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Original Research Article

Efficacy of a novel supplement GlucoSEB PB™ for glucose management: an *in vitro* and clinical study approach

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ABSTRACT

Background: The objective of the study was to perform a comprehensive investigation of GlucoSEB PB™ using in-vitro digestion and a clinical study for evaluating its effects on sugar digestion and associated metabolic responses.
Methods: *In-vitro* digestion of a bread-chicken-patty as a food-matrix was performed using INFOGEST simulated semi-dynamic digestion protocol in presence and absence of GlucoSEB PB™. The sugars released were quantified. Further, for the clinical trial, a double-blind, randomized, crossover, placebo-controlled study was performed by randomizing 35-prediabetic subjects into test and placebo groups. Subjects were instructed to consume 2-capsules (test or placebo), 30-min prior to consumption of standard-meal, and blood-glucose related parameters were monitored.
Results: GlucoSEB PB™ effectively caused a net reduction in the available simple-sugars by 19.40% post in-vitro gastro-intestinal digestion. This was due to formation of oligosaccharides with dietary-fiber potential conferring prebiotic benefits. The findings of the clinical-study indicated an increase in blood-glucose levels until 45 and 60-min in the GlucoSEB PB™ and placebo groups, followed by a continuous decline for 3-h post-consumption of the standard-meal. GlucoSEB PB™ supplementation resulted in a 16.90% reduction in AUC over the placebo, signifying its role in controlling blood-glucose. Additionally, no variations were observed in insulin levels in both arms.
Conclusion: Notably, GlucoSEB PB™ was safe and showcased tolerability at the investigated dosage. No AEs/SAEs were reported during the entire investigation.

Keywords: GlucoSEB PB™, INFOGEST semi-dynamic digestion, Sugar profile, Prediabetes, Postprandial blood-glucose levels

INTRODUCTION

Hyperglycaemia and diabetes have been rising globally, and can potentially lead to life-threatening conditions, both acute and chronic.[1,2] Prediabetes is a borderline clinical state of diabetes where the glucose levels are uncharacteristically elevated, but not enough to be diagnosed as type-2-diabetes.[3] Prediabetes is distinguished as a group of metabolic anomalies, which may collectively place prediabetic patients at an increased risk of diabetes and associated complications.[4] According to the International Diabetes Federation, in 2021 nearly 541-million and 319-million adult population had the prevalence of impaired glucose tolerance (IGT) and impaired fasting glucose (IFG), which is projected to increase to 730-million and 441-million, respectively, by 2045.[5] Prediabetes without adequate intervention could result in several health complications and even cause mortality.[6]

The treatment of hyperglycemia entails precise self-management education, efforts to attain a normal glycemic condition, determining complications at micro- and macro-vascular levels, minimizing health-related risk factors, and excluding drugs involved with lipid and sugar metabolism.[7] Besides, several available approaches include positive modifications in routine and sedentary lifestyles, improved physical activities, and a healthy

diet.[8,9] Additionally, medications and stress-management are imperative in controlling blood sugar.[10,11] However, all the above-mentioned approaches have challenges to ensure efficient management to meet the required glucose levels. Further, regular use of pharmacotherapies could negatively affect the health and body functions.[12] A few effective alternate approaches could be supplementation of exogenous enzymes, herbs, and probiotics that can digest food, utilize the released sugar molecules, and convert them into bioactive components with health-promoting properties.[13]

Enzyme supplements have vital roles in managing the rate and extent of glucose metabolism in GI tract.[14] Whereas, herbal extracts exhibit biological properties promoting various health benefits.[15] Polyphenols in the herbal extract can potentially inhibit the digestive enzymes, glucosidase activity, glucose absorption, and hinder the formation of advanced glycation end products.[16,17] Interestingly, probiotics have also been proven effective in managing blood glucose related parameters.[12,18,19] Thus, further studies are needed to identify the effective combination of these supplements.

