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Antihyperlipidemic activity of myricetin

Z.Z. Yang, J.Q. Zhang, B.B. Shi, J.Q. Qian* ⓘ and H. Guo

College of Pharmaceutical Science, Zhejiang University of Technology, 18 Chaowang Road, Hangzhou 310014, China

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ABSTRACT

Myricetin has been reported to have a wide variety of beneficial physiological functions. The present study investigated the antihyperlipidaemic activity of myricetin against hyperlipidaemia of high-fat diet-fed obese rats. The four-week antihyperlipidaemic activity was assayed by giving different doses of myricetin to hyperlipidaemic rats. Results showed that myricetin could reduce the harm caused by oxidative stress, decrease thiobarbituric acid reactive substances value, and decrease total cholesterol and triacylglycerol levels of hyperlipidaemic rats. Quantitative analysis of gene expression showed that myricetin's lipid-lowering activity can be activated by downregulating gene expression of fatty acid synthase (FAS) and peroxisome proliferator-activated receptor-γ (PPARγ) with upregulation of hormone-sensitive lipase (HSL) mRNA level. Thus, myricetin had significant health benefits and could be explored as a potentially promising dietary supplement for treating hyperlipidaemia.

1. INTRODUCTION

Hyperlipidaemia is a disease characterised by a disorder in lipid metabolism, manifesting as abnormally elevated levels of plasma lipids (including triglycerides and cholesterol) or lipoproteins. Usually, this type of disease is closely associated with cardiovascular disease, fatty liver

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* Corresponding author. E-mail: qianjq757@163.com

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disease, cancer, etc (Gao et al., 2013). The incidence of hyperlipidaemia and its complications has increased significantly in the last few decades. Statins (hydroxy methylglutaryl coenzyme A reductase inhibitors) are typical antihyperlipidaemia drugs, but they account for 61% of side effect types of all antihyperlipidaemic drugs (Jacquet et al., 1993). It can cause certain damage to the skin, digestive system, liver, and kidney. It may be accompanied by severe myolysis side effects and certain neurotoxicity, among which muscle pain caused by myolysis side effects is only triggered by statins. However, plants usually contain phytochemicals with various physiological activities, including some compounds with high activity and almost non-toxic side effects, such as some flavonoids, and appropriate supplementation helps prevent various diseases (O'Day, 2023).

Myricetin (3,3′,4′,5,5′,7-hexahydroxyflavone) is a dietary flavonol without toxicity (Huwait et al., 2023). The compound exhibits many activities, including strong antioxidant, antineoplastic, antihyperlipidaemic, and antiinflammatory (Singh and Bast, 2015; Semwal et al., 2016). Myricetin can reduce blood lipids (He et al., 2016) and improve fatty liver caused by hyperlipidaemia (Xia et al., 2019). The study on myricetin's *in vivo* antihyperlipidaemic activity remains limited, nonetheless. In the present study, we investigated the activity of high-purity myricetin on a high-fat diet (HFD) feeding induced hyperlipidaemia rats to reveal whether myricetin could effectively improve hyperlipidaemia.

Lipogenesis and lipolysis are major factors affecting lipid accumulation in tissues. Fatty acid synthase (FAS) mainly exists in adipose tissues and is critical to lipogenesis, which is an important regulator of triacylglycerol homeostasis (Loftus et al., 2000). Hormone-sensitive lipases (HSL) in the human body mainly catalyse the hydrolysis of triacylglycerol and their metabolites to produce fatty acids, which then enter mitochondria to participate in oxidative reactions and energy supply. This step plays an important role in lipid metabolism (Zechner and Langin, 2014). Peroxisome proliferator-activated receptor gamma (PPARγ), primarily located in adipose and immune tissues, plays an indispensable role in adipogenesis and lipid redistribution (Chen et al., 2014). In this study, we have shown that myricetin may prevent the development of hyperlipidaemia via down-regulating FAS and PPARγ expression and up-regulating HSL expression. The animal experiment shows that myricetin could improve hyperlipidaemia.

