Rubus Suavissimus Alleviates High-fat Diet-induced Lipid Metabolism Disorder via Modulation of the PPAR / SREBP Pathway in Syrian Golden Hamsters

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Research

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Abstract

Background: *Rubus suavissimus* S. Lee (RS), a sweet plant distributed in southwest of China and used as beverage and folk medicine, has been reported to improve the obesity phenotype and hyperlipidemia. However, the exact molecular mechanism remains unknown.

**Aim of the study:** In this study, we aimed to investigate the preventive effects of RS in lipid metabolism disorder golden hamsters caused by high-fat diet and elucidate the potential molecular mechanisms.

**Method:** Five groups of male LVG Syrian golden hamsters were compared: normal diet group (ND), high-fat diet group (HFD), Xuezhikang Cap group (140 mg/kg; HFD+XZK), low dose of RS group (3.6 g/kg; HFD+RSL), high dose of RS group (7.2 g/kg; HFD+RSH). After eight weeks, biochemical and pathological analyses were conducted to evaluate the preventive effect of RS on lipid metabolism. RT-qPCR, and western blotting analysis were used to explore the potential mechanism underlying.

**Results:** Supplementation of a high-fat diet with RS prevented the symptoms of lipid metabolism disorder of golden hamsters and alleviated liver injury. RS upregulated the expression of the PPAR pathway mediators PPARγ and PPARα as well as its downstream targets CCAAT/enhancer binding protein α (C/EBPα), glucose transporter 4 (Glut4), lipoprotein lipase (LPL), and fatty acid binding protein 4 (aP2). Also, RS downregulated the expression of sterol regulatory element binding protein 1 (SREBP1) and its downstream targets acetyl-CoA carboxylase 1 (ACC1), stearoyl-CoA desaturase-1 (SCD1), and fatty acid synthase (FAS).

**Conclusions:** Our data suggest that RS prevents lipid metabolism disorder golden hamsters in high-fat diet and alleviates liver injury through the regulation of the SREBP/PPAR signaling pathway.

Background

Abnormal lipid metabolism results in lipid metabolism disorder, a complex group of pathological conditions closely related to diabetes, obesity, and hypertension, and which is characterized by dyslipidemia, lipoidosis, or fatty acid metabolism disorder [1].

Among others, lipid metabolism is regulated by the peroxisome proliferator-activated receptor (PPAR) and the sterol-regulatory element binding protein 1 (SREBP) signaling pathways. The PPAR pathway is involved in adipocyte differentiation, fatty acid conversion, and lipid synthesis. Upon their activation, the PPARs PPARα, PPARβ, and PPARγ regulate the expression of downstream target genes such as fatty acid binding protein 4 (aP2), glucose transporter 4 (Glut4), lipoprotein lipase (LPL), and CCAAT/enhancer binding protein α (C/EBPα) which, in itself, cooperates with PPARs to regulate the expression of aP2 [2–4]. The SREBP pathway controls liver fatty acid biosynthesis through an interplay of SREBP1, fatty acid synthase (FAS), acetyl-CoA carboxylase 1 (ACC1), and stearoyl-CoA desaturase-1 (SCD1) [5–8]. Therefore, the regulation of PPAR/SREBP signaling pathway will contribute to the regulation of lipid metabolism disorders [9–11].
Nowadays, traditional herbal teas and functional food ingredients once again became important mediators in improving body lipid content. *Rubus suavissimus* S. Lee (Rosaceae), also known as “sweet tea”, is widely distributed in southwest China and consumed as beverage or used for the treatment of clearing heat, moistening lungs, expectorant, relieving cough, as well as an adjuvant treatment of diabetes and hypertension [12]. RS contains diterpene compounds such as rubusoside - a natural sweetener which is 115 times sweeter than sucrose, flavonoids, polyphenols, and triterpenoid compounds [13–16]. Recent research showed that the total extract of RS, the polyphenols of RS, or purified rubusoside affect lipid metabolism disorder and improve the obesity phenotype [17], hyperlipidemia, or reduce blood lipid content and blood pressure [18–20]. However, the exact molecular mechanism still remains unknown.