One such combination, GlucoSEB PB™, is a blend of enzymes, herbal-extract rich in polyphenols, and probiotics. The enzymes aid in the breakdown of food and subsequent release of nutrients, promoting improved digestion.[20] SucroSEB™ in GlucoSEB PB™, basically an alternansucrase primarily transfers the released glucose molecules to specific saccharide/s or non-saccharide/s acceptor moieties to yield bioactive components. SucroSEB™ produce glycans with different molecular weight which exhibits higher dietary fiber potential and are resistant to digestion with intestinal enzymes.[21] Additionally, the herbal extract is rich in polyphenols with the known potential in managing sugar levels.[16,17] Probiotics aid in maintaining a healthy gut microbiome, improves glucose metabolism and reduces systemic inflammation.[12,18,19]

Explicitly, studies have demonstrated that polyphenols, enzymes, and probiotics can reduce glucose levels. Polyphenols, strawberry and apple extracts were found to inhibit glucose uptake at apical and basolateral membranes of Caco-2 cells and brush border membrane vesicles by blocking glucose transporters, and inhibit glucose absorption.[22,23] On the clinical front, earlier studies have revealed the benefits of enzyme transglucosidase to significantly reduces blood glucose and improves associated parameters in T2DM patients.[24] It also enhances the gut microbiota profiles and improves bowel movements.[25,26] Clinical trials involving polyphenols from pomegranate peel have reported significant reductions in inflammatory markers, oxidative stress biomarkers, and homocysteine levels in T2DM patients.[27] Similarly, ellagic acid has shown modest changes in sugar levels, insulin resistance, HbA1c, and antioxidant and anti-inflammatory factors.[28] Moreover, the clinical efficacy of probiotics in lowering glucose levels in T2DM patients is comprehensively addressed in recent systematic-reviews and meta-analyses of RCTs.[12,18,19] However, understanding the combined efficacy through both in-vitro digestive models and clinical studies on postprandial glucose-levels in prediabetic patients remains an area that demands further investigation.

Based on available data and practical considerations, the current study aimed to evaluate both the in-vitro and clinical effects of GlucoSEB PB™. The *in-vitro* study focused on sugar digestion in a complex-food-matrix, a bread-chicken patty meal, while the clinical study assessed its role in controlling postprandial glucose-levels in prediabetic subjects. The harmonized INFOGEST semi-dynamic model was used to carry out in-vitro digestion of a model complex food. The progress of digestion was examined in terms of slow-digested sugars, sucrose reduction percentage, available simple sugars percentage, and net reduction in simple digesting sugars percentage. Further, a double-blind, randomized, crossover, and placebo-controlled clinical study was conducted to understand the actual effect of the GlucoSEB PB™ supplement on postprandial glucose levels in humans. The assessment of efficacy involved enumerating blood glucose after consuming a standard-diet, determining the maximum glucose concentration (Cmax) reached, measuring the time required to attain it (Tmax), and calculating the incremental area-under-the-curve (iAUC). In addition, the changes in insulin levels, safety and tolerability parameters, and adverse events (AEs) and severe adverse events (SAEs) were recorded.

METHODS

Materials

α-Amylase derived from human saliva (300–1500 U/mg), pepsin sourced from porcine gastric mucosa (≥3200 U/mg), pancreatin obtained from porcine pancreas (8×USP specifications), and bile salts were acquired from Sigma-Aldrich, USA. Bread-chicken-patty meal containing a 150-g chicken-patty (2-breaded-chicken-patties, cheese, lettuce, creamy-mayo, and a bun in middle), a carbonated cold-beverage (300 ml), French-fries (100g) and dessert (180g) was purchased from local food restaurant in Thane, India.

All the other chemicals required for the both studies were of AR grade and procured from reliable sources.

Investigational product

The investigational product (IP) (GlucoSEB PB™, 400 mg/capsule) and placebo (maltodextrin, 400 mg/capsule) were provided by Specialty Enzymes and Probiotics, Chino, USA.

The physical appearance, packaging, and labelling of the products were similar, and the coded batch numbers were used for differentiation.

In-vitro study

In-vitro simulated food digestion and sugar analysis

The bread-chicken-patty meal was subjected to the INFOGEST semi-dynamic method for digestion. Experiments were conducted with a control group using standard digestive enzymes, and a test with the standard enzymes plus GlucoSEB PB™ (0.4% w/w of food) to assess the impact of GlucoSEB PB™ on sugar digestion.[20,29]

High-performance liquid chromatography (HPLC) analysis was performed to evaluate the changes in total sugar content (glucose, fructose, sucrose, lactose, maltose, isomaltose, and panose), slow-digested sugars, sucrose reduction percentage, available simple sugars percentage, and net reduction in simple-digesting sugars percentage in intestinal digesta. Size exclusion-HPLC was performed to characterize the different oligomers by separating them based on their molecular weights (sizes) and degree of polymerization.

