the supplement was measured by comparing of blood glucose levels, tested on initiation of the study (*day1*), during placebo treatment (Week1 – Week 3), treatment with the supplement (Week 4 – Week 17); no treatment period (Week 18 – Week 20) and comparing baseline data to the end of the study. All patients were assessed using the following efficacy parameters: (i) reduction in fasting blood glucose level (ii) patient satisfaction measured to demonstrate symptom change and approval of the formulation using a 6-item Likert scale.

### **Treatment Satisfaction**

Patients were asked three questions regarding their satisfaction with treatment at Week 22 using a Likert scale, which is a commonly used psychometric scale in questionnaires. The first item asked patients how satisfied they were with their treatment in reducing measurable BGL, with responses based on a 6-point scale, ranging from "very satisfied" to "very dissatisfied." A second item asked patients whether they would recommend their nutritional supplement treatment to a friend with similar health problems. The response scale ranged between "definitely yes," "probably yes," "probably not," and "definitely not." The third item asked patients how effective their treatment was in eliminating their symptoms (measured clinically as excessive thirst, frequent urination and fatigue), with response options ranging from "very effective, relieved all of my symptoms" to "very ineffective, did not relieve or lessen my symptoms."

### **Dosage**

Two forms of nutritional supplements were provided for the study purposes. A more potent formulation *Sugar Crush (SC)* intended for consumption during meals for the first 12 weeks only, and a less intense maintenance variety *Sugar Crush Daily (SCD)* intended for consumption in conjunction with

potent formulation for the first 12 weeks and then on its own for an additional 10 weeks of the study. Depending on the patient's use of concurrent medication for blood pressure and or cholesterol and weight of the patient, two forms of dosages were employed. *Table 1 and 2* demonstrate dosage instructions for patients enrolled in the study. This dosage protocol was developed to adjust for overweight individuals due to the strong association that exists between these patients and Type 2 diabetes than normal weight individuals.<sup>17,18</sup> It was important to factor these considerations in developing treatment regimens for complex metabolic conditions such as T2DM.

## STATISTICAL ANALYSIS

We used SAS statistical software (version 9; SAS institute, Cary, NC) for all statistical analysis. All the data were compared with regards to the measurements of each parameter taken at each week before and after the use of active supplement. Paired Student's t-test was used for statistical analysis, and all data were expressed as mean (M) ± standard deviation (SD.). A 'p' value of less than 0.05 was considered indicative of statistical significance for the pilot nature of the study.

## RESULTS

A 22-week prospective pilot study of fenugreek based liquid formulation was performed in patients with T2DM. The demographic results of the study population are summarized in *Table 3*. A total of 23 participants were men and 28 were women, with an average age of 52.6 years (range, 28–79 years). Two patients dropped out of the study for travel reasons were not included in the analysis. Estimated duration of diabetes was  $4.8 \pm 0.5$  years, and the body mass index (BMI) was  $32.3 \pm 4.0 \text{ kg/m}^2$ . Nine of the patients had hypertension, defined as blood pressure of 140 and/or 90 mmHg or over, that was being treated by antihypertensive agents. There were ten cases of hyperlipidemia, defined as total cholesterol of 220 mg/dL or over, and/or total triglyceride of 150 mg/dL or over. In addition, there were two cases of hyperuricemia. Fifteen patients (29.4%) were being treated by diet therapy alone, six patients by a  $\alpha$ -glucosidase inhibitor, six patients by a sulfonylurea, three patients by nateglinide, and twenty-one patients (41%) by a biguanide.

*Table 4* gives the fasting BGL in the sample population of the study. The efficacy of the study nutritional supplement showed continued and significant decrease in blood glucose levels during a 22-week period. This was in alignment with the trend line plotted from our unpublished anecdotal data. (*Figure 2*) The mean initial fasting level was high (265.8 mg/dL) as compared to desirable values for

