Hypoglycemic activity of puerarin through modulation of oxidative stress and mitochondrial function via AMPK

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[ABSTRACT] Hyperglycemia is the dominant phenotype of diabetes and the main contributor of diabetic complications. Puerarin is widely used in cardiovascular diseases and diabetic vascular complications. However, little is known about its direct effects on diabetes. The aim of our study is to investigate its antidiabetic effect in vivo and in vitro, and explore the underlying mechanism. We used type 1 diabetic mice induced by streptozotocin to observe the effects of puerarin on glucose metabolism. In addition, oxidative stress and hepatic mitochondrial respiratory activity were evaluated in type 1 diabetic mice. In vitro, glucose consumption in HepG2 cells was assayed along with the qPCR detection of glucogenesis genes expression. Moreover, ATP production was examined and phosphorylation of AMPK was determined using Western blot. Finally, the molecular docking was performed to predict the potential interaction of puerarin with AMPK utilizing program LibDock of Discovery Studio 2018 software. The results showed that puerarin improved HepG2 glucose consumption and upregulated the glucogenesis related genes expression. Also, puerarin lowered fasting and fed blood glucose with improvement of glucose tolerance in type I diabetic mice. Further mechanism investigation showed that puerarin suppressed oxidative stress and improved hepatic mitochondrial respiratory function with enhancing ATP production and activating phosphorylation of AMPK. Docking study showed that puerarin interacted with AMPK activate site and enhancing phosphorylation. Taken together, these findings indicated that puerarin exhibited the hypoglycemic effect through attenuating oxidative stress and improving mitochondrial function via AMPK regulation, which may serve as a potential therapeutic option for diabetes treatment.

[KEY WORDS] Puerarin; Diabetes; Hypoglycemic; Oxidative stress; Mitochondrial function


Introduction

Recently, the world has witnessed an increasing prevalence of diabetes [1]. According to the 9th edition of Diabetes Atlats released by international diabetes federal, diabetes has become one of the fastest growing health challenges in the 21st century, with the number of adults living with diabetes having more than tripled over the past 20 years [2]. The pand-
demonstrated that puerarin has multiple pharmacological activities and has been widely used for the treatment of cardiovascular diseases, including hypertrophic cardiomyocyte [8], myocardial ischemia [9] and pulmonary arteries injury [10]. Emerging evidence proved that puerarin could protect against hyperglycemia-induced injuries in diabetic complication, such as diabetic nephropathy [11], diabetic aorta injury [12]. Both Yang L [13] and Liang T [14] reported the puerarin’s protection on pancreatic β-cells which is closely related with GLP-1R signaling and caspase-AIF-apoptosis pathway. These results indicated beneficial effects of puerarin on glucose consumption of diabetes. However, the exact role of puerarin on glucose consumption and its underlying mechanism remain unclear.

Hence, the present study is aimed to investigate the hypoglycemic effect of puerarin and underlying mechanism. Using type I diabetes mice model, we evaluated the effects of puerarin on blood glucose level and glucose tolerance. In vitro, we tested the ability of puerarin on facilitating glucose consumption in HepG2 cells. To further explore its underlying mechanism, we detected glucogenesis-related genes expression and assayed oxidative stress. In addition, we investigated the modulation of puerarin in mitochondrial function by examining the hepatic mitochondrial respiratory function. Finally, we verified puerarin’s interaction with AMPK by molecular docking and its activation of AMPK phosphorylation. The current study will provide evidence that puerarin might be a potential therapeutic agent for diabetes.

**Material and Method**

**Cell culture and glucose consumption**

Hepatic cell line HepG2 cells were cultured in DMEM supplemented with 10% fetal bovine serum (FBS) (Gibco, Australia) in humidified air at 37 °C supplied with 5% CO₂. HepG2 cells were seeded on 96-well plate and were treated with different concentrated of puerarin (0.1, 1, 10 μmol·L⁻¹) and insulin (3 × 10⁻⁸ mol·L⁻¹) for 24 hours. The supernatant was collected for glucose assay, and cell viability was detected with cell counting kit-8 (CCK-8).

