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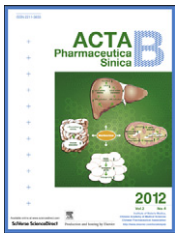

REVIEW

Effects and mechanisms of berberine in diabetes treatment

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Abstract Berberine from Rhizoma Coptidis is an oral hypoglycemic agent with anti-dyslipidemia and anti-obesity activities. Its metabolic activity of regulating blood glucose and lipids has been widely studied and evidenced in patients and various animal models. Berberine is known as an AMP-activated protein kinase (AMPK) activator. Its insulin-independent hypoglycemic effect is related to inhibition of mitochondrial function, stimulation of glycolysis and activation of AMPK pathway. Additionally, berberine may also act as an α-glucosidase inhibitor. In the newly-diagnosed type 2 diabetic patients, berberine is able to lower blood insulin level *via* enhancing insulin sensitivity. However, in patients with poor β-cell function, berberine may improve insulin secretion *via* resuscitating exhausted islets. Furthermore, berberine may have extra beneficial effects on diabetic cardiovascular complications due to its cholesterol-lowering, anti-arrhythmias and nitric oxide (NO) inducing properties. The antioxidant and aldose reductase inhibitory activities of berberine may be useful in alleviating diabetic nephropathy. Although evidence from animal and human studies consistently supports the therapeutic activities of berberine, large-scale multicenter trials are still necessary to evaluate the efficacy of berberine on diabetes and its related complications.

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1. Introduction

Berberine is the major active component of Rhizoma Coptidis, a popular traditional Chinese herb in the treatment of diabetes and inflammation. The content of berberine in Rhizoma Coptidis is 5.2–7.7%. Rhizoma Coptidis is made from several plants including *Coptis chinensis* French, *Coptis deltoidea* C. Y. Cheng *et* Hsiao and *Coptis teetoides* C. Y. Cheng. The earliest record of Rhizoma Coptidis as a medicinal herb was in A.D. 200 in *The Herbal Classic of the Divine Plowman* (*Shen Nong Ben Cao Jing*). In about A.D. 500, the anti-diabetes activity of Rhizoma Coptidis was recorded for the first time in a book titled "*Note of Elite Physicians*". However, in most ancient books, the major therapeutic activity of Rhizoma Coptidis is considered as anti-infection or anti-inflammation because infectious diseases were much more popular than diabetes in ancient time[1,2].

Although the Chinese name of berberine, Huangliansu, means element of Rhizoma Coptidis, most berberine used in medical practice are not extracted from this herb because of high cost. Usually, it is prepared from other herbs such as *Berberis amurense* Rupr. and *Phellodendron amurense* Rupr. Among many chemical forms of berberine, i.e., berberine hydrochloride, berberine sulfate, berberine citrate or phosphate[2], berberine hydrochloride is the most common form. The antimicrobial activity of berberine is well-established in treatment of infection caused by bacteria, viruses, fungi, protozoans and helminthes. In China, berberine is an over-the-counter drug for the treatment of bacterial diarrhea. In 1988, the hypoglycemic effect of berberine was firstly reported when berberine was prescribed to treat diarrhea in diabetic patients[3]. Since then, berberine has been used as an anti-diabetic agent in folk medicine of China.

2. Efficacy of berberine on diabetic patients

Numerous clinical reports about the hypoglycemic action of berberine can be found in Chinese literatures. Berberine was claimed to have a comparable activity to sulphonureas or metformin in reducing blood glucose, although most of the studies were not well designed. Up to now, berberine has been tested in several clinical trials. Our study confirmed that administration of berberine (0.5 g t.i.d.) at the beginning of each meals was able to reduce fasting blood glucose (FBG) and postprandial blood glucose (PBG) in patients with newly-diagnosed type 2 diabetes[4]. Hemoglobin A1c (HbA1c) levels were dropped by 2.0%, which is comparable to the effect of metformin. In poorly-controlled diabetic patients with insulin injection, berberine reduced HbA1c by 0.8%. In addition to the hypoglycemic action, plasma triglycerides, total cholesterol and low-density lipoprotein (LDL) were decreased with berberine treatment, too[4,5]. The similar results were also reported by another group[6]. In this two-center, randomized, double-blind trial, HbA1c decreased by 0.9% after berberine (0.5 g b.i.d.) treatment. All parameters including blood glucose and lipids were improved significantly. In short-term clinical trials, only minor gastrointestinal adverse events, such as constipation, flatulence and diarrhea, were observed. In our study, no significant changes of plasma alanine aminotransferase (ALT), γ-glutamyl transpeptidase (γ-GT), and creatinine were observed. In another study, serum ALT, aspartate aminotransaminase (AST) and γ-GT were significantly reduced in the berberine group. This indicates berberine has no liver or kidney toxicity at the dose given in above studies. Although hypoglycemic effect of berberine was reported in mounting Chinese literature evidence, large scale, long-term clinical trial are still needed to evaluate the efficacy of berberine in the treatment of diabetes.

