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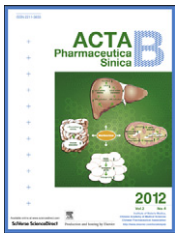

REVIEW

Berberine in type 2 diabetes therapy: a new perspective for an old antidiarrheal drug?

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Abstract Type 2 diabetes mellitus (T2DM) and dysglycemia (impaired glucose tolerance and/or impaired fasting glucose) are increasingly contributing to the global burden of disease. Despite the continued introduction of hypoglycemic drugs, intervention in diabetes and its related complications remains a major global medical problem. Traditional Chinese medicine offers a number of potential candidates for developing hypoglycemic drugs. Berberine (BER), an isoquinoline alkaloid extract, has been commonly used as an oral drug to treat gastroenteritis and diarrhea for more than 1400 years. Although the antidiabetic effect of berberine has been noted in diabetic patients and demonstrated diabetic animal models in the last decade, its use is not yet accepted in the general medical community, for two reasons: its mechanism of action remains to be determined, and its bioavailability is low. Therefore, characterization of its mechanism of action and enhancement of its bioavailability are most important and the subject of current investigations. Recent studies have also revealed beneficial effects of berberine on diabetic complications. In this review the antidiabetic mechanism of action of berberine, its effect on diabetic complications, and efforts to improve its bioavailability are summarized. These studies may lead to its wider use for the treatment of type 2 diabetes mellitus and its complications.

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1. Introduction

Diabetes is one of the earliest diseases to be recognized, and can be traced to 400 BCE where it was described by Indian physicians. The term ''diabetes'' or ''to pass through'' was first used in 230 CE by the Greek Appollonius of Memphis[1]. Effective treatments were not available until the early part of the 20th century, when the Canadians Frederick Banting and Charles Best developed insulin in 1921 and 1922[1].

According to statistics, world-wide there were 285 million people with type 2 diabetes, making up about 90% of diabetes cases in 2010. In China, the prevalence of diabetes is also high and is increasing; the incidence of diabetes in 2010 was estimated at 92.4 million adults with 43.1 million rural and 49.3 million urban patients. Nearly one third of the diabetic patients in the world live in China, the most of any country[2]. This high and increasing incidence of diabetes is believed primarily to be due to global population aging, a decrease in exercise, smoking, elevated cholesterol levels, high blood pressure, and increasing rates of obesity.

In the majority of patients with type 2 diabetes (T2D), oral antidiabetic drug (OAD) treatment is the first-line treatment after lifestyle measures fail. The most commonly prescribed blood-glucose lowering agents, metformin, sulfonylurea and thiazolidinedione, may temporarily improve blood glucose control. However, despite the continuing introduction of hypoglycemic drugs, intervention in diabetes and its related complications remains a major global medical problem. Traditional Chinese medicine has the potential to contribute new candidates for the development of hypoglycemic drugs.

Berberine (BER) is the major active component of Rhizoma Coptidis which can be prepared from rhizomes of several herbs including *Coptis chinensis* French, *Coptis deltoidea* and *Coptis teetoides*. Rhizoma Coptidis was recorded as a medication as early as 200 A.D. In about 500 A.D., the anti-diabetic activity of Rhizoma Coptidis was noted; however, in most books the major therapeutic activity of Rhizoma Coptidis is for the treatment of infection and inflammation. In China, berberine is an over-the-counter drug for the treatment of gastrointestinal infections, such as bacterial diarrhea. The antidiabetic effect of berberine was noted in 1988 in treating gastrointestinal infections patients with diabetes in China. Berberine has been used as an anti-hyperglycemic agent by many physicians in China for many years, with many clinical reports on the hypoglycemic action of berberine. However, berberine has low bioavailability ($<5\%$)[3] due to poor absorption. High dose oral administration usually causes gastrointestinal side effects, which greatly limit its clinical application. In the following sections we will systemically review the antidiabetic mechanism of action of berberine, its effect on diabetic complications, and studies on its formulation. It is hoped that these studies may contribute to the wider use of berberine for the prevention of type 2 diabetes mellitus and its complications.

