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Modulation of Postprandial GLP-1 Secretion and Glycemic Responses by a Food-Grade GLP-1 Formula in Human Subjects

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Abstract

Obesity and overweight remain major public health concerns, driving interest in gut hormone–based strategies for metabolic regulation. Glucagon-like peptide-1 (GLP-1) plays a central role in insulin secretion, appetite control, and postprandial glucose homeostasis. However, pharmacological GLP-1 agonists are limited by injectable administration and adverse effects, highlighting the need for food-grade alternatives. This study aimed to evaluate whether a food-grade multi-component GLP-1 Formula could modulate enteroendocrine hormone secretion and improve postprandial glucose metabolism in vitro and in humans. In vitro experiments were performed using human NCI-H716, HskMC, and HepG2 cells to assess GLP-1/PYY secretion and GLUT4/GLUT2 expression. A randomized, controlled, crossover trial was conducted in 25 adults who received the GLP-1 Formula or water before a 75 g oral glucose challenge. Plasma GLP-1, glucose, insulin, and subjective appetite were measured. GLP-1 Formula significantly increased GLP-1 and PYY secretion and upregulated GLUT4 and GLUT2 in vitro. In humans, GLP-1 Formula enhanced postprandial GLP-1 levels, attenuated glucose excursions, amplified early insulin responses, and showed a sustained trend toward reduced hunger and appetite. A food-grade multi-component GLP-1 Formula improved enteroendocrine and postprandial metabolic responses, supporting food-based GLP-1 modulation as a complementary strategy for metabolic health management.

Keywords: Glucagon-like peptide-1 (GLP-1); Postprandial glycemic response; GLP-1 formula; Gut–endocrine axis

Introduction

Over the past decade, the global prevalence of obesity and overweight has continued to increase, becoming a major public health concern affecting metabolic health, cardiovascular diseases, and type 2 diabetes mellitus [1]. Along with the westernization of lifestyles and the widespread consumption of high-calorie diets, the weight management–related market expanded rapidly, among which strategies targeting gut hormones attracted particular attention [2]. Glucagon-like peptide-1 (GLP-1), an incretin hormone secreted by intestinal L cells, was known to stimulate insulin secretion, suppress glucagon release, delay gastric emptying, and enhance satiety [3]. Accordingly, GLP-1 played a critical role in glucose homeostasis and body weight regulation and was regarded as a central therapeutic target in recent research on weight loss and metabolic modulation [4].

Given the well-defined physiological functions of GLP-1, multiple GLP-1 receptor agonists had been widely applied in weight management and diabetes treatment, demonstrating pronounced weight-reducing effects [5]. However, these pharmacological agents generally required injectable administration and were frequently associated with adverse effects, including nausea, vomiting, gastrointestinal discomfort, and excessive appetite suppression [6]. Long-term use was also reported to compromise treatment adherence and quality of life. In addition, weight regain following drug discontinuation had emerged as a growing concern. Therefore, maintaining the metabolic benefits of GLP-1 modulation while reducing inconvenience and potential side effects became an important research focus in the field of weight management [7]. In contrast, regulating endogenous GLP-1 secretion through food-grade ingredients was considered a milder, more sustainable, and commercially viable alternative strategy [8].

Previous studies indicated that gut microbiota and plant-derived bioactive compounds could influence GLP-1 secretion and energy metabolism through multiple pathways. Bifidobacterium breve, a commonly used probiotic species [9], was shown to improve intestinal barrier function, modulate short-chain fatty acid production, and activate signaling pathways associated with enteroendocrine L cells, thereby promoting GLP-1 release [8, 10]. Meanwhile, Rocket apple extract (Malus pumila fruit), which was rich in polyphenols and dietary fiber, was suggested to contribute to body weight and glycemic regulation by inhibiting carbohydrate absorption, modulating gut hormone responses, and improving insulin sensitivity [11]. In addition, Probio-Kombu Black Tea Powder, derived from fermented black tea (Camellia sinensis leaf), was proposed to affect lipid metabolism, exert anti-inflammatory effects, and modulate gut microbial composition, thereby creating a gut environment favorable for GLP-1 secretion [12, 13]. Collectively, these components exhibited potential synergistic effects and were hypothesized to co-regulate energy metabolism via the gut–endocrine axis.

Based on this background, the present study employed a food-

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grade GLP-1 Formula. This formulation was developed and supplied by TCI Co., Ltd. In vitro cell-based experiments were first conducted to verify whether this formulation could stimulate GLP-1 secretion at the cellular level. Following confirmation of its GLP-1–enhancing potential in vitro, a human clinical trial was subsequently performed to evaluate whether supplementation with the GLP-1 Formula prior to a 75 g oral glucose challenge could increase circulating GLP-1 levels and improve glucose and insulin responses. The findings of this study were expected to clarify the scientific basis of food-grade GLP-1 modulation strategies in weight management and glucose metabolism and to provide empirical evidence for the future development and clinical application of functional foods.

