

# The Role of the Herbal Medicines, *Rehmanniae Radix*, *Citrus unshiu Peel*, and *Poria cocos Wolf*, in High-Fat Diet-Induced Obesity

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## ABSTRACT

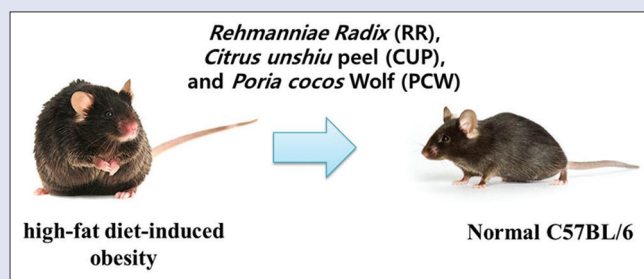
**Background:** Herbal medicine has been used for the treatment of obesity. Obesity is a very common global health problem, and it is known to be linked to metabolic diseases. **Objective:** To investigate on the anti-obesity effects of herbal medicines such as *Rehmanniae radix* (RR), *Citrus unshiu peel* (CUP), and *Poria cocos wolf* (PCW) in high-fat diet (HFD)-induced obese mice. **Materials and Methods:** C57BL/6 mice were fed a normal diet (ND) or an HFD for 6 weeks, and herbal medicines were administered orally three times a week for 8 weeks. Serum biochemical parameters were detected by measuring glucose, triglycerides, and total cholesterol. In addition, histological changes were observed in epididymal adipose tissues. **Results:** The RR, CUP, and PCW effectively lowered both the body weight and epididymal adipose tissue weight and reduced the adipocyte enlargement. In addition, we examined the serum biochemical profiles of HFD-induced obese mice to confirm the anti-obesity effects of RR, CUP, and PCW. Compared to the ND mice, the administration of RR, CUP, and PCW efficiently reduced the glucose, triglyceride, and total cholesterol serum levels in HFD-induced obese mice. **Conclusion:** These findings suggested that the herbal medicines, such as RR, CUP, and PCW, are potential novel agents for the prevention and treatment of metabolic diseases, especially obesity.

**Key words:** *Citrus unshiu peel*, high-fat diet, obesity, *Poria cocos wolf*, *Rehmanniae radix*

## SUMMARY

- Rehmanniae radix* (RR), *Citrus unshiu peel* (CUP), and *Poria cocos wolf* (PCW) effectively lowered both the body weight and epididymal adipose tissue weight and reduced the adipocyte enlargement

- The administration of RR, CUP, and PCW efficiently reduced the glucose, triglyceride, and total cholesterol serum levels in high-fat diet-induced obese mice
- PCW, CUP, and RR are potential novel agents for the prevention and treatment of metabolic syndrome.



**Abbreviations used:** RR: *Rehmanniae radix*; CUP: *Citrus unshiu peel*; PCW: *Poria cocos wolf*; HFD: High-fat diet; ND: Normal diet.

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## INTRODUCTION

Obesity is a metabolic disorder characterized by an excess accumulation of fat in the body due to energy intake exceeding energy expenditure<sup>[1]</sup> and is an increasingly common phenomenon all over the world. Obesity is assumed to be a product of imbalanced caloric intake and expenditure. Therefore, increased physical activity, coupled with a calorie-restricted diet, remains the mainstay of treatment in obese individuals.<sup>[2]</sup> Obesity is becoming increasingly serious and is an independent risk factor for metabolic syndromes such as hypertension, type 2 diabetes, dyslipidemia, sleep apnea, respiratory disorders, cardiovascular disease, stroke, and certain types of cancer.<sup>[3-5]</sup>

Herbal medicines have been used for the treatment of obesity, diabetes, and metabolic syndrome.<sup>[6]</sup> Based on the theory of Traditional Chinese Medicine (TCM), by adjusting patients' body balance as a holistic therapy in obesity management, herbal medicines could be safe and effective to use in obesity.<sup>[6,7]</sup> However, little is known about the effects of herbal medicines in obesity. In the present study, we investigated the

anti-obesity effects of herbal medicines such as *Rehmanniae radix* (RR), *Citrus unshiu peel* (CUP), and *Poria cocos wolf* (PCW) in high-fat diet (HFD)-induced obese mice.