2. Antidiabetic effects and the mechanism of action of berberine

Type 2 diabetes mellitus is a complicated metabolic disease characterized by impairment of both glucose utilization and gluconeogenesis. It has been reported that berberine has activity comparable to sulphonureas and metformin in reducing blood glucose in diabetic patients in China. Yin et al.[4] reported that administration of berberine (0.5 g, t.i.d.) at the beginning of each major meal was able to reduce fasting blood glucose (FBG) in adult patients with newly-diagnosed type 2 diabetes. HbA1c of the patients was also decreased with berberine treatment, and is comparable to that of metformin. In animal studies, berberine treatment reduced weight gain, enhanced insulin sensitivity and decreased blood glucose in both dietary and genetic animal models of type 2 diabetes. Our study in rats with type 2 diabetes induced by a high-fat diet and a low dose of streptozotocin (STZ) showed that FBG was decreased and insulin tolerance was improved significantly by berberine[5]. Numerous investigations on the antidiabetic mechanism of berberine have been undertaken in the last several decades. The antidiabetic effect of berberine was most often noted on skeletal muscle and adipose tissue glucose uptake and liver gluconeogenesis[6] (Fig. 1). It has been shown that activation of AMP-activated protein kinase (AMPK) plays an important role in these processes[6–10].

2.1. *Berberine activates AMPK*

AMPK is an important energy-sensing protein in mammalian cells. It acts as a fuel gauge by monitoring cellular energy levels, such as AMP/ATP ratio. AMPK is thus an attractive drug target that plays a key role in regulation of whole-body energy homeostasis. Activation of AMPK in skeletal muscle and adipose tissue leads to increased glucose uptake. Meanwhile, some studies reported that activation of hepatic AMPK leads to increased fatty acid oxidation and simultaneously inhibition of hepatic glucose production as well as lipogenesis and cholesterol synthesis. Recently, activation of AMPK was found to phosphorylate transducer of regulated CREB protein 2 (TORC2), which mediates cAMP response element binding protein (CREB)-dependent transcription of peroxidome proliferator-activated receptor-γ coactivator-1 (PGC1) and its subsequent gluconeogenic targets PEPCK (phosphoenolpyruvate carboxykinase) and G6Pase (glucose-6-phosphatase), thus inhibiting hepatic gluconeogensis. It has been consistently demonstrated that AMPK is a target for berberine in the regulation of glucose metabolism. The most recognized theory for the activation of AMPK by berberine is *via* increasing AMP/ATP ratio by inhibiting ATP biosynthesis in mitochondria. As early as 1985, berberine was shown to inhibit NAD-linked respiration in isolated liver mitochondria. In 2003 this observation was confirmed.

Berberine inhibited oxygen consumption and enhanced glycolysis, thus increased AMP/ATP ratio. Berberine also could dose-dependently inhibited respiration in L6 myotubes and muscle mitochondria through a specific effect on respiratory complex I, rather than by the activity of either liver kinase B1 (LKB1) or CAM kinase kinase (CAMKKβ) which are the upstream kinases responsible for the regulation of AMPK. Based on these studies, it might be speculated that activation of AMPK by berberine may contribute to regulation of glucose and lipid metabolism *via* mitochondrial inhibition. However, this possibility needs to be further studied.

2.2. *Effect of berberine on glucose uptake*

Skeletal muscle and adipose tissue are important target tissues for insulin-stimulated glucose consumption. Many studies have showed that berberine can increase glucose uptake in

