The Fang’s hypoglycemic formula improves insulin resistance in type 2 diabetes mellitus by regulating mitochondrial autophagy

Jia Zhu1, Xu-Dong Chen2, Jie Zhao3

1Department of Respiratory, Jiaxing Hospital of Traditional Chinese Medicine, Jiaxing 314001, China. 2Department of Endocrinology, Jiaxing Hospital of Traditional Chinese Medicine, Jiaxing 314001, China. 3Department of Endocrinology, The First Affiliated Hospital of Yunnan University of Chinese Medicine, Kunming 650500, China.

*These authors contributed equally to this work and are co-first authors.

Corresponding to: Jie Zhao, Department of Endocrinology, The First Affiliated Hospital of Yunnan University of Chinese Medicine, No. 1076 Yuhua Road, Chengqiang District, Kunming 650500, China. E-mail: 907507885@qq.com.

Author contributions
Jia Zhu and Jie Zhao contributed to study concept; Jia Zhu and Xu-Dong Chen contributed to study design and performance; Jie Zhao and Jia Zhu contributed to analysis of data; Jia Zhao contributed to drafting of the paper; Jie Zhao contributed to study supervision.

Competing interests
The authors declare no conflicts of interest.

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Abbreviations
IDF, International Diabetes Federation; T2DM, type 2 diabetes mellitus; ROS, reactive oxygen species; PTUP, protein tyrosine phosphatase 1B; FSJT, Fangshi Jiangtang decoction; MET, metformin; TG, triglycerides; TC, total cholesterol; IL-1β, interleukin-1β; IL-6, interleukin-6; TNF-α, tumor necrosis factor-α; MDA, malondialdehyde; SOD, superoxide dismutase; GSH-Px, glutathione peroxidase; TOM20, translocase of outer mitochondrial membrane 20; LC3, light chain 3; FSJT-I, Fangshi Jiangtang decoction-low dose; FSJT-M, Fangshi Jiangtang decoction-medium dose; FSJT-H, Fangshi Jiangtang decoction-high dose; OGGT, oral glucose tolerance test; HOMA-IR, homeostatic model assessment for insulin resistance index.

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Abstract
Background: To investigate the pharmacological effects of Fangshi Jiangtang decoction (FSJT) on type 2 diabetes mellitus (T2DM) model rats and explore its mechanism of action from the perspective of mitochondrial autophagy. Methods: Sixty Sprague Dawley rats were randomly divided into six groups after one week of adaptive feeding: Control group, T2DM model group, metformin group (0.2 g/kg by gavage), and FSJT low, medium, and high dose groups (9.5, 19, 38 g/kg by gavage). Except for the Control group, the other five groups were given a high-fat diet. The treatment lasted for 8 weeks, and blood glucose levels were measured weekly. Eight weeks later, blood samples were collected from the rats, and serum was separated for the determination of HbA1c, oral glucose tolerance test, and homeostatic model assessment for insulin resistance index. The pancreas of the rats was collected, weighed, and fixed. The same part of the pancreas was used for hematoxylin-eosin. Kits were used to detect triglycerides, total cholesterol, interleukin-1β, interleukin-6, tumor necrosis factor-α, malondialdehyde, glutathione peroxidase, and superoxide dismutase in pancreatic tissue to assess the effects of FSJT on inflammation and oxidative stress in T2DM rats. Western blot analysis was performed to detect the expression of VDAC1, TOM20, COXIV, PINK1, Parkin, beclin1, lchaine 3, and selective autophagy adaptor protein P62 to evaluate the effects of FSJT on mitochondrial autophagy in T2DM model rats. Results: Compared with the T2DM model group, FSJT intervention significantly reduced blood glucose, HbA1c, oral glucose tolerance test, and homeostatic model assessment for insulin resistance index in T2DM model rats, alleviated pancreatic tissue lesions, reduced levels of total cholesterol, triglycerides, interleukin-1β, interleukin-6, tumor necrosis factor-α, and malondialdehyde, increased glutathione peroxidase and superoxide dismutase activities, downregulated the expression of VDAC1, TOM20, COXIV, and P62 proteins, and upregulated the expression of PINK1, Parkin, beclin1, and light chain 3 proteins. Conclusion: FSJT can improve insulin resistance in T2DM by promoting the activation of mitochondrial autophagy.