Materials and methods

Cell culture

The human enteroendocrine L-cell line NCI-H716 was cultured in RPMI-1640 medium. To induce an adherent phenotype, cells were seeded onto poly-L-lysine–coated culture plates and allowed to attach for 24 h prior to treatment. The human skeletal muscle cell line HSkMC was maintained in Dulbecco's modified Eagle's medium (DMEM). For myogenic differentiation, cells were grown to confluence and differentiated into myotubes using differentiation medium consisting of DMEM supplemented with 2% horse serum for 5–7 days before experimental treatments. The human hepatocellular carcinoma cell line HepG2 was cultured in DMEM. All cell lines were maintained at 37°C in a humidified incubator with 5% CO_2 and cultured in medium supplemented with 10% fetal bovine serum (FBS) and 1% penicillin–streptomycin unless otherwise specified.

Quantification of gene expressions by real-time PCR

The treated cells were harvested, and total RNA was isolated from cells using an RNA purification kit (Geneaid, Taiwan). DNA-free total RNA was reversely transcribed to cDNA using a SuperScript™ Reverse Transcriptase kit (Invitrogen, Life Technologies Co., CA, USA). Quantitative real-time PCR was conducted using an ABI StepOnePlus™ Real-Time PCR System (Thermo Fisher Scientific, Inc., CA, USA) and the SYBR Green Master Mix (KAPA Biosystems, MA, USA) for transcript measurements. The reaction mixture was cycled as follows: one cycle at 95°C for 20 s, followed by 40 cycles of 95°C (1 s), 60°C (20 s), and a plate reading was conducted after each cycle. The melting curves of the PCR products were analyzed during the quantitative real-time PCR. The gene-specific primers used in this study were as follows: for PYY, forward 5′-GCT GCT GTC TTC TCC TTC CT-3′ and reverse 5′-TGA GGA GGA GGA GAA GGT GA-3′; for GLUT4 (SLC2A4), forward 5′-TGG TGT TCC TGT TCT TCC AG-3′ and reverse 5′-GGA GGA GAG GAT GAC GAT GA-3′; for GLUT2 (SLC2A2), forward 5′-GCT GGT TCT TCT TCT GCT GG-3′ and reverse 5′-AGG GAT GGA GGA GAG GAT GT-3′. GAPDH was used as the internal control with primers forward 5′-AAG GTG AAG GTC GGA GTC AA-3′ and reverse 5′-AAT GAA GGG GTC ATT GAT GG-3′. Real-time PCR reactions were performed using the ABI system. GAPDH was used as the reference gene to normalize relative expression. Data were analyzed using the ABI StepOne™ Software v2.2.3 (Thermo Fisher Scientific, Inc., Carlsbad, CA, USA). All PCR assays were performed in duplicate three times.

Clinical Trial Design

The study was registered at ClinicalTrials.gov (NCT07082062) and was conducted under a protocol approved by the Institutional Review Board of Chung Shan Medical University Hospital (CSMUH No. CS2-24173). All procedures were performed in accordance with the ethical principles outlined in the Declaration of Helsinki (1964) and its subsequent amendments, and written informed consent was obtained from all subjects prior to study initiation after a full explanation of the study procedures. This study was designed as a randomized, controlled, crossover clinical trial to evaluate the efficacy of a food-grade GLP-1 Formula on postprandial glycemic regulation. A total of 25 subjects were enrolled. Eligible subjects were men or women aged 18–50 years with a body fat percentage greater than 25%. Subjects were excluded if they had used probiotics, weight-loss products, or gastrointestinal health–related foods or medications within one month prior to enrollment; had a history of diabetes mellitus, autoimmune diseases, cancer, or chronic gastrointestinal disorders, including but not limited to irritable bowel syndrome, inflammatory bowel disease, Crohn's disease, lactose intolerance, chronic diarrhea, gastrointestinal motility disorders, fecal incontinence, pancreatitis, peptic ulcer disease, colorectal cancer, short bowel syndrome, or ulcerative colitis; had undergone gastrointestinal surgery; or were pregnant or lactating. Each subject participated in two intervention phases according to a crossover design, with the intervention order randomized and separated by a 7-day washout period. Subjects were instructed to fast for at least 8 hours prior to each test visit. At the beginning of each visit, fasting venous blood samples were collected. Subjects then consumed either 100 mL of water (control condition) or one bottle of GLP-1 Formula (GLP-1 Formula condition) according to the randomized sequence, and a second blood sample was obtained 30 minutes after consumption. Subsequently, subjects ingested a solution containing 75 g of glucose, and venous blood samples were collected at 15, 30, 45, 60, 90, 120, and 240 minutes following glucose ingestion. During the testing period, subjects were instructed not to consume any additional food, and water intake was standardized to 100 mL per hour. After completion of the first intervention phase, subjects entered a 7-day washout period, after which they returned to the study site to complete the alternate intervention following the same experimental procedures and sampling schedule. The primary outcome measures included plasma GLP-1 concentration, blood glucose levels, and serum insulin levels, which were analyzed to assess the effects of GLP-1 Formula supplementation on postprandial metabolic responses.

Supplement formulation

The intervention was a 50 g ready-to-drink liquid containing GLP-1 formula premix with primary actives (Bifidobacterium breve, Probio-Kombu Black Tea Powder, and Rocket Apple Extract Powder), blended into a liquid carrier matrix (acidulants, sweeteners, flavoring components, and pectin).