Clinical study

Ethics and informed consent

The Institutional Ethical Committee, Charak Hospital reviewed the protocol and provided the approval before the commencement of the trial.

The trial was registered in Clinical Trial Registry, India (CTRI/2023/10/058380) on 06/10/2023, before enrolling the subjects. The protocol was designed according to the principles of Declaration of Helsinki (2013) (Ethical principles for medical research involving human subjects, revised by the 64th WMA General Assembly, 7th revision, Fortaleza, Brazil, October 2013, ICH-GCP E6-R2, Step 5) guidelines, along with the local regulatory requirements of GCP for Clinical Research in India (2004, CDSCO), New Drugs and Clinical Trials Rules (2019) along with its amendments and ICMR guidelines for Biomedical Research on Human Subjects (2017).

All participants were given clear insights and made aware of the study. The required details were explained orally and in written format, in a language familiar and understandable to the participants.

After thoroughly understanding the information, including the related objectives, possible health risks, and benefits, each participant submitted a written informed consent.

Study design and selection of study subjects

A double-blind, randomized, crossover, placebo-controlled study was designed, and the registered participants were included/excluded based on pre-defined criteria.

Inclusion criteria

Inclusion criteria included male and female subjects (age ≥30 years), participants with limited physical activity, body mass index (BMI): 25-40 kg/m^2, consuming a diet rich in carbohydrates (>60%), consuming a stable medicine dose for past 3-months, FBG and HbA1c levels: 100–125 mg/dl and 5.7–6.4%, willing and able to provide written informed consent prior to any study-related activities and adhere to all the protocol requisites.

Exclusion criteria

Exclusion criteria included pregnant/lactating females, BMI >40 kg/m^2, type-I diabetic, currently receiving sugar managing supplements. Major chronic complications (including but not limited to) autoimmune disease, and inflammation, organic insufficiency (cardiac, hepatic, renal, respiratory), consuming fibers/polysaccharides containing food supplements, addicted to smoking, alcohol, and drugs, known hypersensitivity and allergy to ingredients of IP, history of any surgery in past 3-months, currently consuming and/or having GI related probiotics/prebiotics or enzymes in the past 30-days (prescription or over-the-counter) and participation in any other clinical study within 30-days before the first dose of the IP.

Study protocol and randomization

The clinical study was conducted as per the detailed schedule in Table 1.

Eligible participants were screened, randomized to either the test/placebo group or the placebo/test group for a 4-day study. 35 participants were enrolled in the clinical study based on pre-defined selection criteria. 17 participants were allocated to test/placebo, while and 18 to placebo/test group. The clinical trial consisted of a 2-day treatment period, followed by a 2-day crossover treatment.

Participants, investigators, physicians, and officiers involved in this clinical trial were blinded till the completion of the trial. Unblinding was done strictly after completion of the post-clinical phase of the trial to the authorized personnel. Participants were asked to consume IP (2-capsules, 30-min before a meal) with water. A standard meal (750 g-serving containing 150.1 g-carbohydrates, 68.2 g-sugars, 59.3 g-added sugars, 22.8 g-proteins, and 35.6 g-fats) was provided. Supportive treatment, if needed, were suggested and provided to the participants by the physician/investigator.

The designed protocol was strictly implemented, and no further alterations/amendments were made once the trial commenced, and no intermittent analyses were made during the entire study period. The clinical investigation was initiated on 14 October 2023 and completed on 31 December 2023.

Table 1: Schematic schedule of the clinical trial.

Parameters	Screening and randomization	CGM installation	Treatment 1/2 (placebo/test)	Treatment 2/1 (test/placebo)	CGM removal
Visits	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
Day (±days)	Day −2 to −1	Day 0	Diet 1 (day 01-03)	Diet 1 (day 07-09)	Day 13 (±2 days)
Written informed consent	✓				
Inclusion/exclusion criteria	✓				
Randomization	✓				
Physical examination	✓				
Vitals signs	✓	✓	✓	✓	✓
Blood sample collection (FBG and Hb1Ac)	✓				
Demographic information	✓				
Body height and weight	✓				
Medical and surgical history	✓				
Prior medication history	✓				
Instructions for the supplementation	✓				
CGM installation		✓			
Placebo/test capsule administration			✓		
Test/placebo capsule administration				✓	
Blood glucose monitoring with CGM device		✓	✓	✓	
Blood sample collection (0, 2, and 4 h) for insulin analysis			✓	✓	
Product tolerability questionnaires			✓	✓	
Urine pregnancy test (female)	✓				
AEs	✓	✓	✓	✓	✓
Concomitant medications		✓	✓	✓	✓
CGM removal					✓