fasting blood glucose (70-110 mg/dL).<sup>19</sup> During the first three weeks of the study (placebo phase) all participants were acting as their self controls and were followed during this period of time without any dietary counseling and or nutritional intervention except the standard recommendations by the treating physician. There was a mild increase of 8.7% in BGL during this period in time. Between week 1 and week 10 when the first interim analysis was performed, the mean fasting glucose decreased significantly by 46.7% (*paired t-test statistic = -11.8, p<0.001*). This phase included supplementation with 2.5mL dosage of active formulation as directed depending on the subject's current use of blood pressure and or cholesterol medications and weight. After the completion of 17 weeks of study (3 weeks of placebo use and 14 weeks of active supplement use) fasting BGL decreased by a mean of 59% (*p<0.001*) demonstrating continued efficacy of the nutritional supplement on glucose metabolism. There was a moderate leveling of glucose levels at the end of a three week period (between week 18 through week 20) where patients received no supplement treatment (mean BGL change = 22.4% ) with scaling down BGL again upon supplement re-initiation. Overall, at the conclusion of the study after 22 weeks, the average BGL demonstrated a statistically significant reduction by 46.7% (*paired t-test statistic = -14.7, p<0.001*) (*Figure 3*) Comparison of blood glucose level and corresponding change at different time intervals is demonstrated in *table 5 and 6*. No side effects were reported in any patient at the end of the study.

With respect to satisfaction with treatment using the Likert scale, 94% of the patients were satisfied and this was corresponding to their reduced BGL. Statistically significant differences in scores were observed between those who indicated that they would recommend the treatment to a friend compared to those who would not. (*p < 0.001*)

## DISCUSSION

Exponential rise in worldwide cases of disorders in glucose and insulin metabolism, overweight, mild dyslipidemia, and hypertension has led to the enormous problem of type 2 diabetes mellitus. *Trigonella foenum-graecum* appears to exhibit a range of actions of potential benefit to control glucose metabolism in diabetes. In the present study, the effects of a combination of organic herbal products with fenugreek as the key ingredient were evaluated on glucose metabolism.

An active component of *T. fenugreek* seeds has been found to be associated with a defatted fraction, rich in fiber containing steroidal saponins and proteins.<sup>20</sup> Sauvaire and his colleagues<sup>9</sup> have demonstrated a novel amino acid derivative, 4-hydroxyisoleucine, also extracted from fenugreek seeds,

to stimulate glucose-dependent insulin secretion from isolated rat and human islets.<sup>8</sup> Additionally, fenugreek acts by delaying glucose absorption and enhancing its utilization in non-insulin dependent diabetic patients.<sup>21</sup> All other ingredients have also been extensively documented in the literature to improve glucose and lipids in subjects with type 2 diabetes.<sup>22,23</sup> Foeniculum vulgare is widely used traditional medicinal plant for its antibacterial potential.<sup>24</sup> Common sage (*Salvia officinalis* L.) is among the plants that are claimed to be beneficial to diabetic patients, and previous studies have suggested that some of its extracts have hypoglycaemic effects in normal and diabetic animals.<sup>25</sup> Sage has a high essential oil content that has also been tested and proved to be hypoglycaemically active in diabetic rats.<sup>26-28</sup> Similarly Aqueous extracts from cinnamon have been shown to increase in vitro glucose uptake and glycogen synthesis and to increase phosphorylation of the insulin receptor; in addition, cinnamon extract likely aid in triggering the insulin cascade system<sup>29,30</sup>

Our findings coincide with those of earlier studies, which reported that fenugreek in the diet reduced plasma glucose in diabetic human subjects.<sup>31,32</sup> When using ancillary measures as benchmarks for patient improvement, the Likert satisfaction scale was able to demonstrate levels of change in patient-reported overall treatment effect and satisfaction. Similarly, with respect to overall treatment effect and recommending the treatment to a friend, the nutritional supplement was able to demonstrate significantly greater improvements in >90% of the participants.

Medical conditions that require strict control of nutrient intake may be facilitated greatly by the use of a liquid formula diet, regular food and additional nutritional supplementation such as the current investigational product. Calorie controlled portions can be useful for controlling calories and initiating weight loss. Although not clinically tested, liquid formulations seem to boast faster absorption rates than pill-form supplements. Pill supplements often contain soluble excipients termed as a *binder* to help hold the tablet together and give it strength and to improve the dissolution of poorly soluble ingredients.<sup>33</sup> A wide variety of binders may be used, including lactose, dibasic calcium phosphate, sucrose, corn (maize) starch, microcrystalline cellulose. However, in a diseased condition, these binding ingredients may make absorption slower and more difficult. Conversely, we hypothesize that liquid forms may begin absorbing through the buccal mucosa rather than being slowly broken down in the digestive track. Although there are limited data, one disadvantage with liquid formulations is that they tend to expire much faster than pill-form. It is important to note here that the current supplement of investigation has a shelf life of 2 years.

