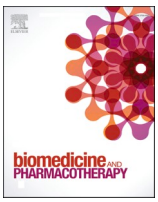
Biomedicine & Pharmacotherapy 187 (2025) 118102

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

journal homepage: www.elsevier.com/locate/biopha



# HG043, a potent thienopyrimidine GPR119 agonist, demonstrates enhanced anti-diabetic and anti-obesity effects in preclinical models

Sangdon Lee [a,b,c], Heecheol Kim [a,b,c], Inyoung Choi [a], Sanghyun Lee [a], Kyung Hoon Min [b,c,*]

[a] Hanmi Pharm. R&D Center, Hanmi Pharm. Co., Ltd, Hwaseong-si 18469, Republic of Korea
[b] College of Pharmacy, Chung-Ang University, Seoul 06974, Republic of Korea
[c] Department of Global Innovative Drugs, Graduate School of Chung-Ang University, Seoul 06974, Republic of Korea

ARTICLE INFO

*Keywords:*
HG043
GPR119
Incretin
Diabetes
Obesity

ABSTRACT

GPR119 is a promising therapeutic target for type 2 diabetes because of its role in enhancing glucose-stimulated insulin secretion and GLP-1 release. We investigated the anti-diabetic and anti-obesity effects of HG043, a novel and potent thienopyrimidine-based GPR119 agonist, by comparing its pharmacological activities to those of MBX-2982 (a known GPR119 agonist) and sibutramine (an appetite suppressant) in both *in vitro* and *in vivo* models. HG043 exhibited potent agonistic activity for human GPR119 and demonstrated enhanced efficacy compared to MBX-2982 in stimulating incretin secretion in pancreatic β-cell lines. Single and long-term treatment with HG043 resulted in significant improvements in diabetic and obesity parameters compared to both MBX-2982 and sibutramine in both healthy and disease models. Furthermore, HG043 demonstrated synergistic glucose-lowering effects when combined with metformin or sitagliptin. These findings suggest that HG043 may serve as a promising therapeutic option for the treatment of type 2 diabetes with obesity patients.

## 1. Introduction

Diabetes, a common chronic condition affecting over half a billion individuals globally [1], poses a significant public health burden [2]. It is a major risk factor for serious complications, including neuropathy, atherosclerosis, and vascular events like ischemic heart disease, stroke, and peripheral artery disease [3]. The global prevalence of type 2 diabetes (T2D) is rapidly increasing, with projections suggesting it will reach approximately 800 million by 2045 [4]. This prevalent trend underscores the urgent need for effective disease management strategies.

While lifestyle modifications, including dietary changes and regular physical activity, are essential components of managing diabetes [5], pharmacological interventions are often necessary to achieve and maintain optimal blood glucose levels. Obesity, a key factor closely linked to T2D, has been a major contributor to the rising prevalence of diabetes in recent decades [6]. The global obesity epidemic exacerbates this issue, as excess adiposity, particularly visceral fat, is associated with insulin resistance in both the brain and peripheral tissues [7]. Weight reduction has thus become a crucial target in improving insulin sensitivity and mitigating the progression of metabolic diseases [7,8].

In clinical practice, various anti-diabetic agents, including sulfonylureas, are commonly prescribed to manage T2D [5]. However, despite these efforts, diabetes remains a leading cause of mortality, with approximately 4 million deaths attributed to the disease in 2019, accounting for nearly 10 % of all deaths globally [9]. This underscores the need for novel therapies that not only improve glycemic control but also promote weight loss and reduce the risk of hypoglycemia.

A promising therapeutic target for T2D is the G protein-coupled receptor 119 (GPR119), primarily expressed in pancreatic β cells and intestinal L cells [10,11]. Activation of GPR119 stimulates glucose-dependent insulin secretion (GSIS) and indirectly enhances the secretion of glucagon-like peptide-1 (GLP-1), a key hormone involved in glucose homeostasis [12]. GPR119 agonists have demonstrated significant anti-diabetic effects in preclinical models, and several such agents have undergone clinical investigation [13]. For instance, MBX-2982 has shown promise in clinical trials by improving glucose control and stimulating GLP-1 secretion [14]. Furthermore, the GPR119 agonist APD668 has exhibited therapeutic potential in treating non-alcoholic steatohepatitis and dyslipidemia in preclinical models [15]. In this context, we identified a novel class of small-molecule GPR119 agonists, including HG043 [16], with significant potential for the treatment of T2D and obesity. In this study, we describe the pharmacological characterization of HG043 in both normal and obese,

* Correspondence to: College of Pharmacy, Chung-Ang University, Unit 408, building 102, 84 Heukseok-Ro, Dongjak-Gu, Seoul 06974, Republic of Korea.
*E-mail address:* khmin@cau.ac.kr (K.H. Min).

https://doi.org/10.1016/j.biopha.2025.118102
Received 10 February 2025; Received in revised form 14 April 2025; Accepted 24 April 2025
Available online 29 April 2025

diabetic rodent models, highlighting its potential as an innovative therapeutic approach for managing these chronic conditions.

## 2. Materials and methods

### 2.1. Animals, cell lines and chemicals

Male C57BL/6 mice and Sprague-Dawley (SD) rats were obtained from Orient, Inc. (Gyeonggi-do, Korea) and were fed Picolab rodent diet 5053 (Lab Rodent Diet, St. Louis, USA). Male diabetic *db/db* (BKS.Cg-+*Lepr*$^{db}$/+*Lepr*$^{db}$/OlaHsd) mice, Zucker (ZDF-Lepr$^{fa}$/Crl) rats, and ZDF control (Lean fa/+) rats were purchased from Jackson Laboratory, Inc. (Yokohama, Japan) and fed the Harlan 2918 C diet (Harlan Lab, Indianapolis, USA; Composition: protein 18.6 %, fat 6.2 %, carbohydrates 58 %) and the Purina #5008 diet (LabDiet, St. Louis, USA; Composition: protein 23.0 %, fat 6.5 %, fiber 4.0 %) to maintain hyperglycemia. A diet-induced obese (DIO) rat model was obtained by feeding normal SD rats a high fat diet (composition: protein 18 %, fat 60 %, carbohydrate 20 %) from Lab Rodent Diet for 12 weeks. All animal experimental procedures were approved by the Hanmi Research Center Institutional Animal Care and Use Committee (IACUC) and were carried out in accordance with the Guide for the Care and Use of Laboratory Animals [17] and institutional standard operating procedures (TE094).

The CellSensor® CRE-*bla* CHO-K1 cell line, purchased from Invitrogen (Carlsbad, CA, USA), contains a β-lactamase reporter gene under the control of a cyclic AMP (cAMP) response element (CRE) stably integrated into CHO-K1 cells [18]. The MIN6 cell line was derived from a transgenic mouse expressing the large T-antigen of SV40 in pancreatic β cells [19].

The GPR119 agonist HG043 was synthesized according to a previously reported method [16]. The Metformin (Sigma-Aldrich®, USA, Cat# No. D150959) and Sitagliptin (Sigma-Aldrich®, USA, Cat# No. PHR1857) were purchased. The MBX-2982 and Sibutramine were synthesized according to published procedures (US 8815886 B2 and WO2004099119A1, respectively).