CGM analysis

The change in glucose after consuming a standard diet was monitored for 3 hours at 15-min intervals on a continuous-glucose-monitoring system (FreeStyle Libre Pro, Glucose sensor and reader, procured from Abbott). Cmax, Tmax, and iAUC were determined. The changes in insulin levels were analysed by chemiluminescence immunoassay.

Safety and tolerability variables

Safety of IP was assessed by physical examination and recording vital signs such as body temperature, respiration rate, pulse rate, systolic blood pressure, and diastolic blood pressure, along with recording of AEs and SAEs. Tolerability of IP was assessed for any side effects experienced by the participants during the study. Further, physical functioning of the different organs was also assessed.

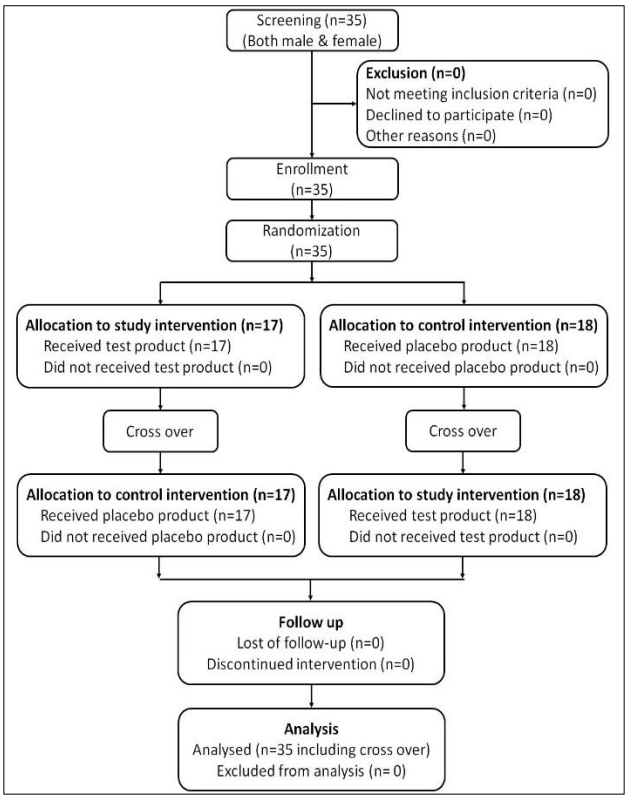

Figure 1: Flow diagram of clinical study.

Data analysis

The data was analyzed using Microsoft Excel 2016, and the findings are presented as mean±standard error.

RESULTS

The potential of digestive supplements to enhance digestion under both *in-vitro* conditions and clinical investigation has not been previously explored. The system becomes too complicated to comprehend the actual impact on the digestion process when exogenous digestive enzymes are added along with indigenous digestive enzymes. Therefore, in-vitro investigation along with clinical study can provide a better understanding.

Effect of GlucoSEB PB™ on in-vitro sugar digestion

The INFOGEST simulated semi-dynamic sugar digestion of complex food was analysed after 120-min of gastric digestion and 120-min of gastrointestinal digestion. A considerable change was observed in total sugar content of the digesta treated with GlucoSEB PB™.

Sucrose content significantly reduced after GlucoSEB PB™ treatment by 92.5±0.71% and 93.1±9.7%, whereas control had a reduction by 51.8±5.80% and 17.35±4.5% after gastric and gastrointestinal digestion (Figure 2a). This higher reduction in sucrose in the GlucoSEB PB™ digesta resulted in a considerable gastric digestion and a significant reduction in gastrointestinal digestion over the placebo. A net difference of 40.70% and 75.75% in sucrose reduction between the GlucoSEB PB™ and control post-gastric and gastrointestinal digestion clearly indicates that sucrose is effectively minimized by GlucoSEB PB™. Whereas, the percentage of available simple sugars was higher in the control (41.50±0.14% and 57.7±1.5%) than the GlucoSEB PB™ supplemented digesta (28.70±0.14% and 38.3±2.7%) after the gastric and gastrointestinal digestion (Figure 2b). Correspondingly, a net reduction of 12.80% and 19.40% in available simple sugars was recorded for GlucoSEB PB™ and control-treated samples after the gastric and gastrointestinal digestion, respectively. Furthermore, the reduction in free sugars in the GlucoSEB PB™ group indirectly contributed to the formation of slow-digesting sugars.

