



A review of the effects of *Berberis vulgaris* and its major component, berberine, in metabolic syndrome

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ABSTRACT

Metabolic syndrome (MetS), characterized by a cluster of metabolic abnormalities including hypertension, obesity, type 2 diabetes mellitus (T2DM) and dyslipidemia, is a well-known cardiovascular risk factor (CVRF). Cardiovascular disease (CVD) represents a massive healthcare burden worldwide. In recent years, with regard to the adverse effects of synthetic drugs, increasing attention has been paid by researchers to herbal medicines for a variety of disorders such as CVD. A large body of literature supports different pharmacological actions of *Berberis vulgaris* (*B. vulgaris*) and its active component, berberine (BBR), such as antidiabetic, antiobesity, hypotensive and hypolipidemic properties that could be interesting in the management of MetS associated with high CVD risk. Numerous preclinical *in vitro* and *in vivo* studies support all these effects. In this review, we evaluated the most related original articles to discover the role of *B. vulgaris* on various constituents of MetS and CVRF comprising dyslipidemia, obesity, high blood pressure and high blood glucose. This review suggests a potential role of *B. vulgaris* and BBR in the managing of MetS; nevertheless more investigations, especially reliable clinical trials, need to be accomplished to evaluate their effectiveness.

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Introduction

Metabolic syndrome (MetS), also described as 'insulin resistance syndrome' (1), 'syndrome X' (2), 'hypertriglyceridemic waist' (3) and 'the deadly quartet' (4) characterized by a cluster of metabolic abnormalities including hypertension, obesity, insulin resistance and dyslipidemia, is a well-known risk factor for type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD) (5). On the word of the International Diabetes Federation (IDF) (6) and the American Heart Association/National Heart, Lung, and Blood Institute (7), manifestation of any 3 of 5 risk factors establishes a diagnosis of MetS (8). Criteria for clinical diagnosis of the MetS are shown in Table 1.

Statistics show that 20–25% of adults are suffering from MetS in the world and its presence should be considered as an indicator of long-term risk (9). So, it is a life-threatening disease and seems to be of vital importance to reach an appropriate remedy. Present and future trends in CVD mortality will require growing attention in the 21st century. Therefore, preventive strategies should be considered to decrease the future CVD burden (10) and nowadays there is a rising demand for plant bio-resources in the management of

chronic diseases such as MetS, instead of synthetic drugs, to avoid adverse effects (11). Furthermore, traditional medicinal plants are often cheaper and more locally available (12). It is a fact that one quarter of all medical prescriptions are formulations based on plant-derived synthetic analogs, and as stated by the WHO, 80% of the world's population; mainly those of developing countries; trust in plant-derived medicines for their healthcare (11). A number of plants and/or their constituents such as *Vitis vinifera* (Grapes) (13), *Nigella sativa* (14), rutin (15) and *Allium sativum* (Garlic) (16) have shown beneficial effects in the treatment of MetS.

In line with this, "zereshk" which is the Persian name for *Berberis vulgaris* (*B. vulgaris*), is extensively cultivated in Iran (typically in Birjand and Qaen cities), central and southern Europe and the northeastern of the United States (17-19). The fruit of *B. vulgaris* (Figure 1) has long scarlet colored berries (20) which are oblong, slightly curved, about 0.5 inches long and edible (21).

B. vulgaris has played an important role in herbal therapy for more than 2500 years. Russian therapists have utilized it for treatment of inflammations, high

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Figure 1. *Berberis vulgaris* plant: showing leaves, flowers and fruits

Table 1. Criteria for clinical diagnosis of the metabolic syndrome according to International Diabetes Federation (IDF) and National Cholesterol Education Program-Adult Treatment Panel III (NCEP-ATPIII) (8)

Measure	Cut points
Elevated waist circumference	Population and country-specific ≥ 150 mg/dl
Elevated triglycerides (or on therapy for hypertriglyceridemia)	Population and country-specific ≥ 150 mg/dl
Reduced HDL-C* (or on therapy for reduced HDL-C)	< 40 mg/dl in males > 50 mg/dl in females
Elevated blood pressure (or on therapy with known history of hypertension)	SBP ≥ 130 and/or DBP ≥ 85 mm Hg
Elevated fasting glucose (or on therapy for hyperglycemia)	≥ 100 mg/dl

*HDL-C= high-density lipoprotein cholesterol

blood pressure, and abnormal uterine bleeding (21). Different parts of this plant including fruits, leaves and roots, have been used in traditional medicine for a long time (22). For instance its dried leaf and stem bark are utilized as antiedema and antihypertensive in varicose veins, respectively. In gastrointestinal system, dried root is used as choleric, laxative, antidiarrheal, anti-hepatitis, anti-hemorrhoid, and also its fruit is used in treatment of painful menstruation, whooping cough, hepatic malfunctions (23). Numerous investigations have earlier indicated that *B. vulgaris* has further medicinal properties such as antihyperglycemic, hypolipidemic, antioxidant, anticholinergic, anticancer, antipyretic, antihistaminic, antimicrobial, hypnotic, jumping and locomotion decreasing activities, and also reduction in the acquisition and reinstatement of morphine-induced conditioned place preference (24-27), which confirm the traditional use of this plant in Ayurveda and Chinese medicine (28).