### 2.2. In vitro cellular assays for GPR119 agonist activity and incretin secretion

The agonistic activity of HG043 on human GPR119 was evaluated using GPR119-CRE-*bla* CHO-K1 cells, as previously described [20]. GPR119-CRE-*bla* CHO-K1 cells ($5.0 \times 10^4$) were plated to black clear-bottom 96-well plates and incubated for 20 hrs at 37°C. Cells were then treated with HG043 at concentrations ranging from 0.1 nM to 10 μM in 0.1 % dimethyl sulfoxide for 5 hours. Subsequently, the LiveBLAzer™-FRET B/G substrate was added to the cells for 2 h. Fluorescence was measured at excitation/emission wavelengths of 409/460 nm and 409/630 nm using a SpectraMax Gemini EM microplate reader (Molecular Devices, San Jose, CA, USA). Insulin secretion was evaluated using the MIN6 cell lineas described previously [21]. MIN6 cells were cultured in Dulbecco's Modified Eagle Medium (DMEM) containing 10 % FBS and 25 mmol/L glucose at 37°C in a humidified atmosphere of 5 % $CO_2$. Cells ($2.5 \times 10^5$) were seeded into wells of poly-D-lysine-coated 24-well plates and incubated for 48 hrs. After incubation, the culture medium was removed, and the cells were washed with Krebs-Ringer bicarbonate buffer (KRBB; composition: 120 mM NaCl, 5 mM KCl, 2 mM $CaCl_2$, 1 mM $MgCl_2$, and 25 mM $NaHCO_3$). Cells were preincubated at 37°C for 30 minutes in KRBB containing 2.8 mmol/L glucose, followed by stimulation with HG043 at concentrations ranging from 0.01 nM to 200 nM in KRBB with 16.8 mmol/L glucose for 20 minutes at 37°C. The supernatants were collected, and insulin concentrations were measured using a mouse insulin ELISA kit (Shibayagi Co., Ltd., Japan) according to the manufacturer's instructions. Absorbance was measured at 450 nm using a SpectraMax i3x (Molecular Devices).

### 2.3. Pharmacokinetic study

Oral pharmacokinetic properties of HG043 were investigated in male Sprague-Dawley (SD) rats. Before oral administration of HG043, the animals were fasted overnight. Food was provided to the rats two hours after dosing. Blood samples (0.3 mL) were collected from the jugular vein at 0.5, 1, 2, 4, 7, 24, and 30 h post-dosing. Blood samples were collected into heparinized tubes (1000 IU/mL heparin), centrifuged at 17,000 × g for 2 min at 4°C, and the resulting plasma was stored at −20°C until analysis. Plasma concentrations of HG043 were determined using liquid chromatography-tandem mass spectrometry (LC-MS/MS). The LC-MS/MS system comprised an Agilent 1100 series HPLC system equipped with a quaternary pump, a column heater, and an autosampler with a temperature-controlled tray (CTC PAL; CTC Analytics, Switzerland). Chromatographic separation was achieved using a reversed-phase phenyl hexyl column (50 mm × 2.0 mm, 5.0 μm; Phenomenex, USA). Mass spectrometric detection was performed using an API 4000QTRAP mass spectrometer (Applied Biosystems, MDS Sciex) equipped with an electrospray ionization source operating in positive ion mode. Pharmacokinetic parameters of HG043 were determined by non-compartmental analysis using Phoenix™ WinNonlin® 6.1 (Pharsight, USA).

### 2.4. Oral glucose tolerance test in C57BL/6 mice

Male C57BL/6 mice (8 weeks old) were fasted for 16 h prior to undergoing an oral glucose tolerance test (OGTT). Two hours prior to an oral glucose challenge (2 g/kg body weight), mice received a single oral dose of either HG043 (30 mg/kg), Metformin (70 mg/kg), Sitagliptin (10 mg/kg), various combinations of these drugs, or a vehicle control (carboxymethylcellulose (CMC): Tween 80: distilled water, 1:2:97). Doses of metformin and sitagliptin are selected based on previous studies [22,23] for preclinical evaluation of their anti-diabetic effects. Blood glucose levels were measured at 0, 15, 30, 60, and 120 mins after glucose administration using tail-nick blood samples obtained from mice and analyzed with a OneTouch® Ultra glucometer (Life Scan, Inc., USA). The area under the curve ($AUC_{0-2\ h}$) of blood glucose levels during the OGTT were calculated using the trapezoidal rule.

### 2.5. Effects of 4-week repeated administration on glycemic control in db/db mice

Eight-week-old male *db/db* mice were grouped based on their baseline blood glucose levels. Animals received daily oral administrations of HG043 (30 mg/kg) or MBX-2982 (30 mg/kg) via gavage for 28 consecutive days. The dose of MBX-2982 was selected based on previous studies [24,25] Clinical observations were conducted throughout the dosing period. Blood glucose levels were measured in a blood drop from the tail vein on days 0, 2, 4, 8, 11, 16, 19, 22, and 25. On day 28 of administration, an OGTT was performed using OneTouch® Ultra glucometer (LifeScan, Inc., USA). Hemoglobin A1C (HbA1c) was analyzed on day 28 using a Hitachi 7020 clinical analyzer (Hitachi, Japan). Body weight was measured daily before each dosing using a BSA224S-CW balance (Sartorius, Germany).

### 2.6. Effects of 7-week repeated administration on glycemic control in Zucker diabetic fatty (ZDF) rats

Eight-week-old male Zucker (ZDF) and ZDF control (LEAN) rats were grouped based on their baseline blood glucose levels. Animals received daily oral administrations of HG043 (30 mg/kg) via gavage for 56 consecutive days. Clinical observations were conducted throughout the dosing period. Blood glucose levels were measured in a blood drop from the tail vein on days 0, 3, 10, 17, 24, 31, 38, 45 and 52. Hemoglobin A1C was analyzed on pre, day 28 and 56 using a Hitachi 7020 clinical analyzer (Hitachi, Japan). Body weight was measured daily before each

dosing using a BSA224S-CW balance (Sartorius, Germany). At the end of the repeated dosing study, rats were fasted overnight and euthanized under deep anesthesia. Whole pancreata were rapidly excised, weighed, and fixed in 4 % paraformaldehyde (PFA) in phosphate-buffered saline (PBS) at 4°C for 24 hours. Tissues were then processed for paraffin embedding and sectioned at 5 μm thickness at 200 μm intervals throughout the entire pancreas. For immunohistochemical analysis, deparaffinized and rehydrated sections were subjected to antigen retrieval in citrate buffer (pH 6.0) and incubated with 3 % hydrogen peroxide to block endogenous peroxidase activity. Non-specific binding was blocked using 5 % normal goat serum. Sections were incubated overnight at 4°C with a primary antibody against insulin (rabbit Anti-Insulin antibody Cat# No. 3014S; 1:500 dilution; Cell Signaling Technology, Boston, USA), followed by a biotinylated secondary antibody (biotinylated goat Anti-Rabbit IgG (H+L), Cat# No. BA-1000, Vector Laboratories, California, USA) and visualization with DAB (3,3′-diaminobenzidine) substrate. Hematoxylin was used for counterstaining. Images of insulin-positive islets were acquired using a microscope, and the insulin-positive area was quantified using ImageJ software (National Institutes of Health, USA). The β-cell mass was calculated by multiplying the relative insulin-positive area (%) by the pancreatic weight.