3. Berberine on glucose metabolism in animals

Berberine was shown to decrease blood glucose, enhance insulin sensitivity and reduce weight gain in both dietary and genetic rodent models of type 2 diabetes. In high-fat diet induced obese rats, berberine decreased FBG, PBG, fasting insulin, homeostasis model of assessment-insulin resistance (HOMA-IR) and body weight[4,7,8]. In low dose of streptozotocin (STZ) and high-fat diet induced type 2 diabetic rats, berberine treatment significantly decreased FBG and improved insulin tolerance[8,9]. In leptin receptor-deficient *db*/*db* mice, glucose tolerance was improved and body weight was reduced with berberine[7]. In alloxan-induced type 1 diabetic rats, berberine also restored the injured pancreas[10].

4. Berberine and islet function

Impacts of berberine on islet are controversial. Our previous work showed that berberine had no insulin secretagogue effects on β-TC3 cells *in vitro*[11]. Berberine restored pancreatic islet hyperthophy back to normal. Our clinical trial showed that berberine lowered fasting insulin levels in the newly diagnosed type 2 diabetic patients. However, in the poorly-controlled diabetic patients with insulin injection, berberine did raise the fasting and postprandial C-peptide levels[4]. The data suggest although berberine did not stimulate the insulin secretion directly, it may be able to improve the islet function in patients unresponsive to oral hypoglycemic agents. Dr. Zhou's work[12] indicated that berberine reduced plasma insulin levels in high-fat diet fed rats and blunted insulin secretion in MIN6 β-cells and isolated rat islets directly. However, other groups reported that berberine decreased blood glucose *via* islet protection in Nonobese diabetic (NOD) mice—a spontaneous type 1 diabetic model[13,14]. The effects of increasing islet numbers and blood insulin levels were not observed in berberine treated *db*/*db* mice. Thus, these results indicate berberine may have a two-way regulation in pancreas islets. In typical type 2 diabetes with notable insulin resistance, berberine lowered blood insulin level through increasing insulin sensitivity. However, in type 1 diabetes or the late stage of type 2 diabetes characterized by poor β-cell function, berberine was able to increase insulin secretion *via* repairing destructed or exhausted islets, which may be related to its antioxidant and anti-lipid peroxidation properties[15].

5. Berberine on lipid metabolism

Berberine was reported to improve lipid metabolism in both animals and human subjects. Two clinical trials showed that berberine decreased triglycerides by 35% and 22%, serum cholesterol by 29% and 16%, and LDL-C by 25% and 20% in patients with dyslipidemia[5,16]. In high-fat diet induced obese

rats, berberine decreased plasma triglycerides[8–10]. Furthermore, triglycerides deposition in muscle and liver was reduced significantly, and liver steatosis was prevented with berberine administration[8,17]. In hamster or diabetic rats fed with high-cholesterol diet, berberine was reported to decrease triglycerides, serum cholesterol and LDL-C significantly[5,10,18], although berberine seems to have little effects on high-density lipoprotein (HDL) level[5,16]. In addition, berberine reduced levels of serum free fatty acids (FFA) in normal lean rats[8,9].

Reduction of cholesterol with berberine is related to the induction of LDL receptor (LDLR) expression in liver, which may be due to extended half-life of LDLR mRNA *via* activation of extracellular signal-regulated kinases (ERK) by berberine[5,19]. Since ERK activation was not observed in other type of cells, the activity of berberine may be hepatocyte specific[4,20,21]. One study showed that the effect of berberine on LDLR was blocked by a c-Jun N-terminal kinase (JNK) inhibitor. Activation of JNK by berberine may be involved in the induction of LDLR[22].