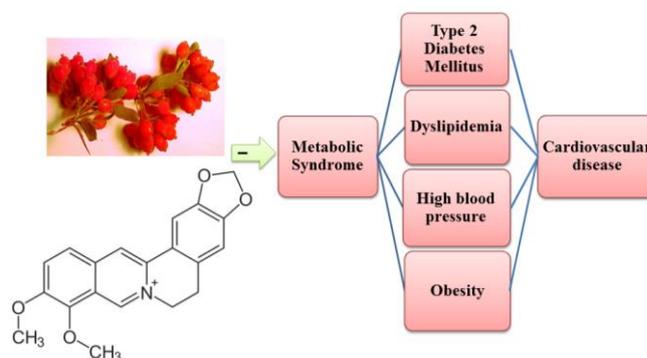


Figure 2. Therapeutic effects of *Berberis vulgaris* and berberine on metabolic syndrome

B. vulgaris contains isoquinoline alkaloids such as berberine (BBR) (29); acanthine, bargustanine, berbamine, berlambine, palmatine and secondary metabolites such as aesculetin, ascorbic acid, caffeic acid, pectin and tannin (23, 30).

BBR, a type of isoquinoline alkaloid with a long history of medicinal application, is the major active component of *B. vulgaris* (31). Recent studies have proved that BBR exhibits several pharmacological activities such as antioxidant, anti-inflammatory, antidiarrheal, antimicrobial and anti-tumor activity (32-35). Furthermore, BBR has a broad range of therapeutic potential uses including lowering blood glucose, adjusting blood lipids, increasing insulin sensitivity and consequently ameliorating insulin resistance (23) (Figure 2).

In this review, we illustrate the most related clinical trials, animal and *in vitro* studies to comprehend the role of *B. vulgaris* and its major active component, BBR, in treatment of various constituents of MetS including dyslipidemia, hyperglycemia, hypertension and obesity. Although the reported biological results indicate that

this plant is a highly promising cardiovascular protective agent, more investigations need to be done to establish its effectiveness and *in vivo* cardioprotective effects, specifically in humans.

Search strategy

This review was carried out by means of the databases of Scopus, PubMed and Google Scholar. All the above databases were searched from the available date of inception until the latest issue up to May 2016. The search words contained MetS, CVD, dyslipidemia, obesity, hypertension, diabetes, *B. vulgaris* and BBR. All articles which included reports of the effect of *B. vulgaris* and BBR on MetS were taken into account. The reference lists of the included articles were also explored to identify additional studies.

Effects on lipid profile

Dyslipidemia is commonly known as an important cardiovascular risk factor (CVRF) with large randomized trials representing significant benefit of lipid modifying therapy in the management of CVD (36). Dyslipidemia is chiefly known as a triad of low HDL-C together with increases in triglycerides (TGs) and LDL (low-density lipoprotein) (37). In animal studies, hypercholesterolemic (HCh) rats which were fed by 30 mg/kg/day of BBR for six weeks showed reduced serum levels of TG and total cholesterol (TC). BBR caused significant increase in cardiac fatty acid transport protein-1, fatty acid transport proteins, fatty acid beta-oxidase, as well as peroxisome proliferator-activated receptor γ (PPAR γ), but decrease in PPAR α mRNA and protein expression (38). Treatment of hyperlipidemic (HL) hamsters with BBR reduced serum cholesterol by 40% and LDL-C by 42%, with a 3.5-fold rise in hepatic LDLR (low-density lipoprotein receptor) mRNA and a 2.6-fold rise in hepatic LDLR protein (39). In a study, it was indicated that because the mechanism of BBR (stabilization of the LDLR mRNA) differs from that of statins, the combination of BBR is more effective than that of the simvastatin or BBR monotherapy (40).

In another study HCh rats which received the alcoholic extract of *B. vulgaris* at minimum (75 mg/kg), moderate (150 mg/kg), and maximum (300 mg/kg) doses by intraperitoneal (IP) injection for three weeks, showed a decrease in serum levels of ALT (alanine transaminase) and ALP (alkaline phosphatase) through antioxidant properties of the plant (41). The mechanism of lowering blood cholesterol levels through inhibiting the intestinal absorption and further by interfering with intraluminal cholesterol micellization and decreasing enterocyte cholesterol uptake and secretion, was indicated in a study in which rats received 50, 100, and 150 mg/kg of BBR by gavage for 8 weeks (42). Furthermore, HFD rats treated with 200 mg/kg/d of BBR remarkably decreased the mRNA levels encoding carnitine palmitoyltransferase-1 α

(CPT-1 α), microsomal triglyceride transfer protein (MTTP) and LDLR in the liver (43).

