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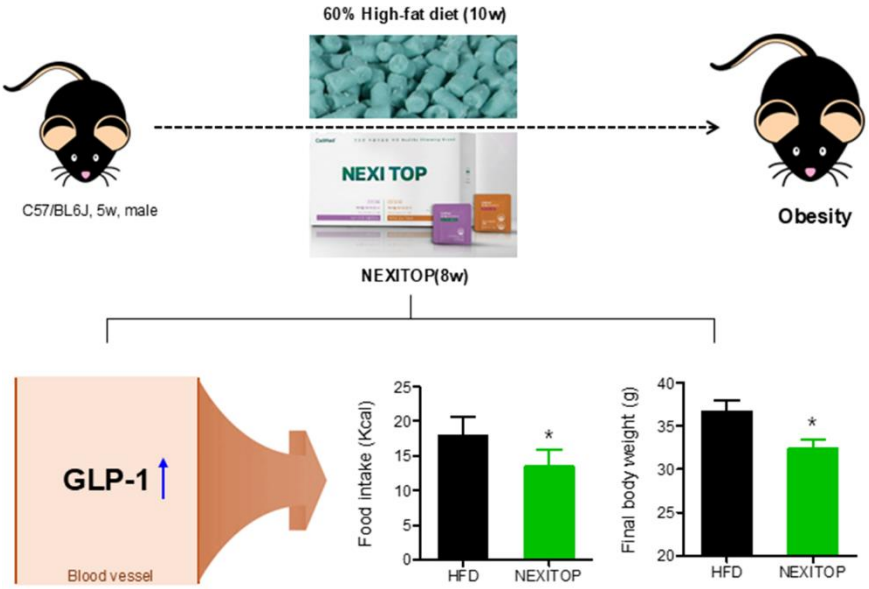
Original article

Anti-obesity effects of an herbal formula NEXITOP through upregulation of glucagon like peptide-1 production in a high fat diet-fed obese mouse model

Graphical Abstract



Highlights

- NEXITOP is novel herbal formula consisting of several natural substances
- NEXITOP administration strongly suppressed both appetite and increase in body weight
- NEXITOP administration decreased abdominal fat accumulation
- NEXITOP administration increased serum GLP-1 levels
- NEXITOP may be a promise therapy modulating GLP-1 derived from natural sources

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In Brief
This study evaluated the anti-obese effects of NEXITOP, a novel herbal formula, in a high-fat diet-induced obese mouse model. NEXITOP decreased body weight and calorie intake while increased serum GLP-1 level, demonstrating therapeutic potential comparable to metformin.

Bong-Keun Jang et al., CellMed. Vol. 15, No. 6, June 2025
http://dx.doi.org/10.5667/CellMed.2025.006

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Anti-obesity effects of an herbal formula NEXITOP through upregulation of glucagon like peptide-1 production in a high fat diet-fed obese mouse model

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ABSTRACT

Objective: Obesity is a complex chronic disease linked to over 200 chronic diseases and has increased in prevalence worldwide to date. This absolutely requires drastic lifestyle changes including practice of exercise and intake of low-calorie diet. However, many pharmacotherapies, approved by FDA, have recently been developed to improve obesity. Especially glucagon-like peptide 1 (GLP-1), a gut hormone that reduces appetite and promotes insulin secretion, has recently attracted much attention as a promising anti-obesity target. We developed 'NEXITOP' consisting of several natural substances that have previously been proven to help with obesity and aimed to evaluate the anti-obesity effects via GLP-1 modulation in high-fat diet (HFD)-induced obese mice.

Materials and Methods: After early feeding HFD for 2 weeks, forty of C57BL/6J mice were divided into five groups: normal diet, HFD control, metformin (200 mg/kg), and NEXITOP (1300 or 2600 mg/kg). And then, NEXTOP and metformin were administered for 8 weeks.

Results: Feeding of HFD for 10 weeks dramatically increased both caloric intake and body weight (1.4 and 1.6-fold, respectively). While the administration of NEXITOP significantly improved both elevated caloric intake (19%) and body weight (12%). The administration of NEXITOP also showed reducible effects of abdominal fats (visceral; 2.1-fold, epididymal; 4.8-fold, retroperitoneal; 1.5-fold) in HFD-fed mice. Also, the administration of NEXITOP greatly elevated serum GLP-1 levels at 2, 4 and 6 weeks as well as its effects were superior to metformin at 2 and 4 weeks.