Our study had several limitations. Data on list and types of foods consumed during the course of the study and frequency categories were not monitored. However, our data can be considered reliable since participants were reminded weekly by telephone calls regarding a controlled diet and non-use of other supplements or drugs during the course of the study period. The study medication was not blinded to investigators and BGL was examined weekly and not daily. The study was also limited in the follow-up, since the beneficial effects of the investigational supplement need to demonstrate efficacy of longer periods than 22 weeks. It is also important to show that efficacy could be better under a 100% diabetic diet regimen. Evidence that the supplement resulted in decreased glycosylated hemoglobin A1C levels in the blood and other markers was not undertaken under the current investigational plan. The small sample size chosen based on pilot data may have been insufficient for a rigorous statistical analysis to demonstrate a clinically significant difference. Although oral glucose tolerance test (OGTT) is more sensitive and modestly more specific than the fasting blood glucose (BGL) to diagnose and detect diabetes, it is poorly reproducible and difficult to perform in practice. Because of ease of use, acceptability to patients, and lower cost, BGL was used in this study as the preferred diagnostic test.<sup>19</sup>

The biological effect of food supplements with the right blend of ingredients, prepared in precise proportion not only allows for patient's meal individualization, but fulfills the deficit of much needed biologically active components. Naturally occurring ingredients in our test product appear to aid in the normalization of carbohydrate metabolism, having a beneficial effect and aid in improved quality of life in T2DM patients.

## **CONCLUSION**

Environmental factors have been implicated in the pathogenesis of type 2 diabetes both as triggers and potentiators of  $\beta$ -cell destruction,<sup>1-3</sup> although the contribution of any individual exogenous factor has not yet been definitely proven. The present study has demonstrated that biologically active food supplement extract significantly reduced blood sugar and a standardized food-grade supplement with such efficacy may offer safety advantages compared to prescription medications.

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**Table 1. Dosage Directions for diabetics *NOT* using blood pressure or cholesterol medications**

<b>Weight of Person</b>	<b>Under 220 lbs</b>	<b>Over 220 lbs</b>
Just before or during breakfast (SC)	2.5 ml along with or followed by 6 oz. of water	5 ml along with or followed by 6 oz. of water
Just before or during dinner (SC)	2.5 ml along with or followed by 6 oz. of water	5 ml along with or followed by 6 oz. of water
Just before or during Lunch Sugar Crush Daily (SCD)	2.5ml along with of followed by 6 oz. of water	5 ml along with or followed by 6 oz. of water

SC =Sugar Crush; SCD= Sugar Crush Daily

**Table 2. Dosage Directions for diabetics using blood pressure or cholesterol medications**

<b>Weight of Person</b>	<b>Under 220 lbs</b>	<b>Over 220 lbs</b>
Just before or during breakfast (SC)	Morning is reserved for blood pressure or cholesterol medication. Do not use Sugar Crush within 2 or 3 hours of medications	Morning is reserved for blood pressure or cholesterol medication. Do not use Sugar Crush within 2 or 3 hours of medications
Just before or during lunch (SC)	2.5 ml along with or followed by 6 oz. of water but no earlier than 2-3 hours after blood pressure or cholesterol medication	5 ml along with or followed by 6 oz. of water but no earlier than 2-3 hours after blood pressure or cholesterol medication
Just before or during dinner (SC)	2.5 ml along with or followed by 6 oz. of water but no earlier than 2-3 hours after blood pressure or cholesterol medication	5 ml along with or followed by 6 oz. of water but no earlier than 2-3 hours after blood pressure or cholesterol medication
Just before bedtime (SCD)	2.5ml along with or followed by 6 oz. of water only if experiencing Unusually high glucose levels. If levels Are not unusually high do not use product before bedtime.	5 ml along with or followed by 6 oz. of water but no earlier than 2- 3 hours after blood pressure or cholesterol medication