## MATERIALS AND METHODS

### Preparation of herbal medicines

Dried RR extract was prepared using ethyl alcohol as described in the previous study.<sup>[8]</sup> The extracts were identified by Dr. Hyungwoo

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Kim and voucher specimens were deposited with Pusan National University School of Korean Medicine. The extract of CUP (CW02-014) and PCW (CW04-009) was obtained from the Plant Extract Bank of the Korea Research Institute of Bioscience and Biotechnology (<https://extract.kribb.re.kr>; Daejeon, Republic of Korea). The powder of RR was immersed in distilled water (DW) and extracted for 2.5 h. After that, it was evaporated under reduced pressure using a DW-290 (Daewoong, Seoul, Republic of Korea) at 100°C. The extract was then lyophilized using a Clean-vac 12 dryer (Biotron Electronics Corporation, Calgary, Alberta, Canada) for 24 h. Next, RR, CUP, and PCW were dissolved in DW at a concentration of 20 mg/mL and stored at 4°C as a stock solution.

## Ethics

Animal care and experiments were conducted in accordance with the guidelines issued by the Ethics Committee of Pusan National University (Busan, Republic of Korea; Approval No. PNU-2018-1832) and the National Institutes of Health "Guide for the Care and Use of Laboratory Animals" (NIH publication No. 85-23; 1996 revision).