Conclusion: Our findings suggest that NEXITOP exerted an anti-obesity effect, and its underlying mechanism may involve regulation of the serum GLP-1 level.

Keywords NEXTOP, glucagon-like peptide 1, body weight, calorie intake, fat

INTRODUCTION

Obesity is a condition of excessive fat accumulation in body that may impair health and defined as the body mass index (BMI) over 30. Its etiology is complex and involves both environmental and genetic factors.[1] The World Health Organization (WHO) has reported that 2.5 billion adults (43% of world population) are overweight, and of these, 890 million (16% of world population) are living with obesity; notably 420 million children under 18 years also suffer from overweight or obesity.[2] The worldwide prevalence of obesity has increased approximately 2.4-fold from 6.6% to 15.8% during the period between 1990 and 2022. It is predicted that by the year 2030, more than one billion adults globally will be obese.[3]

Extracellular energy generated by high caloric diet or irregular eating habits is stored in the form of fat in the adipose tissue and glycogen mainly in the liver and muscle.[4] Fat tissues are broadly classified with white and brown adipose tissues at a ratio of 98% to 2%, and these respectively play main roles in storing lipid contents and consuming energy via thermogenesis.[5,6] Thus, obesity mainly occurs as an imbalance between energy intake and expenditure.[7] Obesity can stimulate immune systems, which provokes an inflammatory condition by generating pro-inflammatory cytokines such as interleukin 6 and tumor necrosis factor alpha.[8] These pathological features in

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Received May 20, 2025; **Revised** May 26, 2025; **Accepted** May 26, 2025; **Published** May 30, 2025
doi: http://dx.doi.org/10.5667/CellMed.2025.006

obesity is complex and multifactorial in nature, disturbing systematic metabolic homeostasis; fact, obesity is known to be associated with over 200 chronic diseases, according to numerous clinical/preclinical studies.[9,10] Especially, type 2 diabetes mellitus (T2D), non-alcoholic fatty liver diseases and cardiovascular diseases are directly linked to obesity.[11–14]

One of the fundamental strategies often employed in the management of obesity is normalizing energy balance by decreasing energy intake while increasing energy expenditure. However, this absolutely requires drastic lifestyle changes including practice of exercise and intake of low-calorie diet.[15,16] Many pharmacotherapies, approved by FDA, have recently been developed as adjuvants to improve obesity. Among these, glucagon-like peptide 1 (GLP-1) has recently attracted much attention as a promising anti-obesity target. GLP-1, as a gastrointestinal peptide hormone released in response to food intake, represses appetite and enhances insulin secretion.[17] Systematic administration of GLP-1 peptide or stimulating endogenous production/release of more GLP-1 has been shown to be effective to prevent or treat obesity and obesity-associated diseases including T2D.[18,19] In addition to synthetic GLP-1 receptor agonists, components of some edible natural products such as berberine, curcumin, and resveratrol may have modulatory effects on GLP-1 expression and secretion in pre-clinical studies.[20–22]

We have developed NEXITOP as a functional food consisting of several natural substances derived from edible plant, *Momordica charantia, Curcuma longa, Berberis asiatica, Camellia sinensis, Hibiscus sabdariffa,* etc. that have previously been proven to help with obesity. In the present study, we investigated the anti-obesity effects of NEXITOP, possibly through upregulation of GLP-1 in 60% high-fat diet (HFD)-fed mice.

MATERIALS AND METHODS

NEXITOP and positive control

NEXITOP was provided by JBKLAB Co., Ltd (Gyeonggi-do, Korea). Briefly, NEXITOP is herbal mixture including *Momordica charantia*, *Curcuma longa*, *Berberis asiatica*, *Camellia sinensis*, *Hibiscus sabdariffa* etc. Metformin (Sigma Aldrich, MO, USA) a well-known anti-diabetic agent, was used as a positive control.