Keywords: Fangshi Jiangtang decoction; type 2 diabetes mellitus; mitochondrial autophagy; oxidative stress
Background

According to a report by the International Diabetes Federation (IDF), approximately 463 million people aged 20–79 globally had diabetes in 2019, with approximately 116.4 million people in China, ranking first in the world [1]. Diabetes can lead to serious complications such as blindness, amputation, kidney failure, coronary heart disease, and stroke, posing a significant threat to patients’ lives and health [2]. Therefore, it is crucial to find practical and effective interventions to block or delay the trend of the epidemic and the progression of the disease. Currently, the treatment of type 2 diabetes mellitus (T2DM) mainly relies on oral hypoglycemic agents and insulin, but there are often issues such as gastrointestinal reactions, large fluctuations in blood glucose, and hypoglycemic events [3]. Traditional Chinese medicine has obvious advantages in relieving clinical symptoms, overall effectiveness, and safety for T2DM. Clarifying the mechanism of action of traditional Chinese medicine on T2DM is of great significance for guiding clinical precision treatment, improving the efficiency of prevention and treatment of T2DM with traditional Chinese medicine, and promoting the modernization of traditional Chinese medicine.

Insulin resistance is the initiating factor of T2DM and persists throughout its entire course. Reactive oxygen species (ROS), as a second messenger, mainly enhances the effect of insulin by inhibiting the activity of protein tyrosine phosphatase 1B (PTP1B) through oxidation [4]. However, long-term hyperglycemia can cause mitochondrial damage due to oxidative stress, leading to the production of a large amount of ROS. Excessive ROS activates multiple serine protein kinases, causing serine phosphorylation of InsR and IRS proteins. Excessive serine phosphorylation blocks insulin signaling, leading to insulin resistance [5]. Mitochondrial autophagy maintains the appropriate quality and quantity of mitochondria by targeted elimination of damaged or excess mitochondria and promoting mitochondrial renewal, limiting the excessive accumulation of ROS [6]. When mitochondrial autophagy function is imbalanced, it cannot initiate mitochondrial autophagy normally, leading to the accumulation of damaged mitochondria and increased ROS production, further exacerbating the occurrence of insulin resistance [7]. This study aimed to establish a T2DM rat model using a high-fat diet and explore whether Fangshi Jiading decoction (FSJT) can improve insulin resistance in T2DM by regulating mitochondrial autophagy.

Materials and methods

Animals

Male Sprague-Dawley rats of specific-pathogen-free grade, aged 8 to 12 weeks, and with a body weight of approximately 200 ± 20 grams, were purchased from Beijing Huafukang Biotechnology Co., Ltd. (Beijing, China) (Experimental Animal Production License Number: SCXK (Dian) 2022-0002). They were housed in the specific pathogen-free environment of the Experimental Center of Yunnan University of Traditional Chinese Medicine (Experimental Animal Use License: SYXK (Dian) 2023-0006), with 5 rats per cage. The temperature was maintained at 22 to 26 °C, humidity at 50% to 60%, and a 12-hour light-dark cycle was applied. The rats had free access to food and water. All animal procedures performed in this study were initially conducted by the National Institutes of Health Guide for Care Use of Laboratory Animals and approved by the animal experiment was approved by the Ethics Committee of Yunnan University of Traditional Chinese Medicine (approval number: R-0620Z3G300).