Measurement of GLP-1 secretion

GLP-1 secretion was quantified using a commercial human GLP-1 sandwich ELISA kit (Elabscience®, Houston, TX, USA; Cat. No. E-EL-H6025) according to the manufacturer's instructions[14]. Briefly, standards or samples (100 µL per well) were added to antibody-precoated 96-well plates and incubated at 37°C for 90 min. After removal of the liquid, 100 µL of biotinylated detection antibody working solution was added to each well and incubated at 37°C for 60 min, followed by washing three times with wash buffer. Subsequently, 100 µL of streptavidin–HRP conjugate was added and incubated at 37°C for 30 min, and the plate was washed five times. Then, 90 µL of TMB substrate was added to each well and incubated at 37°C for 15 min in the dark. The reaction was stopped by adding 50 µL of stop solution, and absorbance was measured immediately at 450 nm using a microplate reader. GLP-1 concentrations were calculated from a

standard curve. The assay sensitivity was 0.94 pg/mL, with a detection range of 1.56–100 pg/mL. All samples were assayed in duplicate.

Statistical analysis

The comparison of measurement results for skin parameters among groups and between groups was analyzed by Paired t-test or one-way ANOVA followed by GraphPad Prism, as $p < 0.05$ was considered statistical significance.

Results

Effects of GLP-1 Formula on GLP-1/PYY secretion and glucose transporter expression

As shown in Figure 1A, treatment with GLP-1 Formula significantly increased GLP-1 secretion in human enteroendocrine cells compared with the mock control. Relative GLP-1 levels were elevated by 51.8% following GLP-1 Formula treatment, reaching a level comparable to that induced by glucose as a positive control, indicating a potent stimulatory effect of the formulation on GLP-1 release. Consistently, Figure 1B demonstrated that GLP-1 Formula markedly upregulated the expression of peptide YY (PYY), a key anorexigenic hormone involved in appetite suppression. PYY mRNA expression was increased by 79.8% in the GLP-1 Formula–treated group compared with the mock group ($p < 0.05$). To further determine whether the enhanced secretion of GLP-1 and upregulation of PYY were accompanied by improvements in peripheral glucose handling, we next examined the effects of GLP-1 Formula on the expression of key glucose transporters in muscle and liver cells. As shown in Figure 1C, treatment with GLP-1 Formula significantly increased the expression of glucose transporter 4 (GLUT4) in human skeletal muscle cells compared with the mock control. GLUT4 mRNA levels were elevated by approximately 390% in the GLP-1 Formula–treated group ($p < 0.001$), indicating a marked enhancement of insulin-responsive glucose uptake capacity in muscle cells. Similarly, Figure 1D demonstrated that GLP-1 Formula significantly upregulated the expression of glucose transporter 2 (GLUT2) in human hepatocytes. GLUT2 mRNA expression was increased by approximately 110% compared with the mock group ($p < 0.05$), suggesting an improvement in hepatic glucose transport and sensing capacity. Together, these results indicated that the GLP-1 Formula–induced increases in GLP-1 secretion and PYY expression were accompanied by coordinated upregulation of glucose transporters in peripheral tissues, supporting a mechanistic link between enteroendocrine hormone modulation and improved cellular glucose utilization. [Figire 1A,B,C,D]