2. MATERIALS AND METHODS

2.1. Chemicals

The crude extract of myricetin (51.3% content of myricetin) was extracted from *Myrica rubra* in Ningbo, Zhejiang Province with 95% ethanol. High-purity myricetin was prepared by silica gel column chromatography with 70% ethanol as the eluent. The high-purity eluent was pooled, and most of the ethanol was removed by spin evaporation. High purity myricetin sample (98.1%, HPLC) was prepared by vacuum freeze drying of concentrated myricetin aqueous solution. The characterisation data obtained by liquid chromatography, nuclear magnetic resonance, and mass spectrometry were consistent with the literature (Qian et al., 2022).

The DNA Ladder and agarose were purchased from Dalian Takara (Dalian, China). Diethyl pyrocarbonate, TRIzol reagent, M-MLV reverse transcriptase, PCR kit (Cat No. YSP97313), and fluorescent quantitative PCR kit (Cat. No. YSP97316) were purchased from Sangon Biotech (Shanghai, China). Tris base and ethylene diamine tetraacetic acid were from Promega

(Madison, WI, USA). All other reagents were from Sigma–Aldrich (St. Louis, MO, USA), except where specified otherwise.

2.2. Quantitative detection and nuclear magnetic characterisation of myricetin

The High-Performance Liquid Chromatography (HPLC) conditions were: instrument Agilent 1200 (Santa Clara, USA), Eclipse XDB-C18 silica gel column (4.6 × 150 mm, 5 μm); mobile phase: methanol: water: acetic acid = 50:49:1 (v/v/v); injection volume: 5 μL; column temperature: 30 °C; flow rate: 1.0 mL min^{-1}; UV absorption detector; detection wavelength: 292 nm. The myricetin sample obtained by purification was detected qualitatively using a standard substance of 99.5% purity. The purity of the myricetin sample was 98.1% by HPLC (Fig. 1).

The nuclear magnetic spectrum (Avance III 500 MHz, Bruker, Billerica, USA) of myricetin is shown in Fig. 2A (^{13}C NMR) and Fig. 2B (^{1}H NMR). The peaks around the δ40 of the chemical shift were solvent DMSO-d6 peaks, and δ93.1 to 175.7 representing 15 carbons with 13 different chemical shifts (Fig. 2A). The δ2.51 and 3.36 in Fig. 2B were solvent DMSO-d6 and water peaks, respectively. δ6.18 to 12.51 represent 10 hydrogens with 8 different chemical shifts, respectively. The NMR data are as follows: ^{13}C NMR (500 MHz, DMSO-d6): 93.1 (C-8), 98.1 (C-6), 102.9 (C-10), 107.1 (C-2′, C-6′), 120.7 (C-1′), 135.8 (C-3, C-4′), 145.7 (C-3′, C-5′), 146.8 (C-2), 156.0 (C-9), 160.7 (C-5), 163.8 (C-7), 175.7 (C-4). ^{1}H NMR (500 MHz, DMSO-d6): 6.18 (d, J= 1.85 Hz, 1H, H-6), 6.37 (d, J = 1.80 Hz, 1H, H-8), 7.25 (s, 2H, H-2′, 6′), 8.84 (s, 1H, 4′-OH), 9.24 (s, 2H, 3′, 5′-OH), 9.36 (s, 1H, 3-OH), 10.80 (s, 1H, 7-OH), 12.51 (s, 1H, 5-OH).

The molecular formula of myricetin is $C_{15}H_{10}O_{8}$. The molecular structure is 3,5,7,3′,4′,5′ hydrogen atoms at the aromatic ring skeleton formed by hydroxyl substitution. The nuclear magnetic spectrum of the sample and the standard nuclear magnetic data (Devi et al., 2015) were compared and the structure of myricetin was qualitatively analysed to confirm the molecular structure of the myricetin sample.
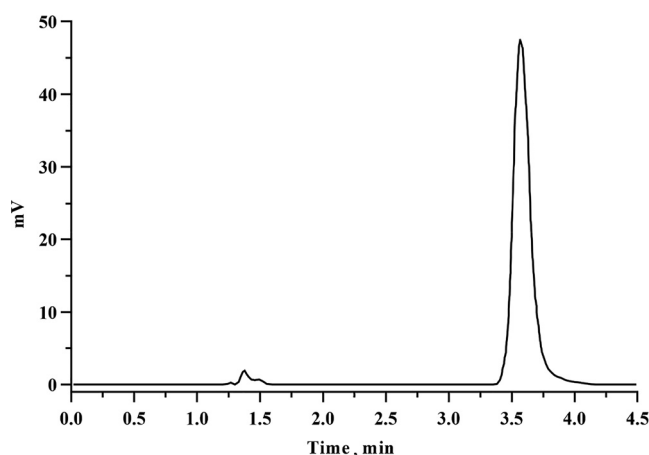