Medicines and reagents

FSJT is composed of 15 g of *Atractylodes Macrocephala Rhi*zoma, 30 g of *Astragalus Radix*, 12 g of *Bupleuri Radix*, 12 g of *Aurantii Immaturus Fructus*, 15 g of charred medicated leaven, 10 g of *Pinelliae Rhi*zoma, 12 g of *Anemarrhenae Rhi*zoma, 15 g of *Alliiat Rhi*zoma, 30 g of *Cocis Semen*, 15 g of *Poria*, 6 g of *Coptidis Rhi*zoma, 6 g of *Amomi Fructus*, 6 g of *Chuanxiong Rhi*zoma, 12 g of *Magnoliae Officinalis Cortex*, 5 g of *Euodiae Fructus*, 6 g of *Rhei Radix et Rhi*zoma, 15 g of *Lablab Album Semen*, 10 g of *Cirti Sarco*dyctis Fructus, and 5 g of *Glycerrhizae Radix*, purchased from Jiaxing Traditional Chinese Medicine Hospital (Jiaxing, China). High-fat food was purchased from Spebio Biotechnology Co., Ltd. (Beijing, China) (batch number: S08050). Metformin (MET), bicinchoninic acid protein quantification kit, triglycerides (TG), total cholesterol (TC), interleukin-1β (IL-1β), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), malondialdehyde (MDA), superoxide dismutase (SOD), and glutathione peroxidase (GSH-Px) kits were all purchased from Nanjing Jiancheng Bioengineering Institute (Nanjing, China) (batch numbers: 2400801, ab105135, A110-1-1, A111-1-1, R013, H007-1-2, R019, ab238537, A001-1-1, A005-1-1). Antibodies for translocase of outer mitochondrial membrane 20 (TM20) and beta-actin (β-actin) were purchased from Affinity Biosciences (Liyang, China) (batch numbers: AF5206, AF7018). Antibodies for voltage VDAC1, CoxIV, PINK1, light chain 3 (LC3), and P62 were purchased from Hangzhou Boao Biotechnology Co., Ltd. (Hangzhou, China) (batch numbers: ab217029, ab164645, ab30903-200ug, ab114219, Ab228525, ab128025, ab280086).

Methods

**Modeling, grouping, and drug administration.** After one week of adaptive feeding, 60 Sprague-Dawley rats were randomly selected, with 50 receiving a high-fat diet (consisting of 17.7% sucrose, 17.7% fructose, 19.4% protein, and 40% fat) for 8 weeks to induce T2DM. The remaining 10 rats served as the Control group and were fed a normal diet. After modeling, the rats were randomly divided into the T2DM group, MET group, and FSJT-low dose (FSJT-L) group, FSJT-medium dose (FSJT-M) group, and FSJT-high dose (FSJT-H) group, with 10 rats in each group. The Control and Model groups were given a daily gavage of 0.2 ml of 0.9% sodium chloride injection, while the MET group received a daily gavage of 0.2 g/kg MET. The FSJT-L, FSJT-M, and FSJT-H groups received daily gavages of crude drugs at 9.5, 19, and 38 g/kg, respectively, for 8 weeks. Blood glucose levels were measured weekly. The doses of FSJT were calculated using the equivalent dose conversion formula, with the medium dose being equivalent to the human dose. After 8 weeks, the rats were anesthetized with pentobarbital sodium, blood was collected from the aorta, and the animals were sacrificed. The pancreas was quickly removed, weighed, and a pancreatic sample from the same location was fixed in 4% paraformaldehyde. The remaining pancreas was stored at −80 °C.

**Biochemical indicator testing.** The pancreas was mixed with 0.9% sodium chloride injection at a ratio of mass to volume of 1:9, and then ultrasonically disrupted on ice to prepare a pancreatic tissue homogenate. The levels of TG, TC, MDA, IL-1β, IL-6, and TNF-α, as well as the activities of SOD and GSH-Px, were measured according to the instructions provided in the kit.

**Histological staining of pancreatic tissue.** The fixed pancreatic tissue was dehydrated with ethanol and paraffin sections were prepared. Histopathological changes were observed under a light microscope after hematoxylin-eosin staining. Fresh frozen pancreatic tissue was also used to prepare frozen sections.

**Immunoblotting analysis of autophagy-related protein levels.** Using immunoblotting, the expression levels of autophagy-related proteins VDAC1, CoxIV, TM20, PINK1, Parkin, Beclin1, LC3, and P62 were detected in pancreatic tissue. Thirty milligrams of frozen rat pancreatic tissue were collected by centrifugation at low temperature. The concentration of total protein was determined using the bicinchoninic acid method, and proteins were separated by electrophoresis. The membrane was then transferred, blocked with 5% skim milk at room temperature for 2 hours, and incubated with primary antibodies overnight at 4 °C. The primary antibodies used were PINK1, Parkin, LC3, P62 (dilution ratio: 1:1000), TM20, VDAC1, CoxIV, Beclin1 (dilution ratio: 1:2000), and β-actin (dilution ratio: 1:3000). After washing the membrane, the corresponding secondary antibodies (dilution ratio: 1:20,000) were
added and incubated at room temperature for 2 hours. The membrane was then washed with tris buffered saline with tween 20, and the proteins were detected using enhanced chemiluminescence imaging. β-actin was used as an internal reference, and the relative expression levels of the target proteins were quantified using Image J software.

