Effects of a fermented buckwheat flower and leaf extract on the blood glucose and lipid profile of type 2 diabetic db/db mice

Wang Jianxing, Yu Xiaohan, Jiang Yan, Wang Yan, Li Ying, Han Shuying

OBJECTIVE: To determine the efficacy of a fermented buckwheat flower and leaf extract (EFBFL) for the reduction of blood glucose and lipid dysregulation in spontaneously obese type 2 diabetic db/db mice, and to explore the possible mechanisms involved.

METHODS: Forty 9-week-old male db/db mice were randomly allocated to a high-dose EFBFL group (EFBFL-H), a low-dose EFBFL group (EFBFL-L), a metformin hydrochloride positive control group (MEG), and a db/db control group (MG), and there was also a db/m negative control group (NCG) (n = 10). Oral glucose tolerance tests (OGTT) were performed after 7 weeks of treatment. At the end of 8 weeks of treatment, random blood glucose (RBG), glycosylated hemoglobin (HbAlc), fasting plasma glucose (FPG), fasting serum insulin (FINS), triglyceride (TG), serum total cholesterol (TC), free fatty acids (FFA), high-density lipoprotein-cholesterol, and low-density lipoprotein-cholesterol (LDL-c) were measured, the homeostasis model assessment-insulin resistance (HOMA-IR) was calculated, immunohistochemistry and western blotting measured the expression of glucose transporter4 (GLUT4) and peroxisome proliferator-activated receptor γ (PPAR-γ) by in skeletal muscle.

RESULTS: The MG mice had a significantly increased in RBG, HbAlc, the HOMA-IR level, the serum of TG, TC, LDL-c, but a decreased in glucose tolerance and the protein expression of GLUT4 and PPAR-γ compared with the NCG. Compared with the MG, EFBFL groups significantly decreased RBG, HbAlc, and the HOMA-IR level, increased glucose tolerance. Meanwhile EFBFL groups reduced the serum TG, TC, and LDL-c in a dose-dependent manner. In addition, EFBFL increased the protein expression of GLUT4 and PPAR-γ in the skeletal muscle of db/db mice. There was significant difference between the MG group and EFBFL groups.

CONCLUSION: These findings suggest that EFBFL has anti-diabetic effects in db/db mice, ameliorating glucose intolerance, lipid dysregulation, and insulin resistance.
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Keywords: Eriogonum; Diabetes mellitus, type 2; Muscle, skeletal; Glucose transporter type 4; PPAR gamma

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is now a worldwide epidemic. It is a syndrome that comprises disorders of sugar, fat, and protein metabolism, and is caused by insulin deficiency and/or a reduction in insulin sensitivity of the target tissues. T2DM represents a serious threat to human health, but a number of conventional medications have been developed that can effectively control T2DM and its complications. However, the long-term use of such drugs can be associated with adverse reactions. Therefore, with the increase in the number of patients with T2DM, research efforts have focused on the production of safer, but effective drugs.

Buckwheat (Fagopyrum pentagonaceae) is a plant with medicinal properties. It has attracted attention recently for its anti-hyperglycemic, anti-dyslipidemic, and antioxidant effects. Previous studies have shown that buckwheat flower and leaf flavones (FBFL) reduce blood glucose and lipid concentrations, dilate blood vessels, improve microcirculation, and have antioxidant and anti-inflammatory effects. In the present study we aimed to determine whether an extract of fermented buckwheat flower and leaf (EFBFL) would reduce blood glucose and ameliorate lipid dysregulation in spontaneously obese type 2 diabetic db/db mice, and to identify a potential mechanism for its effects.

MATERIALS AND METHODS

EFBFL extract

EFBFL was prepared by the fermentation of dried buckwheat flower and leaf, which was purchased from Tongliao, Kulun City, Inner Mongolia. To 50 g of dried buckwheat flower and leaf powder, activated yeast, 30 mL ddH2O, 4 g peptone, and 4 g glucose were added, and the mixture was incubated at 37 °C for 48 h, to obtain fermentation products of buckwheat flower and leaves. Next, we added 10 volumes of 70% ethanol and the suspension was extracted twice for 2 h each. The product was then centrifuged, and the supernatant concentrated and dried at 70 °C to obtain the final fermented alcoholic extract.