SEC-HPLC analysis clearly revealed substantial changes in sugar breakdown in the presence of GlucoSEB PB™ during gastric digestion. A monosaccharide peak (DP1) appeared at 12.964 min in the GlucoSEB PB™ treated samples, which was clearly absent in the control (Figure 3). Further, the disaccharide peak (DP2) at 12.46 min was substantially reduced in the GlucoSEB PB™ treated sample compared to that in the control sample, indicating the utilization of sucrose to produce fructose as a side product. Other additional peak at 11.435 min can be distinguished as a peak corresponding to oligosaccharides (DP=5) as a result of the action of GlucoSEB PB™ in sugar reduction.

Clinical study

35-subjects (19-male (M) and 16-female (F)) with an "intention-to-treat", and an average age and BMI of 46.46±10.78 years and 28.91±3.99 kg/m^2 participated in the trial (Table 2). Of the 2-treatment groups, the test/placebo group was assigned 17-subjects (8-M and 9-F), whereas the placebo/test group was assigned 18-subjects (11-M and 9-F). Study was performed as per planned schedule of events (Table 1). The final data analysis was initiated after removal of the CGM system (on visit 7), and all 35-participants followed the study through to completion.

Changes in blood glucose levels (%)

The change in blood glucose after consuming IP and the standard-meal was measured. An increase in the glucose level was noted until 45 and 60-min in the test and placebo, respectively, followed by a continuous decline till 3-hours (Table 3). The percent change in blood glucose (from baseline) was similar during the initial phase post-consumption of the standard meal (until 45-min) in both groups. However, after 45-min, the change was consistently lower in the test over the placebo (Figure 4).

Cmax of glucose in the test and placebo arms was 127.31±6.69 and 121.17±6.36 mg/dl, corresponding to the Tmax values of 45 min and 60 min, respectively. Slightly higher Cmax value in the test over the placebo could be ascribed to the variations in the baseline, which were

100.37±4.63 and 95.89±4.86 mg/dl in the test and placebo, respectively. Percent change in the glucose levels in the test and placebo relative to their baseline values at corresponding Tmax was 29.04% and 31.48%, respectively.

Total iAUC of glucose released after 3-hour post-consumption of standard meal was 2436.86 and 2932.29 (mg×min/dl) in the test and placebo, respectively (Table 3). The decrease in total iAUC led to a 16.90% higher reduction in the test group compared to the placebo group.