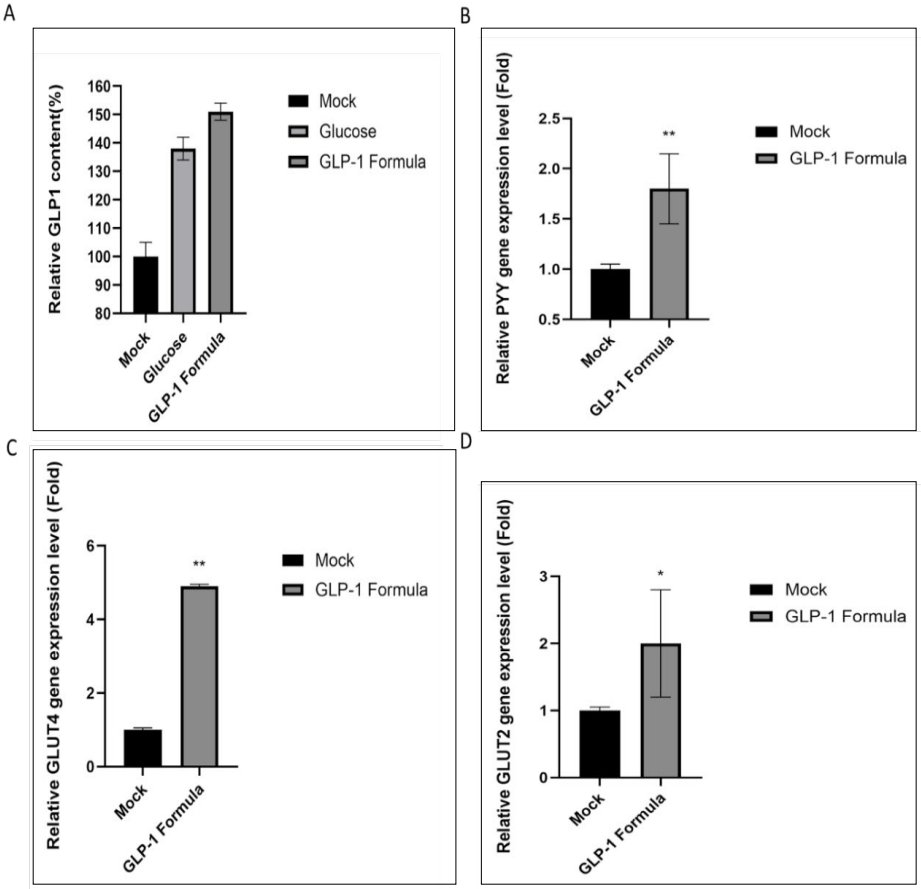

Figure 1. Effects of GLP-1 Formula on GLP-1 secretion and the expression of appetite- and glucose metabolism–related genes in vitro. (A) Relative GLP-1 content in the culture supernatant of NCI-H716 enteroendocrine L cells after treatment with glucose (positive control) or GLP-1 Formula, expressed as percentage relative to the mock control. (B) Relative mRNA expression level of *PYY* in NCI-H716 cells treated with GLP-1 Formula compared with the mock control. (C) Relative mRNA expression level of *GLUT4* in differentiated human skeletal muscle cells (HSkMC) treated with GLP-1 Formula. (D) Relative mRNA expression level of *GLUT2* in human hepatocellular carcinoma cells (HepG2) treated with GLP-1 Formula. Gene expression levels were determined by quantitative real-time PCR and normalized to the internal reference gene. Data are presented as mean ± SD from three independent experiments. $p < 0.05$ and $p < 0.01$ compared with the mock control.

Effects of GLP-1 Formula on Postprandial Plasma GLP-1 Levels

To translate the in vitro findings into a clinical context, we next evaluated the acute effects of GLP-1 Formula on postprandial plasma GLP-1 responses in human subjects. A total of 25 subjects (24 females and 1 male) were enrolled in the study. The participants had a mean age of 27.3 ± 6.6 years and were predominantly overweight, with a mean body mass index of 25.9 ± 4.7 kg/m² and a mean body fat percentage of 37.1 ± 6.8% (Table 1). As shown in Figure 2A, subjects receiving the GLP-1 Formula exhibited a pronounced increase in plasma GLP-1 concentrations following glucose challenge. Prior to glucose ingestion, GLP-1 levels in the GLP-1 Formula group showed a modest elevation at 30 minutes, corresponding to an approximately 16% increase compared with water control group, indicating an early stimulatory effect before glucose loading. After ingestion of 75 g glucose, plasma GLP-1 concentrations in the GLP-1 Formula group increased rapidly and reached peak levels between 75 and 90 minutes, with consistently higher absolute values than those observed in the water control group throughout the postprandial phase. Fold-change analysis relative to baseline further highlighted the enhanced GLP-1 response induced by the GLP-1 Formula (Figure 2B). At 60 minutes post-glucose ingestion, GLP-1 levels in the GLP-1 Formula group increased to approximately 10.96-fold of baseline. This response was further amplified at 75 minutes and 90 minutes, reaching 12.15-fold and 12.45-fold of baseline, respectively. Compared with the control condition, these increases corresponded to approximately 3.8-fold and 4.7-fold greater elevations in GLP-1 levels at 75 and 90 minutes, respectively. Thereafter, plasma GLP-1 concentrations gradually declined but remained numerically higher in the GLP-1 Formula group than in the water control until late postprandial time points, approaching baseline levels by 270 minutes. [Table 1], [Figure 2 A,B].

Effects of GLP-1 Formula on Postprandial Blood Glucose Responses

As shown in Figure 3A, subjects receiving the GLP-1 Formula exhibited a lower postprandial blood glucose response following ingestion of the 75 g glucose solution compared with the water control. Blood glucose levels in the GLP-1 Formula group increased after glucose ingestion, reaching a peak at 60 minutes, but the peak magnitude was numerically lower than that observed in the control condition. Thereafter, blood glucose concentrations in the GLP-1 Formula group declined more rapidly and remained lower during the postprandial phase, particularly between 75 and 120 minutes.

Consistent with the absolute glucose values, analysis of the percentage change in blood glucose relative to baseline (Figure 3B) demonstrated an attenuated glucose excursion in the GLP-1 Formula group. At 60 minutes, the increase in blood glucose was approximately 59.67% in the GLP-1 Formula group, representing an approximate 8% reduction compared with the water control (67.65%). This attenuation persisted at 75 minutes, where the glucose increase was 53.78% in the GLP-1 Formula group, corresponding to an approximate 5% reduction relative to the control (58.83%). The difference became more pronounced at 90 minutes, with the glucose increase reduced to 40.99% in the GLP-1 Formula group compared with 50.65% in the water control, representing an approximate 9.7% reduction. Blood glucose levels in both groups continued to decline thereafter and approached or fell below baseline values by 270 minutes post-glucose ingestion. [Figure 3 A, B]

Table 1. Baseline characteristics of the subjects (n = 25).