Experimental animals

Male, spontaneously obese type 2 diabetic db/db mice (33-38 g, 7-8 weeks old) and male db/m control mice (18-22 g, 7-8 weeks) were supplied by Cavens Ltd. (Changzhou, China; license No. SCXK 2001-0003). The animals were kept in the Laboratory Animal Center at North China University of Science and Technology at 25-30 °C and 45%-55% relative humidity. They were fed standard chow (lot 2015103001MF01; Nanjing Bei Si Fu, Nanjing, China) ad libitum and maintained under a 12-h light-dark cycle. The experimental procedures were performed in accordance with the World Health Organization International Guiding Principles for Biomedical Research Involving Animals and the study protocol was approved by the Joint Ethical Review Committee of North China University of Science and Technology (approval No. 2016056, approval date: May 11th, 2016). The experiment was started after 1 week of adaptation.

Experimental treatments

After a 1-week adaptation period, db/db mice (10 weeks old) that had 2-h postprandial plasma glucose concentrations > 16.7 mmol/L on at least three occasions were randomly allocated to four groups (n = 10 per group): a model group (MG), a high-dose EFBFL group (EFBFL-H, 100 mg·kg⁻¹·d⁻¹), a low-dose EFBFL group (EFBFL-L, 50 mg·kg⁻¹·d⁻¹), and a metformin hydrochloride positive control group (MEG, 160 mg·kg⁻¹·d⁻¹). In addition, db/m mice (n = 10) were used as a negative control group (NCG). EFBFL and MEG mice were administered treatments intragastrically every day at 08:00 h for 8 weeks, and MG and NCG mice were administered the same volume of ddH2O.

Blood and tissue measurements

We aimed to determine the effects of EFBFL on glucose and lipid metabolism, and insulin resistance on a whole-body basis and in skeletal muscle. Therefore, we assessed random blood glucose (RBG), glycated hemoglobin (HbAlc), Oral glucose tolerance tests (OGTT), homeostasis model assessment-insulin resistance (HOMA-IR), and skeletal muscle glucose transporter 4 (GLUT4) and peroxisome proliferator-activated receptor (PPAR-γ) protein expression, to determine whether EFBFL has an anti-hyperglycemic effect and ameliorates insulin resistance by upregulating GLUT4 and PPAR-γ in the skeletal muscle. In addition, we measured the serum concentrations of total cholesterol (TC), triglycerides (TG), low-density lipoprotein-cholesterol (LDL-c), high-density lipoprotein-cholesterol (HDL-c) and free fatty acids (FFA), to determine whether EFBFL ameliorates dyslipidemia, potentially through PPAR-γ.

Measurement of RBG and HbAlc

RBG was measured in blood collected from a tail vein before, and after 2, 4, 6, and 8 weeks of treatment using a Roche Accu-Chek Active blood glucose meter (Abbott, Chicago, IL, USA). HbAlc was measured in blood samples obtained after 8 weeks of treatment.
Oral glucose tolerance testing (OGTT)
OGTT was performed after 7 weeks of treatment. The mice were fasted for 16 h, then administered 2.5 g/kg glucose 30 min after drug administration. Blood glucose was then measured 0, 30, 60, and 120 min later.

Measurement of serum parameters
The mice were fasted for 12 h after 8 weeks of treatment, then serum was prepared from blood obtained from a retro-orbital sinus of each mouse and stored at –20 °C until analysis. The serum concentrations of TC, TG, FFA, HDL-c, and LDL-c were measured using an automated biochemical analyzer (BioSino Ltd., Beijing, China). Fasting plasma glucose (FPG) was measured using an glucose oxidase method kit and fasting serum insulin (FINS) was measured using an enzyme-linked immunomassay (ELISA) kit (Beijing Kai NuoChun Tian of Biological Technology). The level of insulin resistance was calculated using HOMA-IR as follows:
HOMA-IR = FPG (mmol/L) × FINS (mU/L) / 22.5

Immunohistochemistry for GLUT4 in skeletal muscle
The mice were anesthetized and put to death by cervical verteb dislocation, skeletal muscle of femur in mice were isolated, snap-frozen in liquid nitrogen, and then used for immunohistochemistry and western blotting for GLUT4 (Abcam, Cambridge Science Park, England) and PPAR-γ (St. Louis, MO, USA) protein expression.