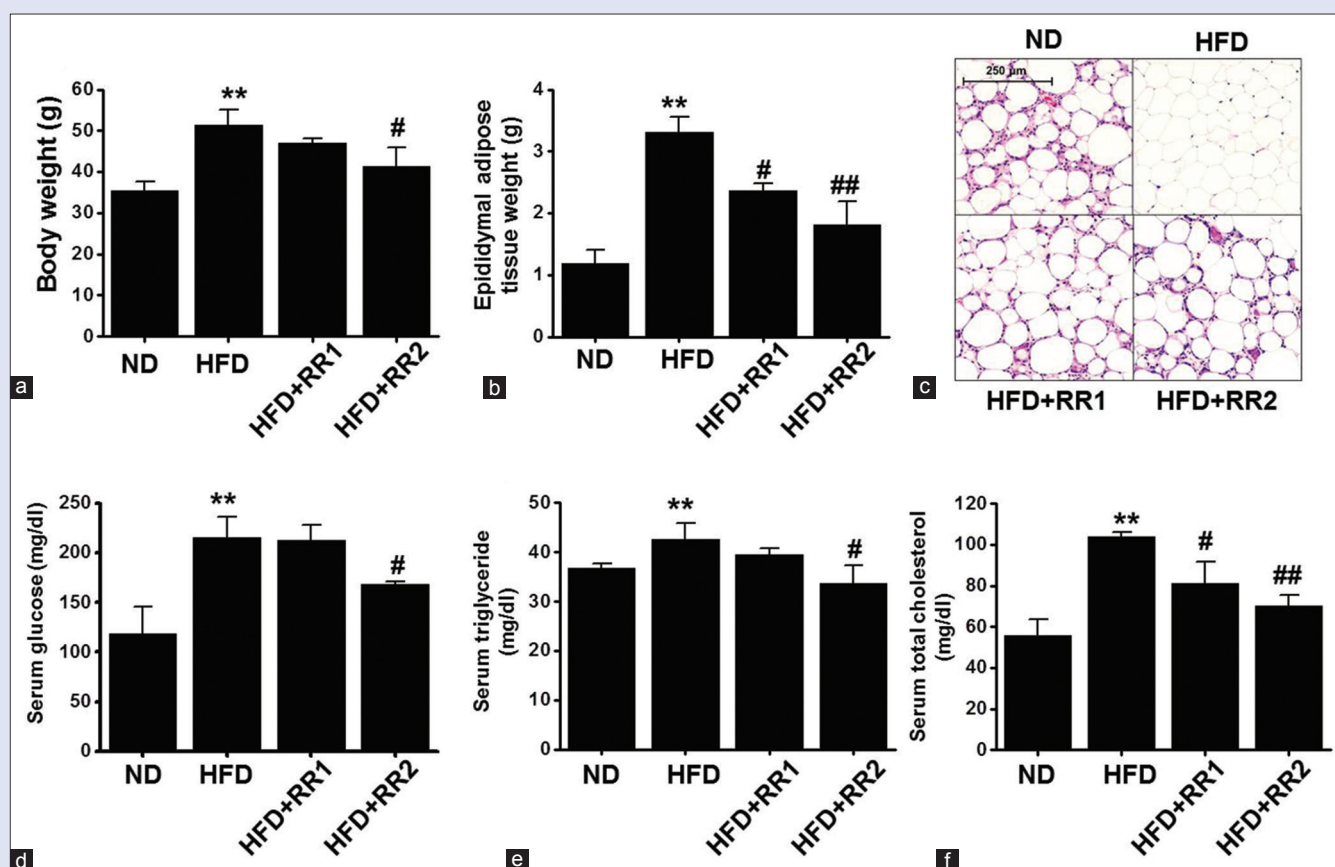
## Animal experiments

C57BL/6 mice (male, 6-week-old) were purchased from Jung Ang Lab Animal, Inc. (Seoul, South Korea). The animals were housed in a conventional state at a temperature of 20°C–23°C and humidity of