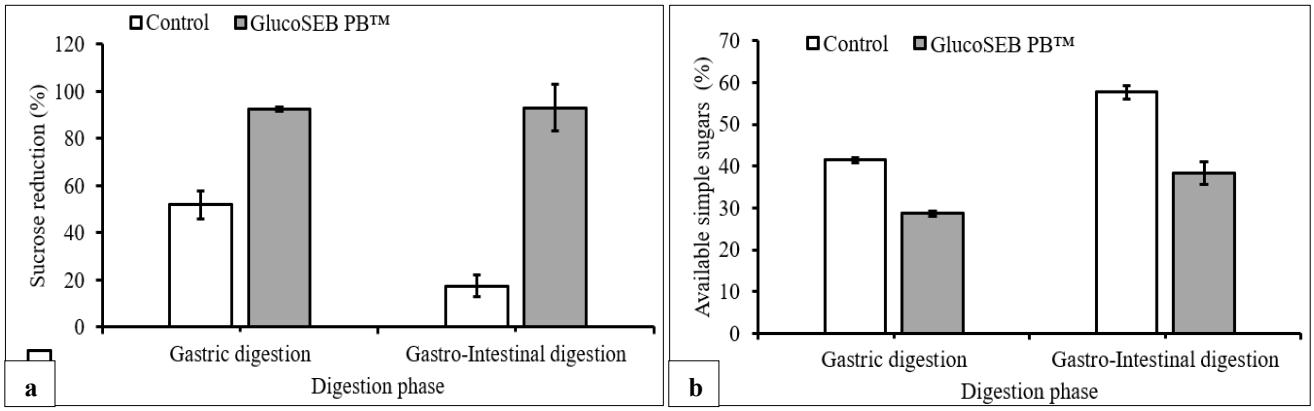

Figure 2: (a) Percent reduction in sucrose content, and (b) percent available simple sugars in GlucoSEB PB™ and control groups post gastric and gastro-intestinal digestion (semi-dynamic digestion). Statistical analysis performed by t-test (paired two sample for means).

Table 2: Demographic and clinical characteristics of subjects under study at baseline.

Demographic characteristics	GlucoSEB PB™/placebo	Placebo/GlucoSEB PB™	Total
Number of subjects	N=17	N=18	N=35
Age (years)	46.29±11.34	46.61±10.55	46.46±10.78
Gender, n (%)			
Male	8 (47.06)	11 (61.11)	19 (54.29)
Female	9 (52.94)	7 (38.89)	16 (45.71)
Height (cm)	164.12±5.41	161.33±6.61	162.68±6.13
Weight (kg)	78.65±11.84	74.44±9.73	76.49±10.86
BMI (kg/m^2)	29.27±4.91	28.57±2.99	28.91±3.99

Table 3: Changes in blood glucose levels and incremental AUC in prediabetic subjects after supplementation (data is represented as mean±SE).

Time (min)	Blood glucose level (mg/dl)		iAUC (mg×min/dl)	
	GlucoSEB PB™ arm	Placebo arm	GlucoSEB PB™ arm	Placebo arm
0	100.37±4.63	95.89 ±4.86	0.00±0.00	0.00±0.00
15	109.83±5.01	104.63±5.39	70.93±16.99	65.57±16.81
30	121.11±5.96	113.86±6.11	226.50±48.84	200.36±48.60
45	127.31±6.69	119.54±6.54	357.64±76.88	312.21±72.60
60	124.94±6.66	121.17±6.36	386.36±93.42	367.07±84.74
75	120.03±6.55	119.69±6.55	331.71±99.39	368.14±95.68
90	117.20±6.19	117.83±6.66	273.64±99.63	343.07 ±103.23
105	113.74±5.71	116.74±6.45	226.50±100.07	321.00±102.43
120	110.20±5.39	113.77±6.03	174.00±103.19	290.57±98.69
135	107.83±5.37	109.69±5.42	129.64±106.43	237.64±94.65
150	106.86±5.27	106.54±5.07	104.57±105.62	183.43±92.92
165	106.09±5.06	103.97±4.86	91.50±99.72	140.57±91.50
180	103.17±4.61	101.49±4.57	63.86±92.44	102.64±87.61
Total			2436.86	2932.29
Change (%)			16.90	

Table 4: Changes in blood glucose levels and incremental AUC in prediabetic subjects after supplementation (data is represented as mean±SE).

Parameters	Arms	Baseline	EOT	Mean change
Body temperature (°F)	GlucoSEB PB™ to placebo	96.81±1.65	97.22±1.27	0.42
	Placebo to GlucoSEB PB™	97.09±1.16	96.77±1.60	-0.32
Respiratory rate (breaths/min)	GlucoSEB PB™ to placebo	17.24±1.75	16.71±1.53	-0.53
	Placebo to GlucoSEB PB™	17.39±2.40	16.28±2.32	-1.11
Pulse rate (beats/min)	GlucoSEB PB™ to placebo	84.76±8.29	85.65±8.75	0.88
	Placebo to GlucoSEB PB™	85.00±7.97	86.78±7.30	1.78
Systolic blood pressure (mmHg)	GlucoSEB PB™ to placebo	125.12±7.18	126.41±7.84	1.29
	Placebo to GlucoSEB PB™	126.50±10.76	126.39±12.35	-0.11
Diastolic blood pressure (mmHg)	GlucoSEB PB™ to placebo	77.06±6.10	78.88±3.89	1.82
	Placebo to GlucoSEB PB™	79.11±8.63	76.72±8.29	-2.39