**RNA extraction and quantitative real-time PCR**

Total RNA of HepG2 was extracted using TRIzol (Life Technologies, Grand Island, NY), followed by reverse transcription of total RNA to cDNA using a high-capacity cDNA reverse transcription kit (Takara, Japan). cDNA subsequently underwent quantitative real-time polymerase chain reaction (qPCR) with TB green (Takara, Japan). qPCR reactions were run in triplicate and quantitated using CFX96™ real-time system (Bio-Rad, Singapore). Relative amounts of mRNA were normalized to TATA box-binding protein (TBP) expression and expressed as arbitrary units.

**Animals and treatments**

Male C57BL/6 mice (20–22 g) were obtained from Beijing HFK Bioscience Co., Ltd. (Beijing, China). Animals were held in a SPF environment of temperature 22–25 °C, humidity 60%–70%, 12 h light/12 h dark cycle for one week to acclimate the environment. All animal experiments were carried out under the guidelines approved by the animal care committee of the Institute of Materia Medica, Chinese Academy of Medical Sciences. Mouse model of type I diabetes was induced as previously reported with minor modification [15]. Briefly, mice were intraperitoneal injected streptozotocin (STZ) at 60 mg·kg⁻¹ and mice with fasting blood glucose (FBG) higher than 11.1 mmol·L⁻¹ and lower than 25 mmol·L⁻¹ were considered as diabetes. Diabetic mice were randomly assigned into five groups: diabetic model group (DM) treated with vehicle, diabetic mice with oral administration of puerarin at 100, 200, and 400 mg·kg⁻¹·d⁻¹, and diabetic mice with oral administration of metformin (Met) at 20 mg·kg⁻¹·d⁻¹ for 3 weeks. Meanwhile, age-matched normal mice received an equal volume of normal saline serving as control group. Body weight as well as water and food consumption were measured every week. Liver coefficient was calculated by the ratio of liver weight to body weight.

**Determination of blood glucose and oral glucose tolerance test**

Fasting blood glucose measurement was conducted with an ACCU-CHEK® Active glucometer (Roche, Hoffmann, Germany) every week. Fed blood glucose samples were collected from tail and were detected with an automatic analyzer (TOSHIBA Acute TBA-40FR, TOSHIBA CORPORATION, Tokyo, Japan). Oral glucose tolerance test (OGTT) was conducted as previously described with minor modification [16]. Briefly, glucose solution (2.0 g kg⁻¹) was administrated orally after 4 h-fasting. Blood glucose were detected at 0, 30, 60, 120 min after glucose loading.

**Examination of MDA, GSH and SOD**

The specific markers for oxidative stress including plasma level of malondialdehyde (MDA) and glutathione (GSH) as well as the activity of superoxide dismutase (SOD) were measured according to the manufacturer’s instructions (Jiancheng Biotech Co., Ltd., Nanjing, China).

**Measurement of mitochondrial respiratory function**

Mitochondria was isolated and its respiratory activity was analyzed as previously reported [15]. 60 mg of mice liver was finely minced and homogenized (10%, W/V) in cold isolation buffer (0.25 mol·L⁻¹ sucrose, 10 mmol·L⁻¹ Tris-HCl, 1 mmol·L⁻¹ EDTA, 1 g·L⁻¹ BSA, pH 7.4) with glass homogenizer. After centrifugation at 1000 g for 10 min, the supernatant underwent another centrifugation at 10 000 g for 10 min. The lower precipitab as mitochondria was resuspend in 1 mL respiration buffer (225 mmol·L⁻¹ sucrose, 5 mmol·L⁻¹ potassium phosphate buffer pH 7.4, 10 mmol·L⁻¹ Tris-HCl, 10 mmol·L⁻¹ CL, 0.2 mmol·L⁻¹ DTA, 0.1 mg·L⁻¹ BSA) for the further measurement.

Mitochondrial respiratory activity was calibrated as oxygen consumption using Clark type oxygen electrodes (Strathkelvin Instruments, British) at 25 °C. After adding complex I substrate (10 μmol·L⁻¹ l-glutamate, 5 μmol·L⁻¹ L-malate), the mitochondrial respiration was initiated. Then followed by adding ADP to induce state 3 respiration and trans-
formed to state 4 respiration after ADP ran out.