In vitro study also showed that BBR increased the LDLR mRNA and protein levels in a time- and dose-dependent manner and exhibits lipid-lowering effects by up-regulating LDLR expression in HepG2 cells (44).

Clinical studies also indicated the beneficial effects of this plant on dyslipidemia in human beings. Oral administration of BBR (0.5 g twice per day) in 32 HCh patients for 3 months reduced serum cholesterol by 29%, TGs by 35% and LDL-C by 25% compared to the control subjects (39). In another study, subjects on the BBR therapy were given 0.5 g of BBR hydrochloride orally twice a day for 3 months and it significantly lowered blood cholesterol, TG, LDL-C, ALT and AST, but increased HDL compared to the control subjects (45). Besides, decrease in TC (19.2%), TG (16.3%) and LDL-C (17.4%) compared to the control subjects was observed in a clinical study which BBR tablets (500 mg) were administered orally to HCh patients daily for 6 months (46). In several clinical studies, BBR has shown reduction in serum levels of TC, TG and LDL levels. Nevertheless, HDL level showed increase in some and no significant change in some other studies (47, 48).

The proposed mechanisms of protective effects of *B. vulgaris* and BBR on dyslipidemia may be associated with increase in hepatic LDLR mRNA and hepatic LDLR protein (39), a significant increase in adenosine monophosphate-activated protein kinase (AMPK) phosphorylation and activity (49) (Table 2).

Effects on obesity

The increasing prevalence of obesity is associated with many diet-related chronic diseases including T2DM, CVD, stroke and hypertension (50). BBR successfully decreased body weight, fasting blood glucose (FBG), postprandial blood glucose (PBG), fasting insulin (FI) and homeostasis model assessment (HOMA IR) in obese rats fed on high fat diet (32). In a study, insulin resistance was developed by feeding the female rats a high fat diet (HFD) for six weeks, then treating them with *B. vulgaris* extract (0.2 g/Kg body weight) or vitamin A (12.8 μ g/Kg/day) for two weeks. Co-administration of vitamin A and *B. vulgaris* extracts reduced body weight, blood glucose level, insulin, and retinol binding protein4 (RBP4) expression before, during and after HFD period (51). In another study when HFD-induced obese mice were treated with 0.75, 1.5 and 3 mg/kg/day (IP) of BBR for 36 days, it was demonstrated that BBR reduced mouse weight gain, food intake and serum glucose, TG and TC levels accompanied with a down-regulation of PPAR γ expression and an up-regulation of globin transcription factor 3 (GATA-3) expression (52).

In a clinical trial which was conducted on 80 patients (case and control groups), a significant decrease was observed in weight, TG and cholesterol in patients who

received two capsules (750 mg) containing *B. vulgaris* extract every day for 3 months (53).

Effects on high blood pressure

Hypertension is also one of the main CVRFs (54), which leads to increase in incidence of myocardial infarction and cerebrovascular disease, as well as heart failure and chronic renal disease (55).

Hypotensive effects of BBR have been observed in different animal models. In a study, the delay of the onset and attenuation of the severity of hypertension as well as amelioration of hypertension-induced renal damage were observed following the administration of BBR [per os (p.o.), 100 mg/kg/d body weight] to spontaneously hypertensive rats. Furthermore, BBR could inhibit the activities of renin-angiotensin system and pro-inflammatory cytokines interleukin 6 (IL-6), IL-17 and IL-23, which are involved in the pathophysiology of hypertension (56). Besides, intravenous (IV) administration of *B. vulgaris* (17–33 mg/100g) significantly reduced the rat arterial blood pressure (57). In another study, IV infusion of BBR (10 mg/kg in one hr) to rats lowered the blood pressure in a dose-dependent manner and a significant hypotensive effect was followed by bradycardia (58). The results of an experiment on rats also suggested that BBR has a hypotensive effect, via the inhibition of angiotensin-converting enzyme and direct release of NO/cGMP in the vascular tissues (59). In a dog ischemic heart failure model, IV administration of BBR, increased cardiac output; and decreased left ventricular end diastolic pressure and systemic vascular resistance (60).

Examination of hemodynamic parameters in humans revealed similar results with increased cardiac index and left ventricular ejection fraction, decreased systemic and pulmonary vascular resistance and left ventricular end-diastolic pressures (61). BBR also showed hypotensive effect in combination therapy. In a clinical study, a nutraceutical composition including policosanol, red yeast rice extract, BBR, folic acid and coenzyme Q10 with *Orthosiphon stamineus* was administered to grade I essential hypertensive patients for a month and an antihypertensive effect along with lipid lowering effect was revealed (62).