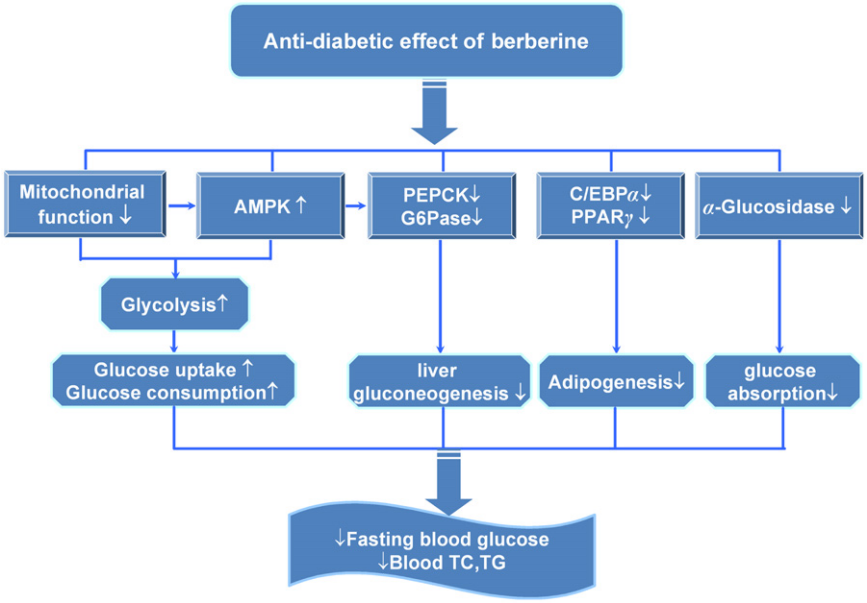

Figure 1 Anti-diabetic effect of berberine: (1) Berberine inhibited mitochondrial function and activated AMPK to enhances glucose uptake; (2) Berberine decreased the PEPCK and G6Pase gene expression to inhibit the gluconeogenesis; (3) Berberine decreased adipogenesis through inhibition of PPARγ and C/EBPα function; (4) Berberine might decrease intestinal glucose absorption by inhibition of α-glucosidase.

skeletal muscle cells such as L6 and C2C12 cell lines. The molecular mechanisms of insulin-dependent glucose uptake have been broadly studied. The effect of berberine on glucose uptake in skeletal muscle cells and adipose cells has been shown to be *via* an insulin-independent way[4,8–13]. Several groups investigated the effect of berberine on glucose transporters. Results are controversial, with some labs finding that berberine could stimulate glucose transporters (GLUT4/1) activity[10,13], while others found no stimulation of the GLUT4/1[9,11]. On balance, only a weak effect of berberine on the activity of glucose transporters appears likely, which suggests that the regulation of GLUTs is not the major mechanism by which berberine stimulates glucose metabolism[4]. Berberine mimics insulin by increasing the glucose uptake of 3T3-L1 adipocytes and L6 myocytes by inhibiting the phosphatase activity of protein tyrosine phosphatase 1B (PTP1B) and increasing the phosphorylation of IR, IRS1 and Akt. Their results suggest that berberine represents a different class of anti-hyperglycemic agents[14]. Berberine exhibited a synergistic effect on insulin-induced glucose uptake and GLUT4 translocation in an insulin-resistant state accompanied by enhancement of insulin-induced PKCδ and PKB activity. The key mechanism was related to the inhibition of mTOR by berberine, which attenuated serine-phosphorylation of IRS-1. It was suggested that berberine may overcome insulin resistance by modulating key molecules in the insulin signaling pathway, leading to increased glucose uptake in insulin-resistant cells[15]. Further study on this aspect of berberine's actions needs to be conducted, and the direct targets of berberine remain unknown. At the beginning of this year a study on microRNA has been reported which suggests a new target of berberine in glucose uptake[16].

2.3. *Effect of berberine on liver gluconeogenesis*

Gluconeogenesis in the liver plays a key role in the pathogenesis of type 2 diabetes. Fasting blood glucose is determined by glucose production in liver and glucose deposition in peripheral tissues. In the insulin resistance state, enhanced glucose output by liver contributes to hyperglycemia together with reduced glucose uptake in skeletal muscle and adipose tissue. Inhibition of hepatic glucose production is important for glycemic control in diabetic patients. It has been clearly reported that inhibition of transcription factors including forkhead transcription factor O1 (FoxO1), hepatic nuclear factor 4 (HNF4), and peroxisome proliferator-activated PGC-1α are related to decreased expression of PEPCK and G6Pase, two regulatory genes in gluconeogenesis. A recent paper reported that berberine could suppress the transcription factor FoxO1 and decrease the expression of key gluconeogenic genes such as PEPCK and G6Pase. They measured the expression of AMPK in the liver of a diabetic model and speculated that berberine activated the expression of AMPK and inhibited the liver gluconeogenesis[17]. Investigations from our group further noted the effect of berberine on liver gluconeogenesis *in vivo* and *in vitro*; we found that berberine decreased gluconeogenesis by activation of AMPK. The inhibitory effect of berberine on gluconeogenesis could be diminished by the application of AMPK inhibitor compound C. Our group also reported that the regulatory role of berberine on glucocorticoid metabolism might be another mechanism by which berberine acts on liver gluconeogenesis[18].