6. Insulin-independent effects of berberine *in vitro*

In the first *in vitro* study using hepatocytes (HepG2 cell line), berberine was shown to stimulate glucose consumption in an insulin-independent manner, and the activity was similar to that of metformin[11]. Several studies confirmed the insulin-independent activity of berberine in other cell models e.g., muscle cells (L6 and C2C12 cell lines) and adipocytes (3T3-L1 cell line)[7,23–28]. In the presence of insulin, berberine exhibited synergetic effect on insulin-induced glucose consumption and glucose uptake. Since berberine stimulated glucose uptake markedly, it is of interest whether the effect is attributed to the regulation of glucose transporters. Berberine was shown to induce glucose transporter type 4 (GLUT4) translocation or elevate GLUT4 protein level in some studies[7,28,29], while others failed to confirm that[24,26]. It is reported that berberine enhanced glucose transporter 1 (GLUT1) expression and promoted GLUT1 activities[24,30]. However, the effects were not consistent[25,26]. Our study suggests that regulation of GLUTs may not be the major mechanism involved in glucose-lowering effect of berberine, which is evidenced by that the effect of berberine on the translocation or expression of glucose transporters is only detectable with high concentration of berberine (≥ 10 μM)[25].

7. Berberine activates AMPK

Berberine is characterized as an AMP-activated protein kinase (AMPK) activator. AMPK is a key energy-sensing/signaling system in the cells and acts as a fuel gauge by monitoring cellular energy levels, e.g., AMP/ATP ratio[31]. Activation of AMPK is well known to increase insulin sensitivity and regulate mitochondrial function[32]. Phosphorylation of Thr-172 within the catalytic domain of the α subunit (AMPKα) is necessary for AMPK activity. Various studies demonstrate that berberine is a strong inducer for Thr-172 phosphorylation of AMPK[7,18,23–25]. Our data showed that the AMPK phosphorylation was increased at 0.5 h after exposure to berberine and the increase was maintained for at least 16 h in cells[25].

AMPK is formed by α, β, and γ subunits, and the α subunit can exist as either the α1 or α2 isoform. In skeletal muscle, berberine acutely stimulated both AMPKα1 and AMPKα2 with a reduction of the intracellular energy status[33]. Liver kinase B1 (LKB1) and Ca^{2+}calmodulin-dependent kinase II (CaMKK II) are two major upstream kinases for AMPK activation. Interestingly, berberine not only stimulated AMPK (Thr172) phosphorylation, but also induced LKB1 (Ser428) and CaMKK II (Thr286) phosphorylation[34]. However, in $LKB1^{-/-}$ cells with or without the CaMKK inhibitor STO-609, AMPK activation by berberine was not affected. This suggested the effect of berberine on AMPK is independent of either LKB1 or CaMKKβ[35]. Berberine was shown to protect against endothelial injury, enhance the endothelium-dependent vasodilatation, and downregulate proinflammatory responses through activation of the AMPK signaling cascade[34,36,37].

8. Berberine inhibits mitochondrial function

Berberine may activate AMPK through increasing AMP/ATP ratio, which is mediated by inhibition of ATP biosynthesis in mitochondria[23,25]. As early as 20 years ago, scientists observed that berberine inhibited NAD-linked respiration in isolated mitochondria of rat liver *in vitro*[38,39], which was confirmed by later studies[40]. In the mitochondria, berberine inhibited monoamine oxidase directly[41–43]. Our study demonstrated that berberine also inhibited mitochondrial function in living cells[25]. We observed that oxygen consumption was decreased and glycolysis was enhanced with berberine as indicated by increased lactate production. This alteration is responsible for the upregulated AMP/ATP ratio. Thus, we hypothesized that AMPK activation may be a consequence of mitochondrial inhibition by berberine[25]. The results also indicate that modest inhibition of mitochondrial function may contribute to improvement of glucose metabolism. This is supported by the fact that inhibition of oxidative phosphorylation protected mice from diet-induced insulin resistance, obesity and type 2 diabetes[44]. Recently, one group reported that berberine suppressed respiration in L6 myotubes and isolated muscle mitochondria, through an inhibitory effect on electron transporter chain complex I, similar to that observed with metformin and rosiglitazone[35,45].

