Hypoglycemic and hypolipidemic effects of rutin on hyperglycemic rats


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Abstract

OBJECTIVE: To study the effects of rutin on serum glucose and lipid levels in hyperglycemic rats.

METHODS: Male Wistar rats were subjected to intraperitoneal streptozotocin injections and a high-sugar, high-fat diet to establish a hyperglycemic and hyperlipidemic model. The model was considered to be successfully established in rats with fasting blood sugar (FBS) ≥ 11.1 mmol/L. The study included 6 groups with 10 rats each: a blank control group, a model group, a metformin group, and groups on large, medium and small doses of rutin. The groups received intraperitoneal streptozotocin or normal saline for 21 d. FBS, serum lipids, serum insulin, insulin sensitivity index (ISI), and levels of catalase (CAT), glutathione peroxidase (GSH-Px), superoxide dismutase (SOD) and malondialdehyde (MDA) levels were evaluated in all rats. Pancreatic tissue samples were harvested to observe structural changes in islet cells.

RESULTS: Large, medium, and small doses of rutin were associated with significantly reduced FBS (P < 0.05), and increased levels of ISI, CAT, GSH-Px and SOD, as well as decreased MDA (P < 0.05). Rutin administration was also related with reduced total cholesterol, triglycerides and low density lipoprotein cholesterol, as well as increased high density lipoprotein cholesterol (P < 0.05). Histologic evaluation revealed rutin induced repair of damaged islet cells.

CONCLUSION: In diabetic rat models, rutin can significantly reduce FBS and blood lipids, improve anti-oxidant activity, increase insulin sensitivity, and induce repair of damaged islet cells.

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Keywords: Hyperlipidemias; Rutin; Hypoglycemic agents; Hypolipidemic agents; Blood glucose; Insulin resistance

INTRODUCTION

Type 2 diabetes mellitus (T2DM) has been related to unhealthy lifestyle patterns, such as high-sugar, high-fat diets and physical inactivity. Diabetes has become the third leading cause of mortality worldwide, under only cancer and cardiovascular disease; thus rep-
resenting a major public health problem. In addition, the incidence and prevalence of T2DM is increasing, while the population diagnosed with this disease has become steadily younger. Moreover, approximately 500 million people in the world are estimated to have prediabetes. Diabetes greatly lowers patients’ quality of life, especially when complications appear. Hyperlipidemia is the result of abnormal lipid metabolism; and is considered a major risk factor for atherosclerosis, and one of the most important risk factors for cardiovascular disease, which has become increasingly frequent in our country. The 2015 China Health and Nutrition Survey revealed the prevalence of total cholesterol (TC) levels ≥ 6.22 mmol/L to be 4.7% and 5.1% in adult males and females, respectively; and the prevalence of triglyceride (TG) levels ≥ 2.26 mmol/L to be 16.7% and 9.8%, in adult males and females, respectively. Traditional Chinese herbs have been widely used to treat T2DM in China. Most of their active components appear to positively impact hyperglycaemia and hyperlipidemia. In particular, natural flavonoids can modulate glucose metabolism, having therapeutic effects on diabetes. Among Chinese herbs, rutin appears to have very important anti-oxidant, anti-inflammatory, hypoglycemic and hypolipidemic effects. The purpose of this study was to explore the therapeutic effects of rutin on hyperglycaemia and hyperlipidemia, and its potential mechanisms of action.

**MATERIALS AND METHODS**

**Chemicals and reagents**

Rutin was purchased from Sigma-Aldrich Co., LLC. (St. Louis, MO, USA). Kits for the measurement of fasting blood glucose (FBG), malondialdehyde (MDA), superoxide dismutase (SOD), glutathione peroxidase (GSH-Px), catalase (CAT), serum insulin (SI), TC and TG were purchased from Jiancheng Bioengineering Institute (Nanjing, China). Streptozotocin (STZ) was purchased from Sigma-Aldrich Co., LLC. (St. Louis, MO, USA). All solvents used in this study were of analytical reagent grade. Column chromatography was performed with macroreticular resin HPD-400 (Chemical Plant of Baoen, Hebei, China).

