Magnesium lithospermate B improves metabolic changes in high-fat diet-fed rats with metabolic syndrome

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ABSTRACT

Danshen, the roots of Salvia miltiorrhiza, is a natural food and traditional Chinese herb possessing antidiabetic and antilipidaemic activities. In the present study, the beneficial effects and possible mechanisms of Magnesium lithospermate B (MLB), the major soluble constituent in Danshen, were investigated in a rodent model of metabolic syndrome induced by a high-fat diet (HFD). Daily supplementation of MLB improved obesity, hyperlipidaemia, hyperglycaemia, glucose intolerance, insulin resistance, and hepatic steatosis caused by HFD. Mechanistic studies showed that MLB caused a down-regulation of fatty acid transporter CD36 and lipogenic transcription factor sterol regulatory element-binding transcription factor 1c (SREBP1c) expression and an up-regulation of lipolytic transcription factor peroxisome proliferator-activated receptor-α (PPARα) expression and post-receptor insulin signalling. In addition, MLB supplementation attenuated proinflammatory cytokine and adipokine expression. These results suggest that MLB may be an active ingredient contributing to the beneficial effects of Danshen on insulin resistance as well as on metabolic syndrome.

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Keywords: High fat diets, Insulin resistance, Magnesium lithospermate B, Metabolic syndrome, Steatosis

1. Introduction

Herbal plants are important sources of biologically active compounds. Many functional foods based on traditional Chinese herbs promote human health beyond basic nutrition (Gao, Zhang, Liu, Xu, & Yang, 2013; Lee & Pan, 2013; Shashidhar, Giridhar, Udaya Sankar, & Manohar, 2013; Shi, Shahidi, & Ho, 2005). Danshen, the roots of medicinal plant Salvia miltiorrhiza, is traditionally regarded as an effective functional food for improving body function and has been utilized to treat a wide variety of diseases, particularly cardiovascular diseases (Chen et al., 2011; Huang et al., 2012; Lei & Chiou, 1986; Xie & Du, 2011). In China, numerous dosage forms of Danshen are commercialized and widely used, including tablets, capsules, granules, oral liquids, sprays, and dripping pills (Zhou, Zuo,
2. Materials and methods

2.1. Animals and drug treatment

Male Sprague-Dawley rats, weighing 150 ± 10 g, were purchased from BioLasco, Taiwan Co., Ltd. (Taipei, Taiwan) and housed in a standard controlled environment of 23 °C, 60% humidity and 12-h light/dark cycle. Rats were fed with a standard chow diet (calories provided by 28.5% protein, 13.5% fat, and 58% carbohydrate, 5001 Rodent LabDiet, St. Louis, MO, USA) or HFD (calories provided by 16% protein, 39.4% fat, and 44.6% carbohydrate, high-fat SSBX Rodent TestDiet, St. Louis, MO, USA) for 4 weeks according to previously reported paper (Hsu, Liao, Lee, Hsu, & Pan, 2013; Ji & Gong, 2008). This experimental course has been shown to significantly promote the development of obesity, liver injury, and relative metabolic abnormalities in animals. During the experimental period, animals were allowed free access to rat chow and tap water. The rats were randomly assigned into five groups (n = 6 per group): (i) normal diet control (NC) group: rats were fed with a normal control diet; (ii) HFD control (HC) group: rats were fed with a HFD; (iii) MLB 5 group: rats were fed with a HFD and supplemented with 5 mg/kg BW/day of MLB; (iv) MLB 10 group: rats were fed with a HFD and supplemented with 10 mg/kg BW/day of MLB; (v) MLB 20 group: rats were fed with a HFD and supplemented with 20 mg/kg BW/day of MLB. MLB, purified from KO DA Pharmaceutical Co., Ltd. (Taoyuan, Taiwan) with a purity of approximately 85%. Generally, the content of MLB in Danshen dry root was about 5 mg/g (Kasimu et al., 1998). The animal experiments were approved by the Institutional Animal Care and Use Committee of the National Chung-Hsing University (IACUC Approval No: 103-31).