Mitochondria are the major apparatuses for ATP production through oxidative phosphorylation. ATP is required for nearly all metabolic processes including gluconeogenesis, adipogenesis, cholesterol and extracellular matrix syntheses. Various effects of berberine, such as reduction of above metabolic processes, may be related to its inhibitory effect on mitochondrial function. Furthermore, complex I of electron transport chain, the major place of superoxide production[46], is the target of berberine[35,45]. Antioxidant activity of berberine may directly result from complex I inhibition. Mitochondrial inhibition may play a key role in the activities of berberine such as preventing fatty liver, reducing blood glucose and decreasing blood lipids. The details of the regulation remain to be explored.

9. Berberine inhibits mitogen-activated protein kinases (MAPK)

MAPK signaling pathway is shown to be involved in diabetic nephropathy *via* inducing extracellular matrix. In rat glomerular

mesangial cells cultured under high glucose condition, increased fibronectin protein expression and collagen synthesis were reversed after berberine treatment. This was at least partly mediated by inhibitory effect of berberine on phospho-p38MAPK and phospho-CREB[47]. In RAW264.7 macrophages, berberine was also reported to suppress the phosphorylation of MAPKs, such as p38, ERK, and JNK, and the level of reactive oxygen species[37]. It is known that type 1 diabetes is resulted from autoimmune disorders. Berberine prevented the progression of type 1 diabetes in half of the NOD mice and suppressed Th17 and Th1 differentiation, which was associated with downregulating of signal transducer and activator of transcription 1 (STAT1) and signal transducer and activator of transcription 4 (STAT4) activities through the inhibition of p38 MAPK and JNK activation[48].

10. Effects of berberine in gut

It is interesting that berberine also acts as an α-glucosidase inhibitor. α-Glucosidase is an intestinal enzyme that breaks down carbohydrates into monosaccharides. Inhibition of the enzyme will lead to diminished absorption of dietary carbohydrates. One group reported that berberine was hardly absorbed in rat intestine. Sucrase and maltase activities were inhibited by berberine[49]. Berberine also effectively inhibited the activity of disaccharidases in Caco-2 cells[50]. The results were confirmed by other groups. Berberine significantly decreased the disaccharidase activities and sucrase-isomaltase (SI) complex mRNA expression both in STZ-induced diabetic rats and normal rats[51,52]. In addition to the α-glucosidase inhibitory activity, berberine has significant antimicrobial activity *via* inhibiting the assembly function of FtsZ and halting the bacteria cell division in the gastrointestinal tract[53]. Berberine was able to completely antagonize the tumor necrosis factor-α (TNFα)-mediated barrier defects in HT-29/B6 human colon monolayers and in rat colon[54]. The antibiotic activity and protection of tight junction barrier may partially contribute to the anti-diabetic effect of berberine.

11. Effect of berberine in liver

Since liver plays a central role in glucose metabolism, numerous studies focused on effects of berberine especially in fatty liver disease. In newly diagnosed type 2 diabetics with nonalcoholic fatty liver disease as a comorbidity, berberine obviously ameliorated liver steatosis in ultrasonic images, decreased AST and ALT, reduced hemorheology indicators, and improved lipids profile[55]. Similar results were obtained in another study. Berberine lowered FBG effectively in chronic hepatitis B and hepatitis C patients with T2DM or impaired fasting glucose. Liver function was improved greatly in these patients as indicated by the reduction of liver enzymes[56]. Our data showed that hepatic steatosis was alleviated by berberine through inhibition of fatty acid synthase (FAS) expression. Berberine decreased fasting blood glucose by direct inhibition of gluconeogenic genes, phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase (G6Pase) in liver. The activities of transcription factors involved in gluconeogenesis, lipid and cholesterol syntheses, such as Forkhead transcription factor O1 (FoxO1), sterol regulatory element-binding protein 1c (SREBP1) and carbohydrate responsive element-binding protein (ChREBP), were decreased with berberine, too[57]. Other studies showed that in obese and diabetic rodent models, berberine treatment reduced liver weight, hepatic and plasma triglycerides, and cholesterol contents[58,59]. The effects may be due to upregulated liver X receptor α (LXRα), peroxisome proliferator-activated receptor α/δ (PPARα/δ) expression and downregulated PPARγ expression in the liver[59,60]. In mouse primary hepatocytes, berberine enhanced hepatocyte nuclear factor 4 α (HNF4α) expression and induced the activity of hepatic glucokinase. The effects were not observed in metformin treated hepatocytes[61].