**Animals**

Male Wistar rats weighing 200-250 g were obtained from the SPF Animal Lab of the Xi’an Jiaotong University (Xi’an, China). The rats were housed and kept for one week in standard polypropylene cages, five rats per cage, in a room at a controlled temperature of (22 ± 2) °C and a humidity of 55% ± 5%. All rats received commercially available whole grain feed stuff (Xi’an Jiaotong University) and water ad libitum, prior to manipulation of their dietary patterns. All procedures conducted on animals followed the protocols approved by the Institutional Ethical Committee of the Shaanxi University of Chinese Medicine.

**Development of experimental rat models with hyperglycemia and hyperlipidemias induced by administration of streptozotocin and a high-glucose high-fat diet**

Rats were randomly assigned either a normal diet or a high-glucose-high-fat diet, with a caloric composition of 30% fodder, 15% fat, 15% sugar, 20% protein and 20% carbohydrates, provided ad libitum for an initial period of 21 d. During this period, rats on the high-glucose-high-fat diet received intraperitoneal injections with low doses of STZ (35 mg/kg) on days 1, 4, 7, 14, and 21; while controls received normal saline (NS) volumes of 1 mL/kg through the same route on the same days. FBG, TC and TG levels were measured after the final injection on day 21 in both groups. Rats with FBG ≥ 11.1 mmol/L were classified as diabetic and selected for further pharmacological study. The control group continued to receive a normal diet; all other rats received the high-glucose-high-fat diet until the end of the experiment.

**Experimental design**

A total of 60 mice were divided into 6 groups of 10 subjects each: the model group, the blank control group, the positive control group which received metformin doses of 125 mg/kg, and three groups which received rutin in large (155 mg/kg), medium (125 mg/kg), or small doses (95 mg/kg). Rats were evaluated daily. The effects of rutin on rats were demonstrated by measuring changes in FBG, insulin sensitivity index (ISI), antioxidiant index, TC, TG and body weight. All biochemical parameters were determined on day 21 after the animals were fasted overnight and sacrificed by decapitation.

**Determination of biochemical metabolic parameters**

On day 21, retro-orbital blood was drawn from the rats after 24 h of fasting. Samples were centrifuged at 3000 rpm and 4 °C for 10 min to obtain serum for the measurement of TG and TC levels. Then, levels of SOD, CAT, GSH-Px and MDA were determined with UV-vis spectrophotometry. ISI was calculated based on serum insulin levels obtained through enzyme-linked immunosorbent assay, with the following formula: ISI = ln [1/(insulin x FBG)].

**Histological analysis**

After sacrificing the rats on day 21, the pancreases were harvested, washed and soaked in 10% formal indiluted with NS. The soaked pancreatic tissue was then sent to Xi’an Jiaotong University for assessment of the number and repair rate of pancreatic islet cells.

**Statistical analysis**

Statistical analysis was conducted using spss 22.0
RESULTS

Body weight
There was no significant intra-group variation in basal body weight. However, the body weight of the animals in the blank control group increased significantly from (203 ± 6) to (268 ± 7) g (Figure 1), while the weight of the model group decreased from (206 ± 7) to (179 ± 6) g. Treatment with rutin was associated with a slight increase in body weight compared with the model group, and the body weight tended to return to normal in this group in comparison with the blank control group.

Fasting blood glucose
Successful induction of diabetes was confirmed in the experimental rats by corroborating the presence of high FBG levels. Compared with the blank control group, FBG was significantly higher in the model group (P < 0.01); whereas compared with the model group, the rutin and metformin groups showed significantly lower FBG (P < 0.05, Table 1). Therefore, administration of rutin significantly reduced FBG in diabetic rats.

Glycosylated serum protein
GSP is a metabolite of advanced glycated end products which reflects FBG levels from the previous 3 weeks. GSP was significantly higher in the model group compared with the blank group (P < 0.01, Figure 2). The groups on rutin or metformin administration had significantly lower GSP levels than the model group (P < 0.05). GSP levels tended to decrease as rutin doses increased.

Serum insulin and insulinsensitivityindex
After 21 d of treatment, the model groups that received rutin or metformin showed significantly lower serum insulin levels and ISI values (P < 0.05, Figure 3).