### 2.7. Body weight and fat mass reduction upon repeated dosing in a diet-induced obese rat model

Five-week-old male SD rats were fed a 60 kcal% fat diet (Research Diet) for 8 weeks to induce obesity. The rats were orally administered HG043 (30 mg/kg) or sibutramine (10 mg/kg) [26] by gavage daily for 24 days. Clinical observations were monitored throughout the dosing period. The body weight was measured on days 0, 3, 7, 10, 14, 17, 21, and 24 using a BSA224S-CW balance (Sartorius, Germany). On day 25, the rats were sacrificed, and the weights of epididymal and mesenteric adipose tissues were determined using a BSA224S-CW balance (Sartorius, Germany).

### 2.8. Evaluation of incretin secretion after a single dose

For plasma level evaluation of glucagon-like peptide-1 (GLP-1), glucose-dependent insulinotropic polypeptide (GIP), peptide YY (PYY) and insulin was referred to previously performed study method [27]. Rats were fasted overnight, weighed, and administered a single dose of HG043 (30 mg/kg), MBX-2982 (30 mg/kg), or the vehicle (CMC/Tween 80/DW, 1:2:97). An oral glucose load of 2 g/kg was administrated 2 hrs after drug administration. Blood was collected from the left subclavian artery at 0, 3, 5, 15, 30, and 60 mins after the glucose challenge into ethylenediaminetetraacetic acid (EDTA)-coated tubes. Plasma was separated by centrifugation at 12,000 × g for 5 min at 4℃ and stored at −80℃ until analysis. Plasma levels of GLP-1, GIP, PYY and insulin were measured using the Milliplex MAP Rat Metabolic Hormone Magnetic Bead Panel (Cat# RMHMAG-84K, Millipore, USA) according to the manufacturer's instructions.

### 2.9. GLP-1 secretion after a single direct injection to the ileum or duodenum

The surgical procedure has been described in detail elsewhere [28]. Eight-week-old male SD rats were fasted overnight and anesthetized with diethyl ether inhalation. In the duodenum injection group, an abdominal incision was made, and approximately 1 cm of the duodenum immediately below the stomach and another 1 cm of the duodenum in the lower 10 cm of the duodenum were ligated. In the group of ileum injections [29], an abdominal incision was made, and approximately 1 cm of the ileum just above the appendix and another 1 cm of the ileum in the upper 10 cm of the ileum were ligated. A single dose of HG043 (30 mg/kg) or vehicle (CMC/Tween 80/DW, 1:2:97) was administered to the ligated intestinal segments using a 26 G syringe. The incision site was immediately sutured. Blood was collected from the left subclavian artery into EDTA-coated tubes 1 hr after dosing. Plasma was separated by centrifugation at 4℃, 12,000 × g for 5 mins and stored at −80℃ until analysis with an active GLP-1 rat ELISA kit (Cat# EGLP-35K, Millipore, USA).

### 2.10. Gastric intestinal motility after a single administration of HG043 in normal rats

After an overnight fast, rats were weighed and received a single dose of HG043 (30 mg/kg) or vehicle (CMC/Tween 80/DW, 1:2:97) 2 hrs prior to oral gavage of a charcoal meal (10 % charcoal, 5 % gum Arabic, and 1 % CMC) [30]. 20 mins after charcoal meal administration, the rats were euthanized by cervical dislocation. The small intestine was dissected, and the distance traveled by the charcoal meal was measured. The data were expressed as a percentage of the total small intestinal length.

### 2.11. Statistics

All data are expressed as the mean ± standard deviation (SD). Statistical significance among experimental groups was evaluated using a one-way analysis of variance (ANOVA) followed by multiple comparison tests, as well as independent sample t-Tests where appropriate. All statistical analyses were conducted using GraphPad Prism software version 6.0 (GraphPad Software, La Jolla, CA, USA). A p-value of less than 0.05 was considered indicative of a statistically significant difference. To facilitate interpretation of the data, specific symbols were used to denote statistically significant differences between experimental groups: an asterisk (*) indicates a significant difference compared with the vehicle control group; a hash ($^{\#}$) denotes significance compared with the MBX-2982 treated group; an ($^{x}$) indicates significance relative to the group receiving a combination of HG043 and Sitagliptin; and a plus sign ($^{+}$) represents a significant difference compared with the group that received HG043 *via* direct injection into the duodenum.

## 3. Results

### 3.1. HG043, a potent stimulator of insulin secretion via GPR119 activation

The chemical structure of HG043 is presented in Fig. 1. The agonist activity of HG043, a novel small-molecule GPR119 agonist, was evaluated in GPR119 CRE-*bla* CHO-K1 cells using a cAMP assay. HG043 exhibited potent and dose-dependently agonistic effect at human GPR119 with an $EC_{50}$ value of 2.0 nM (Table 1, Fig. 2A), significantly more potent than MBX-2982, which displayed an $EC_{50}$ value of 10.0 nM (Table 1).

To further assess the functional activity of HG043, its ability to enhance glucose-stimulated insulin secretion (GSIS) was investigated using the MIN6 pancreatic β-cell line, a well-established *in vitro* model for studying insulin secretion [31]. HG043 potently stimulated insulin secretion with an $EC_{50}$ value of 0.1 nM (Table 1, Fig. 2B), demonstrating approximately 100-fold higher potency compared to MBX-2982 ($EC_{50}$ = 17.65 nM)

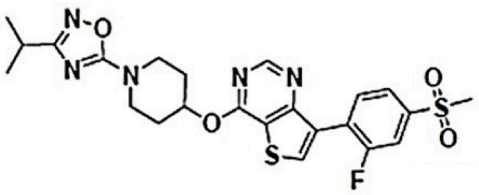



**Fig. 1.** Chemical structure of HG043.

**Table 1**
$EC_{50}$ of HG043 for GPR119 activation (CHO-K1) and insulin secretion (MIN6).

| Compound | $EC_{50}$ (nM) | |
|---|---|---|
| | GPR119 activation | Insulin secretion |
| HG043 | 2.0 | 0.1 |
| MBX−2982 | 10.0 | 17.65 |

### 3.2. Pharmacokinetics of HG043 in rats

The $AUC_{0-24\,h}$ values of HG043 increased in a dose-dependent manner. However, $C_{max}$ values were higher at 10 and 30 mg/kg compared to 60 and 100 mg/kg. Furthermore, the plasma concentration of HG043 exhibited a rapid increase at 30 mg/kg ($t_{max}$ value of 1.1 ± 0.5 h) compared to the other doses (Table 2, Fig. 3). The observation of a reduction in initial systemic exposure of HG043 with increasing dosage may be attributed to dose-dependent inhibition of gastrointestinal motility. A delay in gastric emptying caused by higher doses of HG043 may prolong drug residence in the acidic gastric environment, potentially resulting in chemical instability, degradation, or reduced dissolution ultimately limiting the bioavailability of the drug. Additionally, delayed transit through the intestines could shift absorption away from the optimal intestinal absorption window, further reducing systemic exposure [32]. Based on these results, a dose of 30 mg/kg was selected for subsequent *in vivo* investigations of HG043.