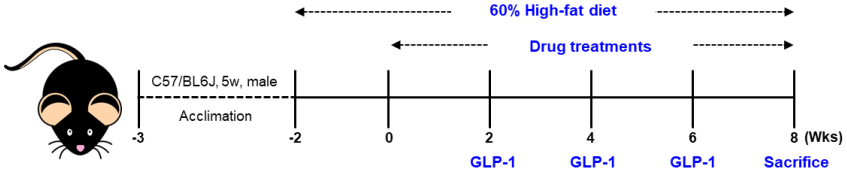
Animal and diet

A total of forty C57BL/6J male mice (5-week-old, 21–23 g body weight) were purchased from DBL Co., Ltd. (Chung-Buk, South Korea) and were housed with free access to diet and water in a room maintained at 22 ± 2 °C under a 12 h light: 12 h dark cycle. The normal diet (ND) and 60% HFD were obtained from DBL Co., Ltd. and Research diet Inc. (NJ, USA) and contained 3 and 5.1 kcal/g, respectively.

Experiment design

After acclimatization for one week, 35 mice, except ND group (n=5) were fed HFD for 2 weeks. In the third week, HFD-fed mice were divided based on the average body weight into 4 groups: HFD with distilled water (DW) (n=10), HFD with 200 mg/kg of metformin (n=8), HFD with 1300 mg/kg of NEXITOP (n=9), HFD with 2600 mg/kg of NEXITOP (n=8). Five groups of mice including those in the ND group were orally administered with DW, NEXITOP or metformin daily for 8 weeks in a volume of 10 mL/kg. The animal experiment protocol was approved by the Institutional Animal Care and Use Committee of JBKLAB Co., Ltd (JBK-25-05-001) as summarized in Fig. 1. On the final day of the experiment, the mice were euthanized in an isoflurane chamber, and blood was collected from the abdominal vein. And then three abdominal fats (epididymal, retroperitoneal and visceral) were removed and weighed.

<Experiment scheme>



Groups	60% High fat diet	Drug treatment	Number of mouse
Normal	X	D.W, p.o	5
Control	O	D.W, p.o	10
Metformin	O	Metformin 200 mg/kg, p.o	8
NEXITOP Low	O	NEXITOP 1300 mg/kg, p.o	9
NEXITOP High	O	NEXITOP 2600 mg/kg, p.o	8

Fig. 1. Experiment scheme adopted in the present study.

Measurements of food intake and body weight

Food intake and body weight were measured in the morning every Monday and Thursday for 8 weeks. Briefly, the food containing 100 g of ND or HFD was supplied into each cage on Monday, and then on Thursday, residual food was weighed and replaced with a new diet. Food intake was calculated as calories and presented as accumulation, changes and average for 8 weeks. Also, body weight was presented as changes and final body weight gain for 10 weeks.

Measurements of serum GLP-1 and blood cell counting

Orbital blood collection was performed at 2, 4, 6 weeks of NEXITOP of metformin administration. All collected blood were separated by centrifugation (8000 rpm, 15 min) after clotting (40 min). Serum GLP-1 was measured using a commercially available ELSIA kit (Invitrogen, MA, USA). On the final day, bloods were exsanguinated from inferior vena cava and analyzed using BC-5000 vet (Mindray PLC, Shenzhen, China).

H&E staining

For H&E staining, formalin-fixed epididymal fat tissues were sectioned at 6 μm thickness and stained with Mayer's hematoxylin solution (Sigma-Aldrich, MO, USA). The stained samples were then mounted on silane-coated slides using Aqueous-Mount (Scytek Laboratories Inc., UT, USA). All slides were examined under an IX70 microscope at 200× magnification (Olympus, Co., Ltd., Tokyo, Japan), and the fat droplet size was determined using ImageJ software following NIH guidelines.

Statistical analysis

All results are expressed as the mean ± standard deviation (SD). Group differences were assessed using one-way analysis of variance (ANOVA). Post-hoc multiple comparisons for each group using Tukey's Honestly Significant Difference (HSD) test was performed with Prism version 8.0. (GraphPad software Inc., CA, USA). Statistical significance is expressed as $^{\#}p<0.05$, $^{\#\#}p<0.01$ and $^{\#\#\#}p<0.001$ for Normal vs. Control groups, and $^{*}p<0.05$, $^{**}p<0.01$ and $^{***}p<0.001$ for Control vs. each group, $^{\dagger}p<0.05$ and $^{\dagger\dagger\dagger}p<0.001$ for metformin vs. each group.