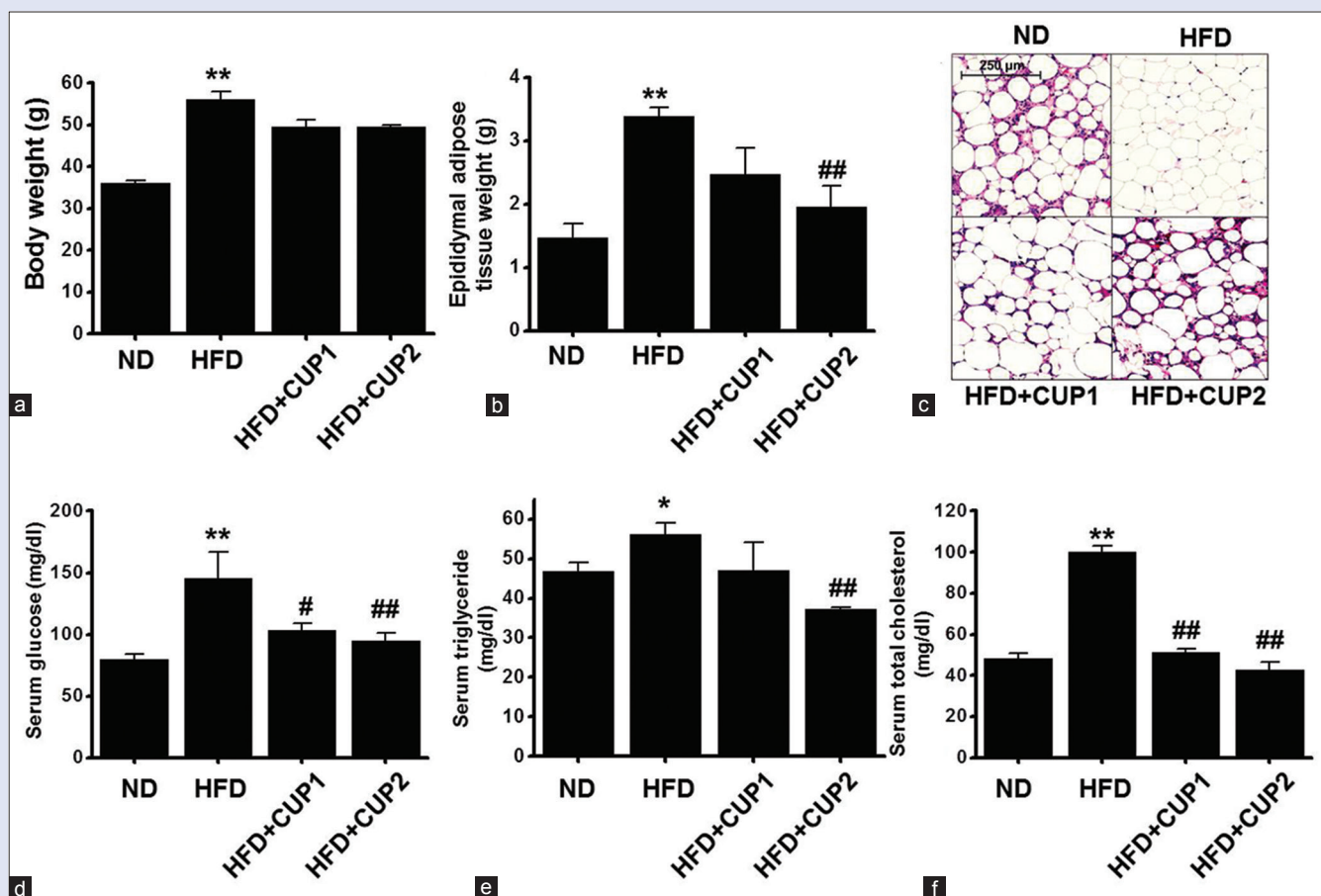
45%–61%, with a 12-h light/dark cycle, and were given free access to food and water. C57BL/6 mice were fed a normal diet (ND) or an HFD for 6 weeks. Thereafter, the HFD-fed mice were randomly divided into the following three groups ( $n = 6/\text{group}$ ): HFD (DW treated) group, HFD + low-dose herbal medicines (250  $\mu\text{g}/\text{mL}$ ) group, and HFD + high-dose herbal medicines (500  $\mu\text{g}/\text{mL}$ ). The experimental diets were the AIN93G diet, which contained 60% kcal fat, and the control diet contained 10% kcal fat. Herbal medicines were administered orally three times a week for 8 weeks. Animal care and experiments were conducted according to the guidelines issued by the Institutional Animal Care and Use Committee of Pusan National University (Busan, South Korea; Approval no. PNU-2018-1832) and those issued by the National Institutes of Health in the Guide for the Care and Use of Laboratory Animals.

## Histological analysis

Epididymal adipose and liver tissues were isolated from the mice, dissected, and fixed in 10% buffered formalin. Fixed tissues were embedded in paraffin and 5- $\mu\text{m}$  sections were prepared using a frozen microtome (HM560H, Microm Laboratory, Walldorf, Germany). Epididymal adipose sections were stained with hematoxylin and eosin (H and E).



**Figure 1:** *Rehmanniae radix* prevents high-fat diet-induced obesity and ameliorates serum biochemical parameters. C57BL/6 mice were fed a normal diet or high-fat diet for 6 weeks, and a low (*Rehmanniae radix* 1, 250  $\mu\text{g}/\text{mL}$ ) or high (*Rehmanniae radix* 2, 500  $\mu\text{g}/\text{mL}$ ) dose of *Rehmanniae radix* was administered to the high-fat diet-fed mice for an additional 8 weeks. (a) Final body weight. (b) Final epididymal adipose tissue weight. (c) H and E staining (scale bar, 250  $\mu\text{m}$ ). (d) Serum glucose level. (e) Serum triglyceride level. (f) Serum total cholesterol level. The data are presented as the mean  $\pm$  standard errors of means for 6 mice. \*\* $P < 0.01$  vs. normal diet fed mice. # $P < 0.05$ , ## $P < 0.01$  versus high-fat diet-fed mice alone