### 3.3. Glycemic control efficacy of HG043 in normal and diabetic mice and rats models

In an oral glucose tolerance test (OGTT) conducted in normal C57BL/6 mice, a single oral dose of HG043 (30 mg/kg) significantly reduced the $AUC_{0-2\,h}$ of blood glucose levels following glucose loading (2 g/kg) compared with the vehicle control group (635.29 ± 14.1 mg·min/dL vs. 844.64 ± 36.1 mg·min/dL, $p < 0.001$), representing about a 25 % reduction (Fig. 4). This effect was significantly greater than that observed with single doses of metformin (75 mg/kg; 709.71 ± 27.5 mg·min/dL) and Sitagliptin (10 mg/kg; 710.86 ± 29.4 mg·min/dL). Furthermore, combinations of HG043 (30 mg/kg) with either Sitagliptin (10 mg/kg) or metformin (75 mg/kg) resulted in a significant and synergistic reduction in $AUC_{0-2\,h}$ compared to both the control group and treatment with either drug alone. Notably, the combination of HG043 with sitagliptin demonstrated a greater synergistic effect than the combination with metformin (Fig. 4A-B).

In diabetic *db/db* mice, long-term repeated administration of HG043 (30 mg/kg) significantly reduced mean blood glucose levels (Fig. 5A), and HbA1c levels compared to both the vehicle control group and the MBX-2982 treatment group (Fig. 5B). Furthermore, an OGTT performed on day 28 after the final dose of the 4-week treatment regimen demonstrated a significant reduction in $AUC_{0-2\,h}$ in the HG043-treated group compared to both the control and MBX-2982-treated groups (Fig. 5C-D). These findings suggest that HG043 exhibits sustained anti-diabetic effects following long-term repeated administration.

8-week-old ZDF rats were orally administered HG043 once daily for 7 weeks. The LEAN group (fa/+) served as the non-diabetic control. Fasting blood glucose levels were significantly elevated in the ZDF control group compared to the LEAN group, confirming the development of hyperglycemia. HG043 treatment led to reduction in blood

**Table 2**
Pharmacokinetic profile of HG043 in rats.

| Parameter | Dose | | | |
|---|---|---|---|---|
| | 10 mg/kg | 30 mg/kg | 60 mg/kg | 100 mg/kg |
| $AUC_{0-24\,h}$ (ng·h/mL) | 12,597 ± 6422 | 14,433 ± 5949 | 16,046 ± 4328 | 19,539 ± 3386 |
| $C_{max}$ (ng/mL) | 2535 ± 943 | 2528 ± 1343 | 2023 ± 827 | 1926 ± 389 |
| $t_{max}$ (h) | 1.6 ± 0.5 | 1.1 ± 0.5 | 2.1 ± 1.2 | 1.4 ± 0.5 |
| $t_{1/2}$ (h) | 3.1 ± 0.3 | 4.4 ± 0.7 | 6.5 ± 2.9 | 10.0 ± 2.2 |

Data represent mean ± SD (n = 5)

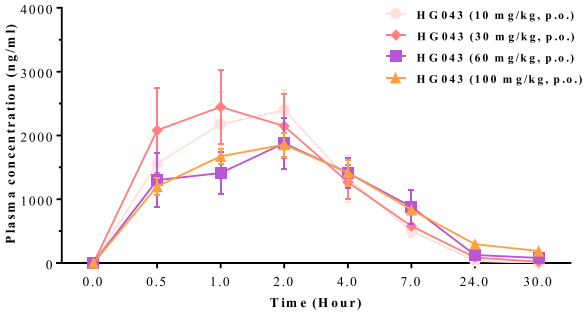



**Fig. 3.** Plasma concentrations of HG043 in normal SD rats after a single oral (p.o) administration. Data represent mean ± SD (n = 5).

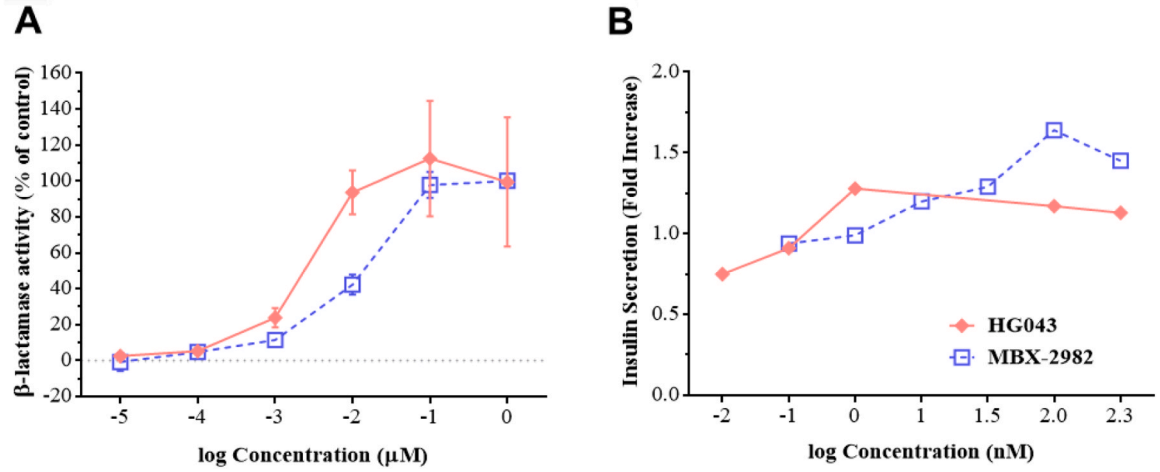



**Fig. 2.** *In vitro* GPR119 activation and stimulation of incretin secretion by HG043 and MBX-2982 treatment in the CRE-*bla* CHO-K1, and MIN6 cell lines. (A) β-Lactamase activity induced by HG043 and MBX-2982 in GPR119-expressing CRE-*bla* CHO-K1 cells (n = 2) (B) Insulin secretion from MIN6 mouse pancreatic β-cells stimulated by HG043 and MBX-2982 (n = 1). Data represent mean ± SD in β-lactamase activity.