Western blotting for GLUT4 and PPAR-γ
Frozen Skeletal muscle tissue were homogenized in ice-cold radioimmunoprecipitation (RIPA) lysis buffer. Total protein concentrations were determined by the bicinchoninic acid (BCA) method. Samples (100 µg) were separated by 10% SDS-PAGE geland were then transferred onto polyvinylidene fluoride (PVDF) membrane.
The membranes were blocked with 5% dried skimmed milk for 1 h, then incubated with primary antibody against GLUT4 (1:1000) or PPAR-γ (1:500) for 12 h at 4 °C, washed three times (5 min each) in tris-buffered saline containing 0.1% Tween-20 (TBST), incubated with secondary antibody (goat anti-rabbit IgG/ horseradish peroxidase; A5316) at 37 °C for 1 h at room temperature, and washed a further 3 times (5 min each) in TBST. Densitometric analysis was performed using Image Lab (Bio-Rad, Hercules, CA, USA). Bands were analyzed using Image J (National Institutes of Health) and the relative density of each band was normalized to that of the corresponding glyceraldehyde 3-phosphate dehydrogenase (GAPDH) loading control band.

Statistical analysis
Data are presented as mean ± standard deviation ( x ± s). Data were analyzed using SPSS v.16.0 (SPSS Inc., Chicago, IL, USA). One-way analysis of variance (ANOVA) was used to identify differences between groups. P < 0.05 was accepted as indicating statistical significance.

RESULTS
Evaluation of RBG and HbA1c
As shown in Table 1, there were no significant changes in RBG concentration in the NCG group during the study. RBG and HbA1c were higher in the MG than the NCG group (P < 0.01). In addition, EFBFL treatment reduced RBG and HbA1c vs the MG group (P < 0.01). Moreover, there were no significant differences between the EFBFL-H and MEG groups (P > 0.05).

Evaluation of glucose tolerance
After 7 weeks of treatment, the blood glucose of the MG peaked after 30 min, and started to decline after 60 min. However, it remained high even after 120 min (Figure 1). In contrast, blood glucose had decreased in the NCG, EFBFL, and MEG groups by 120 min (P < 0.05). There were no significant differences in blood glucose between the EFBFL and MEG groups (P > 0.05).

Effect of EFBFL treatment on FPG FINS, and HOMA-IR
The data in Table 2 show that the FPG and FINS in the MG group were significantly higher than in the NCG group (P < 0.01), and HOMA-IR was also significantly higher in the MG group (P < 0.01). EFBFL treatment significantly reduced HOMA-IR, and there was no significant difference between the EFBFL-H and MEG groups (P > 0.05). These results imply that insulin sensitivity is increased by EFBFL treatment, and the effect of high-dose EFBFL was particularly marked.

Effect of EFBFL treatment on blood lipids
The data in Table 3 show that the serum concentrations of TC, TG, LDL-c, HDL-c, and FFA in the MG
Table 1 Effects of EFBFL treatment on RBG and HbAlc ( x ± s)

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>0 week (nmol/L)</th>
<th>2 weeks (nmol/L)</th>
<th>4 weeks (nmol/L)</th>
<th>6 weeks (nmol/L)</th>
<th>8 weeks (nmol/L)</th>
<th>HbAlc (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCG</td>
<td>10</td>
<td>5.2±0.8</td>
<td>5.6±0.8</td>
<td>5.5±0.6</td>
<td>6.0±1.0</td>
<td>5.9±1.1</td>
<td>4.3±0.3</td>
</tr>
<tr>
<td>MG</td>
<td>10</td>
<td>19.3±2.6</td>
<td>19.8±5.8</td>
<td>19.6±4.6</td>
<td>19.1±3.1</td>
<td>20.1±4.9</td>
<td>5.8±0.4</td>
</tr>
<tr>
<td>MEG</td>
<td>10</td>
<td>19.4±2.2</td>
<td>16.0±5.4</td>
<td>14.1±4.1</td>
<td>13.4±5.1</td>
<td>13.6±4.1</td>
<td>4.6±0.4</td>
</tr>
<tr>
<td>EFBFL-H</td>
<td>10</td>
<td>19.3±2.4</td>
<td>16.2±4.6</td>
<td>15.4±4.9</td>
<td>14.4±4.1</td>
<td>14.8±3.2</td>
<td>4.7±0.4</td>
</tr>
<tr>
<td>EFBFL-L</td>
<td>10</td>
<td>19.2±2.3</td>
<td>17.1±4.0</td>
<td>16.0±5.1</td>
<td>16.6±3.2</td>
<td>16.1±4.6</td>
<td>5.2±0.4</td>
</tr>
</tbody>
</table>