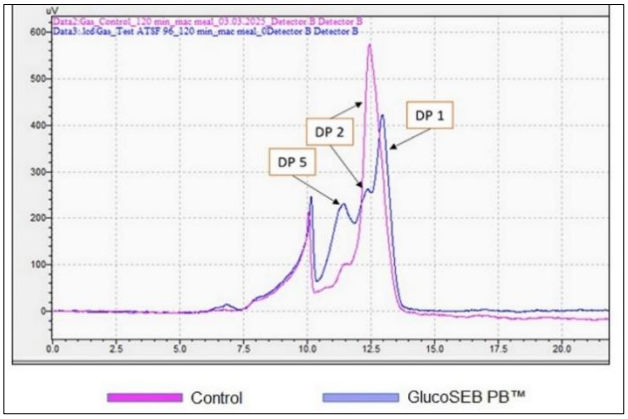

Figure 3: Size exclusion-high-performance liquid chromatography analysis of bread chicken patty meal (control and GlucoSEB-treated) after gastric digestion (120 min).

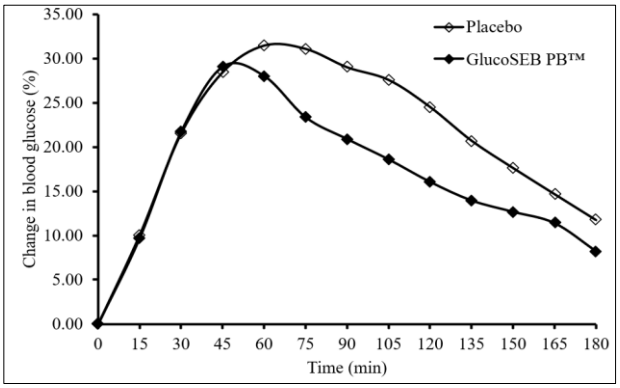

Figure 4: Percent change in blood glucose levels with time in participants after intervention.

Assessment of IP tolerance, adverse events, and serious adverse events

The IP was well tolerated by all the subjects. Insulin levels during the postprandial period were similar, and there were very negligible changes after 3-hour. Additionally, no side effects, were reported by any participant. Further, zero-reports related to AEs/SAEs were observed during the entire clinical study.

The medical outcomes such as physical functioning of vital organs, musculoskeletal-system, and extremities, were normal, and no variations were observed during each visit. Vital physical indicators of each participant indicated them to be in the normal range of the reference values, and no noticeable significant difference in the vital indicators was observed in both groups (Table 4).

DISCUSSION

The present study elucidates the imperative role of GlucoSEB PB™ in enhancing sugar digestion and regulating postprandial glucose levels. The in-vitro experiments provided valuable insights of sugar breakdown during the digestion of complex-foods. These results were further supported by the clinical study, which demonstrated the efficacy of IP in managing postprandial glucose. Throughout the *in-vitro* digestion, sugars within the bread-chicken-patty meal were effectively broken down into simpler forms, and the resulting total sugar content was precisely analyzed using HPLC.[20] After 120-min of in-vitro digestion, a significant increase in sucrose reduction percentage was observed, indicating the efficient breakdown of sucrose into glucose and fructose.[30] Further, the oligosaccharides with a DP-5 were formed by the transglycosidic action post sucrose hydrolysis. These oligosaccharides could pose prebiotic effects and help the growth of probiotics. An increase in sucrose reduction percentage is specifically beneficial for prediabetic patients, as effective sucrose breakdown can aid in blood sugar level regulation.[31]

On the other hand, the available simple sugar was reduced in food digested with GlucoSEB PB™. Thus, the difference in free sugar indirectly indicates the formation of slow-digesting sugars, which allows blood glucose levels to remain more stable with time.[32] Slow digesting carbohydrates help prevent postprandial hyperglycaemia, regulate emptying of the stomach, enhance insulin sensitivity by reducing demand of insulin production, and maintain steady energy level.[33,34] The increase in sucrose reduction and decline in simple sugar intake hold promise for managing glucose levels.