2.4. *Effect of berberine on adipogenesis*

Adipose tissue is now recognized as a major endocrine organ, releasing a wide range of protein factors including adipokines and leptin, which regulate appetite and energy metabolism in human and rodents[19] through a variety of transcription factors such as SREBP-1c, C/EBPα and PPARγ. SREBP-1c accelerates adipogenesis through the overexpression of adipogenic enzymes such as tumor necrosis factor receptor superfamily member 6

(FAS), Acetyl-CoA carboxylase (ACC) and Acetyl-CoA synthetase (ACS). These factors alone cannot promote differentiation of non-adipogenic fibroblasts, but when coexpressed in fibroblasts expressing PPARγ cell differentiation is enhanced. PPARγ appears to function as both a direct regulator of many fat-specific genes and also as a "master" regulator that can trigger the entire program of adipogenesis. In cells treated with berberine, expression of several lipogenic genes including PPARγ, C/EBPα, SREBP-1c, fatty acid synthase, ACC, ACS, lipoprotein lipase, aP2 and CD36 are suppressed[20]. Berberine exerts an anti-adipogenic activity that is associated with the down-regulation of C/EBPα and PPARγ. This result suggests that berberine-activated AMPK might play a role in its inhibitory effect on the adipogenesis. Their data show that berberine up-regulated the expression of two different sets of C/EBP inhibitors, CHOP and DEC2, while down-regulating C/EBPα, PPARγ and other adipogenic markers and effectors in differentiating 3T3-L1 preadipocytes and mature adipocytes. Furthermore, the anti-adipogenic activity of berberine was diminished remarkably by adjusting the differentiation culture media and also by knockdown of CHOP expression. Up-regulation of C/EBP inhibitors appears to underlie the berberine-induced repression of C/EBPα and PPARγ and the inhibition of adipogenesis[21]. Therefore, the inhibition of PPARγ and C/EBPα is likely the key mechanism for inhibition of adipogenesis by berberine, which was closely related to the activation of AMPK by berberine.

2.5. *Effect of berberine on glucose absorption*

It has been reported that carbohydrates need to be broken down into smaller sugar molecules like glucose by α-glucosidase in the small intestine. α-glucosidase inhibitors reduce the postprandial peak in blood sugar and are useful for patients with predominantly postprandial hyperglycemia because it decreases glucose absorption by inhibition of α-glucosidase. The Caco-2 cell model system has been used to evaluate the bioactivity of α-glucosidase inhibitors. The Pan group reported that α-glucosidase activity was inhibited by berberine in the Caco-2 human enterocytic cell line. Further, they found that berberine treatment could decrease glucose uptake at the intestinal epithelium. These two mechanisms may be involved in control of blood glucose by berberine[22].

2.6. *Effect of berberine on pancreatic β-cells*

Type 2 diabetes mainly results from insulin resistance and β-cell dysfunction. β-cell failure is responsible for progressive loss of metabolic control in type 2 diabetic patients and the eventual need for insulin treatment. Therefore, agents to protect β-cell function might be a better choice for diabetic treatment. Berberine treatment could promote pancreatic β cell regeneration and functional recovery. Berberine reduced the fasting serum insulin of diabetic rats and decreased the blood sugar by improving insulin sensitivity of insulin receptors, rather than by stimulating the pancreatic β cells to secrete insulin. This might reduce the burden on the islet β-cells and play a protective role for islet β-cells. However, interestingly, Ko et al.[13] reported that berberine can cause glucose-stimulated insulin secretion in Min6 islet β-cell lines, and promote pancreatic β-cell proliferation, and activation of cell regulatory proteins (ERK1/2), so that the insulin receptor substrate IRS-2 expression increases activation of the insulin/insulin-like growth factor signaling cascades, which serve to reduce blood sugar[23,24].