**Measurement of ATP production**

HepG2 cells were incubated with puerarin (0.1, 1 μmol·L⁻¹) for 6, 12, 24 and 48 h. ATP production were measured using CellTiter-Glo reagent (Promega, USA) and the luminescence was recorded by Spectra Max M5 microplate reader (Molecular Devices, USA)

**Western blot analysis**

Drug-stimulated cells were lysed with RIPA supplement with complete protease inhibitor cocktail as well as phosphatase inhibitor cocktail (CWBIO, China). Cell lysates (30 μg) was subjected to SDS polyacrylamide gel. After electrophoresis and blotting, protein was immunoblottedted with antibodies for phospho-AMPK, total-AMPK and β-actin. The ratio of protein interest was desitometrically analyzed by Gel pro.

**Molecular docking**

LibDock was performed by Discovery Studio software (BIOVIA, USA). The crystal structure of AMPK (PDB id: 5UFU) was used as target protein after removing water molecular, adding hydrogen and computing charges. AMPK agonist AICAR was referenced as positive docking control. Puerarin was docked into the binding pocket of AMPK catalyze domain. LibDock score was applied to evaluate the affinity of molecular conformation.

**Statistical analysis**

All data were expressed as mean ± SEM. Unpaired 2-
tailed Student’s t tests was used to determine statistically significant differences. A value of P < 0.05 was considered statistically significant.

**Results**

**Puerarin promoted glucose consumption in HepG2 cells**

Puerarin, a natural flavone (Fig. 1A), was subjected to glucose consumption of HepG2 cells. The results showed that the glucose consumption of HepG2 cells increased after treated with different doses of puerarin, with no influence on cell viability (Figs. 1B–1C). Especially, 1 μmol·L⁻¹ puerarin significantly improved 12.5% of glucose consumption than control group. This result suggested a hypoglycemic activity of puerarin.

**Puerarin upregulated glucose metabolism-related genes in HepG2 cells**

We then examined the expression of key genes regulating glucose metabolism including alpha-ketoglutarate dehydrogenase complex (Kgdhc), phosphoenolpyruvate carboxykinase (Pck), isocitrate dehydrogenase (Idh1/2). The results showed that Kgdhc, which is believed to have an important role in the regulation of the tricarboxylic acid (TCA) cycle flux, was upregulated by puerarin (Fig. 2A). Pck, which catalyzes the first rate-limiting step in hepatic gluconeogenesis pathway to maintain blood glucose levels, also increased dose-dependently by puerarin (Fig. 2B). However, puerarin tended to elevate Idh1 and Idh2 expression, which catalyzes the first

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![Fig. 1](image1.png)

**Fig. 1** Puerarin enhanced glucose consumption in hepatic cells. HepG2 cells were treated with indicated concentration of puerarin (0.1, 1, 10 μmol·L⁻¹), insulin (3 × 10⁻⁸ mol·L⁻¹) for 24 h. (A) Structure of puerarin, (B) glucose consumption, (C) cell viability of HepG2 cells. Data are presented as mean ± SEM, n = 3. *P < 0.05, ***P < 0.001 vs control group. Ctrl: Control; Ins: Insulin; Pur: Puerarin

![Fig. 2](image2.png)

**Fig. 2** Puerarin upregulated gene expression of glucose metabolism. HepG2 were treated with indicated concentration of puerarin (1, 10 μmol·L⁻¹) for 24 h, key genes regulating glucose metabolism of (A) Kgdhc, (B) Pck, (C) Idh1, (D) Idh2 were measured by qPCR. Data are presented as mean ± SEM, n = 3. *P < 0.05 vs control group. Ctrl: Control; Pur: Puerarin
rate-limiting step of TCA, yet lack of statistical significance (Figs. 2C–2D). Together, Puerarin mainly enhanced the gene expression on gluconeogenesis. **Puerarin ameliorated the general parameters of diabetic mice**

As is shown in Fig. 3, STZ-induced type I diabetic mice displayed constantly reducing body weight and the typical characters of diabetes in polydipsia as well as polyphagia. After oral administration for three weeks of differently doses of puerarin, the losing tendency of body weight was effectively controlled (Fig. 3A). We compared the final body weight reduction and found that puerarin 400 mg·kg⁻¹ effectively stopped the diabetes-induced weight losing (Fig. 3B). Consistently, puerarin 400 mg·kg⁻¹ significantly reduced liver hypertrophy induced by diabetes (Figs. 3C–3D). Despite both puerarin and Met had little influence on the food intake, they markedly ameliorated the polydipsia of diabetic mice. In general, puerarin moderated the general status of diabetic mice (Figs. 3E–3F). **Puerarin alleviated the hyperglycemia of diabetic mice**