**Figure 2:** *Citrus unshiu* peel prevents high-fat diet-induced obesity and ameliorates serum biochemical parameters. C57BL/6 mice were fed a normal diet or high-fat diet for 6 weeks, and a low (*Citrus unshiu* peel 1, 250  $\mu$ g/mL) or high (*Citrus unshiu* peel 2, 500  $\mu$ g/mL) dose of *Citrus unshiu* peel was administered to the high-fat diet-fed mice for an additional 8 weeks. (a) Final body weight. (b) Final epididymal adipose tissue weight. (c) H and E staining (scale bar, 250  $\mu$ m). (d) Serum glucose level. (e) Serum triglyceride level. (f) Serum total cholesterol level. The data are presented as the mean  $\pm$  standard errors of means for 6 mice. \* $P < 0.05$ , \*\* $P < 0.01$  versus normal diet fed mice. # $P < 0.05$ , ## $P < 0.01$  versus high-fat diet-fed mice alone

### Analysis of serum biochemical parameters

After fasting for 12 h, the mice were sacrificed. Blood samples were collected and centrifuged at 1000  $\times$ g for 15 min at 4°C to obtain serum, and the serum was stored at -80°C until needed for analysis. The concentrations of glucose, triglycerides, and total cholesterol were determined using commercial analysis kits (Asan diagnostics, Seoul, South Korea).

### Statistical analysis

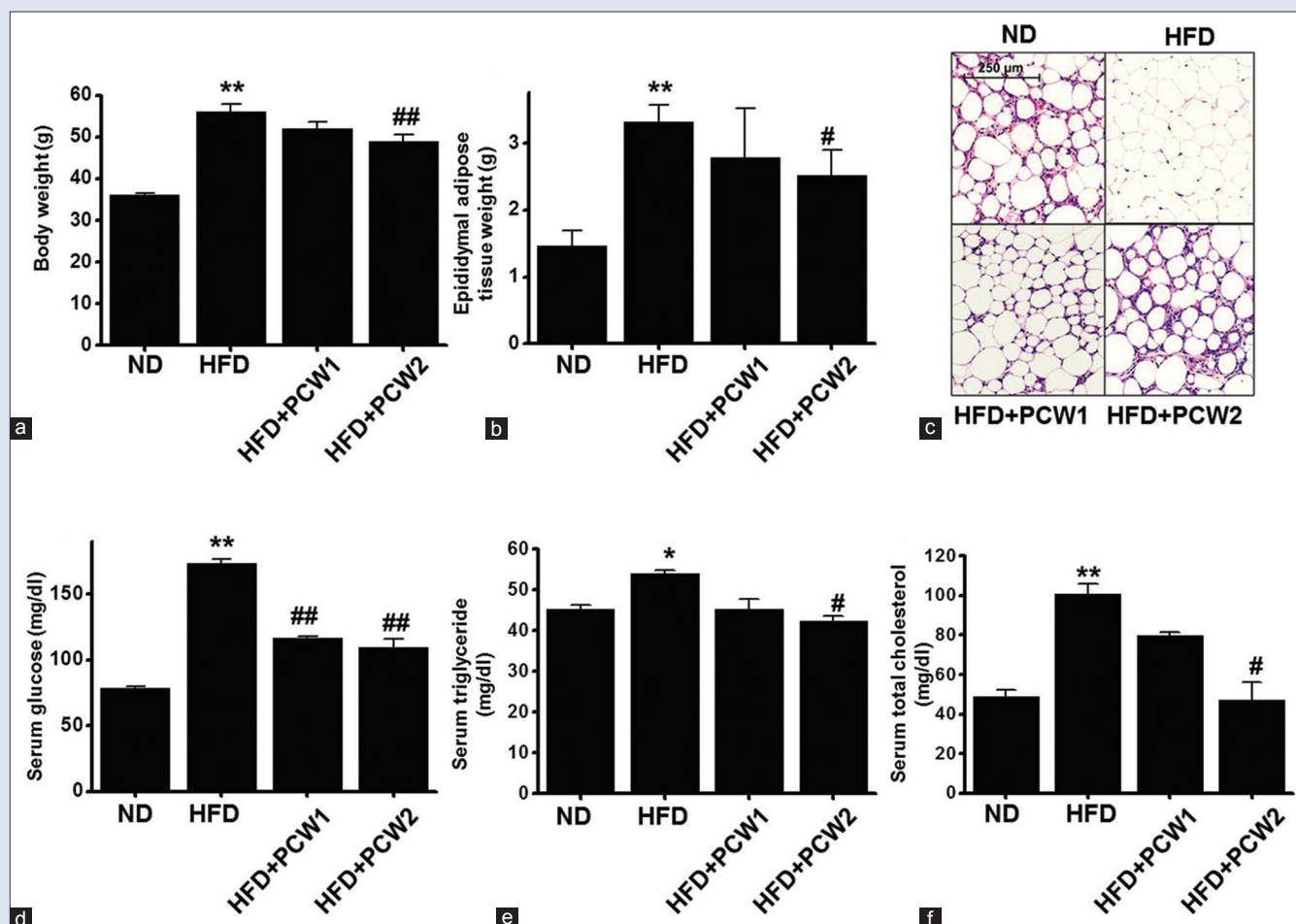
The results are expressed as means  $\pm$  standard errors of means. *N* values refer to the number of separate cells examined. Multiple comparison testing was performed using one-way ANOVA with Bonferroni's *post hoc* comparison.  $P < 0.05$  was considered statistically significant.