RESULTS

NEXITOP reduced body weight

Ten weeks of HFD feeding dramatically elevated the body weight by 1.4-fold compared to ND fed-mice ($p<0.001$). On the other hand, the low dose administration of NEXITOP started to significantly regulate weight from the 5th week and finally decreased the body weight by 12% compared to the control group ($p<0.05$, Fig. 2A to C). Metformin also reduced the final body weight compared to control group ($p<0.01$). A high dose of NEXITOP apparently reduced the body weight, but this was not statistically significant.

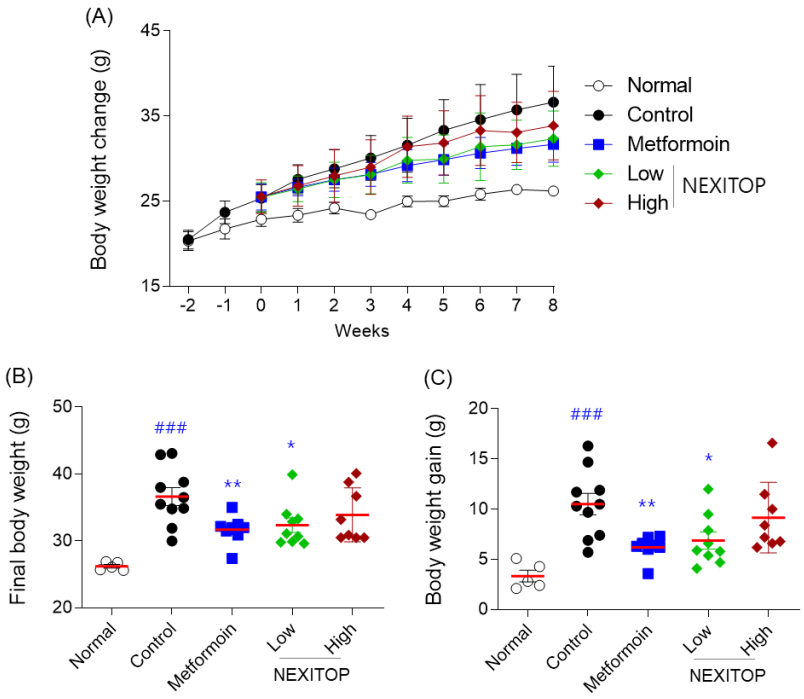


Fig. 2. Effects of NEXITOP on body weight change. Body weights were measured twice a week, in the morning every Monday and Thursday for 8 weeks and were presented as (A) body weight change for 10 weeks, (B) final body weight after 10 weeks and (C) body weight gain. Statistical significance is expressed as $^{\#\#\#}p<0.001$ for Normal vs. Control group, and $^{*}p<0.05$ and $^{**}p<0.01$ for Control vs. each group.

NEXITOP suppressed appetite

Ten weeks of HFD feeding dramatically elevated the calorie intakes by 1.6-fold compared to ND fed-mice. The administration of NEXITOP (low dose) suppressed the average calorie intakes by 29% compared to the control group ($p < 0.01$, Fig. 3A to C). Metformin also showed anorexic effects ($p < 0.01$), and its effects were almost equivalent to those of a low dose NEXITOP. High dose of NEXITOP partially showed anorexic effects, but not significant.

NEXITOP decreased abdominal fat contents

The contents of abdominal fats (visceral, epididymal and retroperitoneal fats) were dramatically increased in mice fed HFD compared to those in the normal group (visceral; 2.1-fold, epididymal; 4.8-fold, retroperitoneal; 1.5-fold). While these alterations were significantly normalized by administration of NEXITOP ($p < 0.05$ for all parameters, Fig. 4C to E). Metformin showed similar effects to NEXITOP ($p < 0.05$ for all parameters). Histological analysis of epididymal fat using H&E staining supported NEXITOP-induced reduction of fat droplets compared to control group ($p < 0.05$, Fig. 4A and B).