Fig. 1. Chromatogram of myricetin sample

Fig. 2. NMR spectra of myricetin sample (A: ^{13}C NMR, B: ^{1}H NMR)

2.3. Animals and experimental design

For this experiment, male Wistar rats (weight 180 ± 10 g) were purchased from the Laboratory Animal Center of Zhejiang Medical Sciences Academy. They were housed at ambient temperature (20 ± 2 °C) with an illumination period of 12 h light per day. Animals were fed standard rat food (Slaccas, Shanghai, China) with unlimited water intake. Food intake and body weight of rats were measured weekly during the experimental period.

After 5 days of adaptive observation, the hyperlipidaemia model in rats was established after confirming that the purchased rats had no abnormal state. The rats were randomly assigned to either the normal diet group (10 rats) fed with standard rat food or the high-fat diet group (50 rats) fed with high-fat forage (Slaccas, Shanghai, China) composed of standard rat food (73.8%, w/w), lard (15%, w/w), powdered egg yolk (10%, w/w), cholesterol (1%, w/w), and bile salt (0.2%, w/w).

Poor water solubility of myricetin results in excessive drug loss during animal gavage. Myricetin powder was weighed precisely and mixed evenly into 1% carboxymethyl cellulose sodium (CMC) to prepare CMC suspension of different drug concentrations to avoid this situation (Fukuchi et al., 2004).

After 2 weeks of feeding, blood samples of HDF group rats were collected by venipunctures of the posterior orbital nerve plexus to measure their lipid levels. The lipid levels of all HFD group rats were in line with the indicators of hyperlipidaemia, which proved that the hyperlipidaemia model was successfully established. The HFD-fed rats were randomly divided into 5 groups with 10 rats in each group (Chat et al., 2013). The model control group, positive control group, and three dosage groups were set up, respectively. The given simvastatin dosage for the positive control group was 50 mg kg^{-1} d^{-1}. The dosage of myricetin in the experimental group was 100, 200, and 400 mg kg^{-1} d^{-1} (He et al., 2016). Myricetin-admin suspensions of 50, 100, and 200 mg mL^{-1} were prepared and administered intragastrically at a volume of 2 mL kg^{-1} once a day. A 25 mg mL^{-1} suspension of Simvastatin-CMC was administered intragastrically at a fixed volume of drug liquid. During the administration period of the drug treatment group, the model control group and the normal group were treated with the same method by gavage of 1% CMC solution with the same volume as administration. In addition, except for the normal group, rats in the other groups were continuously fed with HFD. After 4 weeks of treatment, all animals were fasted for 12 h followed by collection of blood samples. At the end of the study, the animals were euthanised by cervical dislocation under ether anaesthesia. The liver and white adipose tissue (WAT) from the viscera and subcutaneous layer were taken out, rinsed with a physiological saline solution, weighed, and immediately stored at -70 °C.

The experiment was approved by the Experimental Animal Ethics Committee of Zhejiang University of Technology (Ethical approval number: 20200511051).

2.4. Blood lipid detection

After 4 weeks of myricetin treatment, the animals were fasted for 12 h then blood samples were collected without anticoagulation. Serum samples were separated from the blood by clotting for 2 h at room temperature and centrifuging at $1,500\,g$ for 15 min. To assess the serum levels of total cholesterol (TC), triglycerides (TG), and low-density lipoprotein cholesterol (LDL-C), detection kits of TC (Cat. No. A111-2-1, 100T/96 samples), TG (Cat. No. A110-2-1, 100T/96

samples), and LDL-C (Cat. No. A113-2-1, 100T/96 samples) were used (Nanjing Jiancheng Bioengineering Inst., Nanjing, China).

2.5. Lipid peroxidation, SOD, and GSH-Px assays

To assess the activity of two liver antioxidant enzymes, superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px), specific detection kits of SOD (Cat. No. A001-1-2, 100T/96 samples) and GSH-Px (Cat. No. A005-1-2, 100T/48 samples) were used (Nanjing Jiancheng Bioengineering Inst., Nanjing, China). The results were expressed as U/mg protein. Lipid per-oxidation was measured with the thiobarbituric acid reactive substances (TBARS) of commer-cially available kits (Cat. No. A106-1-3, 100T, Nanjing Jiancheng Bioengineering Inst., Nanjing, China) and expressed as nmol of malondialdehyde equivalents (MDAeq) per milligram of protein.