12. Berberine and adipogenesis

Our data showed that berberine reduced waist circumference and waist/hip ratio significantly in the absence of weight change. Similar results were also reported by other groups. It was indicated berberine may inhibit visceral fat accumulation. In diabetic rats, adipocyte size and the ratio of white adipose tissue to body weight were decreased, and adipocyte number was increased with berberine treatment[62]. In addition, berberine derivatives also counteracted the increased adiposity and tissue triglyceride accumulation in high-fat-fed rodents[35,45]. Although berberine was shown to suppress fat accumulation, the current evidence on mechanisms is controversial. *In vitro* experiments showed that berberine inhibited adipocyte differentiation and reduced lipid accumulation in 3T3-L1 adipocytes, which may be due to downregulation of several lipogenic genes including PPARγ, C/EBPα, SREBP-1c, fatty acid synthase, acetyl-CoA carboxylase, acyl-CoA synthase, lipoprotein lipase, aP2 and CD36[7,27,63–65]. Because most lipogenic genes are down-stream target of PPARγ and C/EBPα, suppression of the two genes is considered as the key mechanism for inhibition of adipogenesis by berberine. In contrast, berberine upregulated PPARα/δ/γ liver X receptors (LXRs), CDK9 and cyclin T1 expression in white adipose tissue of type 2 diabetic rodents, although it decreased significantly SREBPs expression[62,66]. The difference between *in vivo* and *in vitro* results may be due to the concentration of berberine. At high concentration, berberine directly inhibits PPARγ activity in adipocytes, whereas it shows an opposite effect at a low concentration *in vivo* study.

13. Effects of berberine on muscle atrophy

Muscle atrophy is a characteristic of chronic diseases including diabetes. Surprisingly, berberine was reported to promote muscle atrophy in both wild-type and *db*/*db* mice through hampering mitochondrial function and stimulating the expression of atrogin-1, which promoted protein degradation and suppressed protein synthesis[67]. However, in another study, berberine improved muscle atrophy, increased glycogen storage and decreased triglycerides content in skeletal muscle of type 2 diabetic rats. Further experiments revealed that reduced expression of CDK9 and cyclin T1 in the muscle was reversed with berberine[68]. Berberine also increased PPARα/δ expression and reduced PPARγ expression in skeletal muscle similar as rosiglitazone or fenofibrate[69]. The controversial data may be due to diverse methods of administration. Muscle atrophy was induced by berberine injection. Oral administration of

berberine led to improvement of muscle atrophy. The actual effects of berberine remain to be explored.

14. Berberine protects cardiovascular system

A growing body of literatures indicated that berberine had beneficial effects on cardiovascular diseases. In STZ-induced diabetic rats, ischemia-induced arrhythmias, prolonged QTc interval and diminished *I*(to) and *I*(Ca) current densities were markedly improved with berberine treatment[70]. Another study showed that berberine recovered arrhythmia scores, resting membrane potential, Kir2.1, *I*(K1) current and current density in rats with myocardial infarctionin the presence or absence of type 2 diabetes[71]. In both cultured endothelial cells and aorta isolated from rat, berberine enhanced phosphorylation of endothelial nitric oxide synthase (eNOS) and promoted the association of eNOS with heat shock protein 90 (HSP90), leading to an increased production of nitric oxide (NO)[36]. Berberine also improved endothelium-dependent vasorelaxation *via* inducing NO, which was due to significantly increased eNOS and decreased NADPH oxidase (NOX4) expression[72]. The results suggest that berberine may improve diabetic cardiovascular complications through restoring endothelial function.

15. Antioxidant and aldose reductase inhibitory activities of berberine

Oxidative stress and aldose reductase activities are closely related to diabetic complications. Several groups have explored obvious beneficial effect of berberine in this field. In STZ and high-carbohydrate/high-fat diet induced diabetic rats with hyperlipidemia, berberine markedly decreased malondialdehyde level and increased catalase, superoxide dismutase, glutathione peroxidase, and glutathione activities[73]. Berberine also improved cognitive performance, lowered hyperglycemia, oxidative stress, and choline esterase activity in diabetic rats[74]. Although most papers indicated that berberine had antioxidant activity, one group reported that berberine did not affect the state of oxidative stress in the liver of a high-fat diet- and STZ-induced diabetic rat model[75]. Thus, effects of berberine on antioxidant remain to be elucidated.