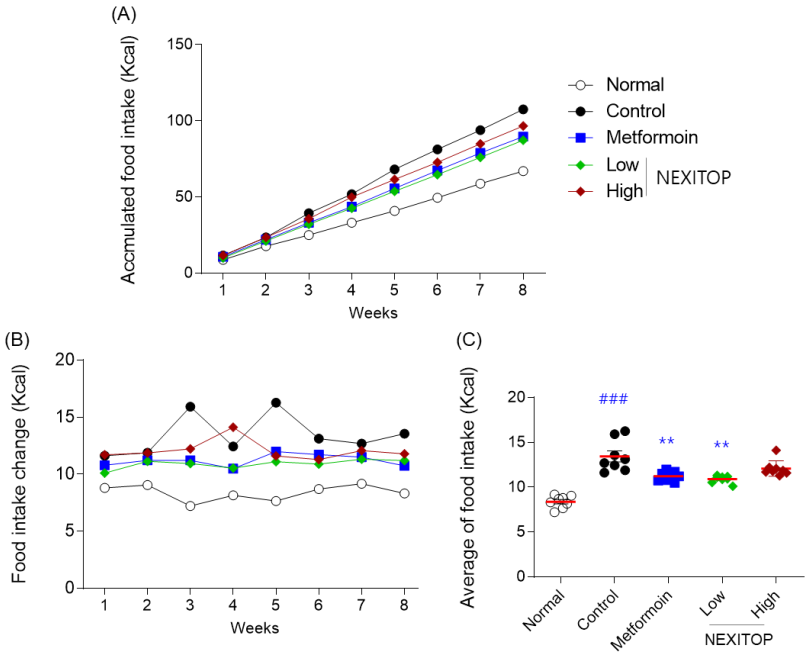


Fig. 3. Effects of NEXITOP on calorie intake. The foods (100g of ND or HFD) were supplied in each cage every Monday and then on Thursday, and residual food was weighed and replaced with new diet. Food intake was calculated as calories and presented as (A) accumulation, (B) change and (C) average for 8 weeks. Statistical significance is expressed as $^{###}p < 0.001$ for Normal vs. Control group and $^{**}p < 0.01$ for Control vs. each group.

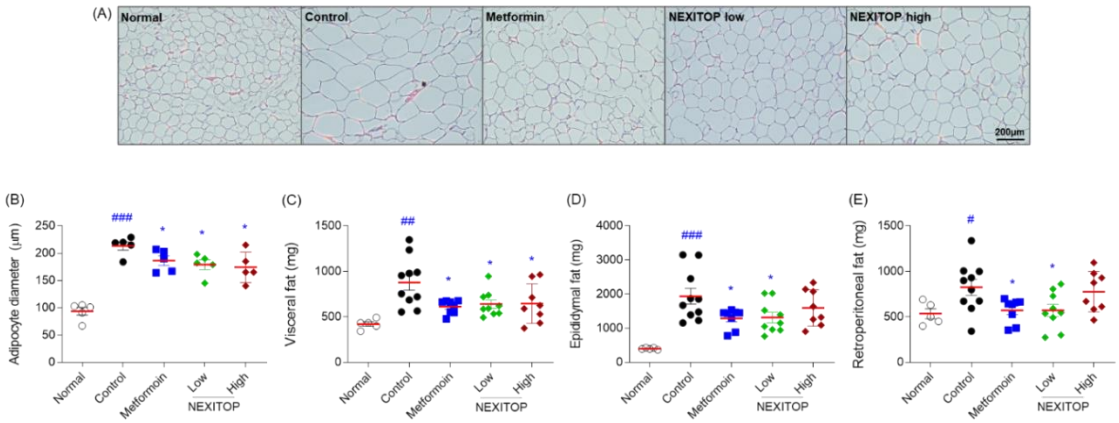


Fig. 4. Effects of NEXITOP on fat contents. (A) H&E staining was performed in formalin-fixed epididymal fat tissues. The sample slide was examined under an IX70 microscope at 200× magnification. (B) The fat droplet size was determined using ImageJ software following NIH guidelines. The (C) visceral, (D) epididymal and (E) retroperitoneal fats were weighed on the final day after sacrifices. Statistical significance is expressed as $^{#}p < 0.05$, $^{##}p < 0.01$ and $^{###}p < 0.001$ for Normal vs. Control group, and $^{*}p < 0.05$ for Control vs. each group.