In the clinical study, GlucoSEB PB™ was investigated for managing postprandial glucose levels of Prediabetic

subjects. The enzymes play a vital role in the digestion of macromolecules in the food-matrix, and subsequently release the nutrients, aiding digestion.[35] The combined action of supplemented exogenous enzymes and endogenous digestive enzymes might have affected the glucose levels during the postprandial-phase. Further, the slightly lower release of glucose with the GlucoSEB PB™ supplementation could be attributed to the action of SucroSEB™. This enzyme is primarily involved in the transfer of released glucose moieties to specific acceptor molecules and leads to the formation of bioactive components such as long-chain fibers or carbohydrate derivatives.[36] SucroSEB™ acts by transferring the glycosyl moieties released from food matrices to various acceptor molecules and further form glycosidic linkages (α-1,2/α-1,3/α-1,4, and/or α-1,6).[37] These oligosaccharides may support the growth of probiotics in the gut, and their digestibility is very slow or negligible, further reducing the rate and extent of glucose absorption in the intestinal tract.[14,38] Earlier study has shown the catalytic action of SucroSEB™ on sucrose under in-vitro gastric conditions, and displayed the formation of glycans that were resistant to digestion.[21] Previously, a clinical trial with the supplementation of transglucosidase for 12-weeks significantly reduced the blood glucose and HbA1c, enhanced the gut microbiota profile and improved the bowel movements in T2DM patients.[24-26] These results were attributed to transglucosidase-induced production of oligosaccharides in GI tract, further supporting the notion of SucroSEB™ reducing the blood glucose levels in the present study.

Further, the ability of polyphenols to induce endogenous antioxidant enzymes, modulate signal transduction, and exhibit anti-inflammatory, neuroprotective, and immune protective properties under in-vivo conditions might have contributed to the results.[15] Previously, the administration of polyphenols from pomegranate peels in patients with T2DM for 8-weeks substantially declined the inflammation, oxidative stress biomarkers, and homocysteine indicating a positive effect on the overall health of diabetic patients.[27] Similarly, the administration of ellagic acid for 8-weeks resulted in significant changes in blood glucose, insulin resistance, and HbA1c ($p<0.05$).[28] These improved parameters were ascribed to the potential of polyphenols in regulating PPAR-γ transcription factors, which might also justify the declined blood sugar observed in the present study.[39] Moreover, the probiotics in GlucoSEB PB™ might have also played a crucial role in managing the glucose levels due to their ability to produce SCFAs, and some bile acids, lipopolysaccharides, and trimethylamine N-oxide. Further, the ability of probiotics to modulate gut microbiota might have contributed to the same. Besides, the glucose-lowering effects of probiotics have been corroborated by in-depth assessments of the clinical efficacies of different probiotics on T2DM by a few systematic reviews and meta-analyses.[12,18,19] Accordingly, probiotics might have also positively contributed in achieving a significant decrease in glucose levels in the present study.

Furthermore, the clinical trial revealed negligible changes in the blood insulin levels. This indicates no prominent role of IP in the secretion and functioning of insulin in both placebo and test groups, revealing the safety of the IP. In addition to the tolerability studies, the values of vital physical indicators were within the normal defined range, and there were no visible significant differences between in both groups at each visit. These clinically important findings clearly demonstrate safety of IP at the given dose upon oral administration. Moreover, during the entire study period, there were zero reports related to AEs or SAEs at the given dose. Nevertheless, the efficacy of GlucoSEB PB™ has been previously proven in a case study on six diabetic patients.[40]

The current clinical study clearly illustrates the efficacy and safety of GlucoSEB PB™ for managing the postprandial blood glucose levels in prediabetic subjects. Evidently, the regular supplementation of the digestive enzymes, probiotics, and herbal extracts, could effectively assist in managing the glucose levels in the body.

CONCLUSION

The *in-vitro* study revealed significant reductions in sugar content, and formation of oligosaccharides with dietary fiber potential in the presence of the GlucoSEB PB™, during the gastric and gastrointestinal digestion. These observations are strongly corroborated by the clinical study, which defined the efficacy and safety of GlucoSEB PB™ via oral consumption in managing blood glucose in prediabetic individuals. The clinical findings revealed excellent efficacy of IP via the noticeable reductions in glucose levels without major variations in insulin levels. Further, the absence of AES/SAEs underlines its tolerability in prediabetic subjects. The in-vitro data align with the clinical outcomes, as both highlight the role of the IP in reducing simple sugar availability, enhancing the digestion of slow-digested sugars, and managing glucose levels effectively. However, further large-scale and long-term clinical investigations are necessary to fully validate the efficacy and potential of GlucoSEB PB™ for broader applications.

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