In this study, we first analyzed RS with ultra-performance liquid chromatography (UPLC) and identified eight constituents. Then, we analyzed the preventive effect of RS on lipid metabolism disorder in Syrian golden hamsters induced by a high-fat diet by comparing the physiological and biochemical indexes, and the gene and protein levels of specific players of the PPAR/SREBP signaling pathway in the liver.

**Materials And Methods**

**Materials and reagents**

*Rubus suavissimus* S. Lee (RS) sample was collected from Dayaoshan Natural Plant Development Co., Ltd. (Guangxi, China) and authenticated by Professor Lanlan FAN. The voucher specimens (voucher number: 0468) were deposited in the Herbarium of School of Pharmacy, Guangxi University of Traditional Chinese Medicine.

Xuezhikang capsules (XZK) were purchased from Beijing Peking University Weixin Biotechnology Co., Ltd (Beijing, 20180809). Gallic acid, caffeic acid, rutin, ellagic acid, hyperin, isoquercitrin, rubusoside, and kaempferol were purchased from Chengdu Pufeider Co., Ltd (Chengdu, China) with purity > 98%. HPLC grade acetonitrile was purchased from Fisher (Fair Lawn, New Jersey, USA). Deionized water was obtained from a Milli-Q water purification system (Millipore, Bedford, MA, USA). The other solvents of analytical grade were purchased from Shanghai Chemical Factory (Shanghai, China).

The antibodies recognizing PPARγ, PPARα, C/EBPα, Glut4, LPL, FAS, and aP2 were purchased from Proteintech (Wuhan, China); the antibodies recognizing β-actin and ACC1 were purchased from BOSTER (Wuhan, China); the antibody recognizing SREBP1 was purchased from Bioss (Beijing, China); and the antibody recognizing SCD1 was purchased from Abcam (United Kingdom).

**Preparation of UPLC fingerprint sample**

RS powder (0.5 g) was dissolved in 10 mL 60% ethanol-water solution, vortexed for 30 s, ultrasonically extracted for 1 h, and filtered through a 0.22 µm filter for analysis. Gallic acid, caffeic acid, rutin, ellagic acid, hyperoside, isoquercetin, rubusoside, and kaempferol were dissolved in methanol.
UPLC analysis conditions

Chromatographic analysis was performed on an Agilent 1290 infinity II UPLC system equipped with a 1290 VWD detector, a 1290 vial sampler, and a 1290 high speed pump. The chromatography separations were performed on an InertSustain C\textsubscript{18} LC column (2 µm, 3.0 × 150 mm, GL Sciences Inc., Japan) with a column temperature of 40 °C. The mobile phase was composed of 0.1% aqueous phosphoric acid (A) and acetonitrile (B) with a gradient elution: 0–6 min, 10% B; 6–21 min, 10% − 24% B; 21–43 min, 24% − 80% B; 43–45 min, 80% − 95% B; 45–46 min, 95% B; 46–46.5 min, 95% − 5% B; 46.5–48 min, 5% B. The flow rate of mobile phase was 0.35 mL/min, the UV detector wavelength was 254 nm, and the injection volume was 1 µL.