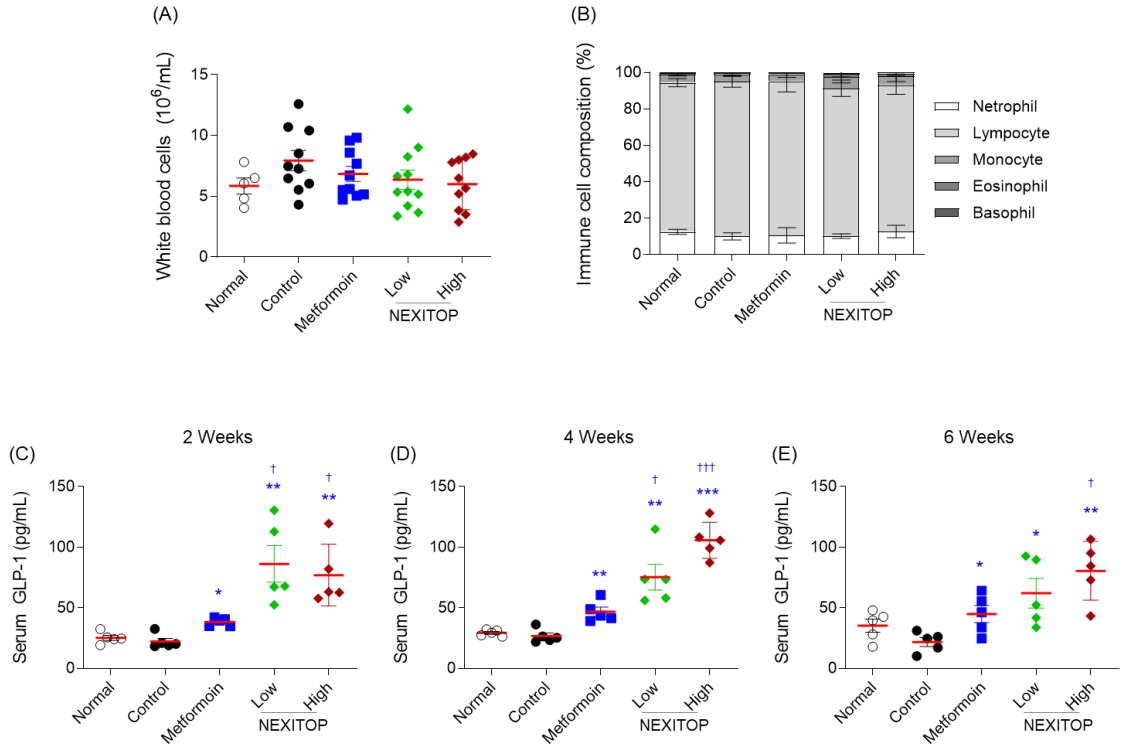


Fig. 5. Effects of NEXITOP on immune cell profiles and serum GLP-1 levels. On the final day, blood was exsanguinated from inferior vena cava. The (A) total white blood cells and (B) individual immune cell populations analyzed using BC-5000 vet. Orbital blood collection was conducted at the (C) 2, (D) 4 and (E) 6 weeks of drug administration. All collected blood were separated by centrifugation as described in Materials and methods. Serum GLP-1 was measured by a common ELSIA kit. Statistical significance is expressed as $^{*}p < 0.05$, $^{**}p < 0.01$ and $^{***}p < 0.001$ for Control vs. each group, $^{\dagger}p < 0.05$ and $^{\dagger\dagger\dagger}p < 0.001$ for metformin vs. each group.

NEXITOP modulated serum GLP-1 levels

The low dose administration of NEXITOP significantly boosted serum GLP-1 at 2, 4 and 6 weeks ($p < 0.05$ or $p < 0.01$), and its effects were superior to metformin at 2 and 4 weeks ($p < 0.05$). Also, the high dose administration of NEXITOP boosted serum GLP-1 in 2, 4 and 6 weeks ($p < 0.01$ or $p < 0.001$), and its effects were also superior to metformin ($p < 0.05$ for 2 and 6 weeks and $p < 0.001$ for 4 weeks). Serum levels of GLP-1 reached a peak at 2 and 4 weeks with low and high doses of NEXITOP, respectively ($p < 0.05$ or $p < 0.001$, Fig. 5C to E). In complete blood counting, total white blood cells and its ratio showed no significant changes with the HFD or metformin administration (Fig. 5A and B).

DISCUSSION

In the past decade, development of anti-obesity drugs has been limited because of ineffectiveness, low-efficacy and numerous safety concerns. Therefore, the development of novel drugs with high efficacy and safety is urgently needed. Recent advances in our understanding of the complex pathophysiology of obesity have led to development of new and powerful therapeutics such as GLP-1 receptor agonist (GLP-1RA) recently approved for the treatment of obesity.[23] In the present study, we confirmed that HFD consumption for early 2 weeks significantly increased tehe body weight (11%) compared to the ND group and that administration of NEXITOP for next 2 weeks (total 4 weeks) significantly increased serum GLP-1 compared to ND and HFD groups (Fig. 2A and 5C). Based on the above observations, we investigated anti-obesity effects of NEXITOP for 8 weeks, in the context of its long-acting effects on expression of GLP-1.