2.6. Gene expression studies

Total RNA was extracted from the WAT of the rat. The first-strand cDNA was synthesised using the Revert Aid First Strand cDNA synthesis kit (Cat. No. 04896866001, Roche, Germany). The expression of selected genes was analysed by real-time PCR (StepOnePlus, Thermo Fisher Scientific, Waltham, USA). PCR conditions were as follows: 1 cycle of 94 °C for 4 min, 36 cycles of 94 °C for 30 s, 55 °C for 45 s, and 72 °C for 60 s, followed by 1 cycle of 72 °C for 10 min. Relative gene expression was calculated by normalising cycle threshold (Ct) values for genes of interest with Ct values for β-actin using the delta-delta Ct method. Primer sequences were as follows: HSL (forward: 5′-GGAGCATACAAA CGCAAC-3′; reverse: 5′-TCCCGTAGGTCATAG-GAGAT-3′); FAS (forward: 5′-CAGA GGGTGGTTGTTAGAAAGAT-3'; reverse: 5′-ACTGCCG-CATCCTCTTCCTC-3′); PPARγ (forward: 5′-CACAAGAGCTGACCCAATGGT-3′; reverse: 5′-CGCAGATCAGCAGACT CTGG-3′); β-actin as a reference gene (forward: 5′-ACTGCCG-CATCCTCT TCCTC-3′; reverse: 5′-CTCCTGCTTGCTGATCCACATC-3′). The PCR products were analysed by agarose gel electrophoresis using 1.5% gel.

2.7. Statistical analysis

All data are represented as the mean ± SD. Statistical analysis was conducted with SPSS 20.0 (SPSS Inc., Chicago, USA). The data were analysed by t-test. P-values less than 0.05 or 0.01 were considered statistically significant.

3. RESULTS AND DISCUSSION

3.1. Effects of myricetin on blood lipid

Serum and liver lipid levels of rats at the end of the experiments showed that the HFD caused the elevation of serum TC, TG, and LDL-C concentrations in rats. Serum TC, TG, and LDL-C levels in all hyperlipidaemic rats were equivalent before being given myricetin. The test results four weeks after the administration are shown in Table 1.

The present study demonstrates myricetin-modified serum lipid levels by reducing TC and TG contents in rats fed a high-fat diet for 4 weeks. This diet, enriched in lard (15%), egg yolk

Table 1. Detection results of blood lipids in 4 weeks of myricetin feeding ($\bar{x} \pm SD$)

Groups	TC (mmol L^{-1})	TG (mmol L^{-1})	LDL-C (mmol L^{-1})
Normal control group	5.05 ± 0.31	1.62 ± 0.57	0.41 ± 0.06
Model control group	9.27 ± 0.54[##]	1.96 ± 0.15[#]	0.82 ± 0.20[##]
Positive control group	6.92 ± 0.56[**]	1.43 ± 0.17[**]	0.42 ± 0.09[**]
100 mg kg^{-1} d^{-1} of myricetin	7.52 ± 0.55[*]	1.54 ± 0.08[*]	0.49 ± 0.21[**]
200 mg kg^{-1} d^{-1} of myricetin	6.83 ± 0.51[**]	1.32 ± 0.23[**]	0.43 ± 0.09[**]
400 mg kg^{-1} d^{-1} of myricetin	5.04 ± 0.42[**]	1.22 ± 0.21[**]	0.36 ± 0.15[**]

TC: total cholesterol; TG: triglycerides; LDL-C: LDL-cholesterol. [#]$P < 0.05$, [##]$P < 0.01$ VS. normal control group. [*]$P < 0.05$, [**]$P < 0.01$ vs. model control group.

powder (10%), cholesterol (1%), and bile salt (0.2%), was used because the combination of these components in a diet is universally used to induce hyperlipidaemia in rats and mice (Zhang et al., 2013). The results showed that the rats fed a high-fat diet had a higher concentration of TC, TG, and LDL-C in their sera than those fed a standard diet, indicating that the hyperlipidaemia model was successfully established.