Notes: the NCG and MG groups were intragastrically administered ddH2O. The MEG group was intragastrically administered metformin hydrochloride (160 mg·kg⁻¹·d⁻¹). The EFBFL-H group was intragastrically administrated EFBFL (100 mg·kg⁻¹·d⁻¹). The EFBFL-L group was intragastrically administrated EFBFL (50 mg·kg⁻¹·d⁻¹). All the mice were administered treatments daily at 08:00 h for 8 weeks. EFBFL: extract from fermented buckwheat flower and leaf; RBG: random blood glucose; HbAlc: glycosylated hemoglobin; EFBFL-H: high-dose EFBFL group; EFBFL-L: low-dose EFBFL group; MEG: metformin hydrochloride positive control group; MG: db/db control group; NCG: db/m negative control group. *P < 0.01 and **P < 0.05 vs the NCG group; ‘P < 0.05 and ‘‘P < 0.01 vs the MG group.

Figure 1 Effect of EFBFL treatment on oral glucose tolerance
The NCG and MG groups were intragastrically administered ddH2O. The MEG group was intragastrically administered metformin hydrochloride (160 mg·kg⁻¹·d⁻¹). The EFBFL-H group was intragastrically administrated EFBFL (100 mg·kg⁻¹·d⁻¹). The EFBFL-L group was intragastrically administrated EFBFL (50 mg·kg⁻¹·d⁻¹). All the mice were administered treatments daily at 08:00 h for 8 weeks. EFBFL: extract from fermented buckwheat flower and leaf; RBG: random blood glucose; HbAlc: glycosylated hemoglobin; EFBFL-H: high-dose EFBFL group; EFBFL-L: low-dose EFBFL group; MEG: metformin hydrochloride positive control group; MG: db/db control group; NCG: db/m negative control group. *P < 0.01 vs the NCG group; **P < 0.05 and ‘‘P < 0.01 vs the MG group.

Group were significantly higher than in the NCG group (P < 0.05). EFBFL treatment significantly reduced the concentrations of TG, TC, FFA, and LDL-c in a dose-dependent manner (P < 0.05), and there were no significant differences between the EFBFL-H and MEG groups (P > 0.05). However, EFBFL had little effect on HDL-c in the serum of db/db mice and there was no significant differences vs the MG group.

Effect of EFBFL treatment on GLUT4 protein expression
The expression of GLUT4 was analyzed using immuno-histochemistry (Figure 2). GLUT4 was highly expressed in NCG mouse muscle, indicated by the presence of a large amount of staining on the membranes of skeletal muscle cells. In contrast, expression was significantly lower in MG mice, demonstrated by lighter and sparser staining. However, the expression of GLUT4 in the EFBFL-treated groups was significantly higher, indicated by deeper and more widely distributed staining, and this was more pronounced in the EFBFL-H group.

Protein expression of GLUT4 and PPAR-γ
The protein expression of GLUT4 and PPAR-γ were analyzed by western blotting (Figure 3). Compared with the NCG group, the expression of both GLUT4 and PPAR-γ was significantly lower in MG mice (P < 0.05 and P < 0.01, respectively). The expression of GLUT4 and PPAR-γ was significantly higher in the EFBFL-H group than in the MG group (P < 0.05 and P < 0.01, respectively) and slightly higher than in the NCG group. Thus, EFBFL increases the expression of both GLUT4 and PPAR-γ in skeletal muscle.

