

Barberry in the treatment of obesity and metabolic syndrome: possible mechanisms of action

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Abstract: Obesity is a consequence of an imbalance between energy intake and energy expenditure. It affects people of both genders and all age groups, ethnicity and socioeconomic groups, and in developed and developing countries. Obesity is often accompanied by the metabolic syndrome (MetS). MetS is characterized by a clustering of cardiovascular risk factors, including high blood pressure, adiposity, dyslipidemia and glucose intolerance, which together increase the risk of atherosclerotic cardiovascular disease, type 2 diabetes mellitus and other causes of mortality. Nowadays, there is a growing interest in the use of plant-based agents instead of synthetic drugs to manage chronic diseases such as MetS; one such example is *Berberis vulgaris*. *B. vulgaris* contains isoquinoline alkaloids such as berberine, berberrubine and berbamine. Recent studies have proved that berberine exhibits pharmacological activities and positive effects on the risk factors of obesity and MetS. We have reviewed original articles related to the possible molecular mechanisms of action of berberine on obesity and MetS. Berberine suppresses adipocyte differentiation and decreases obesity. It also regulates glucose metabolism via decreasing insulin resistance and increasing insulin secretion. Other effects of berberine include antihyperlipidemic and antihypertensive activities and endothelial protection.

Keywords: berberine, syndrome metabolic, obesity

Introduction

Obesity is a consequence of an imbalance between energy intake and energy expenditure. The WHO has identified obesity as a major public health problem because of its associated risk for a number of noncommunicable diseases, which include type 2 diabetes mellitus, hypertension, dyslipidemias and cardiovascular disease, and a reduction in life expectancy.¹ Overweight, obesity and morbid obesity are usually defined using body mass index (defined as the weight in kilograms divided by the height in meters squared) of 25–29.9, 30–39.9 and >40, respectively. Other more sophisticated methods for directly assessing body fat, or adiposity, include bioelectrical impedance analysis, computed tomography and MRI.² Abdominal obesity is an independent predictor of several cancer- and cardiovascular-related outcomes and can be assessed relatively simply by measuring waist circumference or waist-to-hip ratio.³ Obesity is a common public health problem, which is causing an estimated around 2.6 million deaths in the world.² It affects all age, sex, ethnic and socioeconomic groups in both developed and developing countries.⁴ Obesity is a multifactorial disorder due to an interaction between genetic, socioeconomic, environmental and behavioral influences.⁵ Differences in energy metabolism may play a role in long-term body weight regulation

and the pathogenesis of human obesity. Several prospective studies have shown that relatively low energy expenditure and high respiratory quotient due to a low fat to carbohydrate oxidation rate predict body weight gain.⁶ Obesity is often accompanied by the metabolic syndrome (MetS). MetS is determined by a series of factors including physiological, biochemical, clinical and metabolic parameters that together enhance the risk of atherosclerotic cardiovascular disease, type 2 diabetes mellitus and other causes of mortality.⁷ There are several definitions of MetS, but some of the most popular definitions are from the WHO⁸ and the National Cholesterol Education Program Adult Treatment Panel III.⁹

According to the National Cholesterol Education Program Adult Treatment Panel III definition for MetS, the presence of any three of the following five features including waist circumference ≥ 102 cm in men or ≥ 88 cm in women, $\geq 130/85$ mmHg (includes hypertensive patients and patients who received antihypertensive medications), triglyceride (TGs) ≥ 150 mg/dL, high-density lipoprotein cholesterol <40 mg/dL in men or <50 mg/dL in women and fasting blood glucose ≥ 100 mg/dL (includes diabetes).