3. Role of berberine in treatment of diabetic complications

Type 2 diabetes is a chronic disease characterized by multiple metabolic derangements. Patients with diabetes have a ten-year shorter life expectancy. This is partly due to a number of complications including cardiovascular disease, nephropathy and retinopathy[25], and thus a growing number of researchers have focused on diabetes and its complications, with the aim to expand our knowledge about pathogenic and pathophysiological mechanisms, preventive strategies and potential novel therapies.

3.1. *Cardiovascular complications*

3.1.1. *Endothelial dysfunction*

Endothelial dysfunction is a key event that links obesity, diabetes, hypertension, and cardiovascular diseases. Endothelial dysfunction has been known as an initiating, critical factor, and main pathological change during the development of diabetic vascular disease[26], and it has been widely accepted that diabetic vascular endothelial dysfunction is the base of most of other diabetic complications such as diabetic cardiomyopathy, diabetic retinopathy and nephropathy. Endothelial dysfunction in diabetes reflects an imbalance between vasorelaxation and vasocontraction. A considerable body of evidence implicates oxidative stress as a critical pathogenic element in diabetic endothelial dysfunction[27,28].

Our research group has demonstrated that berberine has beneficial effects on the treatment of type 2 diabetes and its cardiovascular complications. Berberine treatment improved glucose and lipid metabolism in type 2 diabetic rats induced by high-fat diet combined with multiple low doses of streptozotocin. The effect of berberine on lipid metabolism, at least partly, contributed to the improvement of endothelial dysfunction. Meanwhile, berberine also significantly protected acetylcholine-mediated vasorelaxation in the aortas of diabetic rats. This protective mechanism can be attributed to increased NO bioavailability by up-regulating eNOS expression and down-regulating expression of NADPH oxidase (NOX4)[29]. In 2012, the latest study from Cheng et al.[30] in humans also further supported our previous findings; they found that berberine treatment ameliorated endothelial function by partially reducing oxidative stress on the vascular endothelium induced by circulating $CD31^{+}/CD42^{-}$ microphages in humans. Their result demonstrated that increased ROS production and Nox4 protein expression, and reduced NO synthesis in human umbilical vein endothelial cells (HUVECs), was reversed in the presence of berberine.

3.1.2. *Diabetic cardiomyopathy*

Cardiovascular complications are major causes of morbidity and mortality in diabetic patients. Diabetic cardiomyopathy (DCM) is the presence of myocardial dysfunction in the absence of coronary artery disease and hypertension, which was first named by Rubler in 1972[31]. Almost two of three patients who present with symptomatic chronic heart disease have abnormal glucose homeostasis. Hyperglycemia seems to

be central to the pathogenesis of diabetic cardiomyopathy and triggers a series of maladaptive stimuli that result in increased oxidative stress, interstitial fibrosis, myocyte death, and disturbances in ion transport and homeostasis. Presently, the pathophysiology of diabetic cardiomyopathy is incompletely understood and several mechanisms are under debate. Early intervention to reverse metabolic toxicity is the most effective method of prevention[32]. Currently,treatment of diabetic cardiomyopathy does not differ from cardiomyopathy of other etiologies, therefore, the principle of treatment has to follow the appropriate guidelines, mainly including diuretics, ACE inhibitors and β-blockers. These drugs also are the choice for patients with diabetes, but the results of the intervention studies for the prevention of diabetic complications have not been satisfied.

Berberine as a new diabetic medicine has garnered increasing attention. Although there is no evidence to prove the direct efficiency of berberine in the diabetic cardiomyopathy, the promising effects of berberine on endothelial dysfunction, anti-oxidative stress, and the regulation of glucose and lipid homeostasis have been demonstrated, all of which involve the pathogenesis of diabetic cardiomyopathy. Berberine has been reported as an effective anti-arrhythmic agent after ischemia-reperfusion heart injury[33]. Wang et al.[34] further reported that berberine suppressed ischemic arrhythmias in a rat model of diabetes mellitus, shortened the prolonged QTc, and reversed the Kir2.1 to normal levels. All the evidence indicates that berberine might be used to manage cardiac disease in diabetic conditions, and suggest further clinical research.