SC =Sugar Crush; SCD= Sugar Crush Daily

**Table 3. Demographic characteristics of the study sample**

Characteristic	Data Value (SD)
Total Sample ( <i>n</i> )	51
Gender	
Male	23
Female	28
Age ( <i>in years</i> )	52.6 (12); range=28-75
Weight ( <i>kg</i> )	171.2 (55)
BMI ( <i>kg/m<sup>2</sup></i> )	32.3 (4.0)
Duration of diabetes ( <i>in years</i> )	4.8 (0.5)

All data is represented as mean (SD) values where indicated

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**Table 4. Effect of supplement use by diabetic subjects at different time points compared to baseline**

<b>Time Point</b>	<b>Mean Blood Glucose Level (SD)</b>	<b>Minimum</b>	<b>Maximum</b>	<b>Mean % Change</b>	<b>p value</b>
Baseline Week 3	265.7 ± 86.2 288.9 ± 90.0	129.0 125.0	477.0 471.0	10.9%	0.003*
Baseline Week 17	265.7 ± 86.2 102.0 ± 24.9	129.0 74.0	477.0 165.0	-59.0%	<0.001
Baseline Week 22	265.7 ± 86.2 102.6 ± 22.5	129.0 76.0	477.0 158.0	-58.5%	<0.001

Baseline= Day 1 (at enrollment); Week 3= Placebo Phase (participants acting as self controls); Week 17= Active Supplement Phase (14 weeks of daily use of nutritional supplement); Week 22= Follow-up Phase; \*Wilcoxon signed rank test used here otherwise paired t-test was used.

**Table 5. Effect of supplement use in diabetic subjects demonstrating sustained efficacy after a 3-week 'non-use' phase**

<b>Time Point</b>	<b>Mean Blood Glucose Level (SD)</b>	<b>Minimum</b>	<b>Maximum</b>	<b>Mean % Change</b>
Week 17	102.0 ± 24.9	74.0	165.0	-59.0%
Week 20	123.2 ± 39.2	80.0	243.0	-50.6%

Week 17= Active Supplement Phase (14 weeks of daily use of nutritional supplement); Week 20= 3 weeks of supplement discontinuation

**Table 6: Comparison of blood glucose level and corresponding change at different time intervals in diabetic study subjects after administration of active nutritional supplement**

Variable	N	Mean	Std Dev	Median	Minimum	Maximum
Baseline	51	265.7	86.2	255.0	129.0	477.0
Week 10	51	131.6	31.7	128.0	76.0	202.0
Change	51	-134.1	80.9	-114.0	-364.0	19.0
%Change	51	-46.7	17.4	-48.3	-80.2	11.9

Paired t-test statistic = -11.8, p<0.001

Variable	N	Mean	Std Dev	Median	Minimum	Maximum
Baseline	51	265.7	86.2	255.0	129.0	477.0
Week 17	51	102.0	24.9	94.0	74.0	165.0
Change	51	-163.8	78.5	-154.0	-384.0	-39.0
%Change	51	-59.0	11.8	-59.1	-82.8	-29.3

Paired t-test statistic = -14.9, p<0.001

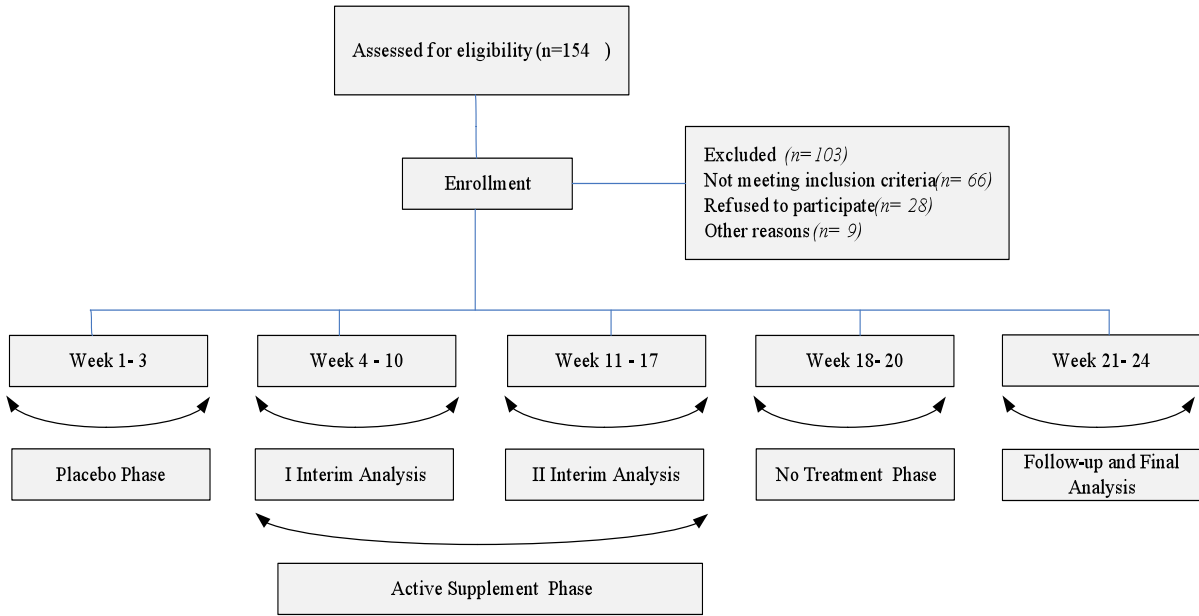
Variable	N	Mean	Std Dev	Median	Minimum	Maximum
Baseline	51	265.7	86.2	255.0	129.0	477.0
Week 22	51	102.6	22.5	97.0	76.0	158.0
Change	51	-163.2	79.1	-150.0	-392.0	-40.0
%Change	51	-46.7	17.4	-48.3	-80.2	11.9