The prevalence of MetS varies widely (10%–84%) and depends on the region, urban or rural setting, individual characteristics, including sex, age, race and ethnicity of the population studied, and the definition of the syndrome used.^{10,11} The International Diabetes Federation estimates that MetS affects approximately one-quarter of the world's adult population.¹² Therefore, many strategies for prevention are being developed to reduce the future MetS burden. Nowadays, there is a growing preference to use plant-based agents instead of synthetic drugs to manage chronic diseases such as MetS because plant-based agents have fewer adverse effects and lesser costs and are more accessible than synthetic drugs in some countries.¹³ Studies show that formulations of one-quarter of all medical prescriptions are derived from plant synthetic analogs, and according to the WHO, 80% of the world population, especially in developing countries, trust in plant-based medicines.¹³

Berberis vulgaris (zereshk in Persian) is widely cultivated in Iran (particularly in South Khorasan province), central and southern Europe and northeastern US.^{14,15} *B. vulgaris* has been used in herbal therapy for >2,500 years, mainly by Russian therapists.¹⁶ The antioxidants present in berberry include berberine, berberrubine and berbamine.¹⁷ Berberine is an alkaloid that is used in Chinese medicine. This herbal ingredient exists in the stem, roots, rhizomes and seven plant species such as *Berberis vulgaris*, *Berberis aristata*, *Mahonia aquifolium*, *Hydrastis canadensis*, *Xanthorhiza simplicissima*, and *Phellodendron amurense* (barberry).¹²

Berberine affects the glucose metabolism by increasing glycolysis and increasing insulin sensitivity,¹⁸ and a recent study has suggested that berberine is both anti-inflammatory and anti-adipogenic. The anti-adipogenic effect may be a result of the downregulation of transcription factors and adipogenic enzymes.¹⁹ Berberine is also used in the treatment of diarrhea, stomatitis, dysentery and hepatitis.²⁰

The polyphenols in barberry juice have been reported to have a positive effect on lipid profiles and diabetes complications.^{21,22}

The chemical structure of berberine is shown in Figure 1.

Inclusion of studies

The keywords including “berberine”, “diabetes”, “insulin-resistance”, “glucose”, hemoglobin A1C”, “dyslipidemia”, “obesity” and “atherosclerosis” were used for an electronic search strategy. All the identified studies and review articles were reviewed. Subsequently, the eligible trials were selected. These are papers reporting original studies on the antidiabetic, antihyperlipidemic and anti-adipogenic mechanisms of action of berberine and almost all available clinical trials. But we mentioned this study is not systematic review.

The mechanisms of action of berberine in obesity

Adipocyte differentiation requires several transcription factors, and key regulators in the process are two adipogenic factors, CCAAT/enhancer-binding protein α (C/EBP α) and peroxisome proliferator-activated receptor γ (PPAR γ). The PPARs function as lipid sensors and regulate lipid and lipoprotein metabolism, glucose homeostasis, adipocyte proliferation and differentiation.²³ C/EBP α -deficient cells are capable of adipocyte differentiation and are also insulin resistant.²⁴ It has been discovered that GATA factors play a role in adipogenesis.²⁵ GATA-2 and GATA-3 are expressed in adipocyte precursors and control the preadipocyte to adipocyte transition. Berberine reduces the expression of C/EBP α and PPAR γ and it has been shown to inhibit

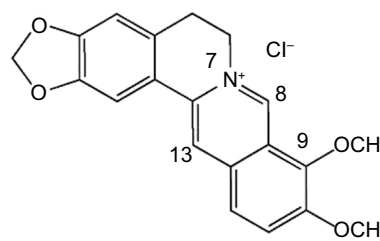


Figure 1 Chemical structure of berberine.

the differentiation of 3T3-L1 cells in murine-derived preadipocytes and human white preadipocytes.²⁶ Furthermore, berberine increases the expression of GATA-2 and GATA-3 and these suppress adipocyte differentiation.²⁴ This mechanism is directly through binding to the PPAR γ promoter and suppression of basal activity of PPAR γ . Also, GATA-2 and GATA-3 form a protein complex with C/EBP α that suppresses the transcriptional activity of PPAR γ .²⁷ It has been reported that berberine reduces weight, the food intake, the ratio of epididymal fat to total weight, as well as the ratio of liver weight to total weight in a murine model. In addition, blood glucose, TG and total cholesterol levels were all reduced in high fat-fed obese mouse, revealing that berberine acts as a potential natural compound for the treatment of obesity.²⁶ The accumulation of TG in adipose tissue leads to obesity, and therefore, reducing the amount of TG in adipocytes may be a way for decreasing obesity. One study showed that berberine increased the adipose TG lipase expression in 3T3-L1 adipocytes and it led to reduced TG accumulation in adipocytes. Berberine also reduced the numbers and size of lipid droplets in 3T3-L1 adipocytes.²⁸