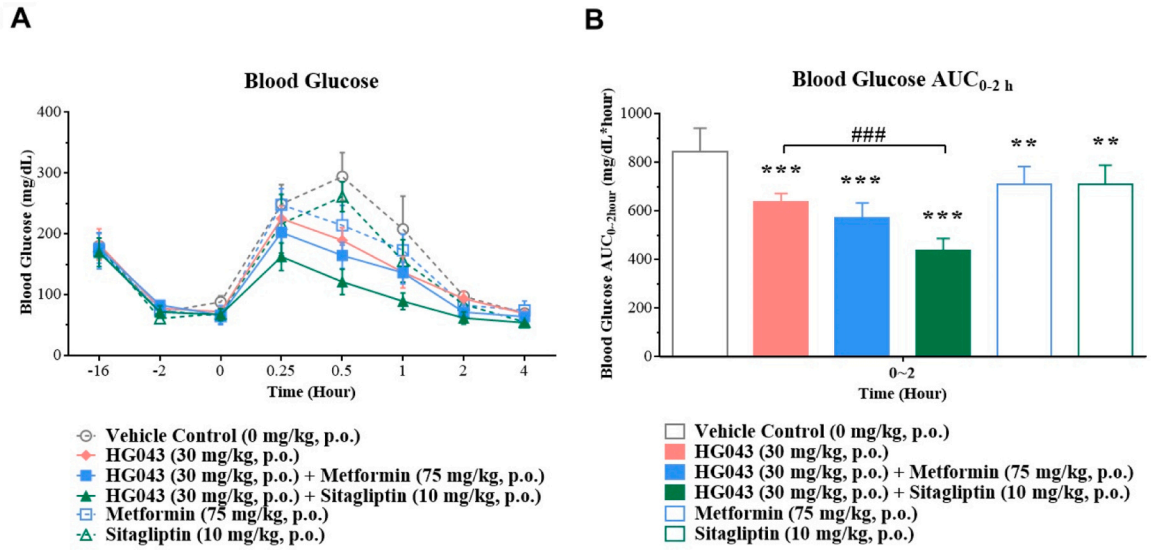



**Fig. 4.** Postprandial glycemic control effects of HG043 and its combinations in normal C57BL/6 mice. Mice received a single oral dose of HG043 (30 mg/kg), Metformin (75 mg/kg), Sitagliptin (10 mg/kg), or their combinations 2 h prior to an oral glucose challenge (2 g/kg). (A) Time-course changes in blood glucose levels during an oral glucose tolerance test (OGTT) in normal C57BL/6 mice. (B) $AUC_{0-2\,h}$ of blood glucose levels during the OGTT. Data represent mean ± SD (n = 7). One-way ANOVA test * $^{*}p < 0.01$ and * $^{**}p < 0.001$ *vs.* the vehicle control group; $^{\#\#\#}p < 0.001$ the HG043 group *vs.* the HG043/sitagliptin combination treated group.

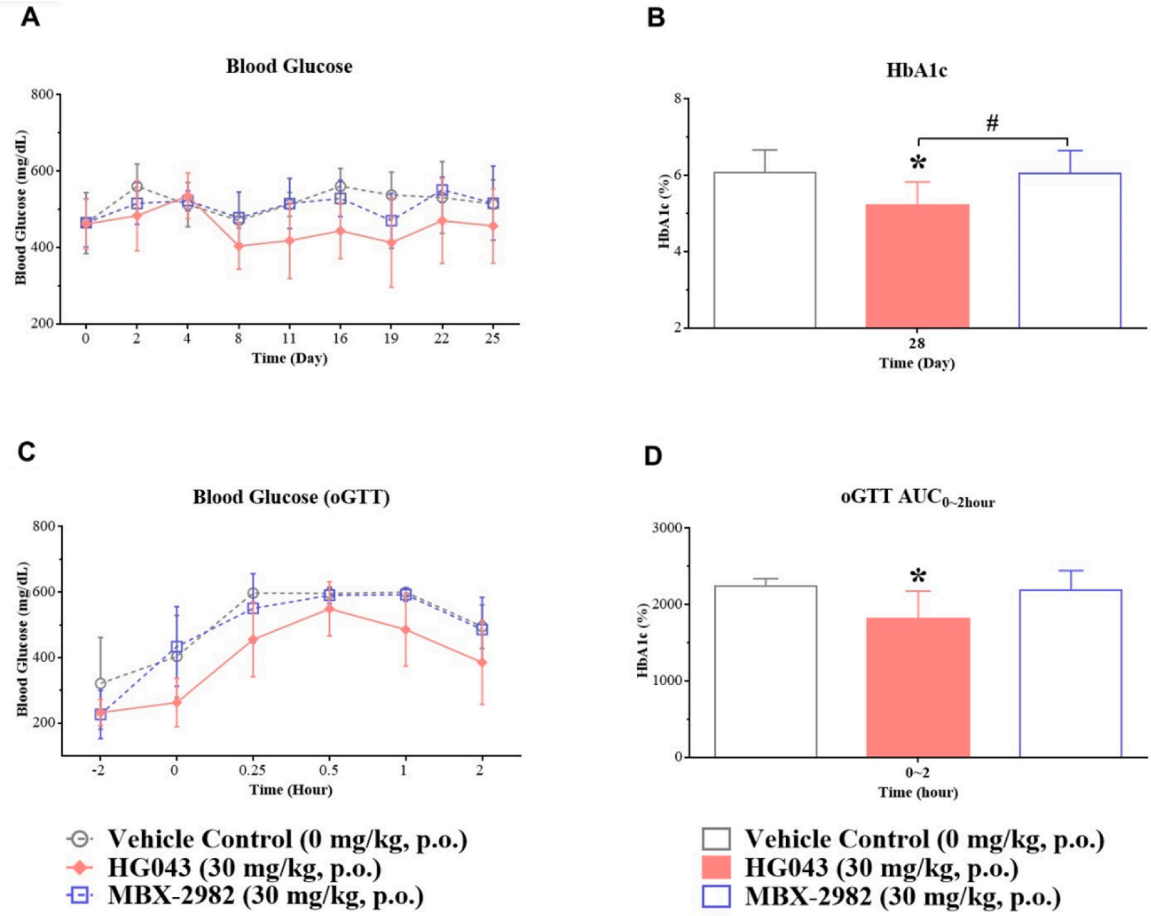



**Fig. 5.** Glycemic control effects of repeated HG043 administration in diabetic *db/db* mice. (A) Time course changes in blood glucose levels during the 4-week treatment period. (B) HbA1c levels on day 28. (C) Time course changes in blood glucose levels during an oral glucose tolerance test (OGTT) performed on day 28. (D) Area under the curve of blood glucose levels during the OGTT performed on day 28. Data represent mean ± SD (n = 7). One-way ANOVA test $^{*}p < 0.05$ and * $^{*}p < 0.01$ *vs.* the vehicle control group; $^{\#}p < 0.05$ *vs.* the MBX-2982 treated group.

glucose levels (Fig. 6A). Similarly, HbA1c levels were markedly ncreased in the ZDF control group, reflecting chronic hyperglycemia. HG043 administration significantly lowered HbA1c levels in treated rats, indicating improved long-term glycemic control (Fig. 6B). In addition, pancreatic histological analysis demonstrated a substantial reduction in β-cell mass in the ZDF control group, characterized by islet shrinkage and loss of cellular density. In contrast, HG043-treated rats exhibited preserved islet morphology and increased β-cell area. Quantitative analysis of immunostained pancreatic sections confirmed a significant increase in β-cell mass in HG043-treated groups compared to the diabetic control (Fig. 6C), suggesting that HG043 not only improves glycemic parameters but also protects against β-cell loss.

### 3.4. Anti-obesity effect of long-term HG043 treatment in diet-induced obese rats

The anti-obesity effects of HG043 were evaluated in a diet-induced obesity (DIO) rat model. Daily oral administration of HG043 (30 mg/kg) for 24 days significantly reduced body weight gain compared to the vehicle-treated group. The anti-obesity effects of HG043 were evaluated in a diet-induced obesity (DIO) rat model. Daily oral administration of HG043 (30 mg/kg) for 24 days significantly reduced body weight gain, demonstrating efficacy comparable to Sibutramine, a selective serotonin and norepinephrine reuptake inhibitor [26], when compared to the vehicle-treated group. (Fig. 7A-B). The anti-obesity effects of HG043 were evaluated in a diet-induced obesity (DIO) rat model. Daily oral administration of HG043 (30 mg/kg) for 24 days significantly reduced body weight gain compared to the vehicle-treated group. In contrast, Sibutramine treatment did not significantly affect adipose tissue mass. (Fig. 7C-D) [33].