Paired t-test statistic = -14.7, p<0.001

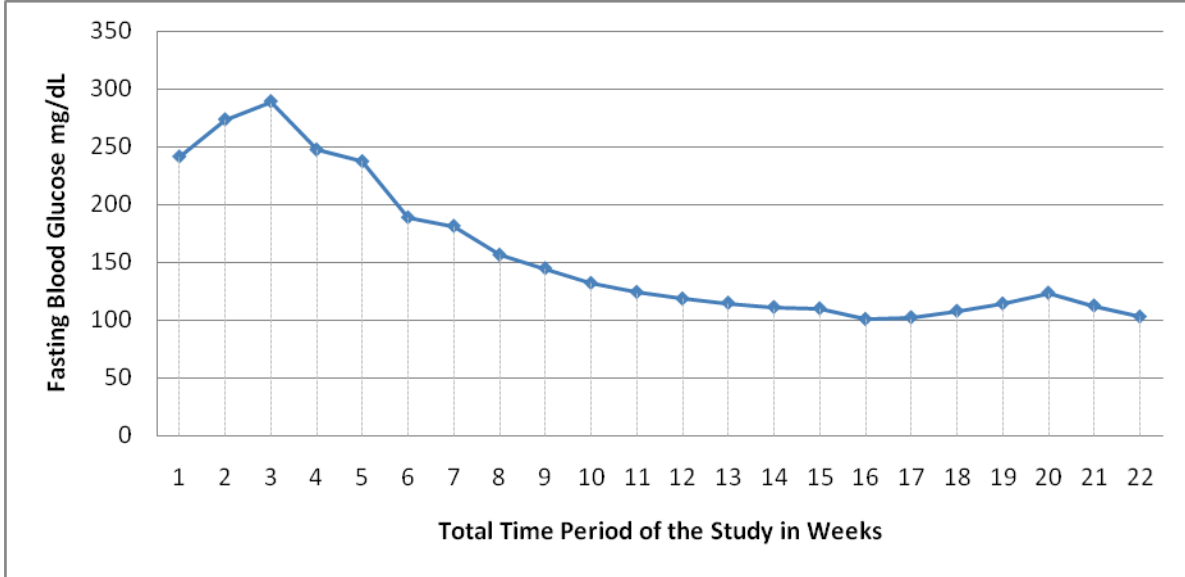
Variable	N	Mean	Std Dev	Median	Minimum	Maximum
Week 17	51	102.0	24.9	94.0	74.0	165.0
Week 20	51	123.2	39.2	112.0	80.0	243.0
Change	51	21.2	32.6	14.0	-32.0	131.0
%Change	51	22.4	32.3	14.9	-19.4	135.1

Paired t-test statistic = 4.6, p<0.001

**Figure 1. Participant Flow Chart and Study Design**



**Figure 2. Effect on Blood glucose in patients after active nutritional supplement use**



**Figure 3. Effect on Blood glucose in patients from baseline to the conclusion of the study at 22 weeks**