3.2. *Diabetic nephropathy*

Diabetic nephropathy is one of the most relevant diabetic complications. In the last decade diabetic nephropathy has become the main cause of end-stage renal disease (ESRD) in the Western world[35,36]. In China, according to a cross-sectional survey in 2012, the prevalence of chronic kidney disease was 10.8%[36]. The pathological changes of diabetic nephropathy include expansion of mesangial cells, accumulation of extracellular matrix protein, thickening of glomerular and tubular basement membranes, tubulointerstitial fibrosis, glomerulosclerosis and renal endothelial dysfunction associated with albuminuria, proteinuria and reduction in glomerular filtration rate[37–39]. It has been accepted that optimal control and maintenance of normal sugar level and blood pressure are prerequisite to prevent the progression of diabetic nephropathy. The combination of ACE inhibitors either with calcium channel blockers or AT1 receptor blockers has been suggested to be a promising therapeutic option to manage patients with diabetic nephropathy.

Berberine as a novel antidiabetic agent has exhibited a positive effect to treat diabetic nephropathy. Berberine decreased the urinary albumin excretion (UAE) and improved the pathological changes in diabetic rats. Oral administration of berberine improved the ratio of kidney to body weight, decreased the glomerular area, glomerular volume, fasting blood glucose, blood urea nitrogen (BUN), blood creatinine (Cr), and 24 h urinary protein in STZ-induced diabetic nephropathy in rats[40]. Moreover, Lan's study[41] also showed that berberine can activate the SphK-S1P signaling pathway (which has been implicated in the pathogenesis of diabetic nephropathy) in alloxan-induced diabetic mice with nephropathy. Furthermore, it has been shown that berberine could prevent renal hypertrophy, TGF-β1 synthesis, fibronectin (FN) and Col IV accumulation. Hao et al.[42] also shows that berberine can improve the diabetic microvascular injury *in vitro* and inhibit the formation of AGEs, suggesting potential clinical therapies with berberine for diabetes and its vascular complications. These result indicated berberine might be an effective agents for diabetic nephropathy. However, the mechanisms of action of berberine on diabetic nephropathy remains to be fully defined.

3.3. *Diabetic neuropathy*

Diabetic neuropathy is the most common complication of diabetes mellitus and up to 50% of patients with type 1 and type 2 diabetes mellitus have neuropathy. Diabetic neuropathy remains an unmet clinical problem and is poorly relieved by conventional analgesics. Neuropathy is diagnosed when diabetic patients complain of symptoms and/or show signs of peripheral nerve dysfunction after the exclusion of other etiologies such as pain, paraesthesiae and loss of sensation[43]. It has been shown that activation of polyol pathway plays a key role in the pathogenesis of diabetic neuropathy.

Although many agents have been shown to be partially effective, clinical studies have reported the difficulty of managing pain caused by these neuropathies[44]. Currently, multiple strategies had been used to treat diabetic neuropathy, such as multivitamins including B1, B2, B6, B12. Recently, aldose reductase inhibitors, such as inositol have been applied to treat diabetic neuropathy. However, there are very few drugs available to directly treat diabetic neuropathy. Recent results indicate that berberine could remarkably improve the nerve conduction velocity[45]. Using berberine to treat diabetic neuropathy in rats induced by STZ and in diabetic patients demonstrated that berberine could significantly improve the median nerve, peroneal in nerve conduction velocity (NCV)[46]. In 2010 and 2012, a study from Lu group reported that berberine suppressed neuroinflammatory responses through AMPK activation in BV-2 microglia and astrocytes, which suggested a anti-neuroinflammatory effect of berberine[47]. However, the mechanism of treatment of diabetic neuropathy by berberine needs further study[47,48].

4. Modification and formulations of berberine

Berberine has poor solubility and bioavailability, limiting its application in the clinic. In recent years, researchers have used various methods to improve the bioavailability of berberine. Chemical modification, dosage form transformation and drug combinations are the most popular methods used.

4.1. *Chemical modification*

Chemical modification is a method that modifies the structure of the existing compounds by adding or removing chemical groups. Through chemical modification, drug properties can be changed, including pharmacological activity, solubility, and bioavailability.