Chronic administration of myricetin for 28 days, at the doses of 100 mg kg^{-1} d^{-1}, 200 mg kg^{-1} d^{-1}, and 400 mg kg^{-1} d^{-1}, provoked a significant reduction in serum levels of TC, TG, and LDL-C compared with vehicle-treated hyperlipidaemic rats. In the study, we showed that myricetin administration lowered lipid profile in HFD-feeding induced hyperlipidaemic rats.

Many researches have demonstrated that HFD-induced hyperlipidaemia has tight relations with oxidative stress (Jenkins et al., 2008). Recently, some preclinical observations have demonstrated that hyperlipidaemia promotes the accumulation of oxidised low-density lipoprotein (Ox-LDL) in the arterial wall, which plays a major role in the initiation and progression of atherosclerosis associated with hyperlipidaemia (Shan et al., 2019). In this work, we investigated the activities of three major defensive antioxidant agents. Our data showed that myricetin exhibited excellent antioxidant capacity to improve the activities of antioxidant enzymes (GSH-Px and T-SOD) and suppress lipid peroxidation (TBARS values) in hyperlipidaemic rats. This result suggest that the potential health benefits associated with myricetin have been partially attributed to its antioxidative properties.

3.2. Effects of myricetin on HFD-induced oxidative stress in liver

The effect of myricetin on the level of MDA equivalents of the rats' liver was determined, and the result is presented in Fig. 3A. The liver MDA equivalents significantly increased from 1.53 ± 0.36 nmol mg^{-1} protein of the normal rats to 2.94 ± 0.47 nmol mg^{-1} protein of the HFD-fed rats. By the administration of myricetin, the increase of MDA equivalents was significantly inhibited compared with the vehicle-treated HFD-fed group. Figure 3B shows the results that GSH-Px activity significantly increased in myricetin-treated groups compared to the vehicle-treated HFD-fed group. Moreover, Fig. 3C shows that an HFD-fed-induced decrease in SOD activity was prevented by the administration of myricetin at moderate (200 mg kg^{-1} d^{-1}) and high doses (400 mg kg^{-1} d^{-1}).

Moreover, myricetin has a unique chemical structure. The combined contribution of hydroxyl groups at the 3 and 5 positions and three continuous hydroxyl groups at positions 3′, 4′,
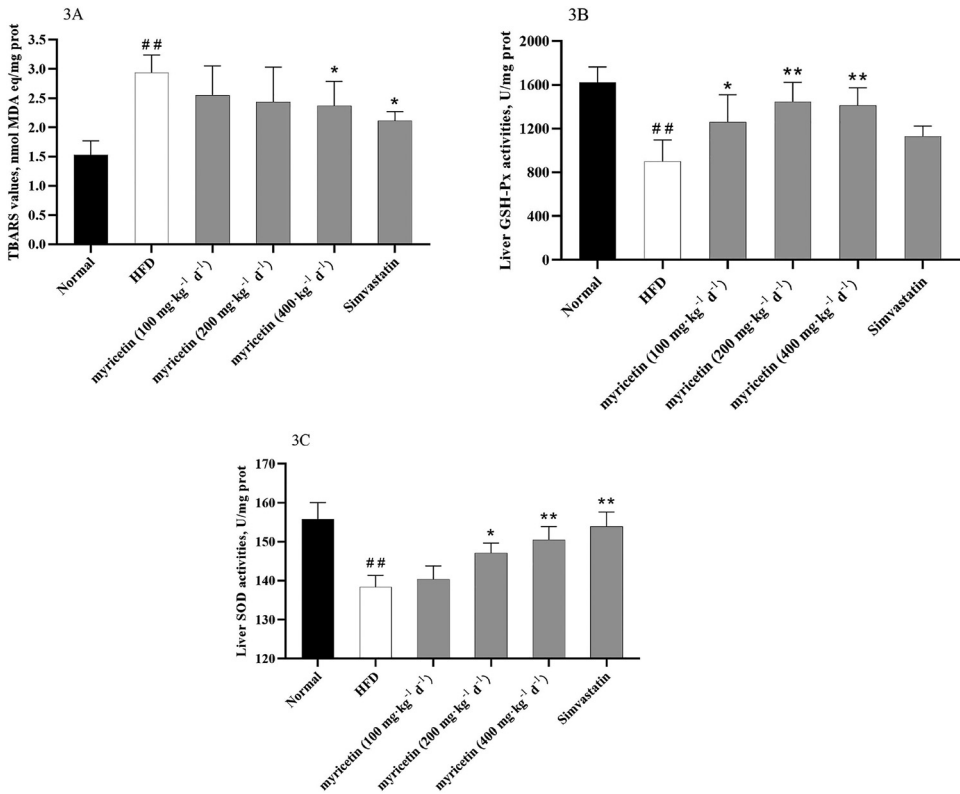
Fig. 3. Effects of myricetin or simvastatin (50 mg kg^{-1} d^{-1}) on liver TBARS (3A), GSH-Px (3B), and SOD (3C) in the rats fed a high-fat diet for 4 consecutive weeks.
All data are presented as the mean $\pm$ SD. [##]$P < 0.01$ VS. normal group. [*]$P < 0.05$, [**]$P < 0.01$ VS. HFD group