Effects on high glucose level

T2DM, a serious, complex metabolic disorder and one of the most common chronic diseases, is an independent CVRF (63-65). The antidiabetic and hypoglycemic effects of *B. vulgaris* and BBR have been described by several clinical, *in vivo* and *in vitro* scientific investigations (32, 33, 66). Many human studies have supported the antidiabetic effect of this plant. For example, in two different diabetic situation (the newly diagnosed T2DM and poorly controlled T2DM patients) who received 0.5 g/three times a day

(t.i.d.) of BBR (orally for 3 months) showed decrease in HbA1c, FBG, PBG, TG, TC, LDL-C; and the authors presented BBR as a potent oral hypoglycemic agent with beneficial effects on lipid metabolism (32). In another clinical study on T2DM patients who were treated with *B. vulgaris* fruit extract (3 g/d) orally for 3 months, reduction in glucose, insulin, TG, TC, LDL-C and apolipoprotein B was indicated (67). In a clinical trial on T2DM patients, BBR was suggested as an ideal medicine with a mechanism different from metformin and rosiglitazone and demonstrated the effect of BBR on increasing insulin receptor mRNA in humans and its relationship with the glucose-lowering effect (68). In another human study, patients who received BBR (0.5 g/twice a day for three months), biomarkers such as TG, TC and LDL-C markedly decreased (69). Also it has been shown that consumption of 1 g/d of BBR in T2DM and DL (dyslipidemic) patients (for 3 months) reduced free fatty acids (64) that can be considered as a mechanism for the antidiabetic effect of BBR. Furthermore, in a meta-analysis, the effect and safety of BBR in the treatment of T2DM, hyperlipemia and hypertension on 2569 patients was investigated. This study indicated that BBR has comparable therapeutic effect on T2DM, hyperlipidemia and hypertension with no serious side effect (70).

Besides, *in vivo* studies have demonstrated this effect. In an animal study, 50 and 100 mg/kg of BBR was intraperitoneally injected to streptozotocin (STZ)-diabetic rats for 4 weeks and decrease in FBG, hepatic gluconeogenesis, glucose 6-phosphatase (G6Pase), weight gain, plasma TG and phosphoenolpyruvate carboxykinase was observed. But glucose tolerance and AMPK activity increased (71). This effect was also observed with a different mechanism in non-obese diabetic mice which were treated orally with BBR (200 mg/kg for 2 weeks) and inhibition of T helper17 (Th17) cell differentiation by activating extracellular signal-regulated kinase1/2 (ERK1/2), inhibition of Th1 cell differentiation by inhibiting p38 mitogen-activated protein kinase (MAPK) and c-jun N-terminal kinase (JNK) activation, was observed (33). In another animal study, BBR (150, 300 mg/kg for 4 months) was IP injected to HCh and T2DM rats and the results showed an increase in insulin expression, β -cell regeneration, antioxidant enzyme activity; and decrease in lipid peroxidation (72). Another mechanism which has been stated on the antidiabetic effect of this plant could be a reduction in FBG and malondialdehyde (MDA), and increase in superoxide dismutase (SOD) and catalase (CAT) activity by treating T2DM mice with BBR (100 mg/kg/d for 2 weeks) (73). The antidiabetic effect of BBR was also demonstrated in a study on mice, accomplished by Zhang *et al* (74). In this study, up-regulated expression of glucose transporter 4 (GLUT4), MAPK14, MAPK8, PPAR α ,

uncoupling protein 2, and hepatic nuclear factor 4 α (HNF4 α); and down-regulated expression of PPAR γ , CCAAT/enhancer-binding protein (C/EBP), PPAR γ coactivator 1 α (PGC1 α) and resistin (which moderates glucose and lipid metabolism), was observed (74). Besides, in adipose and muscle cell, several research projects demonstrated that BBR may stimulate glucose uptake into cell through up-regulating GLUT1 expression and inhibiting RBP4, which can act as an effective insulin sensitizing function (63). BBR treatment in STZ-diabetic rats significantly increases glucagon levels in plasma and intestine through promoting glucagon-like peptide-1 (GLP-1) secretion, accompanied with an increase of proglucagon mRNA expression. Furthermore, BBR raises insulin levels in plasma and pancreas as well as β -cell number in pancreas (75). On GLP-1 receptor activation, adenylyl cyclase (AC) is activated, and cyclic adenosine monophosphate (cAMP) is generated, leading to activation of second messenger pathways and closure of ATP-dependent potassium channels. Increased intracellular potassium causes depolarization, and calcium influx through the voltage-dependent calcium channels occurs. This intracellular calcium increase stimulates the migration and exocytosis of the insulin granules and lowers the blood glucose (76).