Variable	Value
Sex (female / male), n (%)	24 / 1 (96% / 4%)
Age (years)	27.3 ± 6.6
Body weight (kg)	65.1 ± 14.0
Body mass index (kg/m²)	25.9 ± 4.7
Body fat (%)	37.1 ± 6.8

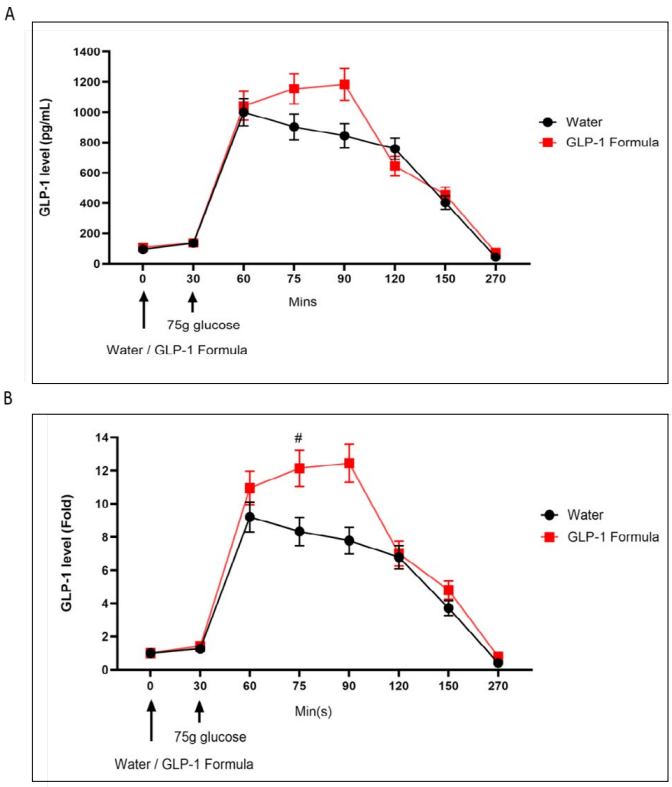

Figure 2. Time-course changes in plasma GLP-1 levels following administration of GLP-1 Formula or water prior to a 75 g oral glucose challenge in human subjects. Subjects received water or GLP-1 Formula at 0 min, followed by oral administration of 75 g glucose at 30 min. Plasma GLP-1 levels were determined by enzyme-linked immunosorbent assay (ELISA). (A) Absolute plasma GLP-1 concentrations (pg/mL) measured at baseline and at indicated time points after glucose ingestion. (B) Relative changes in plasma GLP-1 levels expressed as fold change from baseline (0 min). Data were presented as mean ± SEM. # $p < 0.05$ compared with the water group.

Effects of GLP-1 Formula on Postprandial Insulin and Insulin Resistance Responses

As shown in Figure 4, postprandial insulin dynamics and insulin resistance indices differed between subjects receiving the GLP-1 Formula and those receiving water prior to the 75 g oral glucose challenge. Before glucose ingestion, insulin levels remained close to baseline in both groups at 30 minutes, indicating that administration of the GLP-1 Formula alone did not acutely alter circulating insulin concentrations (Figure 4A). Following glucose intake, insulin levels increased rapidly in both groups; however, subjects in the GLP-1 Formula group exhibited a more pronounced early postprandial insulin response. Insulin levels in the GLP-1 Formula group reached 682.67% of baseline at 60 minutes and peaked at 782.56% at 75 minutes, exceeding the corresponding responses observed in the water control group. Elevated insulin levels were maintained at 90 minutes (707.96%) before progressively declining during the late postprandial period. By

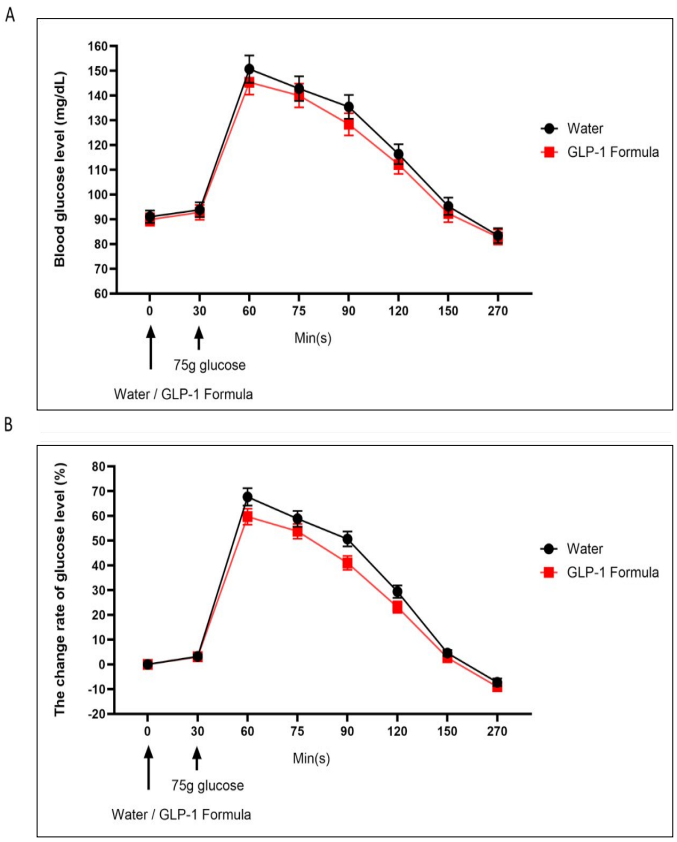

Figure 3. Time-course changes in blood glucose levels following administration of GLP-1 Formula or water prior to a 75 g oral glucose challenge in human subjects. Subjects received water or GLP-1 Formula at 0 min, followed by oral administration of 75 g glucose at 30 min. Blood glucose levels were measured using standard clinical biochemical assays. (A) Absolute blood glucose concentrations (mg/dL) measured at baseline and at indicated time points after glucose ingestion. (B) Relative changes in blood glucose levels expressed as percentage change from baseline (0 min). Data were presented as mean ± SEM.