and 5′ can increase the antioxidant effectiveness of myricetin (Ma et al., 2022). T-SOD and GSH-Px are the major antioxidant enzymes that play a pivotal role in scavenging oxygen free radicals that protect the pancreatic tissue against oxidative stress injury. MDA concentration reflected the degree of the lipid peroxides. In our study, STZ treatment caused significant oxidative stress, indicated by significantly high levels of MDA and low activities of T-SOD and GSH-Px in the diabetic rats relative to the normal rats. Whereas, administration of myricetin prevents hepatic oxidative stress damage *via* normalising MDA, T-SOD, and GSH-Px levels. Complementing our findings, earlier studies have reported that myricetin could have antioxidant activity (Baldissera et al., 2016).

3.3. Effects on gene expression

The effects of myricetin on gene expression of FAS, HSL, and PPARγ are shown in Fig. 4A, all doses of myricetin increased the expression level of HSL. The low (100 mg kg^{-1} d^{-1}), moderate (200 mg kg^{-1} d^{-1}), and high doses (400 mg kg^{-1} d^{-1}) of myricetin significantly increased
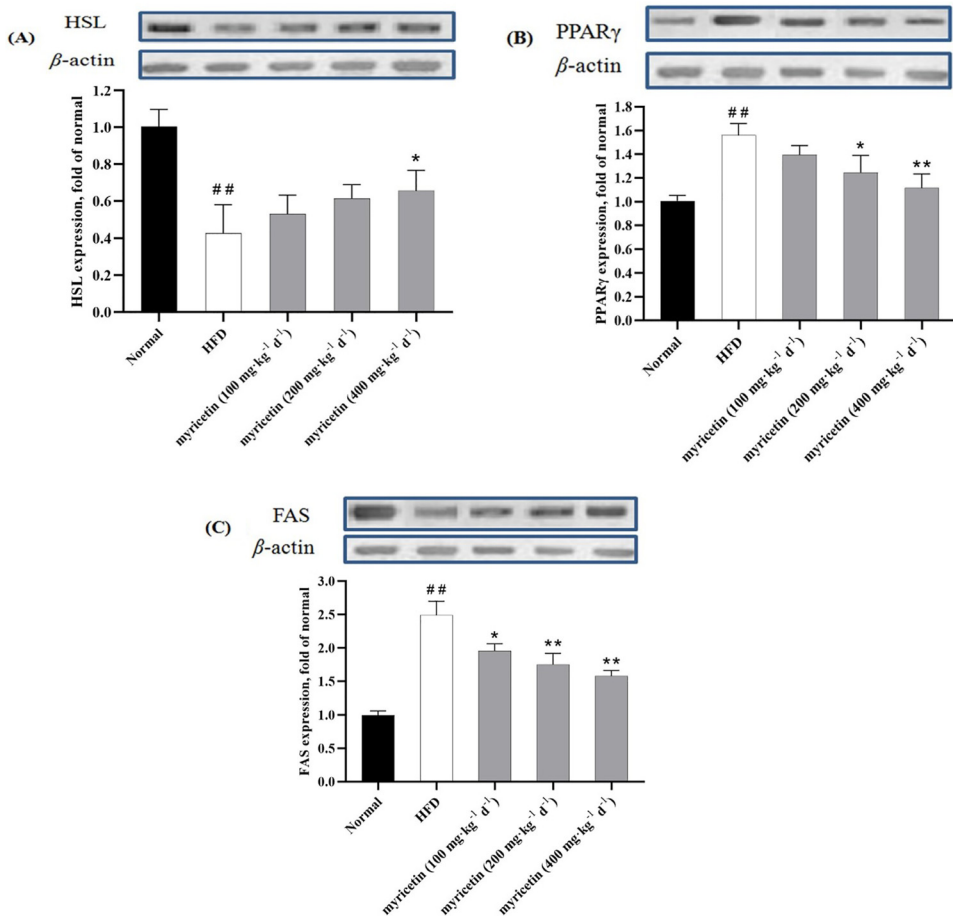
Fig. 4. Effects of myricetin on HSL (A), PPARγ (B), and FAS (C) in the rats fed a high-fat diet for 4 consecutive weeks.
All data are presented as the mean ± SD. $^{##}P < 0.01$ vs. normal group. $^{*}P < 0.05$, $^{**}P < 0.01$ vs. HFD group