In an experiment which was performed on rat H9c2 cardiomyocyte cell line, BBR (5–20 μ M) could increase AMPK activity, glucose consumption and glucose uptake by these cells (77). In another experiment on MCF7, HepG2 and CACO-2 cell lines, the ethanolic extract of *B. vulgaris* and BBR caused the inhibition of α -glucosidase enzyme activity which verifies this effect (66). BBR (50 μ M) also indicated an escalation of insulin sensitizing activity and glucose-stimulated insulin secretion and proliferation; and a diminution of TG in 3T3-L1 adipocytes (78). A proposed mechanism for BBR (0.02–20 μ g/ml) could be a reduction in sucrase, maltase and disaccharidase activity; and the inhibition of α -glucosidase according to an experiment on Caco-2 cell line which lead to reduction in intestinal absorption of glucose (79). The stimulation of palmitate resulted in IL-6 and tumor necrosis factor- α (TNF- α) production in HepG2 cells, and antibody-neutralizing assay further confirms that IL-6 and TNF- α are involved in the development of insulin resistance. BBR effectively inhibits IL-6 and TNF- α production in a concentration-dependent manner, demonstrating its anti-inflammatory activity in hepatocytes (80). BBR augments glucose metabolism through stimulation of glycolysis, which is related to inhibition of glucose

oxidation in mitochondria. BBR-induced AMPK activation is likely a result of mitochondria inhibition that escalates the AMP/ATP ratio (81). The improving effect of BBR on obesity, T2DM and dyslipidemia has been shown through stimulating of AMPK. BBR suppresses pro-inflammatory responses through AMPK activation in macrophages. In adipose tissue of obese db/db mice, BBR considerably down-regulated the expression of pro-inflammatory genes such as IL-1 β , IL-6, TNF α , monocyte chemoattractant protein-1 (MCP-1), inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2). Constantly, BBR inhibited lipopolysaccharide (LPS)-induced expression of pro-inflammatory genes including IL-1 β , IL-6, iNOS, MCP-1, COX-2, and matrix metalloproteinase-9 in peritoneal macrophages and RAW 264.7 cells. Upon various pro-inflammatory signals such as LPS, free fatty acids, and hydrogen peroxide, BBR suppressed the phosphorylation of MAPKs, such as p38, ERK, and JNK, and the level of reactive oxygen species in macrophages (82). BBR also has significant antimicrobial activity against several microbes through inhibiting the assembly function of filamenting temperature-sensitive mutant Z (FtsZ), an essential cell division protein, which results in the cessation of bacterial cell division. Acting topically in the gastrointestinal tract and poorly absorbed, BBR might modulate gut microbiota without systemic anti-infective activity (83), and this could be another mechanism for the antidiabetic effect of BBR (Figure 3).

Conclusion

The use of herbal drugs as complementary medicine is prevalent and gaining worldwide popularity. Many drugs are derived directly from plants; while the others are chemically modified natural products. The original research articles published so far have confirmed the pharmacological potential of *B. vulgaris* and its active component, BBR, which possess remarkable *in vitro* and *in vivo* (clinical studies, in lesser extent) antidiabetic, hypolipidemic, hypotensive and antiobesity effects against MetS. Based on the current review, it can be concluded that *B. vulgaris* may exhibit promise as a medication for modulating different constituents of MetS including T2DM, dyslipidemia, hypertension and obesity, and consequently CVD. However, more clinical trials need to be done for establishing the therapeutic effectiveness of *B. vulgaris* and BBR.

Conflict of interest

None to be declared.