### 3.5. Single administration of HG043 stimulates incretin secretion in normal rats

A single oral administration of HG043 (30 mg/kg) significantly increased plasma levels of active GLP-1 15 minutes after an oral glucose challenge (2 g/kg) in normal SD rats compared to both vehicle and MBX-2982 (30 mg/kg)-treated groups (Fig. 8A). Furthermore, HG043 (30 mg/kg) significantly increased plasma insulin levels at 5 min post-glucose challenge compared to the vehicle group (Fig. 8B). Plasma levels of gastric inhibitory polypeptide (GIP) and peptide YY (PYY) were also significantly elevated in the HG043-treated group compared to the vehicle group at 3 and 5 min after glucose challenge, respectively (Fig. 8C-D).

### 3.6. HG043 stimulates secretion of GLP-1 in normal SD rats

To further investigate the mechanism underlying HG043-mediated GLP-1 secretion, direct intestinal injections were performed in normal SD rats. Direct injection of HG043 into both the duodenum and the ileum significantly increased plasma levels of active GLP-1 compared to vehicle injection (Fig. 9). Furthermore, direct injection of HG043 into the ileum resulted in a significantly greater increase in plasma GLP-1 levels compared to injection into the duodenum, similar to the mechanism of action observed with ZeinH, a potent GLP-1 stimulator.

### 3.7. Suppression of gastric emptying by HG043 in normal SD rats

In the gastrointestinal motility study, the traveled charcoal path in the HG043-treated group was significantly shorter than that in the vehicle group (Fig. 10). These data demonstrate that the administration of HG043 stimulates GLP-1 secretion and its subsequent physiological functions.

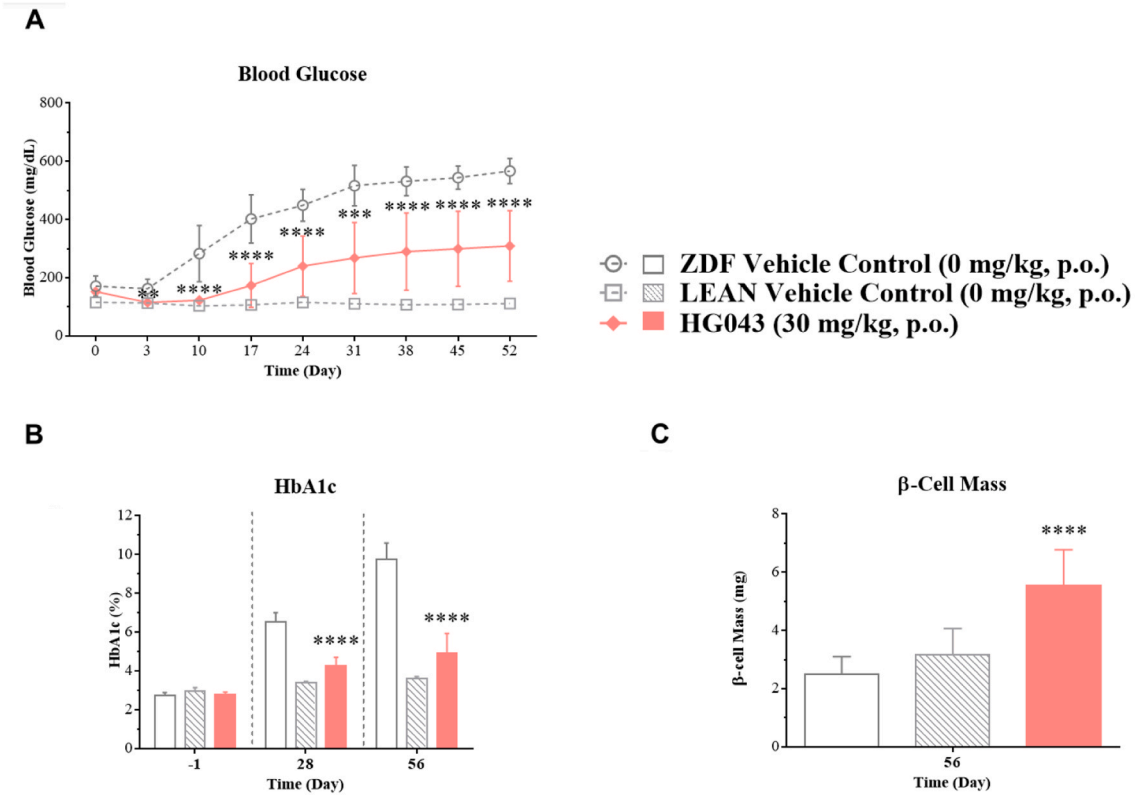



**Fig. 6.** Effects of HG043 on long-term glycemic control and β-cell protection in ZDF rats. Rats received a daily single oral dose of HG043 (30 mg/kg) for 7-week. (A) Time course of blood glucose levels during the treatment period. (B) HbA1c levels on pre, day 28 and 56. (C) β-cell mass on day 56. Data represent mean ± SD (n = 10). t-Test * $^{*}p < 0.01$, * $^{**}p < 0.001$, and * $^{***}$ $^{*}p < 0.0001$ *vs.* the ZDF vehicle control group.