The blood glucose of diabetic mice increased as elongated of the experiment duration, evidenced by results of fasting blood glucose (FBG) and postprandial blood glucose (PBG). Met 20 mg·kg⁻¹ exerted a stable lowering effect of blood glucose on both FBG and PBG as expected. Puerarin dose-dependently decreased the FBG since the second week of administration. Meanwhile, puerarin 400 mg·kg⁻¹ reduced the PBG since the first week of administration (Figs. 4A–4B). At the end of experiment, we tested glucose tolerance of diabetic mice, and the result demonstrated that the impaired glucose tolerance was greatly restored by puerarin (Figs. 4C–4D). These effects of puerarin on blood glucose were confirmed by the result of fructosamine content, which reflected the 2- or 3-week blood glucose level of diabetic mice (Fig. 4E). Taken together, puerarin alleviated the hyperglycemia in type I diabetic mice. **Puerarin attenuated oxidative stress of diabetic mice**

Oxidative stress is the result of chronic hyperglycemia and the major contributor to the diabetic complication with macro- and micro-vascular damages or multiple organic lesions. We next investigated oxidative stress of diabetic mice. The results showed that peroxidation end products MDA significantly increased in diabetic mice (Fig. 5A). Nonetheless, the activities of regulators defending oxidative stress including SOD and GSH decreased. Puerarin administration lowered MDA contents and improved the antioxidant capacity of diabetic mice by elevating the SOD activity and restoring GSH contents (Figs. 5B–5C). Taken together, Puerarin attenuated oxidative stress in type I diabetic mice. **Puerarin improved hepatic mitochondrial function in diabetic mice**

Mitochondria function is closely associated with glucose metabolism. To test the effects of puerarin on mitochondrial function in diabetic mice, we measured the respiratory activity of isolated liver mitochondria. Respiratory control ratio (RCR) is an indicator for mitochondrial structural, functional integrity, and the efficiency of oxidative phosphorylation. As displayed in Figs. 6A and 6D, the lower RCR of chain I and chain II in diabetic mice indicated the mitochondrial dysfunction. Puerarin 400 mg·kg⁻¹ markedly elevated the RCR of chain I and tended to raise the RCR of chain II yet lack of statistical significance. Meanwhile, Puerarin improved the efficiency of oxygen usage by elevating the ratio of ADP concentration to consumption of oxygen (ADP/O) of

![Graphs showing metabolic parameters of diabetic mice](image-url)
mitochondrial respiratory chain I and chain II (Figs. 6B and 6E). These effects were further certified by elevation of oxidative phosphorylation ratio (OCR) by puerarin administration (Figs. 6C and 6F). Taken together, these results suggested puerarin improved hepatic mitochondrial function in type I diabetic mice.

**Puerarin enhanced ATP production of HepG2 cells**

We then examined the effect of puerarin on ATP production of hepatic cells. As displayed in Fig. 7, both puerarin 0.1 and 1 μmol·L⁻¹ significantly elevated the ATP production after incubating 6 and 12 h (Figs. 7A–7B). However, after elongating the incubation time to 12 and 24 h, this improvement was not obvious (Figs. 7C–7D).