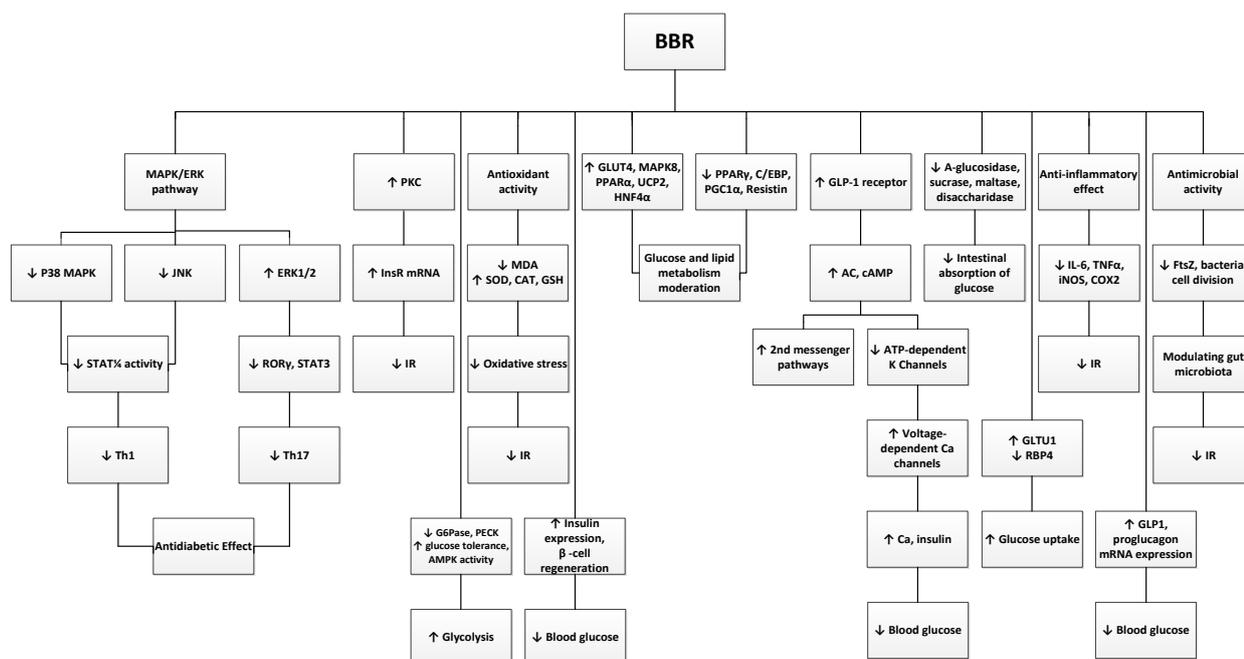


Figure 3. Main mechanisms of berberine on glucose metabolism

MAPK= mitogen-activated protein kinase; ERK= extracellular signal-regulated kinase; JNK= c-jun N-terminal kinase; STAT3= signal transducer and activator of transcription3; Th= T helper cells; PKC= protein kinase C; InsR= insulin receptor; IR= insulin resistance; MDA= malondialdehyde; SOD= superoxide dismutase; CAT= catalase; GSH= glutathione; G6Pase= glucose 6-phosphatase; AMPK= adenosine monophosphate-activated protein kinase; GLUT4= glucose transporter 4; PPARα= peroxisome proliferator-activated receptor α; UCP2= uncoupling protein 2; HNF4α= hepatic nuclear factor 4α; C/EBP= CCAAT enhancer-binding protein; PGC1α= PPARγ coactivator 1α; GLP-1= glucagon-like peptide-1; AC= adenylyl cyclase; cAMP= cyclic adenosine monophosphate; ATP= adenosine triphosphate; RBP4= retinol binding protein4; IL-6= interleukin 6; TNF-α= tumor necrosis factor; iNOS= inducible nitric oxide synthase; COX-2= cyclooxygenase-2; FtsZ= filamenting temperature-sensitive mutant Z; ROR= retinoic acid-related orphan receptors

Table 2. Summary of the effects of *Berberis vulgaris* and berberine in metabolic syndrome

Pharmacological effects	Results	Study protocol	Compound	References
	↓Cholesterol, TG, LDL ↑HDL	<i>In vivo</i> , rats (IP for 21 days)	<i>B. vulgaris</i> extracts (300 mg/kg)	(84)
	↓TC, TG, LDL-C ↑HDL	Human, T2DM patients (p.o. for 2 months)	BBR (0.3 g t.i.d.)	(47)
Hypolipidemic effects	↓Serum cholesterol and dietary cholesterol absorption rate ↓cholesterol uptake and, gene and protein expressions of acyl-coenzyme A cholesterol acyltransferase-2	<i>In vivo</i> , rats (p.o. for 8 weeks) <i>in vitro</i> , Caco-2 cells	BBR (50, 100, and 150 mg/kg twice a day) BBR (5, 10, and/or 15 µg/ml)	(42)
	↓Weight gain, TC, LDL-C, TG, ALT, AST, FI	<i>In vivo</i> , HFD rats (p.o. for 16 weeks)	BBR (200 mg/kg/d)	(43)
	↓TC, TG, LDL-C ↑HDL	Human, HL and IGT patients (p.o. for 13 months)	BBR (0.2 g t.i.d.)	(48)
	↓TC, TG, LDL-C ↑HDL	Human, HL patients (p.o. for 2 months)	BBR (0.4 g t.i.d.)	(85)
	↓TC, TG, LDL-C ↑HDL	Human, T2DM patients (p.o. for 3 months)	BBR (0.5 g t.i.d.)	(86)
	↓Serum cholesterol, TG,	Human,	BBR (0.5 g twice a day)	(39)