Serum lipid levels
The successful establishment of hyperlipidemia model was demonstrated by ascertaining significantly increased TC, TG, low density lipoprotein cholesterol (LDL-C) and decreased high density lipoprotein cholesterol (HDL-C) in the model group. Conversely, in the groups on rutin or simvastatin, TC, TG and LDL-C levels were significantly reduced, and HDL-C was significantly higher (P < 0.05, P < 0.01; Figure 4).

CAT, SOD, GSH-Px, and MDA
Levels of CAT, SOD and GSH-Px were significantly lower in the model group compared with the blank control group (P < 0.01), while MDA was significantly higher in the model group than in the control group (P < 0.01, Figure 5). These results allowed us to deem the models successfully established. Levels of CAT, SOD and GSH-Px were significantly increased in the rutin and model groups (P < 0.05, P < 0.01), while MDA was significantly reduced (P < 0.05, P < 0.01). On the other hand, CAT, SOD and GSH-Px were significantly higher in the metformin group compared with the model group (P < 0.05, P < 0.01), along with a significant reduction in MDA levels (P < 0.05, P < 0.01).

Islet cells
Islet cells were stained with HE to observe structural changes (Figure 6). The blank control group had a large number of regularly-arranged islet cells, while those from the model group underwent degenerative changes, with sparse distribution, decreased islet density, no rounded outlines, and irregular edges. Samples from the groups on rutin showed improvements to a certain extent in comparison with the model group in terms of cell number, morphology, and distribution; thus showing variable degrees of islet cell repair occurred in these groups.

Figure 1 Effect of rutin on body weight
Model: model group on normal saline; blank: blank control group on normal saline; metformin: metformin group (125 mg/kg); large rutin dose (155 mg/kg); medium rutin dose (125 mg/kg); small rutin dose (95 mg/kg). Values are expressed as mean ± standard error of mean (n = 10). aP < 0.05, as compared to the blank control group, bP < 0.05, as compared to the model group.
In this study, we evaluated the hypoglycemic effect of rutin on diabetic rats which were subjected to a high-sugar high-fat diet and received intraperitoneal injections of streptozotocin. We chose this agent because it has been observed to mildly disrupt insulin secretion in a manner similar to that observed in advanced T2DM. Male mice were selected because of their greater sensitivity to drugs and external stimuli. Hyperglycemia causes a variety of symptoms, such as increased urination, thirst, hunger, fatigue and weight loss. These factors should be monitored in order to ensure the success of the modeling process. The antioxidant effect of rutin was evaluated to appraise its impact on the hypoglycemic effect of this substance.

In conclusion, we found the administration of rutin had significant hypoglycemic activity and increase D insulin sensitivity. Rutin also significantly increased CAT, SOD, and GSH-Px; along with a reduction in MDA levels, highlighting its anti-oxidant effect. It also induced a significant reduction of TC, TG and LDL-C, as well as an increase in HDL-C levels. Furthermore, rutin also appeared to induce the repair of damaged islet cells.

**Table 1** Effect of the rutin on fasting blood glucose

<table>
<thead>
<tr>
<th>Group</th>
<th>Dose (mg/kg)</th>
<th>FBG (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blank control</td>
<td>-</td>
<td>5.3±0.4</td>
</tr>
<tr>
<td>Model control</td>
<td>-</td>
<td>13.3±1.07</td>
</tr>
<tr>
<td>Large rutin dose</td>
<td>155</td>
<td>7.9±1.02</td>
</tr>
<tr>
<td>Medium rutin dose</td>
<td>125</td>
<td>8.3±0.82</td>
</tr>
<tr>
<td>Small rutin dose</td>
<td>95</td>
<td>9.6±0.72</td>
</tr>
<tr>
<td>Metformin</td>
<td>125</td>
<td>7.3±0.82</td>
</tr>
</tbody>
</table>

Notes: model: model group on normal saline; blank: blank control group on normal saline; metformin: metformin group (125 mg/kg); large rutin dose (155 mg/kg); medium rutin dose (125 mg/kg); small rutin dose (95 mg/kg). FBG: fasting blood glucose. *P < 0.05, as compared to the blank control group; **P < 0.01, as compared to the model group.

**DISCUSSION**

In this study, we evaluated the hypoglycemic effect of rutin on diabetic rats which were subjected to a high-sugar high-fat diet and received intraperitoneal injections of streptozotocin. We chose this agent because
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