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Animal Models

Vutiglabridin overcomes the GLP-1 RA-associated weight-loss plateau to achieve normal body weight

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BACKGROUND/OBJECTIVES: Although glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are highly effective for body weight reduction, there remains a critical unmet need for complementary strategies that drive selective fat loss and sustain long-term weight reduction. This study aimed to investigate whether Vutiglabridin, a novel oral small-molecule anti-obesity drug, complements GLP-1 RAs to enhance therapeutic efficacy by selectively reducing fat mass and achieving normal body composition.
SUBJECTS/METHODS: 6-week-old mice were fed a high-fat diet (60 kcal% fat) for 11 weeks to generate mice with diet-induced obesity (DIO) and then treated with GLP-1 RAs (Semaglutide, Liraglutide, or Exenatide) either alone or in combination with Vutiglabridin for 3–4 weeks.
INTERVENTIONS/METHODS: Body weight, food intake, fat mass, and lean mass were evaluated during treatment. For the drug discontinuation study, mice were administered Vutiglabridin, Semaglutide, or the combination for 4 weeks, after which treatment was withdrawn on Day 28 and body weight regain was monitored for 21 days.
RESULTS: In DIO mice treated with Semaglutide, weight loss attenuated, and body weight was maintained at a constant level after 2 weeks. In contrast, co-administration of Vutiglabridin overcame this attenuation of efficacy, enabling continuous weight reduction and achieving normal body composition. Vutiglabridin also resolved the diminishing weight-loss effect when combined with comparatively less potent appetite-suppressing GLP-1 RAs, including liraglutide and exenatide. In addition to normalizing body composition, Vutiglabridin mitigated the body weight and fat-mass regain that occurs following Semaglutide discontinuation.
CONCLUSIONS: These findings demonstrate that Vutiglabridin can normalize body composition in combination with multiple GLP-1 RAs, highlighting its potential as a novel therapeutic option for obesity treatment.

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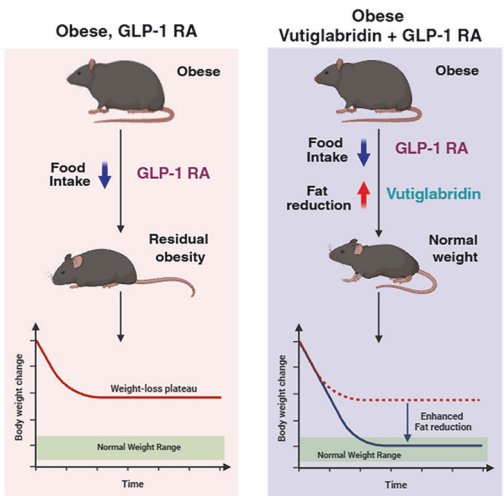
Graphical Abstract



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INTRODUCTION

Obesity is a multifactorial disease with diverse causes. However, most anti-obesity medications primarily rely on appetite suppression as their mechanism of action. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs), such as semaglutide, show robust weight loss efficacy in clinical practice. Tirzepatide, a dual glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptor agonist, further expands the therapeutic potential of incretin-based approaches [1–3]. Their proven efficacy has driven the development of novel obesity pharmacotherapies targeting GLP-1 receptor activity [4–6]. However, even more potent GLP-1 RAs have limitations, including gastrointestinal adverse events and loss of lean mass [7].

Real-world evidence suggests that early-onset side effects are common; they account for <10% of therapy discontinuations within the first 3 months [8]. However, long-term adherence remains limited, with discontinuation rates increasing after 6 months, exceeding 70% of patients within the first year [9]. Notably, most patients discontinuing treatment after 6 months are those whose initial robust weight loss has transitioned into a maintenance phase, where further reduction is no longer achieved [2, 9]. Following discontinuation, a considerable proportion of these patients subsequently regain body weight and fat mass, often returning to their baseline levels within 1–2 years [10]. Furthermore, ~40% of patients who discontinued eventually reinitiate treatment [9]. This cycle of weight loss and regain can further exacerbate obesity. In this study, we define the 'weight-loss plateau' as the stage at which the efficacy of further body weight and fat reduction attenuates despite continued therapy [11, 12], and we emphasize the clinical need for novel approaches capable of complementing GLP-1 RAs to achieve normal body composition [10, 13].

Obesity arises from an imbalance between energy intake and energy expenditure, and the weight-loss plateau similarly reflects disruption in this balance [14, 15]. In particular, this is driven by three primary mechanisms: (i) appetite feedback gain, (ii) energy-expenditure (EE) adaptations and (iii) energy density of weight change. First, appetite feedback increases after weight loss, driven by coordinated neuroendocrine adaptations, receptor-level changes, and recalibration of the brain's reward circuitry [16–20]. Second, reductions in lean mass and neuroendocrine signals lower metabolic rate and overall EE [20]. Lastly, the energy density of weight change is determined by the amount of energy expended through the fat reduction, which provides more energy (9 kcal/g) than glycogen or protein (4 kcal/g), a sustained fat loss is therefore required to sustain metabolic expenditure [21, 22]. When this contribution declines, metabolic rate stabilizes at a lower steady state [23]. Together, these mechanisms indicate that therapeutic approaches that suppress the appetite feedback prevent the decline in energy expenditure and ultimately sustain fat reduction may help to overcome the weight-loss plateau.

Vutiglabridin is a novel anti-obesity drug that promotes fat-selective weight loss, as shown in DIO mice [24]. The condition of obesity directs reduced PON2 activity and mechanistically, Vutiglabridin restores paraoxonase 2 (PON2) activity in the adipose tissue, activating AMPK-mediated lipophagy and lipid degradation. Additionally, this is accompanied by an increase in whole-body EE, suggesting that the fatty acids are preferentially utilized as metabolic fuel rather than stored ectopically or released to blood to induce hyperlipidemia conditions. However, compared with appetite-suppressing drugs, Vutiglabridin produces a slower onset and a smaller magnitude of weight loss [24, 25]. Furthermore, as it does not directly suppress appetite, its efficacy as monotherapy may be limited in obesity driven by hedonic overconsumption [26].

Nevertheless, Vutiglabridin's fat-reducing mechanism complements GLP-1 RA-mediated appetite suppression, enhancing adiposity reduction and overcoming weight-loss plateaus. In this study, combination therapy with semaglutide, liraglutide, and exenatide normalized body composition and attenuated post-discontinuation weight regain. highlighting plateau resolution as key to achieving normal fat mass.

MATERIALS AND METHODS

Test compounds and administration

Vutiglabridin and Vutiglabridin-d11 were prepared by Glaceum Inc. (Suwon, Republic of Korea) according to the protocol in patent US9783551B2. At the time of administration, the doses were calculated in mg/kg based on the daily animal body weight. Vutiglabridin doses of 30 and 50 mg/kg/day were selected based on previous studies demonstrating dose-dependent anti-obesity effects in DIO mice [24, 25].

Semaglutide (Novo Nordisk A/S, Denmark) dose was calculated in nmol/kg based on daily body weight and administrated subcutaneously using an insulin syringe at a final volume of 5 mL/kg. For dose justification, Semaglutide exhibited dose-dependent anti-obesity effects at doses ranging from 0.3 to 30 nmol/kg, and the maximum effective dose of 30 nmol/kg/day was selected from prior DIO mice studies [27]. In the study administering Semaglutide at 30 nmol/kg/day ($n = 11$ for Vehicle group; $n = 10$ for Semaglutide group), dose escalation was performed as follows: Day 0, 0.3 nmol/kg/day; Days 1–2, 1.0 nmol/kg/day; Days 3–5, 10.0 nmol/kg/day; Days 6–28, 30.0 nmol/kg/day. In the study administering Semaglutide at 3 nmol/kg/day ($n = 8$ per group)., dose escalation was performed as follows: Day 0, 0.3 nmol/kg/day; Day 1–8, 1.0 nmol/kg/day; Day 9–19, 1.5 nmol/kg/day; Day 20–21, 1.7 nmol/kg/day; Day 22–25, 2.0 nmol/kg/day; Day 26–28, 3.0 nmol/kg/day.