	LDL-C ↓Serum cholesterol, LDL-C and ↑ hepatic LDLR mRNA, hepatic LDLR protein	HCh patients (p.o. for 3 months) HL hamsters (p.o. for 10 days)	BBR (50 mg/kg/d)	
	↓Cholesterol, TG	<i>In vitro</i> , HepG2 cells <i>in vivo</i> , hamsters (p.o. for 10 days)	BBR (0-15 µg/ml)	(49)
	↓LDL, TG, cholesterol, cholesteryl ester and hepatic fatty acid levels		BBR (100 mg/kg/day)	
	↓TG, cholesterol, LDL-C ↑HDL-C	Human, HL patients (p.o. for 3 months)	BBR hydrochloride (0.5 g twice a day)	(45)
	↓Body weight, TG, serum cholesterol, FBG, ALT, AST	Human, patients with non-alcoholic fatty liver disease (p.o. for 3 months)	Aqueous extracts of <i>B. vulgaris</i> (750 mg capsules twice a day)	(53)
	↓ALP, ALT, cholesterol ↑HDL-C	<i>In vivo</i> , HCh rats (IP for 3 weeks)	Alcoholic extract of <i>B. vulgaris</i> (75, 150 and 300 mg/kg)	(41)
	↑hepatic LDLR expression	<i>In vitro</i> , HepG2 cells	BBR (15 µM)	(44)
Antibesity effects	↓Weight gain, food intake, serum glucose, TG, TC and PPAR γ expression ↑GATA-3 expression	<i>In vivo</i> , mice (IP for 36 days)	BBR (0.75, 1.5, 3 mg/kg/day)	(52)
	↓SBP, IL-6, IL-17, IL-23, angiotensin II and aldosterone	<i>In vivo</i> , HT rats (p.o.)	BBR (100 mg/kg/d)	(56)
	↓ABP	<i>In vivo</i> , rats (IV for 1 week)	Aqueous extracts of <i>B. vulgaris</i> (17-33 mg/100 g)	(57)
	↓SBP, DBP, HR	<i>In vivo</i> , rats (IV)	BBR (10 mg/kg in 1 hr)	(58)
Hypotensive effects	ACE inhibition ↓MAP ↑NO $_x$ and cGMP	<i>In vivo</i> , rats (IV)	BBR (10, 100 µg/ml)	(59)
	↓SBP, DBP	Human, grade 1 essential HT patients (for 1 month)	BBR	(62)
	↑Cardiac contractility and coronary flow	<i>In vivo</i> , dogs (IV)	BBR (2 to 4 µg/ml)	(87)
	Inhibition of Th17 differentiation by activating ERK1/2, inhibition of Th1 differentiation by inhibiting p38 MAPK and JNK activation	<i>In vivo</i> , NOD mice (p.o. for 2 weeks) <i>in vitro</i> , mouse CD4 $^+$ T cells	BBR (200 mg/kg)	(33)
Antidiabetic effects	↓HbA1c, FBG, PBG, TG,	Human, newly diagnosed T2DM patients, poorly controlled type 2 diabetes (p.o. for 3 months)	BBR (0.5 g t.i.d.)	(32)
	↓HbA1c, FBG, PBG, TG, TC, LDL-C,			
	↓Free fatty acids	Human, T2DM and DL patients (p.o. for 3 months)	BBR (1 g/d)	(64)
	↓Serum TG, TC, LDL-C,	Human, T2DM patients	<i>B. vulgaris</i> fruit extract (3	(67)

	apo B, glucose, and insulin	(p.o. for 3 months)	g/d)	
	↓FBG, serum insulin, HbA1c, TG, ALT	Human, T2DM patients (p.o. for 2 months)	BBR (1 g/d)	(68)
	↑Insulin expression, β-cell regeneration and lipid peroxidation ↓lipid peroxidation	<i>In vivo</i> , HCh rats with T2DM (IP for 4 months)	BBR (150, 300 mg/kg)	(72)
	↓FBG, MDA ↑SOD and CAT activity	<i>In vivo</i> , T2DM mice (for 2 weeks)	BBR (100 mg/kg/d)	(73)
	↑Glucagon in plasma and intestine, and proglucagon mRNA expression	<i>In vivo</i> , STZ-diabetic rats (p.o. for 5 weeks)	BBR (120 mg/kg/d)	(75)
	↑AMPK activity, glucose consumption and glucose uptake	<i>In vitro</i> , rat H9c2 cardiomyocyte cells (for up to 24 hr)	BBR (5–20 μM)	(77)
	↑Insulin sensitizing activity and glucose-stimulated insulin secretion and proliferation ↓TG	<i>In vitro</i> , 3T3-L1 adipocytes	BBR (50 μM)	(78)
	↓Sucrase, maltase and disaccharidase activity inhibition of α-glucosidase	<i>In vitro</i> , Caco-2 cells	BBR (0.02- 20 μg/mL)	(79)
	↓FBG, insulin sensitivity ↑glucose consumption	<i>In vitro</i> , HepG2 cells <i>in vivo</i> , rats with T2DM (p.o.) <i>in vivo</i> , mice with T2DM (p.o. for 3 weeks)	BBR (7.5 μg/mL) BBR (75 or 150 mg/kg twice a day) BBR (100 or 200 mg/kg/d)	(88)
	↓FBG, PBG, HOMA-IR ↑insulin sensitivity ↑glucose consumption, AMPK phosphorylation,	<i>In vivo</i> , obese rats (p.o. for 5 weeks) <i>in vitro</i> , mouse fibroblast 3T3-L1 preadipocytes, L6 rat skeletal myoblasts, C ₂ C ₁₂ mouse myoblasts and rat hepatoma cell line H4IIE	BBR (125 mg/kg twice a day) BBR (5 and 20 μmol/l)	(81)
	↓Body weight, adipose tissue mass and FBG ↓body weight and plasma TG	<i>In vivo</i> , obese and diabetic mice (IP for 3 weeks) <i>in vivo</i> , high-fat-fed rats (p.o. for 2 weeks)	BBR (5 mg/kg) BBR (380 mg/kg)	(89)
	↓TG, free fatty acids and adipocyte differentiation	<i>in vitro</i> , 3T3-L1 cells		
Antidiabetic and hypolipidemic effects	↓Body weight, serum insulin and glucose,	<i>In vivo</i> , high fat diet rats (p.o. for 6 weeks)	<i>B. vulgaris</i> extract (0.2 g/Kg)	(51)
	↓FBG, TC, TG up-regulation of GLUT4, MAPK14, MAPK8, PPARα, UCP2 and HNF4α down-regulation of PPARγ, C/EBP, PGC1α and resistin	<i>In vivo</i> , obese and diabetic mice (IP for 4 weeks)	BBR (250 mg/kg/day)	(74)