Dai et al.[49] used berberine as the original starting material and hydrogenated it to yield tetrahydroberberine in the first step of a

synthetic process. They then attached a 4-chlorobenzyl side chain to the N atom, producing a quaternary ammonium salt, which was named CPU86017. This product has improved solubility and oral bioavailability. CPU86017 was shown to protect from malignant arrhythmias and sudden cardiac death by multiple actions at ion channels because of its potent anti-arrhythmic activity as a Class III anti-arrhythmic agent.

A derivative of berberine named dihydroberberine (dhBer) was prepared and its effect on adiposity and glucose metabolism was examined in a rodent model of type 2 diabetes fed a high-fat diet. The results demonstrated that dhBer decreased triglyceride accumulation in adipose tissue and improved insulin resistance in this model. This improvement in *in vivo* efficacy is mainly due to the enhancement of oral bioavailability: dhBer had a bioavailability of 2.65% compared to berberine, which is not detectable in the plasma. However, the bioavailability of dhBer is limited since it can be converted back to berberine in the stomach, which hinders its absorption.

8,8-Dimethyl-13,13a-dihydroberberine is a second newly developed derivative of berberine. Addition of the two alkyl groups was designed to block aromatization of dhBer by 8,8-disubstitution. This new derivative, Di-Me has improved aqueous solubility and acid stability, significantly higher bioavailability, and is not converted back to berberine *in vivo*. Notably, it activates AMPK similarly to berberine and dhBer[50].

4.2. Dosage forms

Dosage form transformation is also a very important way to improve the bioavailability of berberine. The aims are to avoid first pass elimination, increase the absorption and oral bioavailability of berberine, reduce its side effects, as well as increase patient compliance and tolerability.

4.2.1. Solid preparation

Tablets are the most common solid preparations. A large number of new materials and new technologies have appeared. Berberine has been prepared in many new forms on the basis of these developments.

The solid dispersion of berberine was prepared and its dissolution rate *in vitro* was studied. A fusion method with PEG6000 as carrier and dissolvent-fusion method with PVP K30 as carrier were used. The dissolved solution and the *in vitro* dissolution were studied with the ultraviolet spectrophotometric method detecting the concentration of berberine. The results revealed that the solid dispersions with PEG6000 and PVP K30 as carriers improved the dissolution rate significantly, with complete dissolution in 15 min, demonstrating that the technology of solid dispersion can improve the dissolution rate of berberine[51]. Zhang et al.[52] developed a duodenum-specific drug delivery system. They used hydroxypropyl methylcellulose acetate maleate (HPMCAM), a pH-sensitive polymer, as a coating agent which dissolves at pH 3.6. HPMC-K4M and carbopol–934P were used as bioadhesive materials. Within 24 h of fasting the pH value of gastric juice is 1.3–1.8, rarely higher than 2.0. Acid entering into the duodenum is neutralized by heavy carbonate to maintain a pH of 6.0, nearly neutral. The gastric 24 h pH rhythm of duodenal ulcer patients is similar to that of a normal subject, but duodenal pH value can be as low as 3.0–4.0. So when it is used in duodenal ulcer patients, berberine coated in this tablet was carried directly to duodenum without being released in the stomach, and this made berberine release in the duodenum to accumulate at the surface of the pathological ulcer. So the function of a duodenum-specific eradiation therapy was achieving for Hp.

4.2.2. Semi-solid preparation

Liu et al.[53] prepared a suspension concentrate of berberine to study and apply its antifeed activity to *B. brassicae*. First, they screened a suitable moist dispersion making its HLB value above 8 with the flow point method. Then three preparations of 20% berberine chloride suspension concentrate were produced. The result suggest that No. 3 SC of 20% berberine hydrochloride had high bioactivity, with better touch-kill activity and antifeed activity to *B. brassicae*, and higher inhibition rate to *Rhizoctonia DC* and *P. oryzae*.

4.2.3. Particulate delivery system

Nano emulsion is a colloidal dispersed system with the emulsion droplets sized 10 to 100 nm, dispersing in another liquid. It consists of the kernel oil phase and surface-active agent with a hydrocarbon chain. This nano-emulsion increases the solubility of water insoluble drugs.