Animals and treatment

Thirty-five eight weeks old male LVG hamsters (90–110 g, Vital River Laboratory Animal Technology Co., Ltd., Beijing, China) were housed in a temperature-controlled (22–25°C) room on a 12-hour light-dark cycle with free access to food and water. After adapting to the environment for one week, the animals were randomly divided into five groups: normal diet group (ND), high-fat diet (HFD), XZK group (positive drug, a traditional Chinese medicine, 140 mg/kg; HFD + XZK), low dose of RS group (3.6 g /kg; HFD + RSL), and high dose of RS group (7.2 g/kg; HFD + RSH). The high-fat diet consisted of 78.75% basic feed, 10% lard, 10% corn oil, 1% cholesterol, and 0.25% sodium cholate. Throughout the experiment, the food intake, energy intake, and body weight of the animals was recorded daily. At the end of week eight, after withholding food for 12 h, the animals were anesthetized by intraperitoneal injection of 3% pentobarbital sodium (0.3 mL/100 g), and blood samples were taken from the eye nerve plexus veins. Afterwards, the animals were euthanized by cervical dislocation. Serum samples were collected and centrifuged at 3500 rpm for 10 min at 4 °C. Serum total cholesterol (TC), triglyceride (TG), aspartate aminotransferase (AST), and alanine aminotransferase (ALT) were obtained by automatic biochemical analyzer (HITACHI 7600, Hitachi High-Tech Co., Ltd., Japan). The liver was dissected, weighed, frozen sections were taken, and oil red O staining was used to mark the fat. Liver TC and TG were measured with a commercial kit according to the manufacturer's instructions (Applygen Technologies Inc., Beijing, China). The remaining samples were frozen in liquid nitrogen and stored at -80°C.

Real-time quantitative PCR analysis of liver tissues

Total RNA was extracted with Trizol (Tiangen, Beijing) and reverse transcribed into cDNA. The primers of aP2, SREBP1, C/EBP\alpha, PPAR\alpha, LPL, Glut4, PPAR\gamma, ACC1, SCD1, FAS, and \beta-actin genes were designed using Primers3 (www.primer3.ut.ee) and are shown in Supplementary Table 1. PCR reactions were performed in 20 µL containing cDNA, specific primers and ChamQ Universal SYBR qPCR Master Mix (Vazyme, Nanjing, China) on a Light Cycler 96 (Roche) real-time fluorescence quantitative PCR instrument with the following cycling conditions: 120 s at 95 °C, followed by 45 cycles of 95 °C 10 s, 50–57 °C 15 s (Table S1), and 72 °C 30 s. All reactions were conducted in triplicates. Beta-actin was used as an internal reference to calculate the relative expression of the genes of interest.

Western blot analysis of liver tissues
The frozen liver tissue was homogenized in RIPA lysis buffer (Beyotime, Shanghai, China) containing 1% protease inhibitor cocktail (CWBI, Beijing, China) and 1 mM PMSF (Beyotime, Shanghai, China), and centrifuged at 12000 g for 20 min at 4 °C. The supernatant was collected and the total protein concentration was determined with a BCA protein concentration determination assay kit (Beyotime, Shanghai, China). The protein was denatured after mixing with loading buffer (Beyotime, Shanghai, China), separated by 8% or 12% sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE), and transferred to a polyvinylidene fluoride (PVDF) membrane. The membrane was blocked at room temperature for 1–1.5 h with 5% skimmed milk powder and incubated overnight with the respective antibody on a shaker at 4 °C. The next day, the membrane was labeled with an HRP-labeled Goat Anti-Mouse IgG(H + L) for 2 h at room temperature. Protein bands were visualized with enhanced chemiluminescence (ECL, Thermo Scientific) and analyzed with Image Lab software.

Statistical analysis

Data was analyzed with SPSS (IBM, version 24.0). All data were expressed as mean ± SD. One-way ANOVA was used to analyze significant differences among multiple groups, while couple comparisons were performed via the t-test. Statistical values of $P < 0.05$ and $P < 0.01$ were considered significant.

Results

Establishment of RS UPLC fingerprint

Compared to the retention time of each reference substance, the following eight compounds were identified from the extraction of *Rubus suavissimus*: gallic acid, caffeic acid, rutin, ellagic acid, hyperoside, isoquercetin, rubusoside, and kaempferol (Fig. 1).

RS alleviates lipid metabolism disorder in high-fat diet golden hamsters

Next, we verified the preventive effect of RS on the development of lipid metabolism disorder in Syrian golden hamsters fed a high-fat diet. First, we examined the effect of RS on food intake, body weight, and energy intake. At the beginning of the experiment, there were no significant differences in daily food intake, energy intake, and body weight between the groups; however, throughout the later stages of the experiment, the food- and energy intake as well as body weight of golden hamsters in HFD + RSL, HFD + RSH, and HFD + XZK groups were significantly lower compared to the HFD group (Fig. 2a-c). These observations indicated that RS can maintain the body weight of golden hamsters on a high-fat diet and limit their energy intake.