	↓Body weight, TC, TG, free fatty acid, LDL-C, MDA, TBARS, glucose and insulin levels ↑plasma superoxide dismutase activity and 4mRNA	<i>In vivo</i> , high glucose and high fat diet-induced diabetic hamsters (IP for 6 weeks)	BBR (50 and 100 mg/kg)	(90)
	↓LDL-C, FBG and HbA1c	Human, T2DM and HCh patients (p.o. for 6 and 12 months)	BBR (588 mg/tablet)	(91)
	↓FBG, TC, TG, LDL-C and Apo B	<i>In vivo</i> , STZ-diabetic mice (p.o. for 4 weeks)	Aqueous extracts of <i>Rhizoma Coptidis</i> (100 mg/kg/d)	(92)
	↓SBP, DBP, HbA1c and FBG	Humans, HCh patients with T2DM (p.o. for 24 months)	BBR (0.1 g t.i.d.)	(93)
	↑AMPK activation	<i>In vitro</i> , HUVE cells (for 1 hr) <i>in vivo</i> , rats	BBR (25 μM)	(94)
Antidiabetic and hypotensive and antiobesity effects	↓expression of IL-1β, IL-6, TNFα, MCP-1, iNOS and COX-2, phosphorylation of p38, ERK and JNK ↓ TNFα	<i>In vivo</i> , obese db/db mice (IP for 3 weeks) <i>in vitro</i> , 264.7 macrophages and 3T3-L1 adipocytes	BBR (5 mg/kg/d)	(82)
	↓DBP, FBG and TG	<i>In vivo</i> , HG and HCh rats (p.o. for 6 weeks)	BBR (30 mg/kg/day)	(38)
Hypotensive and hypolipidemic effects	↓SBP, PP, TC, LDL-C and TG	Human, grade 1 essential HT and HCh patients (p.o. daily for 6 months)	BBR (500 mg)	(46)

↑= increase; ↓= decrease; FBG= fasting blood glucose; FI= fasting insulin; BMI= body mass index; TG= triglyceride; TC= total cholesterol; LDL-C= low-density lipoprotein cholesterol; LP (a) = lipoprotein (a); HOMA-IR= homeostatic model assessment; PPARγ= peroxisome proliferator-activated receptor γ; HbA1c= hemoglobin A1c; C/EBP= CCAAT enhancer-binding protein; GATA-3= globin transcription factor 3; STZ= streptozotocin; FPG= fasting plasma glucose; SBP= systolic blood pressure; DBP= diastolic blood pressure; MDA= malondialdehyde; TBARS= thiobarbituric acid reactive substances; t.i.d.= three times a day; PBG= postprandial blood glucose; ALT= alanine transaminase; AST= aspartate transaminase; ALP= alkaline phosphatase; p.o.= per os (orally); ABP= arterial blood pressure; SBP= systolic blood pressure; DBP= diastolic blood pressure; HR= heart rate; HUVECs= human umbilical vein endothelial cells; AMPK= adenosine monophosphate-activated protein kinase; ACE= angiotensin converting enzyme; MAP= mean arterial pressure; HT= hypertensive; HCh= hypercholesterolemic; HG= hyperglycemic; HL= hyperlipidemic; PP= pulse pressure; Apo B= apolipoprotein B; IGT= impaired glucose tolerance; UCP2= uncoupling protein 2; HNF4α= hepatic nuclear factor 4α; PGC1α= PPARγ coactivator 1α; TNF-α= tumor necrosis factor; iNOS= inducible nitric oxide synthase; COX-2= cyclooxygenase-2; IV= intravenous; T2DM= type 2 diabetes mellitus; MCP-1= monocyte chemoattractant protein-1

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