## RESULTS

### Effects of *Rehmanniae radix*, *Citrus unshiu* peel, and *Poria cocos* wolf on high-fat diet-induced obesity

We investigated the anti-obesity effect and effect on glucose levels of RR, CUP, and PCW in HFD-induced obese mice. To this end, 6-week-old mice were fed an HFD or ND for 6 weeks, and the HFD-fed mice were further administered a low (250  $\mu$ g/mL) or high dose (500  $\mu$ g/mL) of RR, CUP, and PCW for 8 weeks. As shown in Figures 1-3, HFD

feeding for 14 weeks resulted in a significant increase in body weight [Figures 1a, 2a, and 3a] and epididymal adipose tissue weight [Figures 1b, 2b, and 3b] compared to those in the ND mice. However, the high dose of RR and PCW effectively lowered both the body weight and epididymal adipose tissue weight. H and E staining also indicated that the HFD resulted in increased average adipocyte size in epididymal adipose tissue compared to average adipocyte size in the ND mice, whereas the low and high doses of RR, CUP, and PCW administration efficiently reduced the adipocyte enlargement [Figures 1c, 2c, and 3c]. These results demonstrated that RR, CUP, and PCW prevented HFD-induced body weight gain and adiposity. Furthermore, we examined the serum biochemical profiles of HFD-induced obese mice to confirm the anti-obesity effects of RR, CUP, and PCW. Compared to the ND mice, the mice fed an HFD had significantly higher serum levels of glucose [Figures 1d, 2d, and 3d], total triglycerides [Figures 1e, 2e, and 3e], and total cholesterol [Figures 1f, 2f, and 3f]. However, administration of the low and high doses of RR, CUP, and PCW efficiently reduced the glucose, triglyceride, and total cholesterol serum levels, indicating that RR, CUP, and PCW administration improved glucose and lipid homeostasis in the HFD-induced obese mice. These results suggested that RR, CUP, and PCW ameliorated the increase in glucose levels and prevented the HFD-induced obesity.