Exenatide (PT302) was provided by Peptron Inc. (Daejeon, Republic of Korea). was dosed similarly, administrated subcutaneously at 1 mg/kg/week using a 1 cc syringe with the final volume of 4 mL/kg. The 1 mg/kg/day dose was selected based on the previous study of exenatide in mice ($n = 8$ per group) [28].

Liraglutide (Saxenda, MP5E414, Novo Nordisk) was dosed similarly, administered via subcutaneous injection using an insulin syringe (No.328820, USA, BD), with the final administrated volume of 5 mL/kg at weekly intervals. The 0.3 mg/kg/day was selected based on prior studies in DIO mice ($n = 6$ per group) [29].

Animal model

For the diet-induced obesity mouse efficacy study, male C57BL/6J mice (6 weeks old) were purchased from Jackson Laboratory (Bar Harbor, ME, USA). Mice were fed a high-fat diet (60% kcal fat; D12492, Research Diets) or a normal diet (10% kcal fat; PicoLab5053, LabDiet). At 17 weeks, mice were acclimatized for 1 week, then underwent 1 week of cage adaptation and 2 weeks of drug administration adaptation. Mice were housed at 22 ± 2 °C, 50 ± 10% humidity, 12-h light/dark cycle (dark: 7 PM–7 AM) in individually ventilated cages (IVC Rack, 13 × 34 × 14 cm, UREATAC, Korea). Groups were stratified by body weight and fat mass. At study end, mice fasted 14–16 h and were sacrificed under isoflurane anesthesia. The normal body weight reference used 6-week-old chow-fed mice over 4 weeks, which were age matched to the DIO mice (mean ± SD, Fig. S1). All procedures at Lee Gil Ya Cancer and Diabetes Institute (Gachon University) were approved by Institutional Animal Care and Use Committee (LCDI-2021-0010, -0042, -0108; LCDI-2023-0047). Animals were assigned to treatment groups in a manner intended to minimize baseline differences; formal randomization or blinding was not performed.

Body weight, organ/tissue weight and food intake assessment

Body weight (measured with an FX-2000i precision balance, A&D, 0.01–2200 g) and food intake (measured with a CSG201F balance, OHAUS, 0.1–200 g) were recorded daily from the start of drug administration. Daily dietary intake (in g) was calculated as the difference between food supplied and food remaining for each animal. After 16 h of fasting, animals were anesthetized with inhalational gas, and organs and tissues were collected and weighed.

Whole body fat mass and lean body mass measurements

Whole-body fat and lean mass were measured on Day 0 (baseline), the last day of drug administration, and the last day of the discontinuation period. Mice were placed in an NMR analyzer (Mini-spec, IF-90II, Bruker Optics GmbH; Billerica, MA, USA) without anesthesia for 5 min per scan.

Statistical analysis

Statistical analyzes were conducted using GraphPad Prism 9.5.1 (GraphPad Software Inc., San Diego, CA, USA). Data were analyzed by Ordinary one-way ANOVA followed by Tukey's test as appropriate. The p value of <0.05 was considered statistically significant.

RESULTS

Semaglutide reached weight-loss plateau before achieving normal body weight

DIO mice received semaglutide at its maximal efficacious dose (30 nmol/kg) for 3 weeks using dose escalation: Day 0 (0.3 nmol/kg/day); Days 1–2 (1.0 nmol/kg/day); Days 3–5 (10.0 nmol/kg/day); Days 6–28 (30.0 nmol/kg/day) [27]. At the end of the treatment period, the semaglutide group exhibited a −22.1% mean reduction in body weight compared with the Vehicle group (Fig. 1A). Although semaglutide induced rapid initial body weight loss post-treatment initiation, but efficacy progressively declined, stabilizing despite mice remaining in obesity condition. Body weight changes, analyzed in 3-day intervals throughout treatment, defined plateau as ~0 g change over 3 days while exceeding normal mouse body weight. (Figs. 1B and S1). Using this criterion, semaglutide reached weight-loss plateau by Day 12 despite maximal dosing, precluding further reduction. As semaglutide primarily acts via appetite suppression, food intake was monitored throughout. Cumulative intake was 33.9% lower versus vehicle control. (Fig. 1C). Daily intake analysis further showed that semaglutide markedly decreased food consumption during the early phase of treatment, followed by a partial recovery after approximately 10 days (Fig. 1D). Taken together, semaglutide produces rapid weight loss accompanied by strong early-phase reductions in food intake. However, its appetite-suppressing effects gradually wane, leading to a weight-loss plateau despite the mice remaining obese.

Vutiglabridin mitigates the weight-loss plateau under calorie-restriction conditions

To evaluate its anti-obesity efficacy, DIO mice were treated for 3 weeks with 50 mg/kg Vutiglabridin, a dose effective in a previous study [24]. At treatment end, the Vutiglabridin group showed −18.7% mean body weight reduction versus Vehicle (Fig. 2A). Although significant weight loss occurred by study end, minimal change was seen in the first 6 days, distinct from semaglutide's rapid onset (Figs. 1A and 2A). Three-day weight change intervals revealed steady, continuous reduction from Day 7 without plateau (Fig. 2B). Body composition analysis showed Vutiglabridin selectively reduced fat mass by 36.4% relative to Vehicle, with unchanged lean mass (Fig. 2C, D). This pattern aligned with food intake, showing no significant differences from Vehicle throughout (Fig. S2A, B).

To assess plateau under forced calorie restriction, unlike Semaglutide's appetite suppression in DIO mice received 1.7 g food/day (~60% of 3.0 g average intake) for 3 weeks (Fig. 2E). Daily and 3-day interval analyzes indicated rapid initial weight loss, then diminishing efficacy; by Day 18, no further change occurred, confirming plateau (Fig. 2E, F). In contrast, 50 mg/kg Vutiglabridin with food restriction yielded continuous loss without plateau. The combination group achieved 7.2% additional body weight reduction versus restriction alone (Fig. 2E, F). Overall, Vutiglabridin overcomes food restriction-induced plateau, enabling sustained weight reduction under calorie-restricted conditions.

Vutiglabridin overcomes the semaglutide-associated weight-loss plateau

Vutiglabridin overcomes the semaglutide-associated weight-loss plateau. DIO mice received semaglutide alone (30 nmol/kg) or combined with Vutiglabridin (50 mg/kg). Initial 4-day body-weight changes were comparable. From Day 5, trends diverged and the combination group showed synergy, reaching normal body-weight range by Day 9 (Fig. 3A). Three-day interval analysis confirmed semaglutide monotherapy plateaued after ~2 weeks, while combination avoided plateau (Fig. 3B). In addition to reaching a normal body-weight range without a plateau, Body composition analysis revealed that the combination treatment markedly reduced fat mass than either vehicle or semaglutide monotherapy, while lean mass remained unchanged in all groups (Fig. 3C, D). Further analysis of regional fat depots, including epididymal and retroperitoneal fat, showed significantly reduced fat weights in the combination group (Fig. 3E, F). In addition, liver weight decreased, consistent with our previous findings (Fig. 3G) [30]. Semaglutide alone markedly suppressed daily food intake post-initiation, with significantly reduced cumulative intake over 3 weeks versus Vehicle. Despite greater body weight and fat mass reductions than semaglutide monotherapy, combination showed no reductions in daily or cumulative intake (Fig. 3H, I). Post-Day 9 normal-weight attainment, combination trended toward higher intake than semaglutide. Collectively, Vutiglabridin overcomes semaglutide-induced plateau, enabling additional fat-selective weight reduction without further food intake suppression.

Vutiglabridin overcomes the weight-loss plateau of low-potency GLP-1RAs

Vutiglabridin overcomes the weight-loss plateau of low-potency GLP-1RAs. DIO mice were treated with liraglutide (0.30 mg/kg) alone or combined with Vutiglabridin (50 mg/kg) for 3 weeks. Liraglutide monotherapy reduced body weight by 18.6% versus Vehicle; combination achieved 38.0% reduction (Fig. 4A). Three-day intervals showed liraglutide plateaued by Day 4, while combination continued loss to normal range by Day 9, with minimal further loss thereafter (Fig. 4B). Analysis of regional adipose depots, including epididymal and retroperitoneal fat, revealed significantly reduced fat mass in the combination group, consistent with previous findings (Fig. 4C, D). Liver weight was also decreased, in line with prior results (Fig. 4E). Liraglutide alone reduced cumulative intake 23.8% versus Vehicle; combination enhanced to 40.8% (Fig. 4F). Daily intake suppression by liraglutide waned after Day 6, but combination sustained it as approximately 10 days until normal weight, then normalized to Vehicle levels (Fig. 4G).