Diabetic nephropathy is a representative microvascular complication of diabetes. Several studies indicated that berberine had an obviously beneficial effect on the complication. In STZ-induced diabetic rats, fasting blood glucose, blood urea nitrogen, creatinine, and urine protein over 24 h were significantly decreased, which may be ascribed to the inhibition of aldose reductase (AR) in mesangium, reduction of oxidative stress, and regulation of extracellular matrix synthesis and cell proliferation[76,77]. In alloxan-induced diabetic mice, berberine inhibited the increases in fasting blood glucose, kidney/body weight ratio, blood urea nitrogen, serum creatinine and 24-h albuminuria, and prevented renal hypertrophy, transforming growth factor beta 1(TGF-β1) synthesis, fibronectin and type IV collagen (Col IV) accumulation. Inhibitory effect of berberine on the activation of sphingosine kinase- sphingosine 1-phosphate (SphK-S1P) signaling pathway maybe involved in its renoprotective effects[78]. *In vitro* experiments demonstrated that berberine was able to inhibit the activity of AR directly[79].

16. Berberine derivatives

The bioavailability of berberine is quite low, therefore, investigators are engaged in the research to improve the bioavailability through using its derivatives or novel delivering system. One group synthesized two berberine derivatives e.g., dihydroberberine (dhBBR) and 8,8-dimethyldihydroberberine (Di–Me). Similar to berberine, both inhibited mitochondrial respiration, activated AMPK and stimulated glucose uptake *in vitro*. In diet-induced obese mice, dhBBR and Di–Me counteracted the increased adiposity, tissue triglyceride accumulation and insulin resistance. The highest bioavailability and bioactivity were observed for Di–Me, followed in descending order by dhBBR and berberine[35,45]. Another group developed an anhydrous reverse micelle (ARM) delivery system for berberine administration. Compared to berberine solutions, 2.4-fold enhancement of the oral bioavailability and 2.1-fold of maximum blood concentration of berberine were observed in berberine-loaded ARMs treated mice. Therefore, hypoglycemic effects of berberine were markedly improved with the new delivery system[80].

17. Conclusions

Berberine, a single compound identified from Rhizoma Coptidis, is a promising oral hypoglycemic agent. The metabolic activity in regulating blood glucose and lipids has been widely studied and evidenced in patients and various animal models (Fig. 1). The major mechanism is related to inhibition of mitochondrial function, stimulation of glycolysis and activation of AMPK pathway (Fig. 2). Additionally, berberine may also act as an α-glucosidase inhibitor. In the newly-diagnosed type 2 diabetic patients, berberine is able to lower blood

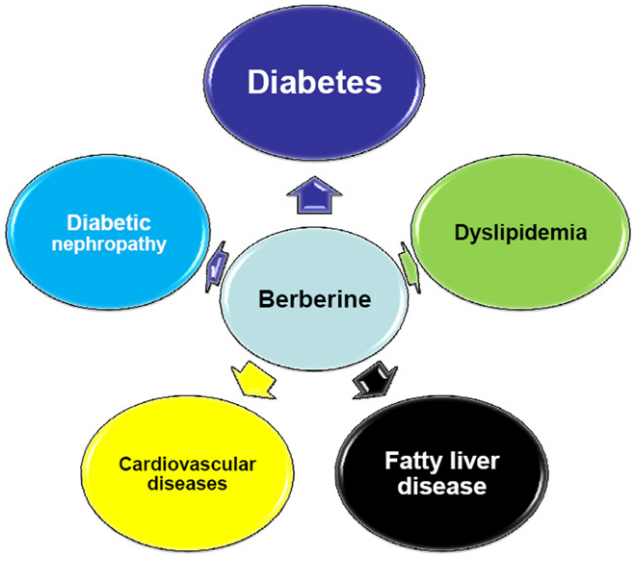

Figure 1 Therapeutic effects of berberine *in vivo*. In medical practice, berberine has been applied to treatment of type 2 diabetes, dyslipidemia, fatty liver disease and cardiovascular diseases. Berberine is also shown to alleviate diabetic nephropathy in animal experiments.