**Puerarin directly bound to AMPK and activated phosphorylation of AMPK**

We then explored whether AMPK, which is the metabolic master switch regulating mitochondria and glucose metabolism, is involved the hypoglycemic activity and the mitochondrial protection of puerarin. We firstly examined the affinity of puerarin with AMPK by molecular docking. As shown in Fig. 8A, LibDock results showed that puerarin was docked into AMPK active pocket at LYS169, TYR164, SO4404 through Pi-Anion bonds. Puerarin showed good LibDock energy (LibDock score = 95.09), which is higher than AMPK agonist AICAR (LibDock score = 81.16) (Figs. 8A–8B). We than run western blot to assay puerarin’s effect on AMPK. The results showed that puerarin activated the phosphorylation of AMPK in a time-dependent manner and reached to a maximum at 30 min (Fig. 8C). In accordance with the previous result of glucose consumption, 1 μmol·L⁻¹ puerarin had best effect on AMPK phosphorylation activation (Fig. 8D). Pretreated with specific AMPK inhibitor compound C significantly inhibited phosphorylation of AMPK, which was ameliorated by co-treatment with 1 μmol·L⁻¹ puerarin (Fig. 8C). Collectively, these results suggested that puerarin interacted with AMPK and activated the phosphorylation...
glucose consumption is the dominant phenotype of diabetes, therefore, inventions are important by targeting the glucose metabolism for the diabetes treatment. In the current study, puerarin effectively decreased both PBG and FBG since the first week of administration till the 21st day with a stronger effect on FBG. Increasing glucose consumption and uptake in periphery tissue, especially liver and skeletal, are major contributor to lowering postprandial glucose. Besides fasting hyperglycemia, postprandial hyperglycemia is one of the earliest abnormalities of glucose homeostasis associated with diabetes and markedly aggravated fasting hyperglycemia. The further investigation in HepG2 cells confirmed that puerarin enhanced the glucose consumption of hepatic cells. Glucose consumption in vitro depends not only on the glucose consumption rate but also on the cell proliferation rate. The CCK-8 result demonstrated that puerarin facilitated glucose consumption rather than cell proliferation. Notably, we also found that puerarin ameliorated the diabetic liver hypertrophy by reducing liver coefficient, the ratio of liver weight-to-body weight, which could be related to its improvement of hepatic glucose metabolism. This was in accordance with our previously finding in high-fat diet combined with low dose STZ-induced type II diabetic rats, in which puerarin improved glucose metabolism and reduced de novo lipogenesis in diabetic liver.

Hepatic glucose production, which is the source of fuel...
for brain and red blood cells, plays important role in maintaining normoglycemia (20). We further investigated the key enzymes regulating hepatic gluconeogenesis such as Kgdh, Pck (21). These enzymes are involved in first rate-limiting step in hepatic gluconeogenesis and TCA cycle flux to maintain blood glucose levels (22-23). Although, Idh was reported to be related to lipid biosynthesis pathway, recently it was found that Idh1 is critical for amino acids utilization in vivo. Its deficiency attenuated gluconeogenesis primarily by impairing α-KG-dependent transamination of glucogenic amino acids such as alanine (24). The improvement of glucose consumption by puerarin may be related to its upregulation of glucogenic genes in hepatic cells.

The impaired redox homeostasis has long been known to play a key part in the pathogenesis of the diabetes and its complications through a variety of mechanisms. Landmark studies by Giacco and Brownlee showed that the increased glycemic load in diabetes overwhelms the Krebs cycle, resulting in the inhibition of electron transfer within the mitochondrial membrane and the accumulation of free radicals (25), which in turn resulting in oxidative damage to membranes and tissues (26). Superoxide induced by hyperglycemia through mitochondrial electron-transport chain is the initial oxygen free radical, which consequently converted to other reactive species damaging cells in numerous ways (26). In the current study, we observed puerarin relieved oxidative stress by reducing MDA and enhancing the antioxidant system. This antioxidant effect of puerarin may be relevant to its hypoglycemic activity. On the other hand, as a natural flavone, puerarin’s ability to suppressed oxidative stress in diabetic conditions remains to be explored.

**Fig. 8** Puerarin interacted with AMPK and activated AMPK phosphorylation. Molecular interaction of (A) Puerarin and (B) AMPK activator AICAR with active site of AMPK using LibDock by Discovery Studio. (C), HepG2 were treated with indicated concentration of puerarin (1 μmol·L⁻¹) from 5 to 60 min, phosphorylation of AMPK at time-response effect determined by western blot. (D), representative blots for dose-response effect of puerarin (0.1, 1, 10 μmol·L⁻¹) at 30 min, after pretreated with AMPK inhibitor compound C (40 μmol·L⁻¹) for 1 h at 37 °C, HepG2 cells were treated with puerarin (0.1, 1, 10 μmol·L⁻¹) for 30 min with or without compound C, phosphorylation of AMPK was detected by western blot. Data are presented as mean ± SEM, n = 3 per group. *P < 0.05, **P < 0.01, ***P < 0.001 vs control group. Ctrl: Control; Pur: Puerarin.
mice, which is in consistent with previously finding in other models [19, 27-29].