Vutiglabridin-mediated mitigation of the weight-loss plateau and its synergistic effects on body-weight reduction were also observed when combined with exenatide. Exenatide was administered using PT302, a long-acting formulation designed for once-weekly injection [28]. Notably, similar synergy occurred with exenatide (PT302 long-acting, 1 mg/kg weekly) plus Vutiglabridin (30 mg/kg) over 4 weeks. Exenatide alone yielded 12.5% weight reduction; combination reached 32.1%, normalizing by Week 3 (Fig. 5A). Exenatide showed minimal change; combination had negligible early change then continuous loss to Day 21 without plateau, slowing post-normalization (Fig. 5B). Fat mass dropped selectively while lean mass remained unchanged (Fig. 5C, D). A similar effect on the regional fat depots and liver weights also observed (Fig. 5E–G). Food-intake analyzes further supported these effects. Cumulative food intake decreased by 6.0% in the exenatide group relative to the vehicle group, whereas the combination group induced a greater food intake reduction of 16.9% (Fig. 5H). Combination sustained significant daily food intake reductions versus both groups (Fig. 5I).

Low-dose semaglutide (3 nmol/kg final, escalated as previous) alone gave 9.9% reduction after 4 weeks; combination with Vutiglabridin (30 mg/kg) achieved 27.1%, normalizing by Week 3 (Fig. 6A). Semaglutide monotherapy stayed near baseline while combination minimal early and then continuous loss Day 7–28 without plateau (Fig. 6B). Consistent with findings from the Exenatide combination, body-composition analysis demonstrated Fat mass reduced 62.6% and lean mass preserved (Fig. 6C, D). Food-intake analysis further revealed that semaglutide 3 nmol/kg

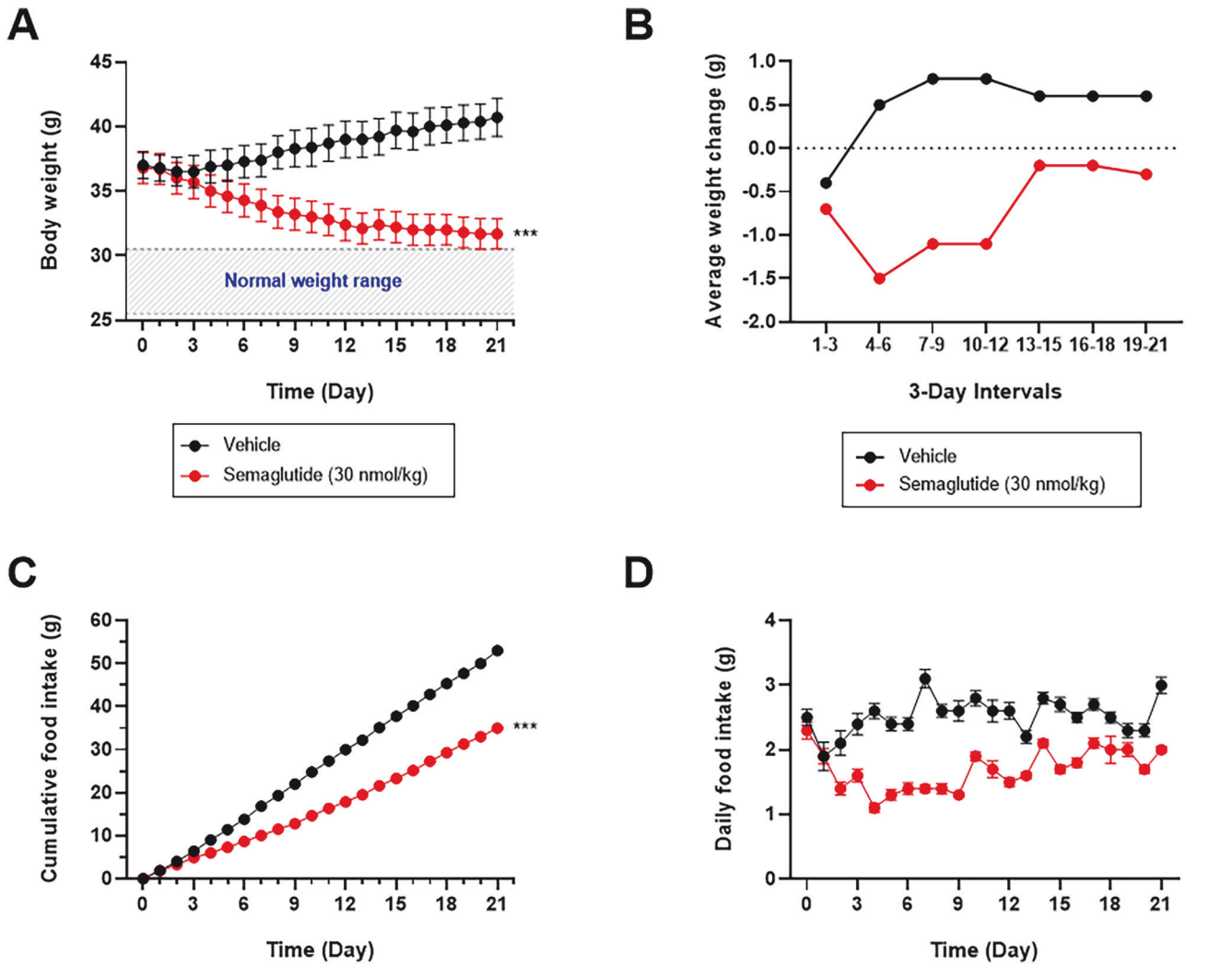
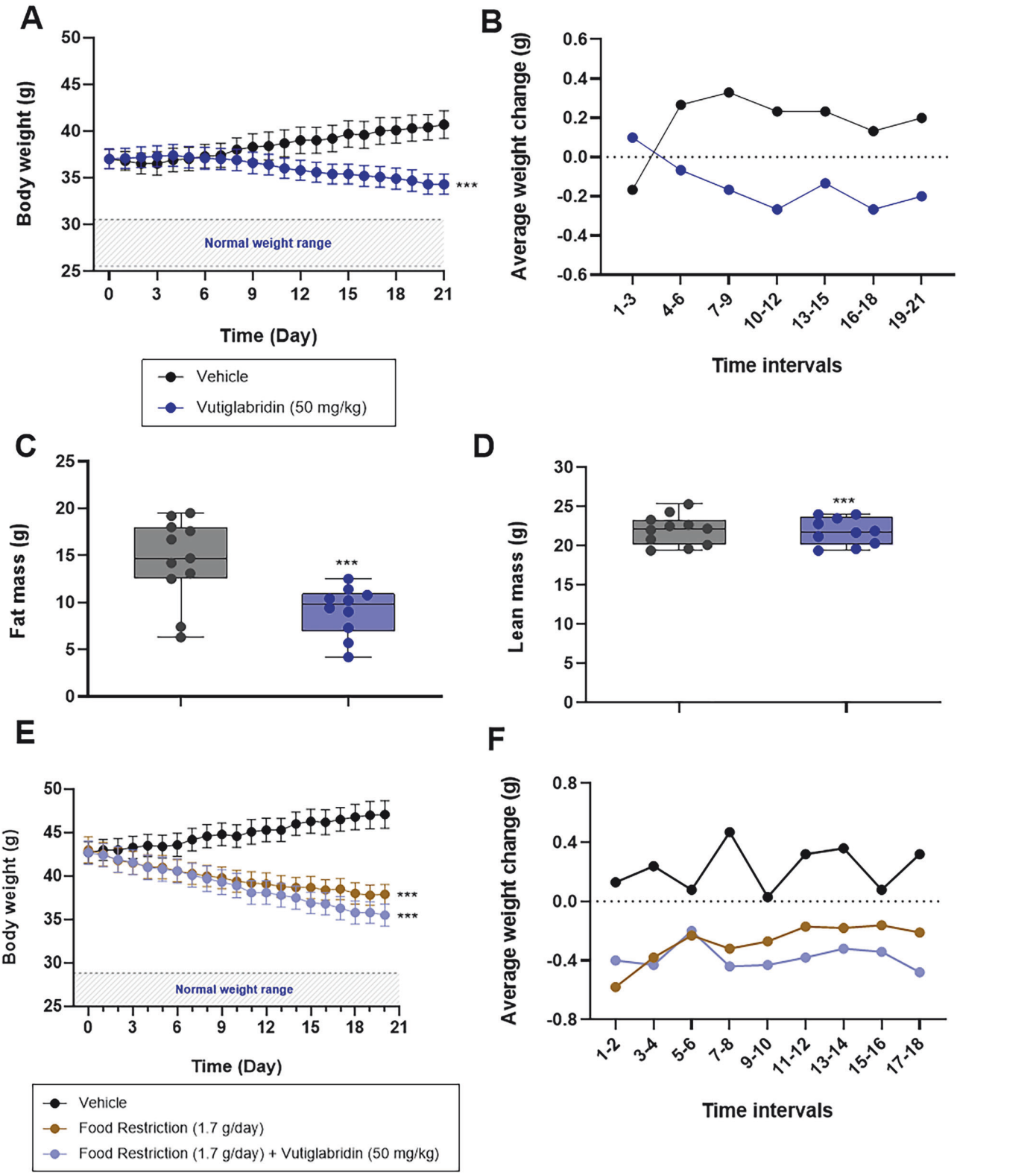