Then, we analyzed whether RS affects the lipid metabolism on hamsters. For that, we analyzed the liver index and measured liver and serum levels of total cholesterol (TC) and triglyceride (TG) as well as serum levels of low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C).
The liver of golden hamsters on a high-fat diet was white and cloudy with a hard texture whereas the livers of animals belonging to the other groups were more ruddy and shiny with a soft texture. Based on oil Red O staining of liver tissue sections, animals in HFD had more liver lipid droplets compared to animals in ND. However, animals on a high-fat diet supplemented with XZK – a preparation of red yeast rice and a traditional Chinese medicine currently used to lower cholesterol – or RS had less hepatic lipid droplets compared to animals in HFD (Fig. 3).

Compared with ND (liver index 2.91%, liver TC and TG were 367.58 and 705.35 µmol/L, serum TC, TG, and LDL-C were 3.35, 1.52, and 0.66 mmol/L, respectively), animals in the HFD group showed an enhanced liver index (4.63%), increased liver TC (1015.62 µmol/L) and TG (838.07 µmol/L) levels, as well as enhanced serum TC (11.71 mmol/L), TG (8.37 mmol/L), and LDL-C (4.43 mmol/L) levels (Fig. 2d-j). Compared to HFD, a high-fat diet supplemented with RS resulted in a dose-dependent reduction of liver TC (779.17 and 757.57 µmol/L for RSL and RSH) and TG (715.67 and 589.57 for RSL and RSH), serum TC (9.68 and 7.71 mmol/L for RSL and RSH), TG (3.51 and 2.18 mmol/L for RSL and RSH) and LDL-C (3.28 or 2.14 mmol/L for RSL and RSH). Of note, supplementation of a high-fat diet with a low-dose RS increased the level of HDL-C (4.47 and 4.01 mmol/L) in serum (Fig. 2g). Whereas animals in HFD had significantly higher serum levels of alanine aminotransferase (ALT, 289.17 U/L) and aspartate aminotransferase (AST, 248.33 U/L) compared to ND (ALT: 183.83, AST: 94.83 U/L), this was prevented by supplementation of the high-fat diet with RS (ALT: 171.57 and 164.63 U/L; AST: 88.83 and 50.55 U/L in RSL and RSH, respectively, Fig. 2k-l). These results indicated that RS can regulate abnormal blood lipids and liver lipids in high-fat diet golden hamsters and attenuate liver injury.

**RS regulates lipid metabolism disorders through an up-regulation of the PPAR signaling pathway**

In order to verify whether the PPAR signaling pathway is involve in the RS-mediated attenuation of the lipid metabolism disorder process, we examined the expression of PPARα, PPARγ as well as their downstream targets aP2, C/EBPα, Glut4, and LPL in the liver of golden hamsters at both the mRNA and protein level. Upon activation, PPARs regulate the expression of their downstream targets such as aP2, Glut4, LPL, and CCAAT binding protein enhancer α (C/EBPα). Interestingly, while being regulated by PPARs, C/EBPα can also bind its recognition site within the PPARγ promoter region and co-regulate the expression of aP2 [4]. Furthermore, activation of PPARα promotes lipid oxidative metabolism through enhancing the expression levels of fatty acid transporters, lipoprotein lipase (LPL), apolipoprotein, and the fatty acid oxidase system in the liver. The above process stimulates the uptake of fatty acids and thus reduces the concentration of blood lipids [22].