**Statistical analysis**
Statistical analysis was performed using SPSS 17.0 statistical software. Measurement data that conformed to a normal distribution were expressed as mean ± standard deviation (± s), and comparisons between groups were made using the t-test. A P-value of less than 0.05 was considered statistically significant.

**Results**
Basic information and changes after treatment in rats changes in behavior, body weight, physiological indexes and pathology of rats after modeling (Table 1).

### Table 1 Basic information and changes after treatment in rats

<table>
<thead>
<tr>
<th>Basic information about rats</th>
<th>Initial state</th>
<th>Post-processing status</th>
</tr>
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<tbody>
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<td>Sprague Dawley</td>
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<td>Gender</td>
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<tr>
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<td>High-sugar and high-fat feed</td>
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<td>Slightly quieter and less active</td>
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<tr>
<td>Weight changes</td>
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<td>Lower</td>
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<tr>
<td>Changes in physiological indicators</td>
<td>Normal</td>
<td>Elevated blood sugar levels</td>
</tr>
<tr>
<td>Pathological changes</td>
<td>Not</td>
<td>The islets β cells have blurred boundaries and vacuole changes</td>
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**Pharmacological effects of FSJT on T2DM rats**
Starting from the beginning of drug administration, the changes in blood glucose levels in rats from each group were dynamically observed weekly. After the end of drug administration, compared with the normal group, the levels of blood glucose, Hba1c, oral glucose tolerance test (OGTT), and homeostatic model assessment for insulin resistance index (HOMA-IR) in the model group were significantly elevated (all P < 0.01). However, the blood glucose, Hba1c, OGTT and HOMA-IR of rats in the MET group and the FSJT medium and high dose groups were significantly reduced (all P < 0.01) (Figure 1a–d).

To evaluate the impact of FSJT on blood lipid levels in T2DM rats, the levels of TG and TC in the serum of rats from each group were measured. Compared with the normal group, the levels of TG and TC in the model group were significantly elevated (both P < 0.01). However, compared with the model group, MET and medium and high doses of FSJT significantly reduced the levels of TG and TC (P < 0.01; P < 0.05; P < 0.01, respectively) (Figure 1e, f).

**Figure 1 Observation of therapeutic effect indicators in rats from each group after modeling and drug administration.**
(a) Blood glucose; (b) Hba1c; (c) HOMA-IR; (d) OGTT; (e) TC level; (f) TG level. Compared with the normal group, **P < 0.01; compared with the model group, *P < 0.05, **P < 0.01 (n = 6 per group). FBG, fasting blood glucose; MET, metformin; TG, triglycerides; TC, total cholesterol; FSJT-L, Fangshi Jiangtang decoction-low dose; FSJT-M, Fangshi Jiangtang decoction-medium dose; FSJT-H, Fangshi Jiangtang decoction-high dose; OGTT, oral glucose tolerance test; HOMA-IR, homeostatic model assessment for insulin resistance index.

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After hematoxylin-eosin staining, the model group exhibited reduced staining intensity in the acini, unclear boundaries of pancreatic islet β-cells, and the presence of vacuolar changes. Following treatment with MET and FSJT, the staining intensity of the acini improved, and the lipid droplet vacuoles in pancreatic islet β-cells decreased, resulting in clearer boundaries and regular arrangement. These improvements in pathological conditions were particularly evident in the high-dose groups of MET and FSJT (Figure 2).