Fig. 1 The appetite-suppressing drug reached a weight-loss plateau before achieving normal body weight. Anti-obesity effect of semaglutide (30 nmol/kg) treatment in mice with diet-induced obesity (DIO). Mice were fed a high-fat diet for 11 weeks to induce obesity, followed by 21 days of semaglutide treatment ($n = 11$ for Vehicle group; $n = 10$ for semaglutide group). **A** Daily body weight change; **B** Average weight change (Δg) calculated over 3-day intervals throughout treatment; **C** Cumulative food intake; **D** Daily food intake change. Each data point represents mean ± SEM. *P*-value was calculated using Student's *t*-test for comparisons between Vehicle group and Semaglutide group: $^{*}P < 0.05$, $^{**}P < 0.01$ and $^{***}P < 0$.

decreased cumulative food intake by only 9.2% relative to Vehicle. In contrast, the combination group showed a 21.7% reduction (Fig. 6E). Daily intake patterns indicated that semaglutide 30 nmol/kg group resulted in little or no sustained appetite suppression throughout the 4-week period, whereas the combination group exhibited significantly reduced food intake across the same duration (Fig. 6F). Taken together, these results demonstrate that Vutiglabridin overcomes the weight-loss plateau not only of semaglutide but also of other low-potency GLP-1 RAs, including liraglutide and exenatide. Moreover, even at a lower dose (30 mg/kg), Vutiglabridin synergizes with multiple GLP-1 RAs to enhance fat-selective weight reduction and achieve the normal body-weight range.

Vutiglabridin attenuates body weight regain after semaglutide discontinuation

Another limitation of GLP-1 RAs, including semaglutide, is the occurrence of body weight regain after drug discontinuation[10]. In this study, We examined 9-day body-weight changes post-discontinuation of semaglutide (after 4-week dose escalation: 0.3–3.0 nmol/kg/day) or Vutiglabridin (30 mg/kg) in DIO mice. Semaglutide triggered marked regain (39.9 g to 43.6 g), while Vutiglabridin showed minimal gain (38.6 g to 39.2 g) (Fig. 7A). Daily food-intake analysis revealed a substantial rise in consumption in the semaglutide group during the discontinuation phase, whereas food intake in the Vutiglabridin group remained comparable to Vehicle levels (Fig. 7B). To further assessment, Vutiglabridin (30 mg/kg) and semaglutide (3 nmol/kg) were administered for 4 weeks before monitoring discontinuation responses for 21 days. When both drugs were discontinued, body weight increased sharply from 32.2 g at treatment end to 39.5 g by Day 21. However, when only semaglutide was discontinued while Vutiglabridin treatment was maintained, body weight initially increased but gradually declined after Day 8, resulting in a modest net increase from 32.2 g to 34.9 g (Fig. 7C, D). Daily food-intake patterns supported these findings: mice in the dual-discontinuation group exhibited a rapid and sustained increase in food intake throughout the 21-day period. Similarly, mice in the semaglutide-discontinuation/Vutiglabridin-continuation group also showed an acute elevation in food intake immediately after semaglutide discontinuation, followed by persistently elevated levels (Fig. 7E). Despite increased food intake post-semaglutide



discontinuation, continued Vutiglabridin attenuated fat accumulation, unlike dual discontinuation, which fully rebounded fat mass to baseline by Day 21. Lean mass remained unchanged across all groups. (Fig. 7F, G). Overall, these results suggest that Vutiglabridin mitigates body weight regain following semaglutide discontinuation by suppressing fat accumulation.

DISCUSSION

Appetite suppression via GLP-1 RAs remains the most effective and widely employed pharmacological strategy for obesity. Semaglutide, in particular, has demonstrated robust and clinically meaningful weight-loss efficacy across human trials by suppressing appetite through central mechanisms in the hypothalamus

Fig. 2 Vutiglabridin mitigates the weight loss plateau. Anti-obesity effect of Vutiglabridin (50 mg/kg) treatment in mice with diet induced obesity (DIO). Mice were fed a high-fat diet for 11 weeks to induce obesity, followed by 21 days of Vutiglabridin treatment ($n = 11$ for vehicle and Vutiglabridin group). **A** Daily body weight change; **B** Average weight change (Δg) calculated over 3-day intervals throughout treatment; **C** Fat mass change; **D** Lean mass change. Anti-obesity effect of food restriction and food restriction combined with Vutiglabridin (50 mg/kg) in DIO mice. Mice were fed a high-fat diet for 11 weeks to induce obesity, followed by 21 days of food restriction and Vutiglabridin treatment ($n = 6$ for food restriction and food restriction combined with Vutiglabridin group). In the food-restriction group, mice were provided only 1.7 g of food daily (compared with the average 3 g daily intake in DIO mice). **E** Daily body weight change; **F** Average weight change (Δg) calculated over 3-day intervals throughout treatment. Each data point represents mean ± SEM. *P*-value was calculated using Student's *t*-test comparing Vutiglabridin, food restriction, and food restriction combined with Vutiglabridin to the vehicle group: $^{*}P < 0.05$, $^{**}P < 0.01$ and $^{***}P < 0.001$.

and brainstem [2, 18, 31–33]. Following semaglutide, numerous anti-obesity drugs have been developed to improve the pharmacological properties of GLP-1 RAs, such as prolonging appetite suppression, increasing potency, or mitigating adverse effects, including gastrointestinal symptoms and lean mass loss [34, 35]. In this context, our study provides the first in vivo evidence that overcoming the GLP-1 RA-associated weight-loss plateau may represent a new strategy for more complete obesity resolution. In DIO mice, Vutiglabridin co-administration eliminated GLP-1 RA weight-loss plateaus, synergistically enhancing anti-obesity efficacy and enabling normal body composition beyond appetite suppression limits alone.

In addition to GLP-1, other hormone targets are being explored to enhance appetite suppression, including amylin analogs such as cagrilintide and melanocortin-4 receptor agonists [35, 36]. Simultaneously, therapies designed to increase EE are under development, featuring glucagon receptor agonists and multi-receptor agonists that target GIP and glucagon receptors [5, 37]. Among these diverse hormone-based therapies, tirzepatide, a dual GLP-1 and GIP receptor agonist with activity biased towards GIP, has demonstrated superior weight-loss efficacy across multiple clinical trials [38]. Oral GLP-1 RAs have been introduced to improve convenience, although their weight-loss efficacy is generally lower and gastrointestinal adverse effects tend to be more pronounced than with injectable formulations [39, 40]. Despite their diversity and potential synergy with GLP-1 RAs, these therapies commonly encounter weight-loss plateaus that limit further reduction before normal body composition is achieved [3, 38, 41].