Compared to ND, animals in the HFD group had significantly lower mRNA levels of PPARα and PPARγ as well as aP2, C/EBPα, Glut4 and LPL (Fig. 4a-f). Relative to HFD, animals in HFD + XZK had similar levels of PPARα and PPARγ, but significantly higher levels of aP2. Compared to HFD, animals in HFD + RSL had significantly higher levels of PPARα and the downstream targets aP2 and Glut4, whereas animals in HFD + RSH had significantly higher mRNA levels of PPARα and PPARγ as well as aP2, Glut4, and C/EBPα.
These observations suggested that supplementation of RS prevents the high-fat diet-induced inhibition of PPARα and PPARγ mRNA in the liver of golden hamster and preserved the expression of aP2, C/EBPα, and Glut4.

At the protein level, animals in HFD had significantly lower PPARγ levels compared to ND as well as significantly lower levels of the downstream targets aP2, Glut4, C/EBPα, and LPL. Animals in HFD + XZK had significantly higher levels of PPARα as well as Glut4, C/EBPα, and LPL compared to HFD. Animals in HFD + RSL had significantly higher levels of PPARα and the downstream targets aP2, Glut4, C/EBPα, and LPL whereas animals in HFD + RSH had significantly higher levels of PPARα as well as Glut4, C/EBPα, and LPL (Fig. 4k).

**RS inhibits lipid synthesis through down-regulation of the SREBP signaling pathway**

Sterol regulatory element binding proteins (SREBPs) are cholesterol-sensitive transcription factors located on the endoplasmic reticulum and nuclear membrane [23] which regulate the metabolism of fatty acids, glucose, and TG by regulating the expression of, among others, fatty acid synthase (FAS), acetyl-CoA carboxylase (ACC1), and stearoyl-CoA dehydrogenase 1 (SCD1) [5–8, 24, 25]. Under normal circumstances, continuous activation of SREBP promotes the expression of key mediators of lipid synthesis leading to lipid accumulation. Upon high cellular cholesterol levels, SREBP shear activation protein (SCAP) and insulin-induced gene (INSIG) form a complex with SREBP and lock the latter on the endoplasmic reticulum membrane thereby reducing the expression of cholesterol and fatty acid synthase [26]. Upon activation, SREBP1 promotes lipid synthesis through upregulation of downstream target genes, such as ACC1, FAS, and SCD-1 [6, 7].

In order to verify whether RS attenuates the lipid metabolism disorder through the SREBP1 signaling pathway, we examined the expression of SREBP1 and its downstream targets in the liver of golden hamsters at both the mRNA and protein level. Compared to ND, animals in HFD had significantly higher mRNA levels of SREBP1 and of its targets FAS and SCD-1 in the liver. Compared to HFD, animals in HFD + XZK, HFD + RSL, and HFD + RSH had significantly lower mRNA levels of SREBP1 as well as ACC1, FAS, and SCD-1 (Fig. 4g-j). At the protein level, animals in HFD had significantly higher levels of ACC1 compared to ND. Compared to HFD, animals in HFD + XZK had significantly lower levels of SREBP1, ACC1, FAS, and SCD-1. Compared to HFD, animals in HFD + RSL had significantly lower levels of ACC1, FAS, and SCD-1 whereas animals in HFD + RSH had significantly lower levels of SREBP1, ACC1, FAS, and SCD-1 (Fig. 4k). These observations suggested that RS can prevent the high-fat diet-induced activation of the SREBP1 pathway.

**Discussion**

In the current study, we evaluated the preventive effect of RS on high-fat diet-induced lipid metabolism disorder in a golden hamster model. Conform previous reports, we showed significantly higher serum HDL-C levels upon a long-term high-fat diet [21]. Additionally, we observed increased levels of TC, TG,
LDL-C, ALT, and AST in serum as well as enhanced levels of TC and TG in liver and a higher liver index in these animals. Supplementation of the high-fat diet with RS preserved liver morphology and prevented the corresponding increase in serum TC, TG, LDL-C, ALT, and AST as well as liver TC, TG, and index. These observations suggest the potential of RS to mediate lipid metabolism disorder and to reduce high-fat diet-associated liver injury.