The impact of FSJT on inflammation and oxidative stress in T2DM rats
To evaluate the anti-inflammatory and antioxidant capabilities of FSJT in T2DM rats, the levels of inflammatory cytokines (IL-1β, IL-6, TNF-α) and oxidative stress-related indicators (MDA, GSH-Px, SOD) in the pancreatic tissue of rats from each group were measured. Compared with the normal group, the levels of IL-1β, IL-6, and TNF-α were elevated in the pancreatic tissue of T2DM model rats (P < 0.01). However, compared with the model group, MET and medium and high doses of FSJT significantly reduced the levels of IL-1β, IL-6, and TNF-α (P < 0.01, P < 0.05). Furthermore, when compared to the normal group, the MDA levels were elevated in model rats (P < 0.01), while the activities of GSH-Px and SOD were reduced (P < 0.01). In contrast, compared with the model group, the MDA levels were significantly decreased in the MET and medium and high-dose FSJT groups (P < 0.01, P < 0.05). Additionally, the SOD activity was significantly increased in the high-dose MET and FSJT groups (P < 0.01), while the GSH-Px activity was significantly elevated in the medium and high-dose MET and FSJT groups (P < 0.01, P < 0.05) (Figure 3).

Figure 2 Pathological changes in rats from each group after modeling and drug administration. (a) HE staining (100×, scale bar = 100 μm; 400×, scale bar = 25 μm); (b) Pancreatic injury quantification table, **P < 0.01; compared with T2DM group, P < 0.05, *P < 0.01 (n = 6 per group). MET, metformin; FSJT-L, Fangshi Jiangtang decoction-low dose; FSJT-M, Fangshi Jiangtang decoction-medium dose; FSJT-H, Fangshi Jiangtang decoction-high dose; HE, hematoxylin-eosin.

Figure 3 Impact on inflammatory and oxidative stress indicators of liver tissue after modeling and drug administration in each group. (a) IL-1β level; (b) IL-6 level; (c) TNF-α level; (d) MDA level; (e) SOD activity; (f) GSH-Px activity. Compared with the normal group, **P < 0.01; compared with the model group, P < 0.05, *P < 0.01 (n = 6 per group). MET, metformin; IL-1β, interleukin-1β; IL-6, interleukin-6; TNF-α, tumor necrosis factor-α; MDA, malondialdehyde; SOD, superoxide dismutase; GSH-Px, glutathione peroxidase; FSJT-L, Fangshi Jiangtang decoction-low dose; FSJT-M, Fangshi Jiangtang decoction-medium dose; FSJT-H, Fangshi Jiangtang decoction-high dose.

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The impact of FSJT on mitochondrial autophagy in T2DM rats

Compared with the normal group, the expressions of TOM20, VDAC1, and COXIV proteins in the pancreatic tissue of the T2DM model group were elevated (all \( P < 0.01 \)). In comparison with the model group, the expressions of VDAC1 protein were reduced in the MET group and the medium and high-dose FSJT groups (\( P < 0.01, P < 0.05, P < 0.01 \)), while the expressions of TOM20 protein were also decreased (\( P < 0.05, P < 0.05, P < 0.01 \)). Additionally, the expressions of COXIV protein were reduced in the MET group and all FSJT dose groups (low, medium, and high) compared to the model group (all \( P < 0.01 \)) (Figure 4).

Moreover, the expressions of PINK1 and Parkin proteins in the pancreatic tissue of T2DM rats were lower compared to the normal group (both \( P < 0.01 \)). In contrast, the expressions of PINK1 and Parkin proteins were upregulated in the MET group and all FSJT dose groups (low, medium, and high) compared to the model group (all \( P < 0.01, P < 0.05, P < 0.01, P < 0.01 \)).

Furthermore, the expressions of Beclin 1 and LC3 proteins were reduced in the model group compared to the normal group (both \( P < 0.01 \)), while the expression of P62 protein was significantly increased (\( P < 0.01 \)). However, when compared to the model group, the expressions of Beclin 1 protein were elevated in the MET group and all FSJT dose groups (low, medium, and high) (\( P < 0.01, P < 0.05, P < 0.01, P < 0.01 \)), and the expressions of LC3 protein were also increased (all \( P < 0.01 \)). Additionally, the expression of P62 protein was reduced in the MET group and all FSJT dose groups (\( P < 0.01, P < 0.05, P < 0.05, P < 0.01 \)) (Figure 4).