Another approach to obesity treatment involves increasing energy expenditure to modulate the underlying energy imbalance [14, 15]. β3-adrenergic agonists enhance thermogenesis by activating Uncoupling Protein 1 (UCP1) in brown adipose tissue, which stimulates PKA-mediated lipolysis and increases energy expenditure [42]. Thyroid hormone receptor agonists mimic endogenous T3 signaling, promoting mitochondrial biogenesis across multiple tissues and raising basal metabolic rate to increase systemic energy consumption [43]. Additional strategies include promoting muscle growth through myostatin and activin blockade [34] as well as enhancing adipocyte lipolysis to induce fat reduction with drugs such as Vutiglabridin [24]. Although these therapies offer distinct mechanisms, their clinical translation remains limited by safety concerns, poor translatability, and inadequate weight-loss efficacy as monotherapies.

Although GLP-1 RAs are highly effective for weight loss, their efficacy often plateaus during continued treatment, with no further loss and sometimes weight regain [2]. This plateau likely reflects metabolic adaptation to sustained appetite suppression. Vutiglabridin, through its direct fat-reducing mechanism, helps overcome this limitation and supports sustained weight loss until normal body weight is reached.

In this study, we evaluated Vutiglabridin's synergy with GLP-1 RAs in DIO mice. GLP-1 RAs induce initial rapid weight loss via appetite suppression but plateau after sustained administration. Vutiglabridin overcomes this plateau across GLP-1 RAs, including liraglutide and exenatide, which plateau earlier despite higher doses, and enabling normal body composition. Pair feeding experiments indicate Vutiglabridin exerts an additional effect beyond food intake suppression, consistent with its distinct metabolic action on fat mass. The fat-selective mechanism driven by PON2 activation, AMPK signaling and lipophagy in adipose tissue complements GLP-1 RAs, representing a novel strategy for complete obesity resolution [24].

In prior work, Vutiglabridin increased energy expenditure in DIO mice, while adipose AMPK/PON2 signaling enhanced lipophagy and reduced adipogenesis [24]. Importantly, the previous results also showed increased VO_2 and VCO_2, indicating that the fatty acid released by Vutiglabridin driven fat loss are likely utilized as metabolic fuel [24].

The present study also suggests that the complementary action between Vutiglabridin and GLP-1RAs depends on the potency and dose of the GLP-1RA used. At higher, maximally efficacious semaglutide doses, food intake suppression appears to approach a physiological lower limit of approximately 1 g/day, beyond which additional anorectic effect is minimal [27]. Under these conditions, Vutiglabridin mainly contributed to further fat-mass reduction rather than additional food intake suppression. In contrast, with lower-dose semaglutide or lower-potency GLP-1RAs such as liraglutide and exenatide, Vutiglabridin further reduced food intake beyond the effect of GLP-1RA alone, consistent with an obesity-dependent secondary metabolic effect. This effect is not interpreted as direct central satiety center action, but rather as a secondary response to sustained fat reduction, potentially involving improved leptin sensitivity in the setting of leptin resistance [24].

Another limitation of GLP-1 RAs is that discontinuation commonly leads to substantial body weight regain, and many patients who regain weight subsequently restart GLP-1 RA therapy, resulting in a recurrent cycle of body weight loss and gain [10]. In our DIO mouse study, semaglutide discontinuation caused rapid increases in food intake and marked weight regain. In contrast, continued Vutiglabridin attenuated post-withdrawal rebound and suppressed the associated fat regain, consistent with its fat-reducing mechanism and obesity-dependent metabolic effects (Fig. 7A, B). A similar pattern was observed in the combination-treatment study. When both drugs were discontinued, food intake increased, leading to rapid weight regain. However, continued administration of Vutiglabridin after semaglutide withdrawal attenuated body weight regain and suppressed rebound-associated fat accumulation (Fig. 7D, E), possibly in line with the previously observed lower plasma leptin levels [24]. Collectively, these findings suggest that Vutiglabridin may provide a useful adjunct for sustaining weight-loss efficacy after GLP-1RA discontinuation.

Excessive weight loss beyond normal BMI risks adverse effects like impaired immunity, hormonal dysregulation, and reduced bone density are key considerations when overcoming plateaus for sustained reduction [44]. To assess safety of sustained weight reduction with Vutiglabridin with Semaglutide combination, we conducted an 8-week study in normal rats using more than 3 times efficacious mouse doses, monitoring body weight, food intake, and safety parameters. Semaglutide monotherapy reduced