Mitochondria, which constitute the main sources of free radicals, generated ROS by mitochondrial oxygen consumption [38]. Consequently, the aggregated oxidative stress extensively affected the mitochondrial function by damaging mitochondrial proteins. Mitochondrial damage has occurred during diabetic complications in liver [31]. In the current study, we observed significant mitochondrial dysfunction evidenced by impaired respiratory activity in both chain I and chain II. RCR were calculated as the ratio of velocity in state 3 (V3)/state 4 (V4). V3 represents the response to oxidative phosphorylation under ADP stimulation, and was regulated by electron transport complex activity, oxidized substrate content as well as ATP synthase activity [32]. On the other hand, V4 represents electrons escaping from complex I to complex III during transformation and leading to increase of superoxide anion and ROS generation [33]. Thus, the reduced RCR indicating the inclined V4 or the declined V3. Puerarin had a stronger effect on amelioration of respiratory chain I than chain II. Puerarin significantly promoted the RCR and OPR of respiratory chain I, suggesting that puerarin treatment was beneficial for structural and functional integrity of mitochondria, and elevated the efficiency of oxidative phosphorylation. Thus, puerarin attenuated oxidative stress may attribute to its protection on mitochondrial function. Further, we observed puerarin promoted ATP production in HepG2 cells, verifying the beneficial effects of puerarin on mitochondria. Glucose metabolism is closely related with mitochondria, thus, facilitating glucose consumption of puerarin may be attributed to its improvement of mitochondrial function.

AMPK is usually regarded as a sensor of adenine nucleotides that is activated in states of low cellular energy, which is signaled by rising AMP/ATP and ADP/ATP ratios. AMPK acts to restore energy balance by turning off anabolic pathways and other processes consuming ATP while turning on alternative catabolic pathways that generate ATP such as glucose uptake, consumption, and glycolysis. Diabetes is closely related with abnormality of AMPK activity. AMPK directly phosphorylates key factors involved in multiple pathways to restore energy balance by stimulation of catabolism to stimulate ATP production [34]. Acute pharmacological activation of AMPK promoted glucose transport and fatty acid oxidation [35]. AMPK stimulates glucose utilization by phosphorylating targets involved in the trafficking of glucose transporters to increase glucose uptake into cells [36]. Many natural products including coptisine [37] and salvianolic acid A [38] were proved to activate AMPK and elevated ATP production and eventually increased glucose uptake or glucose consumption. In the current study, we found AMPK in HepG2 cells was phosphorylated by Puerarin in dose- and time-dependent manner. Meanwhile, the glucose consumption and the key genes regulating TCA cycle flux were elevated. Thus, puerarin activated phosphorylation of AMPK, which triggers intracellular catabolic changes, including increasing glucose consumption and ATP production, and eventually leads to glucose-lowering. Moreover, a growing body of evidence demonstrated that AMPK promoted mitochondrial biogenesis [37] and regulated mitochondrial homeostasis [38]. Thus, the mitochondrial protection of puerarin may also related to its activation of AMPK. Nonetheless, we calculated a fine binding activity of puerarin with AMPK by molecular docking, further investigations are needed to certify whether puerarin directly bind to AMPK and its exact binding sites. However, on the other hand, as a flavone, the poor water solubility or lipid solubility restrained the application of puerarin. We used puerarin at dosage of 100, 200, 400 mg·kg⁻¹ on diabetic mice, and the 400 mg·kg⁻¹ had the best effects. Compared with other natural products such as salvianolic acid, which exert effect at low dosage (1–10 mg·kg⁻¹) [3, 39], the solubility and consequently bioavailability will bring great challenges for the development of puerarin as a chronic administrated agent. Recently, the development of new crystal solid form of puerarin offer new hope in it.

In conclusion, our study demonstrated that puerarin served as a glucose consumption enhancer and ameliorated glucose metabolism of STZ-induced type I diabetic mice through alleviating oxidative stress and improving mitochondrial function via AMPK regulation. Our current studies indicated that puerarin may serve as a prospective anti-diabetic drug.

References