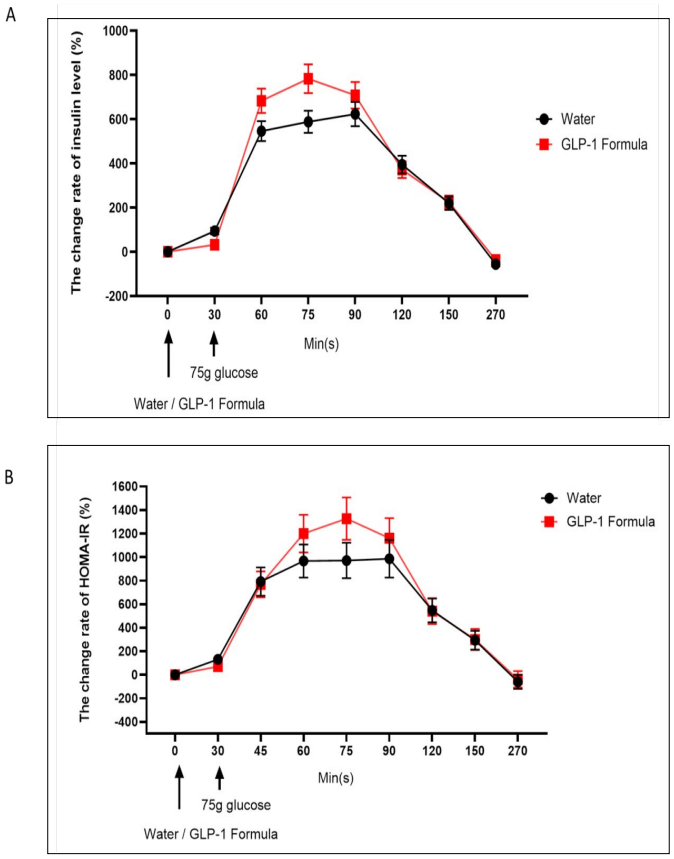

Figure 4. Time-course changes in postprandial insulin response and insulin resistance index following GLP-1 Formula supplementation. (A) Time-course changes in the percentage change of plasma insulin levels following administration of GLP-1 Formula or water prior to a 75 g oral glucose challenge in human subjects. Subjects received water or GLP-1 Formula at 0 min, followed by oral administration of 75 g glucose at 30 min. Plasma insulin levels were measured at baseline and at the indicated time points after glucose ingestion and are expressed as percentage change relative to baseline (0 min). (B) Time-course changes in the percentage change of HOMA-IR following the same intervention protocol. HOMA-IR values were calculated based on plasma glucose and insulin concentrations at each time point and are expressed as percentage change relative to baseline. Data are presented as mean ± SEM.

120 and 150 minutes, insulin levels decreased to 371.40% and 219.37% of baseline, respectively, approaching those observed under the control condition. Consistent with these insulin responses, postprandial changes in insulin resistance assessed by HOMA-IR are presented in Figure 4B. HOMA-IR values remained near baseline in both groups prior to glucose ingestion. After glucose challenge, HOMA-IR increased markedly, reflecting the physiological rise in circulating glucose and insulin. The GLP-1 Formula group displayed a more pronounced elevation in HOMA-IR during the early to mid postprandial phase, reaching 1210.41% of baseline at 60 minutes and peaking at 1334.52% at 75 minutes, whereas the water group exhibited lower peak values of approximately 980–1000% over the same time interval. Elevated HOMA-IR levels in the GLP-1 Formula group were sustained through 90 minutes (1160.63%) before declining during the late postprandial phase. By 120 and 150 minutes, HOMA-IR values decreased to 540.93% and 300.42% of baseline, respectively, and by 270 minutes returned to near or below baseline levels in both groups. Collectively, these findings indicated that GLP-1 Formula supplementation enhanced early-phase postprandial insulin availability and was associated with a distinct temporal profile of insulin resistance dynamics, characterized by an augmented early response followed by a comparable recovery phase during the late postprandial period. [Figure 4 A, B]