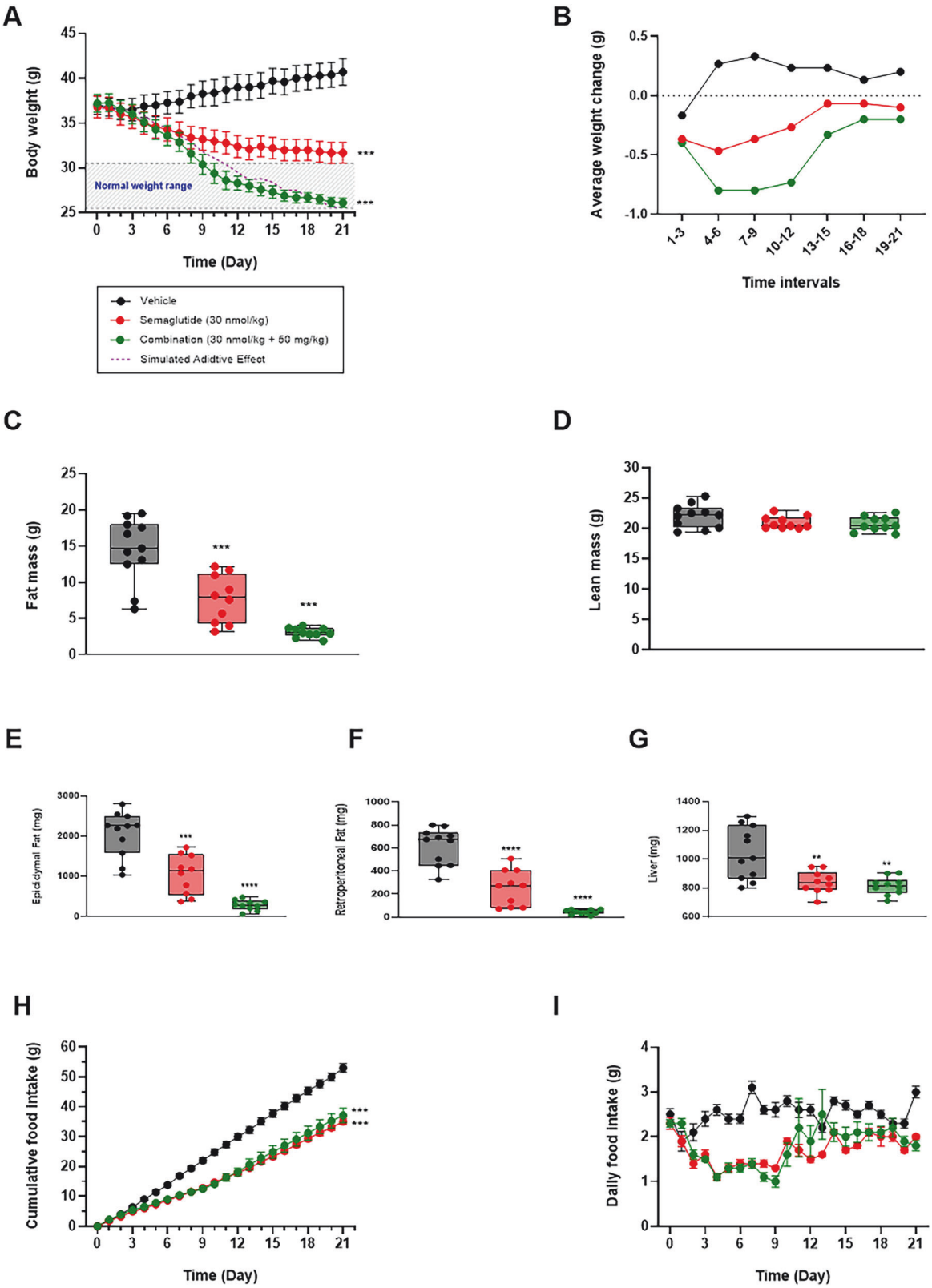


Fig. 3 Combination of Vutiglabridin and semaglutide reduces body weight to the normal weight range. Anti-obesity effect of semaglutide (30 nmol/kg) and the combination of Vutiglabridin (50 mg/kg) and semaglutide (30 nmol/kg) in mice with diet-induced obesity (DIO). Mice were fed a high-fat diet for 11 weeks to induce obesity, followed by 21 days of semaglutide alone or semaglutide combined with Vutiglabridin treatment ($n = 11$ for vehicle group; $n = 10$ for semaglutide and combination group). **A** Daily body weight; **B** Average weight change (g) calculated over 3-day intervals throughout treatment; **C** Fat mass change; **D** Lean mass change; **E** Epididymal fat weight (mg); **F** Retroperitoneal fat weight (mg); **G** Liver weight (mg); **H** Cumulative food intake; **I** Daily food intake change. Each data point represents mean ± SEM. *P*-value was assessed by one-way ANOVA with Tukey's multiple comparison test: $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$ and $^{****}P < 0.0001$.

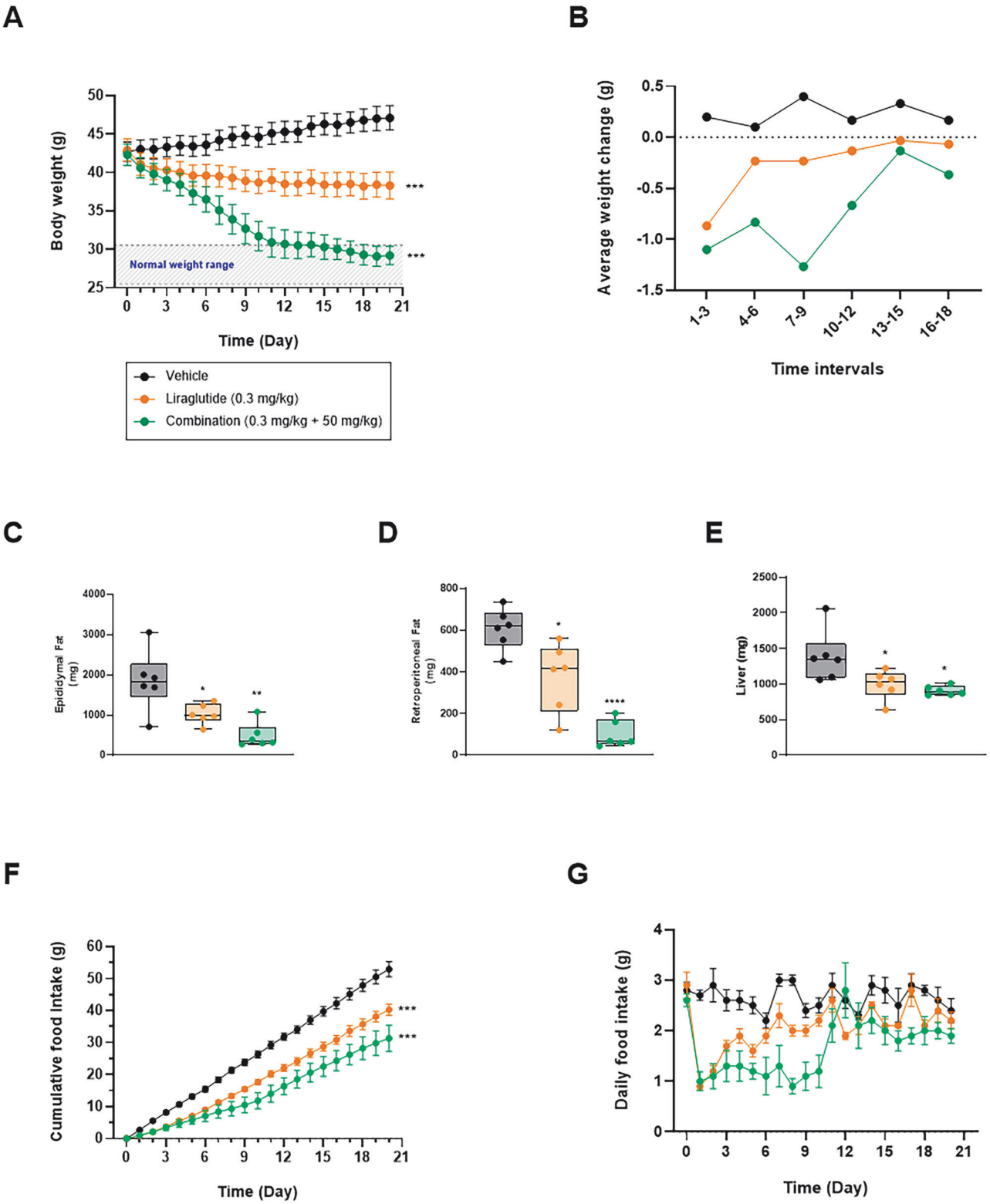


Fig. 4 Vutiglabridin overcomes the weight-loss plateau of the low-potency GLP-1RA liraglutide. Anti-obesity effect of liraglutide (0.3 mg/kg) and the combination of Vutiglabridin (50 mg/kg) and liraglutide (0.3 mg/kg) in mice with diet-induced obesity (DIO). Mice were fed a high-fat diet for 11 weeks to induce obesity, followed by 21 days of liraglutide alone or liraglutide combined with Vutiglabridin treatment ($n = 6$ per group). **A** Daily body weight change; **B** Average weight change (g) calculated over 3-day intervals throughout treatment; **C** Epididymal fat weight (mg); **D** Retroperitoneal fat weight (mg); **E** Liver weight (mg); **F** Cumulative food intake; **G** Daily food intake change. Each data point represents mean ± SEM. *P*-value was assessed by one-way ANOVA with Tukey's multiple comparison test: $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$ and $^{****}P < 0.0001$.