2.2. Intraperitoneal glucose tolerance test (IPGTT)

IPGTT was performed in rats 3 weeks after MLB treatment. The fasting rats were postloaded with 2 gm glucose/kg BW by intraperitoneal injection and the venous bloods were withdrawn at 0, 30, 60, 90, and 120 min. The levels of glucose in blood samples were measured by ACU-CHEK® Active glucose meter with test strip (Roche, Mannheim, Germany). The area under the curve was calculated for glucose tolerance examination.

2.3. Analysis of blood biochemical

Four weeks after treatments, the blood samples were collected from overnight fasted rats. The plasma levels of aspartate transaminase (AST), alanine transaminase (ALT), total cholesterol (TC), triacylglycerol (TG), and high-density lipoprotein cholesterol (HDL-C) were analyzed by automated standardized procedures (Hitachi 717). The levels of insulin (Mercodia AB, Uppsala, Sweden), tumour necrosis factor-α (TNF-α), interleukin-6 (IL-6), and leptin (Quantikine R&D Systems, Minneapolis, MN, USA) were measured by rat enzyme linked immunosorbent assay (ELISA) kits.

2.4. Homeostatic model assessment index

Insulin resistance and β-cell function were validated from fasting insulin and glucose level by homeostasis model
HOMA insulin resistance index (HOMA-IR) was calculated as follows: HOMA-IR = fasting insulin (FPI: μIU/L) × fasting glucose (FPG: mmol/L)/22.5. The function of pancreatic β-cell was assessed by HOMA index (HOMA-B) as follows: [FPI × 20/FPG – 3.5].

2.5. Histological examination

After anaesthesia with Zoletil 50 (40 mg/kg, IP; Virbac Laboratories, Carros, France), the epididymal fats and livers were quickly removed 4 weeks after treatments. The resected tissues were fixed in 10% formalin and embedded in paraffin. The paraffin sections were stained with haematoxylin and eosin (H&E) for histological examination. Histological images were captured by a light microscope (Olympus, BX43, Tokyo, Japan) equipped with a digital camera (Cannon EOS 600D, Tokyo, Japan).

2.6. Liver lipid extraction and measurement

The extraction and measurement of hepatic lipids were carried out in accordance with our previously reported study (Folch, Lees, & Sloane Stanley, 1957). Liver tissues were minced, homogenized in 0.15 M NaCl (Sigma-Aldrich, St. Louis, MO, USA), and then vigorously mixed with equal volume of chloroform/methanol (2:1, v/v) (Sigma-Aldrich). After centrifugation at 400 × g for 5 min, the supernatants were collected for lipid measurement. The levels of hepatic cholesterol and triacylglycerol were analyzed using an enzymatic colorimetric assay, respectively (Human Gesellschaft für Biochemica und Diagnostica mbH, Wiesbaden, Germany).

2.7. Tissue preparation and Western blot analysis

After anaesthesia, the gastrocnemius muscles and livers were quickly removed, frozen in liquid nitrogen, and stored at −80°C until use. The excised tissues were homogenized with T-PER tissue protein extraction buffer (Pierce Biotechnology, Thermo-Fisher, Rockford, IL, USA) containing 1% protease inhibitor cocktail and 1% phosphatase inhibitor cocktail (Calbiochem, Biotechnology, Inc., CA) and 1% phosphatase inhibitor (Calbiochem, Biotechnology, Inc., CA, USA), SREBP1c, CD36 (1:1000; Novus Biologicals, Inc., Littleton, CO, USA), PPARα (1:1000; Pierce Biotechnology, Thermo-Fisher), GLUT2 (1:1000; Pierce Biotechnology, Thermo-Fisher), GLUT4 (1:100, Biovision, Mountain View, CA, USA), or GAPDH (1:20,000; Merck Millipore). After incubation with a 1:5000 dilution of anti-rabbit or anti-mouse IgG HRP-conjugated secondary antibody, the blots were developed using Immobilon™ Western Chemiluminescent HRP Substrate reagent (Merck Millipore) and quantified by chemiluminescence with MiniChemi I system (Beijing Sage Creation Science, Beijing, China). After normalizing with GAPDH, the relative protein intensity was expressed as folds of the content in the NC group.

2.8. Statistical analysis

All the data are presented as mean ± standard deviation (SD). The differences were analyzed by one-way analysis of variance (ANOVA) followed by post-hoc analysis of Duncan’s test to determine significant differences between the five groups. Statistical calculation was performed by SigmaStat (version 3.5). A level of P < 0.05 was considered to be statistically significant.