Figure 4 Impact on mitochondrial autophagy of liver tissue after modeling and drug administration in each group. (a) Western blot results of autophagy-related proteins; (b) VDAC1 level; (c) TOM20 level; (d) COXIV level; (e) Western blot results of PINK1/Parkin pathway-related proteins; (f) PINK1 level; (g) Parkin level; (h) Beclin 1 level; (i) LC3 level; (j) P62 level. Compared with control group, \# \( P < 0.01 \); compared with T2DM group, \( P < 0.05, \# \# P < 0.01 \) (n = 6 per group). MET, metformin; TOM20, translocase of outer mitochondrial membrane 20; LC3, light chain 3; FSJT-L, Fangshi Jiangtang decoction-low dose; FSJT-M, Fangshi Jiangtang decoction-medium dose; FSJT-H, Fangshi Jiangtang decoction-high dose.
Discussion

In this study, a T2DM model was established in rats using a high-fat diet, and FSJT intervention was administered. The results showed that FSJT significantly reduced blood glucose, HbA1c, OGTT, and HOMA-IR levels in T2DM model rats, indicating that FSJT has a beneficial therapeutic effect on T2DM model rats.

Mitochondria serve as the primary site for biological oxidation and energy conversion in mammalian cells, providing the “power” for cellular life activities and maintaining the homeostasis of mitochondrial quality and quantity, which is crucial for life activities [8]. As a selective autophagy mechanism, mitophagy clears damaged or excessive mitochondria from cells, thereby maintaining the homeostasis of mitochondrial quantity and function [9]. Mitochondrial genetic mutations, intracellular high ROS levels, and chemical factors such as anticycin can lower the mitochondrial inner membrane potential, leading to mitochondrial damage and triggering the mitophagy response [10]. When mitochondria function normally, PINK1 is recognized by the translocase of the outer membrane complex on the mitochondrial outer membrane and transported into the intermembrane space. It is then imported into the mitochondria through the translocase of the inner membrane 23 and rapidly degraded on the mitochondrial inner membrane. However, when the mitochondrial membrane potential decreases, PINK1 is activated through self-phosphorylation and stabilizes on the depolarized mitochondrial outer membrane after recognizing damaged mitochondria. Subsequently, PINK1 phosphorylates the ser65 site located in the ubiquitin-like domain of Parkin, and the phosphorylated Parkin is recruited from the cytoplasm to the outer membrane of damaged mitochondria [11]. This further regulates the dynamic changes in mitochondrial morphology, fission, and fusion through ubiquitination of substrates such as VDAC1, Mfn1, and Mfn2 embedded in the outer membrane [12, 13].

Insulin resistance refers to the decreased sensitivity of insulin-responsive target tissues such as the liver, muscles, and adipose tissue to insulin. It is the initiating factor of T2DM and persists throughout the entire disease course. As a second messenger, ROS enhances the effects of insulin mainly by inhibiting the activity of PTP1B through oxidation [4]. Mitochondrial autophagy maintains the appropriate quality and quantity of mitochondria by targeting cleared damage of damaged or redundant mitochondria and promoting mitochondrial renewal, thereby limiting excessive accumulation of ROS [6]. This process regulates insulin signaling and improves insulin resistance [7]. When mitochondrial autophagy function is imbalanced, it cannot properly initiate mitochondrial autophagy, leading to the accumulation of damaged mitochondria and increased ROS production, which further exacerbates the occurrence of insulin resistance. The ratio of LC3-II/LC3-I can be used as an indicator of autophagy levels. P62 can bind to LC3 and be transported to the lysosome for degradation, thus serving as a marker of lysosomal degradation activity. Beclin1 is an important regulatory factor in the autophagy process, and its expression is positively correlated with autophagy activity [14]. Studies have shown that in the pancreas of T2DM model rats, the level of mitochondrial autophagy mediated by PINK1/Parkin is significantly reduced, leading to the accumulation of damaged mitochondria [15]. Activating PINK1/Parkin-mediated mitochondrial autophagy can alleviate fat deposition and mitochondrial damage in T2DM pancreatic cells [16–18]. The results of this experiment showed that after FSJT intervention, the protein expression levels of VDAC1, TOM20, COXIV, and P62 decreased in T2DM model rats, while the protein expression levels of PINK1, Parkin, LC3-II/I, and Beclin1 increased. This suggests that FSJT significantly improves insulin resistance in T2DM rats, which may be closely related to the regulation of mitochondrial autophagy.

In summary, FSJT can alleviate insulin resistance in T2DM rats by mediating the activation of mitochondrial autophagy.

References