Effects of GLP-1 Formula on Subjective Hunger and Appetite Ratings

As shown in Figure 5A, subjects receiving the GLP-1 Formula exhibited lower subjective hunger scores compared with the water control during the postprandial period. At baseline (0 min), hunger scores were comparable between the two conditions. At 150 minutes, hunger scores in the GLP-1 Formula group remained relatively stable, whereas an increase was observed in the water control, indicating a tendency toward reduced hunger in subjects receiving the GLP-1 Formula. By 270 minutes, hunger scores increased in both groups; however, the GLP-1 Formula group continued to demonstrate numerically lower hunger ratings compared with the control condition. A similar pattern was observed for subjective appetite (craving) scores (Figure 5B). Appetite scores in the GLP-1 Formula group remained lower than those in the water control at 150 minutes, suggesting a tendency toward appetite suppression during the mid-to-late postprandial phase. At 270 minutes, appetite scores increased in both groups, yet subjects receiving the GLP-1 Formula continued to report

lower craving scores compared with the water control. Collectively, these results indicated that supplementation with the GLP-1 Formula was associated with a sustained trend toward reduced hunger and appetite during the late postprandial period. [Figure 5 A, B]

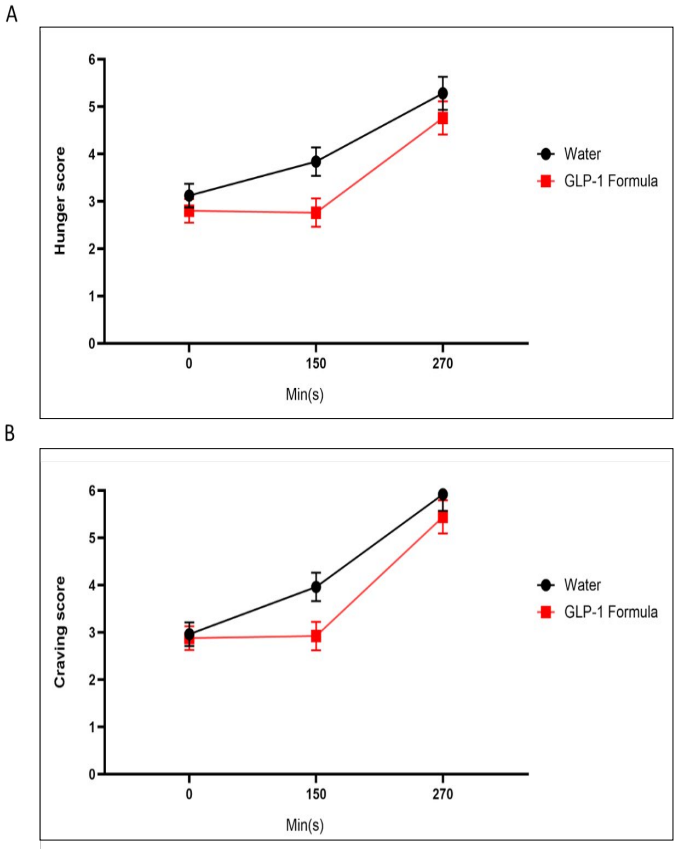

Figure 5. Effects of GLP-1 Formula on questionnaire-based hunger and appetite ratings after oral glucose loading. (A) Changes in self-reported hunger scores assessed at baseline (0 min) and at 150 and 270 min after glucose ingestion. (B) Changes in self-reported craving (appetite) scores assessed at the same time points. Data were presented as mean ± SEM.

Discussion

The present study provided comprehensive translational evidence demonstrating that a food-grade, multi-component GLP-1 Formula modulated enteroendocrine hormone secretion, peripheral glucose transporter expression, and postprandial metabolic responses from in vitro models to human subjects. The major findings of this study were threefold. First, GLP-1 Formula significantly enhanced GLP-1 and PYY secretion in human enteroendocrine cells and concomitantly upregulated GLUT4 in skeletal muscle cells and GLUT2 in hepatocytes. Second, in a human oral glucose challenge test, supplementation with GLP-1 Formula markedly increased postprandial plasma GLP-1 concentrations and attenuated postprandial glucose excursions while enhancing early-phase insulin responses. Despite comparable total GLP-1 AUCs, the two groups exhibited markedly different kinetic topologies. Unlike the transient surge observed in the Water group, the GLP-1 Formula elicited a sustained maintenance of GLP-1 levels from 60 to 120 minutes. This prolonged duration of action—obscured by AUC analysis—may offer greater clinical relevance for appetite suppression and post-prandial glucose clearance than short-term peaks. Third, these endocrine and metabolic changes were accompanied by a sustained trend toward reduced subjective hunger and appetite during the late postprandial period.

Bifidobacterium breve and its associated microbial components have increasingly been recognized as important regulators of enteroendocrine signaling [15]. Previous studies reported that structural components of bifidobacteria, including cell wall fragments, peptidoglycans, and microbial-derived short-chain fatty acids, stimulated L-cell secretion of GLP-1 and PYY through activation of G protein–coupled receptors such as GPR41 and GPR43 [16, 17]. Notably, several investigations demonstrated that heat-killed bifidobacteria retained the capacity to stimulate enteroendocrine responses despite the absence of viable colonization, suggesting that microbial-associated molecular patterns rather than live bacterial metabolism mediated these effects [18]. In the present study, treatment with heat-killed B. breve was associated with significant increases in both GLP-1 and PYY secretion, consistent with these earlier observations. Moreover, the elevation of GLP-1 was accompanied by marked upregulation of GLUT4 and GLUT2, supporting the notion that microbial-induced incretin signaling propagated downstream to peripheral tissues [19]. These findings expanded existing literature by providing direct evidence that non-viable probiotic components could simultaneously modulate enteroendocrine hormone secretion and peripheral glucose transporter expression within an integrated experimental framework.