GLP-1RAs were originally developed to treat T2D. However, their application has been expanded to use as anti-obesity drugs because of their capability to reduce body weight. These GLP-1RAs are classified as short- and long-acting compounds, based on their difference in pharmacodynamic profiles.[24] The short-acting GLP-1RAs lower postprandial blood glucose levels through inhibition of gastric emptying,[25,26] while the long-acting ones lower fasting glucose levels, which is mediated predominantly by elevating insulin secretion.[27,28] Especially, semaglutide, dulaglutide and exenatide as long-acting GLP-1RAs demonstrated both long-term over-expression of GLP-1 and insulin secretion as well as reduction of body weight in clinical trials.[24,29,30] Our data showed that the administration of NEXITOP increased the serum GLP-1 levels in 2, 4 and 6 weeks with notable acceleration from 2 to 4 weeks. (Fig. 5C to E). In addition, the effects were superior to metformin currently used as therapeutic of T2D. Our data indicates that NEXITOP-induced increase of GLP-1 may account for its capability to reduce the body weight in HFD-obesity mice.

In animal models, obesity is assessed by criteria based on the gain of body weight or increase of body fat content, but standard tools for obesity have been developed like BMI in humans. Thus, the degree of obesity in most animals has been evaluated by comparing body weight or fat between ND-fed mice. The HFD-induced C57Bl/6J mouse model is mainly used for studying metabolic disorders such as obesity, hyperlipidemia and diabetes.[31–33] HFD consumption for a total of 10 weeks dramatically accumulated excessive calorie intakes (Fig. 3A to C), and it resulted in an increase of 3-abdominal fats (visceral, epididymal, retroperitoneal) in body (Fig. 4C to E). Finally, these alterations were prominent in terms of the elevation of body weight which is the main feature of obesity compared to the ND group (Fig. 2A to C).[34] It is noticeable that the administration of NEXITOP for 8 weeks significantly attenuated these alterations. These results were consistent with the results of adipocyte diameter in epididymal fat-histological analysis (Fig. 4A and B).

Excessive fat accumulation in body may lead to pathological conditions such as immune-mediated inflammation and hormones imbalance.[35,36] Adipose tissue secretes bioactive molecules with various properties including adiponectin, and they mainly modulate immune response and inflammation.[37] The hypertrophied adipocytes altered secretion of adipokines, and this stimulates macrophages to release pro-inflammatory cytokines and lipolysis of adipocyte.[38] In our present study, the alterations of immune cell population by HFD consumption are unclear. We just noticed that the total white blood cells slightly tend to increase, but this was normalized by administration of NEXITOP (Fig. 5A and B).

NEXITOP is a mixture of natural products consisting of *Momordica charantia*, *Curcuma longa*, *Berberis asiatica*, *Camellia sinensis* and *Hibiscus sabdariffa*. These components revealed pharmacological actions in obesity or metabolic disorders. For instance, *Momordica charantia* and *Curcuma longa* decreased body weight and fat contents in HFD-induced obese mice.[39,40] *Berberis asiatica* and *Camellia sinensis* have been investigated for several metabolic disorders including diabetes and cardiovascular diseases in clinical fields.[41,42] *Hibiscus sabdariffa* also has been considered for therapeutic applications in the management of metabolic syndromes.[43] Several lines of clinical and experimental evidence from the studies and others land support the notion that formulations derived from these natural products, such as NEXITOP, may have fewer side effects and be safer than currently approved synthetic single ingredients.

Further studies are needed to measure the serum or plasma insulin and glucose, GLP-1 receptor expression and fat-metabolic mechanisms associated with overexpression of GLP-1. Nevertheless, our findings strongly showed both an increase in serum GLP-1 and a decrease in the body weight and calorie intake by NEXITOP administration. These results suggest that NEXITOP has an anti-obesity potential. Its underlying mechanisms may involve modulating the release of GLP-1.

ACKNOWLEDGEMENT

None.

RESEARCH FUNDING

This research received no external funding.

CONFLICT OF INTEREST

The authors declare no competing interests.

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