**Figure 3:** *Poria cocos* wolf prevents high-fat diet-induced obesity and ameliorates serum biochemical parameters. C57BL/6 mice were fed a normal diet or high-fat diet for 6 weeks, and a low (*Poria cocos* wolf 1, 250  $\mu$ g/mL) or high (*Poria cocos* wolf 2, 500  $\mu$ g/mL) dose of *Poria cocos* wolf was administered to the high-fat diet-fed mice for an additional 8 weeks. (a) Final body weight. (b) Final epididymal adipose tissue weight. (c) H and E staining (scale bar, 250  $\mu$ m). (d) Serum glucose level. (e) Serum triglyceride level. (f) Serum total cholesterol level. The data are presented as the mean  $\pm$  standard errors of means for 6 mice. \* $P < 0.05$ , \*\* $P < 0.01$  versus normal diet fed mice. # $P < 0.05$ , ## $P < 0.01$  versus high-fat diet-fed mice alone

## DISCUSSION

TCM has a history of more than 3000 years of use in both China and Korea. It is the most important reason for which herbal medicines are widely perceived as natural and safe.<sup>[9]</sup> Herbal medicines are used for health promotion, treatment of various diseases, including metabolic syndromes, and as therapy for chronic conditions.

Metabolic syndrome is a complex disorder consisting of obesity, diabetes mellitus, hyperglycemia, hypertension, and hyperlipidemia.<sup>[10,11]</sup> Obesity and diabetes are two major diseases in the metabolic syndrome. TCM prefers the use of herbology, a Chinese art of combining different medicinal herbs into one treatment through prescription.<sup>[12]</sup> Each patient should receive personalized herbology because of differences in their backgrounds. For personalized treatment, multiple herbs are often prescribed to make up a special formula and a single herb is not often used individually.<sup>[13]</sup> In the present study, we investigated the anti-obesity effects in HFD-induced obese mice.

HFD-induced obese mice are a widely used animal model and show the characteristics of weight gain, hyperlipidemia, hyperglycemia, hyperleptinemia, insulin resistance, and systematic low-grade inflammation associated with obesity in men.<sup>[14-16]</sup>

Obesity is characterized by the accumulation of excessive body fat<sup>[17]</sup> and in Asia is defined as a body mass index of  $>25$  kg/m<sup>2</sup>.<sup>[18]</sup> Various factors contribute to the development of obesity in men, such as food, environment, lifestyle, drugs, and endocrinal disorders.<sup>[19]</sup> Among these factors, changes in dietary habits, particularly with respect to the increased intakes of fat, caloric sweeteners, and animal-sourced food, are considered to be major causative factors of the recent obesity pandemic.<sup>[16,20]</sup> The incidence of obesity and obesity-related diseases, such as type 2 diabetes mellitus and nonalcoholic fatty liver disease, is increasing worldwide, which threatens quality of life and human health.<sup>[21]</sup> In TCM theory, it was believed that the spleen and stomach provide the nutritional basis for the acquired constitution and are the source of qi and blood. The spleen and stomach of TCM are different from those of Western medicine, which generally refers to the gastrointestinal and other digestive organs. In the theory of the spleen and stomach, the authors suggested that weakness of the spleen and stomach was the cause of all diseases.<sup>[22]</sup> Traditional herbal medicine contains fiber, polyphenols, and polysaccharides that exert prebiotic-like activities in the prevention and treatment of obesity-related diseases.<sup>[21]</sup> Recently, obesity and obesity-related diseases have become a worldwide health crisis. It is important for clinical nurses to have a comprehensive understanding of the prevention of obesity and obesity-related diseases. Although lifestyle

modulations are the first-line treatment, clinical nurses should be aware of current and future TCM medication management to help the patient live a healthy life.<sup>[21]</sup>

PCW has been used in China for the treatment of many types of diseases with signs of a deficiency of yin in the kidneys, and it improved insulin resistance in diabetes mellitus, in part, by regulating the canonical PI3K/Akt signaling pathway in the liver.<sup>[23]</sup> Mice supplemented with CUP extract also showed a significant decrease in body weight gain and body fat mass,<sup>[24]</sup> and hepatic steatosis and hypertriglyceridemia were ameliorated via the inhibition of gene expression and increased activation of lipogenic enzymes and fatty acid oxidation in the liver.<sup>[25]</sup> Therefore, CUP had a beneficial effect on the metabolic syndrome.<sup>[25]</sup> In addition, RR is effective for treating patients with various inflammatory and metabolic diseases, such as high blood pressure, diabetes, and obesity.<sup>[26]</sup>