3. Results

3.1. Effects of MLB on animal growth and liver injury

The results showed that four weeks of HFD feeding increased the body weight gain (Fig. 1A) and average food intake (Fig. 1B) compared with rats fed with a normal diet. Daily supplementation of MLB had an inhibitory effect on body weight gain but no apparent effect on average food intake. The liver weight (Fig. 2A), epididymal fat weight (Fig. 1C), AST level, and ALT level

<p>| Table 1 – Effects of MLB on biochemical parameters in rat fed a normal diet or a high-fat diet for 4 weeks. |
|--------------------------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th></th>
<th>NC</th>
<th>HC</th>
<th>MLB 5</th>
<th>MLB 10</th>
<th>MLB 20</th>
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<tbody>
<tr>
<td>AST (U/L)</td>
<td>125.33 ± 18.00</td>
<td>170.17 ± 26.05†</td>
<td>153.33 ± 26.45</td>
<td>164.00 ± 24.02</td>
<td>152.33 ± 25.84</td>
</tr>
<tr>
<td>ALT (U/L)</td>
<td>46.50 ± 7.42</td>
<td>61.17 ± 6.49†</td>
<td>50.83 ± 17.01</td>
<td>44.17 ± 4.79†</td>
<td>38.83 ± 10.65†</td>
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<tr>
<td>Cholesterol (mg/dL)</td>
<td>38.83 ± 11.14</td>
<td>63.00 ± 11.06***</td>
<td>70.50 ± 7.06***</td>
<td>54.83 ± 4.58***†††</td>
<td>46.50 ± 8.26***†††</td>
</tr>
<tr>
<td>Triacylglycerol (mg/dL)</td>
<td>16.83 ± 4.26</td>
<td>47.50 ± 14.82***</td>
<td>56.83 ± 20.17***</td>
<td>31.17 ± 3.82††††</td>
<td>29.33 ± 8.04††††</td>
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<tr>
<td>Non-HDL-C (mg/dL)</td>
<td>11.50 ± 4.04</td>
<td>28.17 ± 9.15***</td>
<td>31.67 ± 5.13***</td>
<td>21.83 ± 3.92***</td>
<td>15.17 ± 2.79***</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>22.67 ± 10.46</td>
<td>13.00 ± 3.69</td>
<td>17.33 ± 1.51</td>
<td>23.00 ± 7.90</td>
<td>24.17 ± 7.19</td>
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<tr>
<td>IL-6 (pg/dL)</td>
<td>49.28 ± 5.04</td>
<td>59.39 ± 7.57</td>
<td>55.06 ± 12.83</td>
<td>47.50 ± 3.34</td>
<td>44.44 ± 3.57</td>
</tr>
<tr>
<td>TNFα (pg/dL)</td>
<td>1.19 ± 0.36</td>
<td>6.13 ± 1.59***</td>
<td>5.98 ± 2.06***</td>
<td>4.33 ± 1.20***††</td>
<td>3.71 ± 0.77***††</td>
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<tr>
<td>Leptin (pg/dL)</td>
<td>50.87 ± 6.09</td>
<td>217.40 ± 42.24***</td>
<td>206.20 ± 63.56***</td>
<td>145.83 ± 38.67***</td>
<td>134.30 ± 14.14***</td>
</tr>
</tbody>
</table>

ALT, alanine transaminase; AST, aspartate transaminase; HDL-C, high-density lipoprotein cholesterol; IL-6, interleukin 6; TNFα, tumour necrosis factors α; NC, normal diet control; HC, high-fat diet control; MLB5, high-fat diet with 5 mg/kg/day of MLB; MLB10, high-fat diet with 10 mg/kg/day of MLB; MLB20, high-fat diet with 20 mg/kg/day of MLB.

Data are expressed as mean ± SD (n = 6 per group).

* P < 0.05 and **P < 0.01 vs. NC group by one-way ANOVA.
† P < 0.05 and †††P < 0.001 vs. HC group by one-way ANOVA.
Table 1 of rats fed with a HFD were significantly higher than those of rats fed with a normal diet. MLB supplementation reduced HFD-induced increases, except AST level. The results suggest that MLB supplementation has beneficial effects in alleviating tissue weight gain and liver injury caused by a HFD.