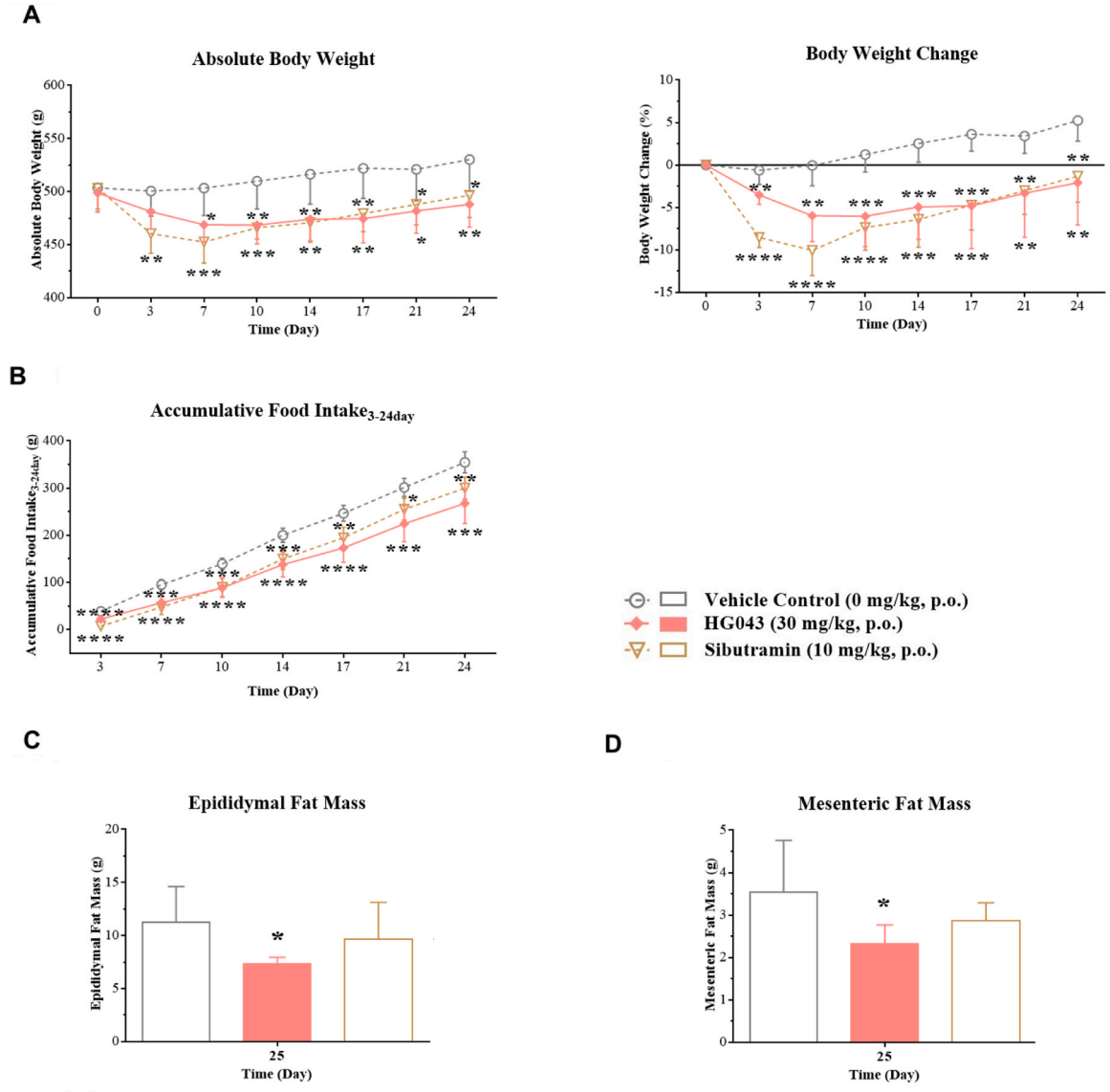



**Fig. 7.** Effects of repeated administration of HG043 on body weight and fat mass in DIO rats. HG043 and sibutramine were orally administered daily for 24 days. (A) Body weight changes and absolute body weight and (B) Cumulative food intake for 24 days. (C) Epididymal and (D) mesenteric fat mass measured on day 24. Data represent mean ± SD (n =7). One-way ANOVA test*$p < 0.05$, * *$p < 0.01$, * **$p < 0.001$, and * *** *$p < 0.0001$ *vs.* the vehicle control group.

## 4. Discussion

In this study, we characterized HG043, a novel GPR119 agonist, and demonstrated its anti-diabetic and anti-obesity effects. HG043 potently activated GPR119 *in vitro*, as shown by cAMP production in GPR119 CRE-bla CHO-K1 cells. Furthermore, HG043 effectively stimulated insulin secretion from MIN6 cells, supporting its role in enhancing GSIS. Following oral administration to SD rats, HG043 exhibited rapid absorption (tmax $\leq$ 1.1–2.1 h) and a moderate-to-long elimination half-life (3.1–10.0 h). In normal C57BL/6 mice, a single dose of HG043 significantly improved postprandial glucose control in an oral glucose tolerance test. Moreover, the combination of HG043 with sitagliptin, a DPP-IV inhibitor, exhibited a synergistic effect on glycemic control compared to monotherapy with either agent. In diabetic db/db mice and ZDF rats, chronic treatment with HG043 significantly improved glycemic control, as evidenced by reductions in blood glucose levels, HbA1c, and postprandial glucose excursions (mice), as well as the prevention of β-cell loss (rats). In contrast, MBX-2982, another GPR119 agonist, did not improve glycemic control in these mice. Notably, HG043 demonstrated significant anti-obesity effects in diet-induced obese (DIO) rats, reducing body weight, food intake, and adipose tissue mass. The effects observed with HG043 were comparable to those of sibutramine; however, HG043 appeared to have a potentially improved satiety profile. Notably, the HG043 treatment group demonstrated a greater reduction in food intake as well as in epididymal and mesenteric fat mass compared to the sibutramine group. The weight loss observed in the HG043 group was primarily due to fat reduction, resulting from decreased food intake [34]. A study on incretin secretion revealed that HG043 stimulates the *in vivo* secretion of multiple incretins, including GLP-1, GIP, and PYY. Plasma levels of GLP-1, insulin, and GIP were significantly higher in the HG043-treatment group compared to the vehicle-treated group. The major metabolic actions of these incretins involve the uptake of glucose from the bloodstream into the liver and muscles to maintain blood glucose homeostasis under postprandial or normal conditions [35,36]. In addition, PYY secretion was significantly increased in the HG043-treated group compared to the vehicle-treated group. Both GLP-1 and PYY play crucial roles in appetite regulation and weight maintenance by inhibiting gastrointestinal motility and directly acting on appetite-regulation centers in the brain [37,38]. The reduction of food intake observed in the HG043-treated group was likely attributable