Polyphenol-rich Kombu Black Tea extracts derived from Camellia sinensis have been widely reported to influence glucose homeostasis and incretin signaling [20]. Tea catechins, theaflavins, and thearubigins present in Kombu Black Tea were shown to activate AMP-activated protein kinase and calcium-dependent signaling pathways in intestinal epithelial cells, thereby enhancing GLP-1 secretion and improving insulin sensitivity [21]. In addition, polyphenols from Kombu Black Tea inhibited intestinal α-glucosidase activity, delayed carbohydrate digestion, and reduced postprandial glucose excursions [22]. At the level of peripheral tissues, Kombu Black Tea extracts were reported to promote GLUT4 expression and translocation in skeletal muscle and to modulate hepatic glucose output [23]. In the present study, the observed increases in postprandial GLP-1 concentrations and the coordinated upregulation of GLUT4 and GLUT2 were consistent with these previously described mechanisms. These findings suggested that Kombu Black Tea contributed not only to the stimulation of enteroendocrine hormone release but also to the enhancement of insulin-responsive glucose transport in peripheral tissues, thereby reinforcing its dual role in both intestinal and systemic glucose regulation.

Apple-derived polyphenols from Malus pumila have similarly been implicated in the regulation of glucose metabolism and incretin signaling [24]. Procyanidins, quercetin, and related flavonoids were shown to improve insulin sensitivity through activation of the PI3K/Akt and AMPK pathways, promote GLUT4 translocation in skeletal muscle, and suppress hepatic gluconeogenesis [25]. Several studies further reported that apple polyphenols stimulated GLP-1 secretion and reduced appetite in experimental models [26]. In the present study, the pronounced upregulation of GLUT4 and GLUT2 and the attenuation of postprandial glucose excursions were in agreement with these reported actions of apple polyphenols [27]. These results supported the interpretation that rocket apple extract primarily contributed to the improvement of peripheral glucose handling and insulin sensitivity, complementing the enteroendocrine effects induced by the other components of the formulation.

An important feature of the present study was the use of a

multi-component formulation rather than a single active ingredient. Heat-killed B. breve primarily targeted enteroendocrine L cells and incretin secretion [28], Kombu Black Tea polyphenols influenced both intestinal nutrient sensing and insulin signaling [29], and apple polyphenols preferentially enhanced peripheral glucose transporter expression and insulin sensitivity [30]. These components appeared to act at distinct yet interconnected regulatory nodes along the gut–pancreas–peripheral tissue axis. The simultaneous increases in GLP-1 and PYY secretion, coordinated upregulation of GLUT4 and GLUT2, and integrated improvements in postprandial glucose and insulin dynamics suggested the presence of complementary and potentially synergistic effects among these components. This multi-target strategy may provide an advantage over single-ingredient approaches by engaging multiple physiological pathways involved in appetite control and glucose homeostasis, thereby achieving a more balanced and physiologically aligned modulation of postprandial metabolism [31].

Several limitations of the present study should be acknowledged. First, the human intervention was designed as an acute postprandial study; therefore, the long-term effects of the GLP-1 Formula on body weight regulation, insulin resistance, and sustained glycemic control could not be evaluated. Second, the sample size was relatively limited, and key physiological parameters such as gastric emptying rate, habitual energy intake, and gut microbiota composition were not directly assessed, all of which may contribute to the observed effects on appetite regulation and glucose metabolism. Third, the recruited cohort likely consisted predominantly of individuals with metabolically healthy obesity (MHO). Such individuals typically retain relatively preserved insulin sensitivity and robust glucose homeostasis, creating a physiological "ceiling effect" that constrains the magnitude of detectable metabolic improvements. This context may partially explain the absence of statistically significant differences in aggregate postprandial AUC parameters, despite the presence of distinct and biologically meaningful kinetic trends in GLP-1 secretion and glucose handling. Fourth, only a single dose of the formulation was evaluated, and dose–response relationships were not examined. Future studies should therefore incorporate longer-term supplementation protocols, larger and metabolically stratified cohorts—particularly individuals with prediabetes or impaired glucose regulation—and comprehensive metabolic phenotyping, including measurements of HbA1c, gastric emptying, energy intake, and gut microbiota profiles. Such investigations will be essential to further define the clinical applicability and therapeutic potential of this multi-component, food-based GLP-1 modulation strategy for metabolic health management.

Conclusion

The present study demonstrated that a food-grade GLP-1 Formula containing heat-killed B. breve, Kombu Black Tea, and rocket apple extract modulated enteroendocrine hormone secretion, enhanced peripheral glucose transporter expression, and improved postprandial glucose and insulin responses in humans. These findings provided proof-of-concept evidence supporting the use of multi-component nutritional strategies to achieve coordinated modulation of the gut–peripheral tissue axis and highlighted the potential of food-based GLP-1 modulation as a complementary approach for metabolic health management.

Declaration of Competing Interest

The authors declare no conflict of interest.

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