### 3.2. Effects of MLB on lipid metabolism

In HFD rats, the plasma levels of cholesterol, triacylglycerol, and non-HDL-C were significantly elevated compared with those of normal diet rats. However, a HFD feeding decreased plasma level of HDL-C (Table 1). Those altered lipid profiles were improved in HFD rats supplemented with MLB. Since livers and adipose tissues are crucial organs for lipid deposition, morphological changes were examined in livers and epididymal fat pads. In examining the epididymal fat pads, H&E staining revealed an increment in adipocyte size in HFD rats compared with those in normal diet rats. The increment in adipocyte size in HFD rats was decreased by MLB supplementation (Fig. 1D). Results of morphological examination in livers showed that no morphological abnormalities were observed in normal diet rats. A substantial fat deposition in the hepatocytes was seen in HFD rats. MLB supplementation remarkably improved the liver histopathological changes induced by a HFD (Fig. 2B). In parallel to the observed histopathological improvement, the biochemical studies showed that MLB supplementation attenuated HFD-induced hepatic accumulation of cholesterol (Fig. 2C) and triacylglycerol (Fig. 2D). These findings suggest that MLB supplementation is capable of improving hyperlipidaemia and lipid deposition in HFD rats.

### 3.3. Effects of MLB on glucose metabolism

To examine the effects of MLB on glucose metabolism, several parameters reflecting insulin action were assessed. The analysis
of glucose tolerance was performed three weeks after treatments. Fig. 3A showed the blood glucose variations during the glucose tolerance test. As observed in Fig. 3B, HFD rats showed impairment in the clearance of blood glucose compared with those of normal diet rats. MLB supplementation improved the impairment in the clearance of blood glucose. At the end of experiment (four weeks), analysis of fasting blood glucose revealed that HFD increased its level and MLB supplementation markedly decreased the glucose level (Fig. 3C), indicating a hypoglycaemic effect. However, there was no significant difference in fasting insulin level among groups (Fig. 3D). Parallel assessments indicated that HFD rats showed impairment in insulin sensitivity and pancreatic β-cell function, as evidenced by increased HOMA-IR (Fig. 3E) and decreased HOMA-B (Fig. 3F), respectively. MLB supplementation improved those HFD-induced impairments. These results show that MLB supplementation may improve glucose intolerance, hyperglycaemia, and insulin resistance in HFD rats.

3.4. Effects of MLB on insulin signalling

Insulin plays a crucial role in the regulation of glucose and lipid metabolism (Saltiel & Kahn, 2001). To elicit the potential mechanisms underlying MLB-mediated improvement in metabolic abnormality of glucose and lipid, intracellular molecules of lipid metabolism and insulin action were analyzed in peripheral insulin targets, livers and skeletal muscles. Evidence suggests an important role of SREBP1c, CD36, and PPARα in regulating fatty acid transport, lipid metabolism, and hepatic lipid accumulation (Nguyen et al., 2008). As shown in Fig. 4A–D, HFD rats showed an up-regulated SREBP1c and CD36 as well as a down-regulated PPARα protein in livers. The alternation of those proteins was improved in HFD rats supplemented with MLB. Representative blots of Western blot analysis of insulin action-related molecules such as IRS1, PI3-k p85α, p-Akt-Ser, Akt, and GLUT2 were shown in Fig. 4A, E–H. Quantitative results showed that HFD significantly decreased hepatic expression...
of IRS1, PI3-k p85α, Akt phosphorylation, and GLUT2 compared with values obtained in normal diet rats. The alternation of these insulin signalling molecules was attenuated by MLB supplementation. Parallel studies showed similar alternations of IRS1, PI3-k p85α, Akt phosphorylation, and GLUT4 expression in gastrocnemius muscles (Fig. 5A–E). These results indicate that MLB supplementation improves lipid abnormality and insulin resistance in HFD rats by enhancing insulin signalling and lipid catabolism and attenuating lipid anabolism.