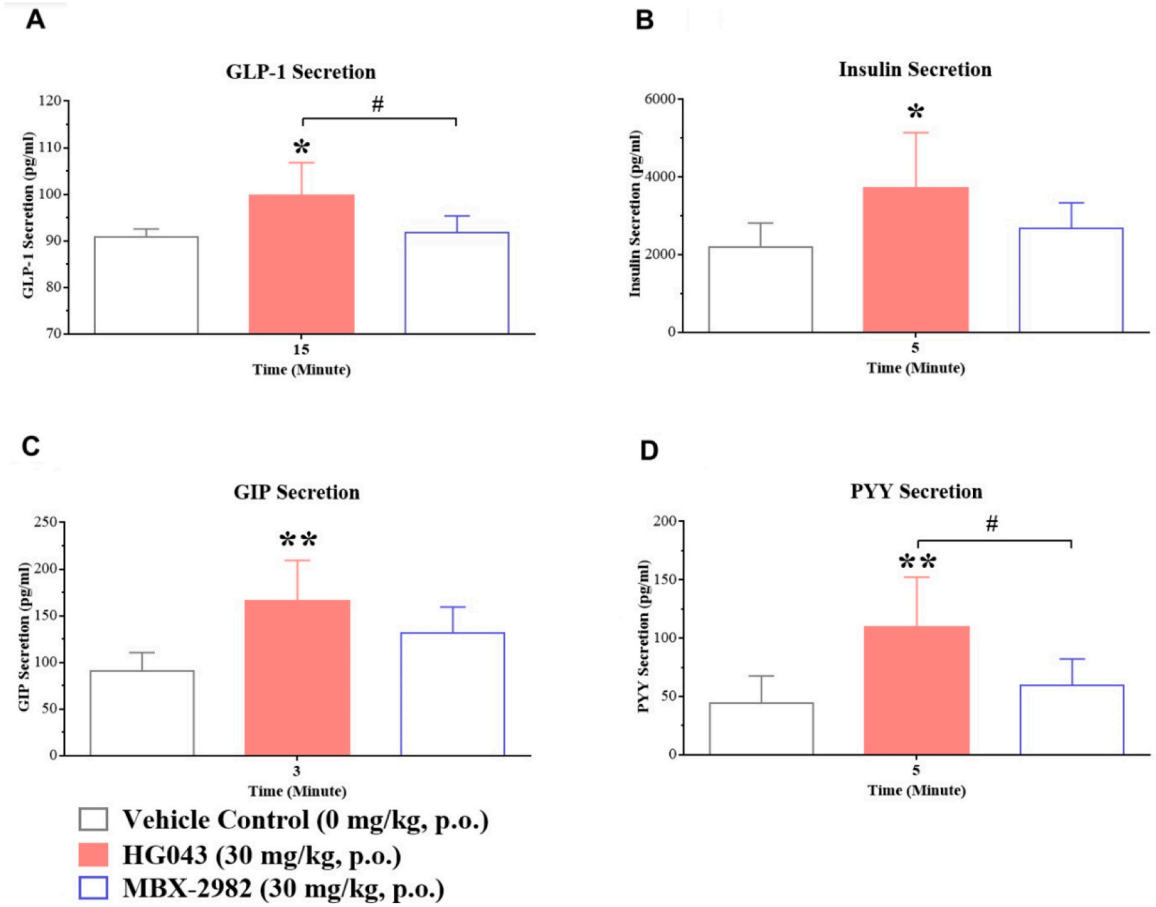



**Fig. 8.** Effects of HG043 on incretin secretion in normal SD rats. Plasma levels of active GLP-1 (A), insulin (B), GIP (C), and PYY (D) were measured in normal SD rats after a single oral administration of HG043 (30 mg/kg), MBX-2982 (30 mg/kg), or vehicle followed by an oral glucose challenge (2 g/kg) at 2 hours post-dosing. Blood samples were collected at15 (GLP-1), 5 (insulin), 3 (GIP), and 5 (PYY) minutes post-glucose challenge, respectively. Data represent mean ± SD (n = 6). One-way ANOVA test $^{*}p < 0.05$ and $^{**}p < 0.01$ *vs.* the vehicle control group; $^{\#}p < 0.05$ *vs.* the MBX-2982 treated group.

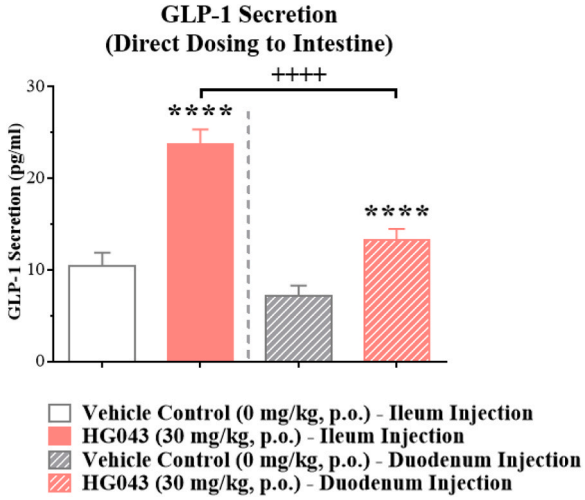



**Fig. 9.** Stimulatory effect of a single direct intestinal injection of HG043 on active GLP-1 secretion in normal SD rats. Active GLP-1 levels were measured 1 hour after direct intestinal administration of HG043. Data are expressed as the mean ± SD (n = 3). *t*-Test $^{**}p < 0.001$ HG043 *vs.* vehicle injection to each the ileum or duodenum; $^{++++}p < 0.0001$ HG043 injection to the ileum *vs.* HG043 injection to the duodenum.

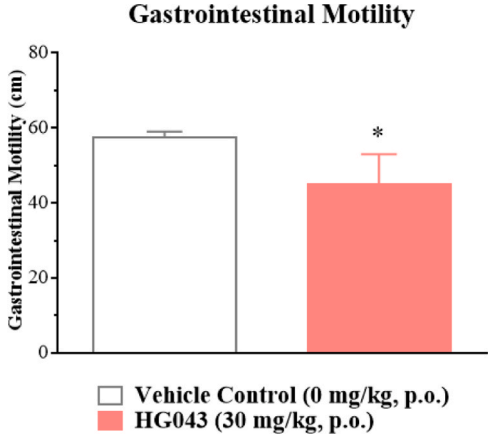



**Fig. 10.** Gastrointestinal motility inhibition effect of a single dose of HG043 in normal SD rats. The percentage of the traveled charcoal distance past the pyloric sphincter after a single oral administration of HG043. Data are expressed as the mean ± SD (n = 3). t-Test $^{*}p < 0.05$ *vs.* the vehicle control group.

to the stimulation of GLP-1 and PYY. Indeed, gastrointestinal motility in the HG043-treated group was significantly slower than in the vehicle-treated group of normal SD rats. Glucose and fatty acids are potent stimulators of GLP-1 release from enteroendocrine L cells in the distal intestine following food ingestion [39]. L-cell density shows a moderate increase along the ileum and is significantly higher in the most

caudal compared to the proximal part of the small intestine [40]. Direct intestinal injection of HG043, particularly into the ileum, significantly increased plasma GLP-1 levels, suggesting that HG043 may directly stimulate GLP-1 secretion from L cells.

HG043 represents a promising class of oral antidiabetic agents that could potentially overcome several limitations associated with subcutaneous GLP-1 analogs. The clinical use of these analogs is often restricted due to the need for injectable administration and associated patient compliance issues [41]. In contrast, oral GPR119 agonists like HG043 offer potential advantages such as improved patient adherence and convenience of administration. Unlike subcutaneous injections, oral formulations eliminate injection-associated discomfort, needle phobia, and skin reactions, which could significantly improve patient acceptability and compliance, especially for long-term disease management. Moreover, HG043 enhances endogenous GLP-1 secretion, providing a more physiological incretin effect compared to the pharmacologically supra-physiological stimulation seen with injectable GLP-1 analogs. This mechanism is potentially associated with fewer gastrointestinal side effects, such as nausea, vomiting, and diarrhea, which are commonly reported with subcutaneous GLP-1 analogs [42,43].

In summary, our study demonstrates the potential of HG043, a novel GPR119 agonist, to effectively manage both diabetes and obesity. HG043 stimulated insulin secretion, improved glucose control in both normal and diabetic mice, and showed synergistic effects when combined with a dipeptidyl peptidase-4 (DPP-4) inhibitor. In preclinical models, HG043 reduced body weight, food intake, and adipose tissue mass, with effects comparable to sibutramine but with a potentially better satiety profile. These beneficial outcomes were attributed to the stimulation of multiple incretins, which subsequently improved glucose homeostasis and reduced appetite. Based on these findings, HG043 holds promise as a new therapeutic agent for the treatment of type 2 diabetes and obesity. Following this study, we plan to conduct a comprehensive evaluation of both efficacy and toxicity, considering sex-specific differences by analyzing male and female subjects separately. The results of these assessments will provide critical supporting data for the design and implementation of future clinical trials, contributing to a more tailored and evidence-based approach in the development of this investigational drug.

## CRediT authorship contribution statement

**Kim Heecheol:** Methodology, Investigation. **Choi Inyoung:** Resources, Methodology. **Lee Sanghyun:** Resources, Methodology. **MIN KYUNG HOON:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization. **Lee Sangdon:** Writing – original draft, Methodology, Investigation, Data curation, Conceptualization.

## Funding

This study was supported by Hanmi Pharm. Co. and the National Research Foundation of Korea (NRF-2022R1A2C2010824.)

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Data availability

Data will be made available on request.

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