DISCUSSION
It has previously been shown that FBFL reduces blood glucose and lipid concentrations, increases insulin sensitivity, and has antioxidant effects. Furthermore, recent research showed that the total flavone concentration in buckwheat leaves is reduced by fermentation, and the fermented extract significantly reduces blood glucose and prevents myocardial injury in spontaneously obese type 2 diabetic db/db mice. In the present study, buckwheat leaves were fermented using a standard Chinese herbal medicine technique and the effect of the generated EFBFL preparation was determined in db/db mice. In particular, on the basis of the previous findings, we wished to determine the mechanism of the anti-hyperglycemic effect of EFBFL. The db/db mouse is a useful model of T2DM, because it manifests many of the pathological features of the hu-
Table 2 Effects of EFBFL treatment on FPG, FINS, and HOMA-IR (± s)

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>FPG (mmol/L)</th>
<th>FINS (mU/L)</th>
<th>HOMA-IR</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCG</td>
<td>10</td>
<td>6.0±0.8</td>
<td>6.2±2.1</td>
<td>1.7±0.7</td>
</tr>
<tr>
<td>MG</td>
<td>10</td>
<td>13.3±2.9</td>
<td>12.6±3.2</td>
<td>7.4±1.5</td>
</tr>
<tr>
<td>MEG</td>
<td>10</td>
<td>9.5±2.9</td>
<td>10.6±2.5</td>
<td>4.5±1.1</td>
</tr>
<tr>
<td>EFBFL-H</td>
<td>10</td>
<td>10.6±2.5</td>
<td>9.8±2.7</td>
<td>4.6±0.9</td>
</tr>
<tr>
<td>EFBFL-L</td>
<td>10</td>
<td>11.8±2.8</td>
<td>9.6±3.1</td>
<td>5.0±1.2</td>
</tr>
</tbody>
</table>

Notes: the NCG and MG groups were intragastrically administered ddH₂O. The MEG group was intragastrically administered metformin hydrochloride (160 mg·kg⁻¹·d⁻¹). The EFBFL-H group was intragastrically administered EFBFL (100 mg·kg⁻¹·d⁻¹). The EFBFL-L group was intragastrically administered EFBFL (50 mg·kg⁻¹·d⁻¹). All the mice were administered treatments daily at 08:00 h for 8 weeks. EFBFL: extract from fermented buckwheat flower and leaf; FPG: fasting plasma glucose; FINS: fasting serum insulin; HOMA-IR: homeostasis model of assessment-insulin resistance; EFBFL-H: high-dose EFBFL group; EFBFL-L: low-dose EFBFL group; MEG: metformin hydrochloride positive control group; MG: db/db control group; NCG: db/m negative control group. *P < 0.01 vs the NCG group; †P < 0.05 and ‡P < 0.01 vs the MG group.

Table 3 Effects of EFBFL treatment on blood lipids (mmol/L, ± s)

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>TC</th>
<th>TG</th>
<th>LDL-C</th>
<th>HDL-C</th>
<th>FFA</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCG</td>
<td>10</td>
<td>3.08±0.36</td>
<td>1.15±0.31</td>
<td>0.22±0.09</td>
<td>2.41±0.25</td>
<td>235.80±31.75</td>
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<tr>
<td>MG</td>
<td>10</td>
<td>5.25±0.49</td>
<td>3.46±0.57</td>
<td>0.48±0.16</td>
<td>3.35±0.41</td>
<td>427.17±34.82</td>
</tr>
<tr>
<td>MEG</td>
<td>10</td>
<td>4.95±0.37</td>
<td>2.33±0.26</td>
<td>0.32±0.07</td>
<td>2.88±0.37</td>
<td>311.57±30.79</td>
</tr>
<tr>
<td>EFBFL-H</td>
<td>10</td>
<td>4.78±0.64</td>
<td>2.19±0.35</td>
<td>0.37±0.12</td>
<td>3.51±0.74</td>
<td>289.58±36.53</td>
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<tr>
<td>EFBFL-L</td>
<td>10</td>
<td>5.01±0.83</td>
<td>2.49±0.41</td>
<td>0.43±0.11</td>
<td>2.93±0.52</td>
<td>302.37±31.38</td>
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</tbody>
</table>