3.5. Effects of MLB on proinflammatory cytokine and adipokine production

Obesity and insulin resistance are accompanied by elevated expression of proinflammatory cytokines and adipokines (Antuna-Puente, Feve, Fellahi, & Bastard, 2008). To further elicit the beneficial effects of MLB supplementation against HFD-induced insulin resistance and lipid abnormality, plasma levels of TNF-α, IL-6, and leptin were measured. Analysis of blood samples revealed that HFD caused an elevation in TNF-α, IL-6, and leptin compared with normal diet and their elevated production was attenuated by MLB supplementation (Table 1). These findings show that MLB supplementation attenuates HFD-induced elevated production of TNF-α, IL-6, and leptin.

4. Discussion

HFD has been shown to induce metabolic syndrome in rodents characterized by obesity, hyperlipidaemia, hyperglycaemia, hyperinsulinaemia, glucose intolerance, insulin resistance, and hepatic steatosis (Buettner, Schölmerich, & Bollheimer, 2007). In this study, HFD developed obesity, hyperlipidaemia, hyperglycaemia, glucose intolerance, insulin resistance, and hepatic steatosis in rats during a feeding course of four weeks.
Fig. 4 – Effects of MLB on insulin signalling in liver. Proteins were extracted from liver tissues and subjected to Western blot analysis with indicated antibodies (A). Bar graphs showed the quantitative results of SREBP1c (B), CD36 (C), PPARα (D), IRS-1 (E), PI3-k p85α (F), p-Akt-Ser/Akt (G) and GLUT2 (H). NC, normal diet control; HC, high-fat diet control; MLB5, high-fat diet with 5 mg/kg/day of MLB; MLB10, high-fat diet with 10 mg/kg/day of MLB; MLB20, high-fat diet with 20 mg/kg/day of MLB. Values are expressed as mean ± SD (n = 6 per group). **P < 0.01 and ***P < 0.001 vs. NC group and ††P < 0.01 and †††P < 0.001 vs. HC group.
Daily supplementation of MLB improved those metabolic alterations caused by HFD. The beneficial effects of MLB were accompanied by enhancement of insulin signalling. In addition to polyphenolic acids, polysaccharides, and tanshinones, our findings suggest that MLB may be an active ingredient contributing to Danshen-provoked beneficial effects on insulin resistance and even metabolic syndrome.

The imbalance between lipogenesis and lipolysis and the favour of the former result in abnormal lipid accumulation and deposition. Hyperlipidaemia is usually accompanied by hepatic lipid deposition and adipocyte hypertrophy (den Boer, Voshol, Kuipers, Havekes, & Romijn, 2004). The reduction of cholesterol, triacylglycerol, non-HDL-C, liver weight, epididymal fat weight, hepatic lipid deposition, and adipocyte hypertrophy and the increase of HDL-C by MLB reflect its hypolipidaemic effect.

The liver plays a central role in regulating lipid metabolism by importing fatty acids, lipogenesis, lipolysis, and storing and exporting lipids. CD36 is an important transporter critical to hepatic influx of free fatty acids (Koonen et al., 2007). Together with the action of CD36, lipogenic transcription factor SREBP1c promotes de novo synthesis of lipids in liver (Ferré & Foufelle, 2010). PPARα shows the opposite actions. It is the most important lipid-activation transcription factor that regulates de novo lipolysis (Tailleux, Wouters, & Staels, 2012). The suppression of hepatic expression of SREBP1c and CD36 and the enhancement of PPARα expression in HFD rats indicated that the hypolipidaemic effect of MLB might be mediated partly through inhibiting lipid anabolism and enhancing lipid catabolism. In hyperlipidaemic rats, supplementation of Danshen extracts improved abnormal lipid profiles accompanied with
a reduction of SREBP1c mRNA level (ji, Chan, & Kaplowitz, 2006). Together with relevant studies, our findings suggest that the biochemical events of hepatic lipogenesis/influx and lipolysis/export might be crucial action targets of MLB to modulate lipid metabolism.

Multiple events transduce signals to regulate homeostatic lipogenesis and lipolysis in liver. Among the candidates involved, the execution of insulin action favours abnormal lipid metabolism (Czech, Tencerova, Pedersen, & Aouadi, 2013). Thus, insulin resistance might be a key player leading to abnormal lipid metabolism. HFD rats showed signs of insulin resistance, as evidenced by glucose intolerance, hyperglycaemia, and increased HOMA-IR and those metabolic abnormalities were improved by MLB supplementation. Improving insulin sensitivity is an effective strategy to alleviate abnormal lipid metabolism (Chen, Chen, Liu, & Mao, 2010). It means that insulin resistance might be an alternative upstream target of MLB to improve hyperlipidaemia and adiposity.