Next, we showed that RS significantly prevented the high-fat diet induced decrease of PPARα, PPARγ, aP2, C/EBPα, and Glut4 mRNA in the liver and verified these observations for PPARα, aP2, C/EBPα, and Glut4 at the protein level. These observations indicate that RS activates PPARα and/or PPARγ paralleled by enhanced expression levels of aP2, C/EBPα, Glut4, and LPL suggesting an alleviation of the lipid metabolism disorder through a participation in adipocyte differentiation and lipid synthesis.

We also demonstrated the capacity of RS to prevent the high-fat diet-induced increase of SREBP1, FAS, and SCD1 mRNA as well as ACC1 protein expression levels in the liver of golden hamsters. The fact that animals receiving RS had even significantly lower levels of SREBP1, SCD, and FAS compared to control animals further suggests that RS efficiently can downregulate the expression of SREBP1, ACC1, and SCD1 through inhibition of the SREBP signaling pathway. Taken together, our data suggest that RS alleviates lipid metabolism disorders through regulation of the SREBP/PPAR signaling pathways and participation in fat differentiation, fatty acid conversion, and fatty acid biosynthesis (Fig. 5).

Finally, based on the UPLC fingerprint of RS, we identified eight compounds and confirmed that RS is rich in rubusoside, flavonoids, and polyphenols. However, the exact potential mechanism of the identified compounds on lipid metabolism still needs to be further analyzed. Also, whether these active compounds act directly or indirectly on the PPAR / SREBP pathway or through alternative mechanisms needs to be further explored.

**Conclusions**

In the current study, we provided evidence that RS alleviates high-fat diet-induced lipid metabolism disorder and liver injury in a golden hamster model. Additionally, at the molecular level, we showed the capacity of RS to upregulate the expression of the PPAR pathway-mediators PPARα, PPARγ, C/EBPα, aP2, Glut4, and LPL as well as to downregulate the expression of the SREBP pathway mediators SREBP1, ACC1, SCD1 and FAS. Taken together, these observations suggest that RS mediates lipid metabolism disorders by interfering in fat differentiation, fatty acid conversion, and fatty acid biosynthesis through regulation of the SREBP/PPAR signaling pathways.

**Abbreviations**

ACC1, acetyl-CoA carboxylase 1; ALT, alanine aminotransferase; aP2, fatty acid binding protein 4; AST, aspartate aminotransferase; C/EBPα, CCAAT/enhancer binding protein α; FAS, fatty acid synthase; Glut4, glucose transporter 4; HDL-C, high-density lipoprotein cholesterol; HFD, high-fat diet; LDL-C, Low-density
lipoprotein cholesterol; LPL, lipoprotein lipase; PPAR, peroxisome proliferator-activated receptors; PPARγ, peroxisome proliferator-activated receptor γ; PPARα, peroxisome proliferator-activated receptor α; PPRE, peroxisome proliferator responsive element; RS, *Rubus suavissimus*; Rbs, rubusoside; RXR, retinoid X receptors; S1P, Site 1 protease; S2P, Site 2 protease; SCD1, stearoyl-CoA desaturase 1; SRE, Sterol-regulatory element; SREBP, sterol regulatory element binding proteins; SREBP1, sterol regulatory element binding protein 1; TC, total cholesterol; TG, triglycerides; XZK, XuezhiKang Cap.

**Declarations**

**Author’s contributions**

Lanlan Fan and Xiaosheng Qu conceived and designed the research. Manjing Jiang and Li Li conducted the experiments. Shuai Huang, Manjing Jiang and Li Li analyzed the data and prepared the manuscript. Wanfang Huang participated in the experimental operation and data analysis. All authors reviewed and approved the manuscript.

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**Availability of data and materials**

All data included in this article are available from the corresponding author upon request.

**Ethics approval and consent to participate**

Animal care and procedures were approved by and conducted according to the standards of the Guangxi University of Chinese Medicine (Nanning, China).

**Consent for publication**

All authors have provided consent for publication in the journal of Chinese Medicine.
Declaration of competing interest

The authors have declared that no competing interest exists.

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