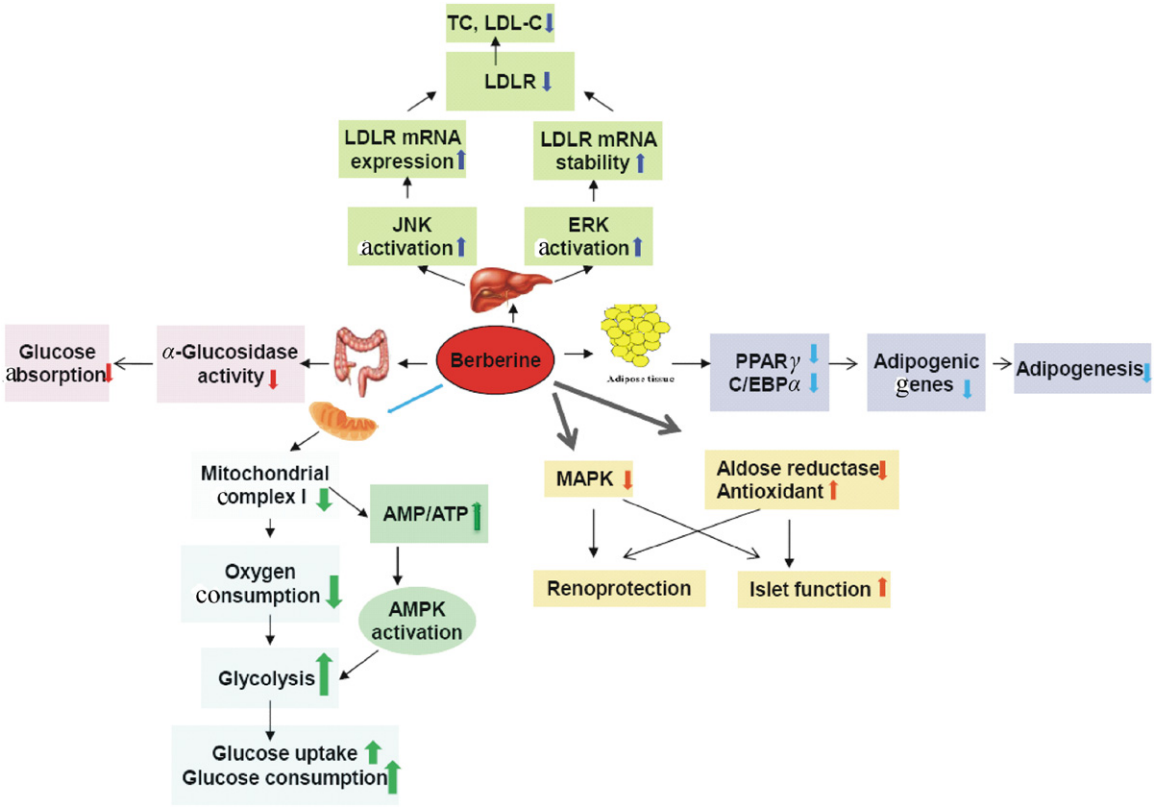

Figure 2 Mechanism of berberine in regulation of metabolism: (1) Berberine enhances glucose uptake through induction of glycolysis, which is due to inhibition of aerobic respiratory. AMPK activation is a consequence of inhibition of mitochondrial electron transport chain complex I; (2) Berberine is able to suppresse adipogenesis through inhibition of PPARγ and C/EBPα function; (3) Berberine decreases intestinal glucose absorption by inhibition of α-glucosidase; (4) Berberine alleviates diabetic nephropathy and improves islet function *via* its antioxidant, aldose reductase and MAPK inhibitory activities; (5) Berberine upregulates LDL receptor (LDLR) expression through increasing LDLR mRNA, which is related to activation of ERK and JNK pathways.

insulin level *via* enhancing insulin sensitivity. However, in patients with poor β-cell function, berberine may improve insulin secretion *via* repairing destructed or exhausted islets. Compared with other hypoglycemic agents used in clinic, berberine is of particular interest and may have extra beneficial effects on diabetic cardiovascular complications because of its cholesterol-lowering property. Berberine is also characterized with the antioxidant and aldose reductase inhibitory activities, through which berberine alleviates diabetic nephropathy in animals. However, it has not been tested in human subjects so far. Since evidence-based medicine is the "gold standard" for clinical practice, large-scale multicenter trials are needed to evaluate the efficacy of berberine on diabetes and the related complications.

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