Sun et al.[54] chose the suitable oil phase, surfactant and cosurfactant to optimize the nano-emulsion drug delivery system of berberine by studying the pseudo-ternary phase diagram. The preparation method was optimized by entrapment efficiency and drug loading as an evaluation standard. Berberine nano-emulsion as a stable delivery system has a good affinity to the gastrointestinal lymphoid tissue, making more of the drug absorbed by lymphatic pathways into the blood, avoiding the liver, intestinal biological conversion and absorption, and avoiding the hepatic first-pass metabolism, thereby improving the bioavailability of berberine. He et al.[55] recast the traditional berberine by using the solid-self-micro-emulsifying enteric bead as a new carrier. The self-micro-emulsifying drug delivery system (SMEDDS) has great ability to improve the oral bioavailability of berberine.

4.3. Complexation

4.3.1. Drug combination

Mo et al.[56] produced a complex prescription metformin and berberine (CPMB) to observe the influence on metabolism of lipid in diabetic rats. CPMB (metformin:berberine = 60:130) was administrated to diabetic rats which were induced by injection of STZ for 3 months. Triglyceride (TG), total cholesterol (TC) and low-density lipoprotein (LDL) were decreased significantly after treatment by CPMB (400 mg/kg), while high-density lipoprotein (HDL) increased. The metabolism disorder of diabetic rats was ameliorated by CPMB. Zhang et al.[57] developed salvianolic acid B-berberine double salt (SBS) to investigate its effects on diabetic nephropathy in diabetic rats. Salvianolic acid B (Sal B) is one of the water-soluble components from TCM-*Salvia miltiorrhiza*. It has been shown that Sal B has multiple effects, including improving renal function, alleviating ischemic damage, and an antioxidative action. SBS is prepared by acid-base reaction. After 8 weeks of treatment with SBS the renal lesions of diabetic rats were significantly reduced.

4.3.2. Drug complexation with adjuvant

Battu et al.[58] developed a complex of berberine with 2-hydroxypropyl-β-cyclodextrin (HPβCD) after evaluating the physicochemical characteristics of berberine. They used cyclodextrins (CDs) to enhance berberine solubility. The phase-solubility studies demonstrated that the aqueous solubility of berberine improved almost 4.5-fold in the presence of 20% HPβCD.

Our research group produced a complex of berberine and a surfactant, sodium caprate, which also used as a intestinal absorption enhancer, to improve the bioavailability of berberine. The results showed that berberine can be absorbed at various intestinal segments; sodium caprate significantly increased the absorption of berberine in intestine *in vitro* and *in vivo* because of its inhibition of P-gp activity. Moreover, both berberine and coadministration with sodium caprate orally significantly decreased fasting blood glucose and improve glucose tolerance in diabetic rats. The hypoglycemic effect of coadministration was remarkably stronger compared with berberine alone[59]. Furthermore, our recent studies demonstrate that sodium caprate augments the hypoglycemic effect of berberine by activation of AMPK and inhibition of hepatic gluconeogenesis.

As noted above, numerous methods were used to reform berberine. The aim is to improve its bioavailability. The results of the research cited above have made outstanding progress, but a high-effect and low-toxicity form of berberine has yet to be developed. This will be a future task for medical researchers.

5. Conclusions

Berberine, a traditional anti-diarrheal drug, has promising activity in the control of blood glucose and lipids in patients. The mechanism of action has been suggested by recent studies. Additionally, the role of berberine in treatment of diabetic complications might be a new application of berberine. Based on the existing literatures, the problems in exploring the berberine as new antidiabetic drug include: (1) lack of a multicenter, well controlled, long-term clinical trial to evaluate the efficacy of berberine; (2) lack of a clear mechanism of action of berberine; (3) low bioavailability of berberine, and lack of long-term and high-dose safety studies; (4), lack of sufficient formulation studies to improve dissolution, solubility, and bioavailability of berberine and its functional derivatives. New formulations of berberine will be the next major task for the research scientist. Berberine remains a promising new drug in the treatment of diabetes and its complications.

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