In the present study, we evaluated the *in vivo* anti-obesity effects of PCW, CUP, and RR in HFD-induced obese mice. Compared to the ND mice, the HFD-fed mice had a higher final body weight, epididymal adipose tissue weight, and serum levels of glucose and triglycerides. However, the administration of PCW, CUP, and RR significantly lowered the final body weight, epididymal adipose tissue weight, and serum levels of glucose and triglycerides [Figures 1-3], demonstrating that PCW, CUP, and RR prevented HFD-induced obesity and ameliorated the serum metabolic parameters. We also determined that the administration of HFD resulted in a white-colored fatty liver in the mice, but the administration of PCW, CUP, and RR to the HFD-fed mice resulted in conversion to a relatively healthy liver (data not shown). Because it is composed of several medicinal herbs which possess beneficial effects against obesity, PCW, CUP, and RR might manage these symptoms of obesity by exerting multidirectional effects. However, we do not currently know the active components of PCW, CUP, and RR. Therefore, in the future, we will determine the efficacious components to clarify the precise mechanisms of these herbal medicines in obesity.

The fruit of *Schisandra chinensis* has been used as a traditional herbal medicine in China, Korea, Japan, and Russia. *S. chinensis* contains various bioactive constituents, including lignans, triterpenoids, polysaccharides, and sterols.<sup>[27]</sup> Gomisin N (GN) is a lignan from *S. chinensis* and was reported to exhibit hepatoprotective,<sup>[28]</sup> anticancer,<sup>[29]</sup> and anti-inflammatory effects.<sup>[30]</sup> Jang *et al.*<sup>[31]</sup> suggested that GN has potential as a novel agent for the prevention and treatment of obesity. The high dose of GN effectively lowered both the body weight and epididymal adipose tissue weight. H and E staining also showed that HFD feeding resulted in increased average adipocyte size in epididymal adipose tissue, compared to average adipocyte size in the ND mice, whereas the high dose of GN administration efficiently reduced the adipocyte enlargement.<sup>[31]</sup> Furthermore, the mice fed an HFD had significantly higher serum levels of glucose, total triglycerides, and total cholesterol. However, the high dose of GN efficiently reduced the serum levels of glucose, triglycerides, and total cholesterol, indicating that GN administration improved glucose and lipid homeostasis in the HFD-induced obese mice.<sup>[31]</sup> In this study, PCW, CUP, and RR to HFD-fed mice resulted in a reduction in the final body weight gain, fat pad weight, adipocyte size, and serum levels of glucose, triglycerides, and hepatic triglycerides in the HFD-induced obese mice. When we compared with GN, the degrees of decrease of these PCW, CUP, and RR were more potent or similar. Therefore, we think that PCW, CUP, and RR are one of the novel agents for the prevention and treatment of obesity.

Metabolic syndrome is a cluster of biochemical and physiological abnormalities associated with the development of cardiovascular disease and obesity.<sup>[32]</sup> In Europe and Asia, the prevalence of metabolic syndrome has been increasing dramatically.<sup>[32]</sup> Metabolic syndrome and associated

diseases are a major burden in the health-care system in many industrialized countries. For the management of metabolic syndrome, TCM is an excellent representative in alternative and complementary medicines with a complete theory system and substantial herb remedies. Therefore, in the treatment of metabolic syndrome, the importance of TCM might be increased.

## CONCLUSION

The present study shows that administrations of PCW, CUP, and RR to HFD-fed mice result in a reduction in the final body weight gain, fat pad weight, adipocyte size, and serum levels of glucose, triglycerides, and hepatic triglycerides in the HFD-induced obese mice. Based on these results, we conclude that PCW, CUP, and RR are potential novel agents for the prevention and treatment of metabolic syndrome.

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## Conflicts of interest

There are no conflicts of interest.

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