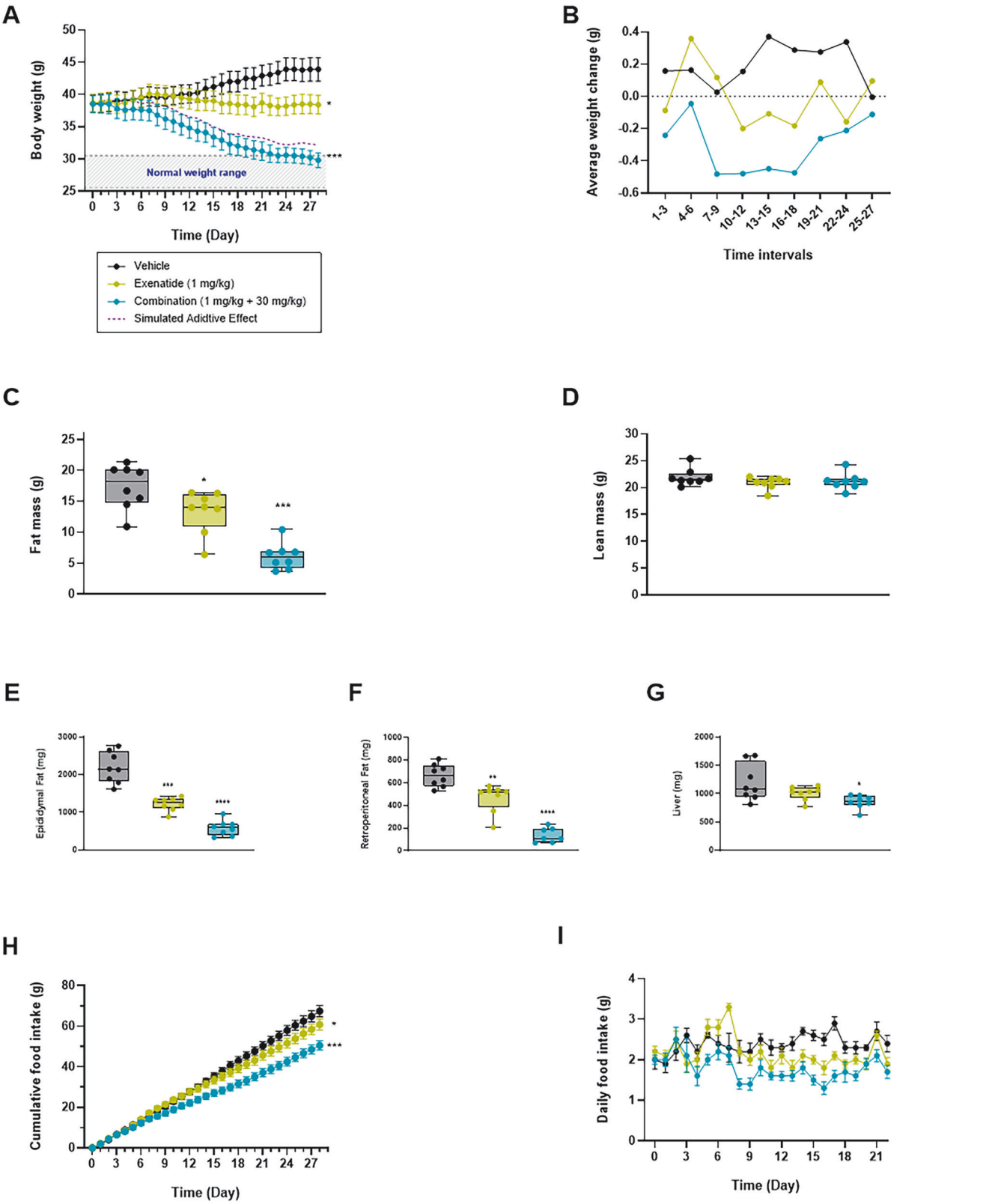


Fig. 5 Vutiglabridin overcomes the weight-loss plateau of the low-potency GLP-1RA exenatide. Anti-obesity effect of exenatide (4 mg/kg) and the combination of Vutiglabridin (30 mg/kg) and exenatide (4 mg/kg) in mice with diet-induced obesity (DIO). Mice were fed a high-fat diet for 11 weeks to induce obesity, followed by 21 days of exenatide alone or Exenatide combined with Vutiglabridin treatment ($n = 8$ per group). **A** Daily body weight change; **B** Average weight change (Δg) calculated over 3-day intervals throughout treatment; **C** Fat mass change; **D** Lean mass change; **E** Epididymal fat weight (mg); **F** Retroperitoneal fat weight (mg); **G** Liver weight (mg); **H** Cumulative food intake; **I** Daily food intake change. Each data point represents mean ± SEM. *P*-value was assessed by one-way ANOVA with Tukey's multiple comparison test: $^{*}P < 0.05$, $^{**}P < 0.01$ and $^{***}P < 0.001$.

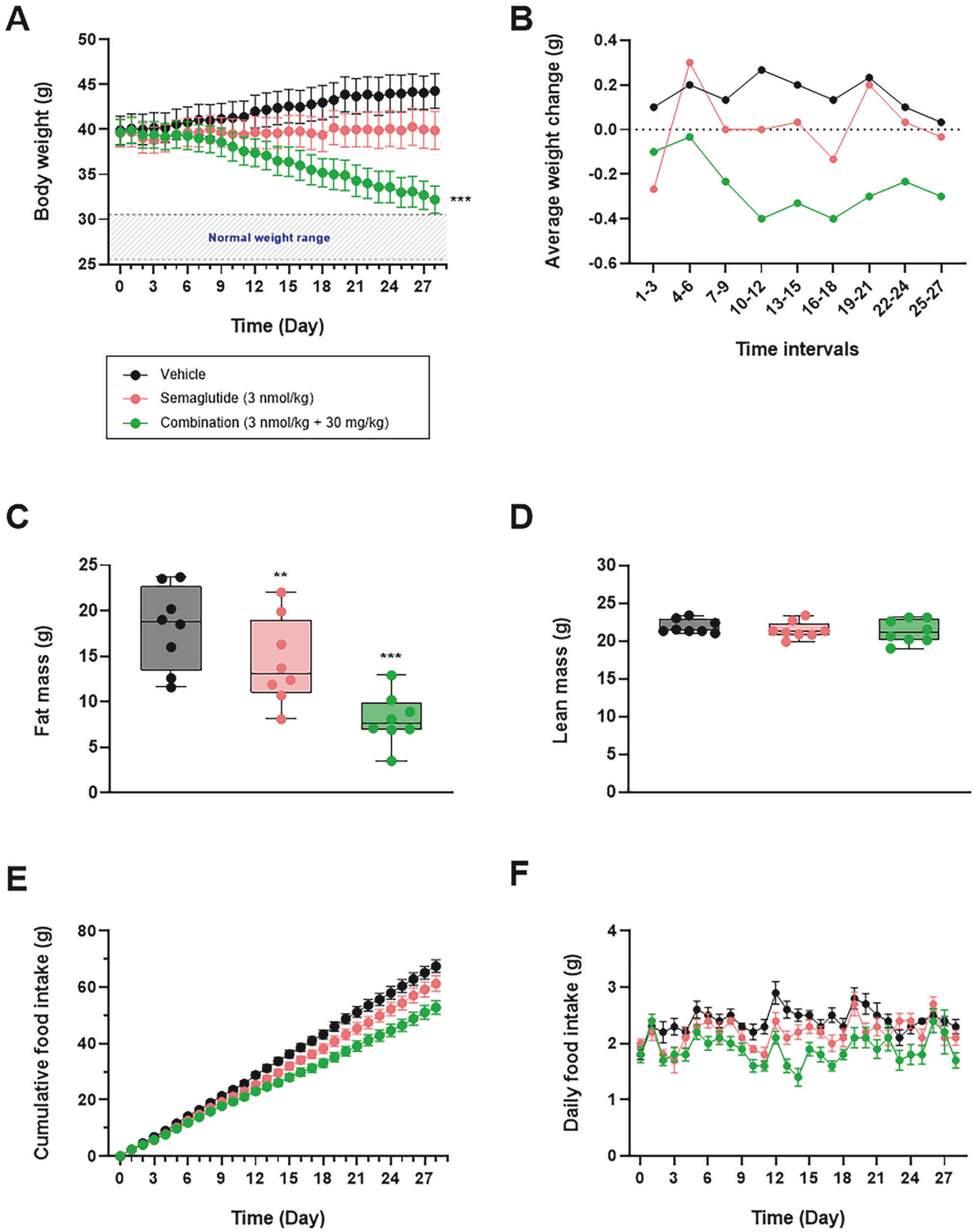
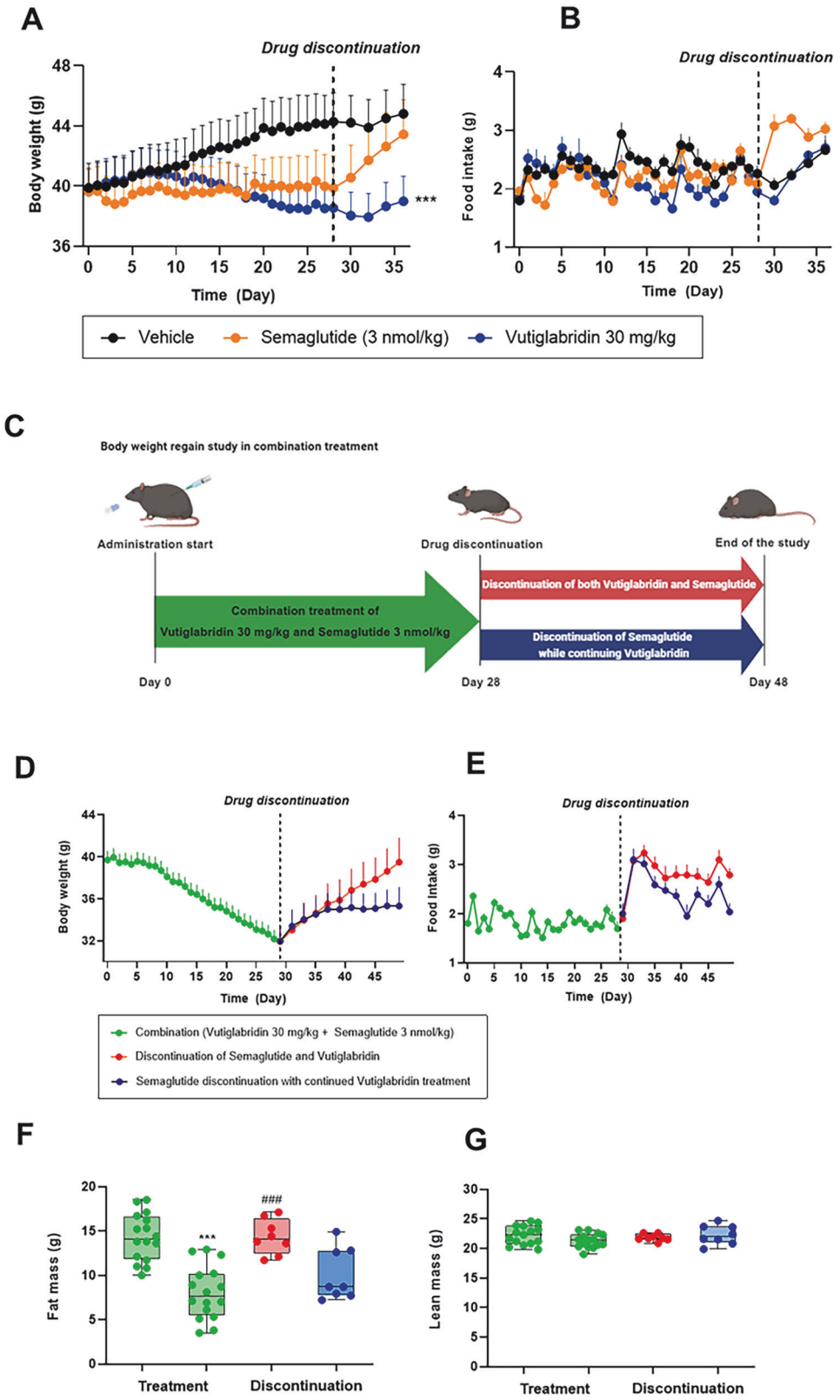