Notes: the NCG and MG groups were intragastrically administered ddH₂O. The MEG group was intragastrically administered metformin hydrochloride (160 mg·kg⁻¹·d⁻¹). The EFBFL-H group was intragastrically administered EFBFL (100 mg·kg⁻¹·d⁻¹). The EFBFL-L group was intragastrically administered EFBFL (50 mg·kg⁻¹·d⁻¹). All the mice were administered treatments daily at 08:00 h for 8 weeks. EFBFL: extract from fermented buckwheat flower and leaf; TG: triglyceride; TC: total cholesterol; FFA: free fatty acids; HDL-C: high-density lipoprotein-cholesterol; LDL-C: low-density lipoprotein-cholesterol; EFBFL-H: high-dose EFBFL group; EFBFL-L: low-dose EFBFL group; MEG: metformin hydrochloride positive control group; MG: db/db control group; NCG: db/m negative control group. *P < 0.01 and †P < 0.05 vs the NCG group; ‡P < 0.05 vs the MG group.

Figure 2 Immunohistochemistry for GLUT4 protein in skeletal muscle (× 400)
A: NCG group; B: MG group; C: MEG group; D: EFBFL-H group; E: EFBFL-L group. The NCG and MG groups were intragastrically administered ddH₂O. The MEG group was intragastrically administered metformin hydrochloride (160 mg·kg⁻¹·d⁻¹). The EFBFL-H group was intragastrically administered EFBFL (100 mg·kg⁻¹·d⁻¹). The EFBFL-L group was intragastrically administered EFBFL (50 mg·kg⁻¹·d⁻¹). All the mice were administered treatments daily at 08:00 h for 8 weeks. EFBFL: extract from fermented buckwheat flower and leaf; GLUT4: glucose transporter 4; EFBFL-H: high-dose EFBFL group; EFBFL-L: low-dose EFBFL group; MEG: metformin hydrochloride positive control group; MG: db/db control group; NCG: db/m negative control group.

EFBFL significantly reduces the RBG and HbAlc of db/db mice, reflecting changes in both current glucose status and the long-term control of blood glucose, which indicates that EFBFL can ameliorate the hyperglycemia of db/db mice. Furthermore, we have shown that EFBFL improves the glucose tolerance of db/db mice and reduces FBG, FINS, and HOMA-IR, which indicates that it increases the utilization of glucose and ameliorates insulin resistance.

Impairments in skeletal muscle glucose uptake and utilization are important manifestations of IR. GLUT4 is the insulin-sensitive glucose transporter and is primarily expressed in skeletal muscle and adipose tissue. When insulin binds to its receptor and activates the insulin signaling pathway, this causes GLUT4 translocation to cell membranes, where it facilitates the entry of glucose into cells.21,22 A reduction in GLUT4 expression in skeletal muscle, and especially its translocation to the plasma membrane of muscle cells, impairs insulin-stimulated glucose uptake and utilization.22 We have shown that EFBFL significantly increases the expression of GLUT4 in the skeletal muscle of db/db mice, which should be associated with increases in the transport and utilization of glucose, which would ameliorate insulin resistance in these mice.23

References:
It regulates lipid metabolism and adipocyte differentiation by affecting the transcription of lipid metabolism genes, and thereby promotes the uptake and metabolism of circulating FFA, reduces circulating blood lipids, and increases the uptake of free fatty acids by adipocytes. Leptin inhibits adipocyte differentiation, whereas PPAR-γ promotes this, but both promote catabolism in adipose tissue. The db/db mice used in this study have leptin receptor defects that cause an appetite disorder in the hypothalamus and leptin resistance in adipocytes. However, there may be some synergy between leptin and PPAR-γ in the catabolism in adipose tissue. Furthermore, PPAR-γ can increase the insulin sensitivity of peripheral tissues. Thus, PPAR-γ regulates glucose metabolism, which may reduce blood glucose. It also directly regulates the expression of GLUT4, increasing glucose uptake. We have shown that EFBFL significantly increases the expression of PPAR-γ in the skeletal muscle of db/db mice. This would be expected to increase the transactivation of PPAR-γ target genes, including GLUT4, and thus the uptake and utilization of glucose. This would also be expected to reduce the accumulation of intracellular lipid, further ameliorating the skeletal muscle IR.

In conclusion, EFBFL ameliorates the disorders in glucose and lipid metabolism and the insulin resistance of type 2 diabetic db/db mice. These effects may be mediated through increases in GLUT4 and PPAR-γ expression, and a reduction in lipid deposition in the skeletal muscle of the mice.

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REFERENCES