After the engagement of ligands and receptors, the classical insulin signalling cascade, IRS1–PI3-κ–Akt, is stimulated by insulin and required for glucose transporter expression and/or translocation in insulin targeted organs (Saltiel & Kahn, 2001). Insulin resistance and glucose metabolism defect are consequences of impaired insulin signalling cascade (Shulman, 2000). In peripheral insulin targeted organs, livers and gastrocnemius muscles, the axis of IRS1–PI3-κ–Akt and expression of glucose transporter isoforms were down-regulated in HFD rats. The down-regulation of insulin signalling and accompanied gene expression was reversed by MLB supplementation. These findings show that the enhancement and/or preservation of insulin signalling appear to be an action mechanism of MLB to combat insulin resistance.

Obesity-associated insulin resistance is associated well with oxidative stress and inflammation. Antioxidants and anti-inflammatory agents increase insulin sensitivity and improve insulin resistance (Furukawa et al., 2004). Evidence suggests that oxidative stress, proinflammatory cytokines and adipokines interfere insulin signalling through multiple steps, including receptor internalization, receptor degradation, IRS1 serine phosphorylation, and IRS1 degradation (Zeyda & Stulnig, 2009). MLB possesses antioxidant and anti-inflammatory activities (Zhao et al., 2008). In our study, we found that the well-documented proinflammatory cytokines and adipokines associated with insulin resistance such as TNF-α, IL-6, and leptin were lowered in HFD rats supplemented with MLB. Together with relevant studies, our findings reveal that the down-regulation of proinflammatory cytokine and adipokine expression by MLB is one of the potential mechanisms that may resolve the blockade of insulin signalling.

In consideration of combating with insulin resistance, pancreatic β-cells are crucial targets for intervention (Ferrannini & Mari, 2014). Plasma cholesterol is regulatory factors in the function of β-cells, particularly, HDL-C has an advantageous effect on glucose metabolism through the elevation of β-cell function (Drew et al., 2009). Literature shows that Danshen has the effect to raise plasma level of HDL-C in the patients with ischaemic cerebrovascular disease (Zhou et al., 2005). Evidence also points out that MLB shows protective effect on β-cells avoiding cytokine-induced apoptosis (Lee et al., 2011). HFD rats showed impairment in the function of β-cells, as evidenced by the decreased HOMA-B. Although there was no significant difference of insulin levels among groups, the preservation of HOMA-B suggested an improvement of β-cell function by MLB supplementation. Thus, pancreatic β-cells might represent an alternative target by which MLB acts to improve insulin resistance.

Danshen is a famous and widely consumed functional supplement, and has been applied to ameliorate human disease for many years now. Its commercial product, Compound Danshen Dripping Pills (CDDP), has been approved by the FDA for entering Phase IV clinical trials (NCT01825759). In the present study, we have shown that MLB supplementation improved several determinants of metabolic syndrome in rats caused by a HFD. The beneficial effect of MLB is accompanied by improvement of insulin resistance and suppression of inflammation. Our findings suggest that Danshen, in particular the MLB ingredient, could serve as a therapeutic agent against insulin resistance and even metabolic syndrome. However, other beneficial mechanisms and action targets by which MLB protects against metabolic syndrome require further investigation.

5. Conclusion

Danshen is an essential and reliable herb or food for the prevention and treatment of metabolic syndrome. In addition to polyphenolic acids, polysaccharides, and tanshinones, using a HFD rat model, our findings provide evidence showing that MLB might be an alternative ingredient actively contributing to Danshen-provoked beneficial effects on insulin resistance and even metabolic syndrome. Results of mechanistic study also show clinical implications highlighting the values of post-receptor insulin signalling, proinflammatory cytokines, and adipokines being therapeutic targets for the prevention and treatment of metabolic syndrome. These results suggest that MLB may be an active ingredient contributing to the beneficial effects of Danshen on insulin resistance as well as on metabolic syndrome.

Conflict of interest

The authors have no conflict-of-interest/financial disclosure.

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