Fig. 6 Vutiglabridin overcomes the weight-loss plateau of low-potency semaglutide (3 nmol/kg). Anti-obesity effect of semaglutide (3 nmol/kg) and the combination of Vutiglabridin (30 mg/kg) and semaglutide (3 nmol/kg) in mice with diet induced obesity (DIO). Mice were fed a high-fat diet for 11 weeks to induce obesity, followed by 21 days of semaglutide alone or semaglutide combined with Vutiglabridin treatment ($n = 8$ per group). **A** Daily body weight change; **B** Average weight change (g) calculated over 3-day intervals throughout treatment; **C** Fat mass change; **D** Lean mass change; **E** Cumulative food intake; **F** Daily food intake change. Each data point represents mean ± SEM. *P*-value was assessed by one-way ANOVA with Tukey's multiple comparison test: $^{*}P < 0.05$, $^{**}P < 0.01$ and $^{***}P < 0.001$.



food intake and body weight gain vs. controls; the combination showed no further reductions in either (Fig. S3A, B). Moreover, necropsy performed in Week 8 revealed no toxicological findings attributable to the combination treatment. Vutiglabridin selectively enhances lipid metabolism in dysfunctional adipocytes of animals with obesity but minimally impacts body weight in the lean physiological range (Fig. S3). Similar patterns occurred with semaglutide/liraglutide combinations, where weight loss continued in mice but plateaued at normal body weight (Figs. 3A and 4A). In addition, stable lean mass was observed with both GLP-1

Fig. 7 Vutiglabridin attenuates body-weight regain after GLP-1RA discontinuation. Body weight changes following discontinuation of Vutiglabridin (30 mg/kg) and semaglutide (3 nmol/kg) in mice with diet-induced obesity (DIO). Mice were fed a high-fat diet for 11 weeks to induce obesity, followed by 28 days of Vutiglabridin or semaglutide treatment. Body-weight regain was assessed for 9 days beginning on Day 28. **A** Daily body weight change; **B** Daily food intake change. Body-weight changes following discontinuation of semaglutide (3 nmol/kg) alone or the combination of Vutiglabridin (30 mg/kg) and semaglutide (3 nmol/kg) in mice with diet induced obesity (DIO). Mice were fed a high-fat diet for 11 weeks to induce obesity, followed by 28 days of semaglutide or combined Vutiglabridin and semaglutide treatment. Body weight regain was assessed for 21 days beginning on Day 28. **C** Experimental design; **D** Daily body weight change; **E** Daily food-intake change; **F** Fat mass change; **G** Lean mass change. Each data point represents mean ± SEM. Groups with different letters statistically differ (for the discontinuation period compared to treatment period: $^{*}p < 0.05$, $^{**}p < 0.01$; for the treatment period compared to baseline: $^{\#}p < 0.05$, $^{\#\#}p < 0.01$). *P*-value was assessed by one-way ANOVA with Tukey's multiple comparison test.

RA monotherapy and combination, with greater fat-mass loss in combination. Together, these findings indicate that the combination of Vutiglabridin with GLP-1 RAs promotes sustained and safe weight reduction until the normal body-weight range is reached, without inducing excessive or undesirable weight loss beyond physiological limits focusing mainly on fat mass reduction.

The current study has several limitations. First, we did not directly measure EE or substrate utilization in the combination regimen. Although prior work showed that Vutiglabridin increases whole-body EE, the contribution of this effect in the present combination study remains to be formally tested by indirect calorimetry. Second, although our data indicate that Vutiglabridin and GLP-1 RAs act through complementary mechanisms, the detailed molecular crosstalk between these pathways has not yet been fully elucidated. Future studies will be needed to define how Vutiglabridin influences adipose remodeling, appetite regulation, and metabolic adaptation in combination with GLP 1RAs.

In conclusion, Vutiglabridin overcomes GLP-1 RA weight-loss plateaus in DIO mice and supports normalization of body composition. Its benefits appear to arise primarily from selective fat reduction, with additional obesity dependent effects on food intake at submaximal GLP 1RA doses and attenuation of rebound weight gain after GLP 1RA withdrawal. Together, these findings support Vutiglabridin as a promising adjunct for sustained obesity treatment.

DATA AVAILABILITY

Additional supporting data the findings of the study are available from the lead contact, Sang-Ku Yoo (skyoo@glaceum.com), upon reasonable request.

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AUTHOR CONTRIBUTIONS

Hyeong Min Lee: Conceptualisation, Methodology, Formal analysis, Writing–Original Draft, Writing–Review & Editing. Kamindu Gayashan Marakkalage, Sang Hyo Kim, Soonje Lee, Jae Ho Lee: Methodology, Data Curation, Validation, Software, Writing–Review & Editing. Hyung Soon Park: Writing—Review & Editing. Sang-Ku Yoo: Supervision, Conceptualisation, Writing–Review & Editing.

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COMPETING INTERESTS

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Sang-Ku Yoo has patent Pyranochromenyl phenol derivative, and pharmaceutical composition for treating metabolic syndrome or inflammatory disease issued to US9783551B2. HML, KGM, SHK, SL, JHL, HSP and S-KY are current employees of Glaceum Inc. and hold Glaceum's stocks/shares. Glaceum Inc. holds the intellectual property rights of Vutiglabridin.

ETHICS APPROVAL

All procedures involving animals at Lee Gil Ya Cancer and Diabetes Institute (Gachon University) were approved by the Institutional Animal Care and Use Committee (Approval No. LCDI-2021-0010, LCDI-2021-0042, LCDI-2021-0108; LCDI-2023-0047). The studies were conducted in accordance with local legislation and institutional requirements.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41366-026-02161-9.

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