expression levels of HSL (23.26%, 41.86%, and 53.49%, respectively). Figure 4B displays that the expression level of PPARγ significantly decreased in myricetin-treated groups compared to the vehicle-treated HFD-fed group. Furthermore, Fig. 4C shows that the expression level of FAS was significantly higher in HFD-fed rats than that in the normal group; and those levels were lower by 36% in the myricetin (400 mg kg^{-1} d^{-1}) treated group.

HSL, abundant in the fatty tissue and other cholesterol-producing tissues, is the catabolic rate-limiting enzyme of lipolysis in animals, and plays a role in many aspects of lipid metabolism, as it hydrolyses triacylglycerol to monoacylglycerol and free fatty acid (Haemmerle et al., 2002; Gong et al., 2010). Recently, an increasing number of natural active substances have been extracted from plant and animal sources with antihyperlipidaemic effects *via* affecting lipolysis in adipocytes and hyperlipidaemic rats (Sarnaizul et al., 2013). In our

study, the expression level of the HSL gene significantly increased in the adipose tissue at myricetin administration. The result showed that myricetin might reduce lipids through increasing HSL gene expression.

Additionally, lipogenesis-associated genes such as FAS and PPARγ have also been reported as key transcriptional factors for lipid accumulation (Mangelsdorf et al., 1995). FAS plays an important role in denoting lipogenesis by converting acetyl-CoA and malonyl-CoA to palmitate and is related to various diseases such as obesity, cardiovascular disease, and cancer (Yeh et al., 2003). FAS may facilitate the synthesis and cytoplasmic storage of large triacylglycerols. When the FAS level is too high, triglyceride synthesis can be enhanced considerably (Zechner et al., 2009). Mice that are genetically engineered to overexpress an exogenous FAS gene, display increased lipid accumulation and lipogenesis (Postic and Girard, 2008). We also assayed the effect of myricetin on the expression of PPARγ, which is a lipid-activated transcription factor and highly expressed in white adipose tissue (Braissant et al., 1996), plays a central role in adipogenesis and lipid repartition (Weigt et al., 2013). Over-expression of PPARγ in adipocytes could selectively induce the production of lipoprotein lipase, regulate the signalling transduction, slow lipolysis speed, and increase the triacylglycerol synthesis (Ying et al., 2013). In macrophages, PPARγ-dependent lipid uptake and storage were initially suggested to increase foam-cell formation and, potentially, atherosclerosis (Lehrke and Lazar, 2005). We found that the expression levels of PPARγ and FAS genes in white adipose tissue in myricetin-treated HFD-fed rats significantly decreased as compared with the vehicle-treated counterparts. The results indicated that the action of myricetin to decrease lipid accumulation in hyperlipidaemic rats involved preventing lipogenesis beside stimulating lipolysis.

4. CONCLUSIONS

Myricetin exhibited excellent antihyperlipidaemic effects *in vivo*, with the improvement of oxidative status. It significantly lowers the concentration of serum TC, TG, and LDL-C. These effects appear to be mediated through down-regulation of adipogenesis-related genes (PPARγ) and downstream genes (FAS), and up-regulation of lipolysis-related genes (HSL). Taken together, our results suggest that myricetin can serve as a dietary supplement in the management of hyperlipidaemia.

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