Several studies have shown that berberine regulates TG, cholesterol and glucose metabolism via AMP-activated protein kinase (AMPK) expression,²⁹ an important regulator of lipolysis in adipose tissue. Hormone-sensitive lipase and adipose TG lipase are phosphorylated by AMPK.^{30,31}

The effects of berberine on insulin resistance and glycemic control

Berberine has been shown to regulate glucose and lipid metabolism in vitro and in vivo (see Table 1). It enhances insulin secretion, stimulating glycolysis, suppressing adipogenesis by inhibiting PPAR γ and C/EBP α function,³² activating the AMPK pathway and increasing glycokinase activity. Berberine stimulates pancreatic G protein-coupled receptor 40 (GPR40), reduces intestinal glucose absorption by inhibiting α -glucosidase activity, and also upregulates the expression of glucose transporter-4 (GLUT-4) and stimulates glucose uptake, and upregulates glucagon like peptide-1 (GLP-1) genes.^{33,34}

Secretagogue effect of berberine on insulin

Berberine increases glucose-stimulated insulin secretion in a dose-dependent manner, enhancing both mRNA expression of hepatic nuclear factor 4- α (HNF-4 α) and glycokinase activity; this provides an insulinotropic effect different from sulfonylureas.³⁵

Table 1 Glycemic control mechanisms of berberine

Upregulation of GLUT-4
Activation of AMPK
Suppression of adipogenesis by inhibiting PPAR γ and C/EBP α function
Stimulation of GLP-1
Suppression of human protein tyrosine phosphatase 1B
Stimulation of the pancreatic GPR40
Reduction of intestinal glucose absorption by inhibiting α -glucosidase activity

Abbreviations: AMPK, 5' adenosine monophosphate-activated protein kinase; GLP-1, glucagon-like peptide-1; GLUT-4, glucose transporter type 4; GPR40, G protein-coupled receptor 40.

Berberine and insulin resistance

In 3T3-L1 adipocytes, with insulin resistance, berberine could inhibit IKB kinase beta (IKK β) Ser(181) and IRS-1 Ser(307) phosphorylation, and could progress glucose transport induced by insulin and rebound insulin resistance due to free fatty acids.³⁶ It also improves insulin sensitivity by upregulating IRS-2 mRNA expression in the expression of PPAR- α / δ and decreases the expression of PPAR- γ in the liver of diabetic rat³⁷ and is also related to the suppression of adipocyte differentiation.³⁸ Also, berberine enhances insulin sensitivity by reducing the homeostatic model assessment-insulin resistance value up to 50%.³⁴

Antihyperlipidemic activity of berberine

Berberine stabilizes low-density lipoprotein (LDL)-R mRNA by reducing the LDL-R mRNA 3' UTR binding of heterogeneous nuclear ribonucleoprotein I and KH-type splicing regulatory protein, which are key modulators of LDL-R mRNA stability in liver cells.³⁹ Berberine also enhances the transcriptional activity of LDL-R promoter by c-Jun N-terminal kinase (JNK) pathway⁴⁰ and reduces the transcription of the PCSK9 gene, the product of which induces LDL-R degradation.⁴¹ Furthermore, berberine decreases the activities of PPAR- γ , fatty acid synthase, acetyl-CoA carboxylase, acyl-CoA synthase and lipoprotein lipase.⁴² Also, berberine decreases lipid profiles by improving the liver function and bile acid secretion, and polyphenolic compound in barberry juice can justify the positive effects on lipid profiles.⁴³

Antihypertensive and endothelium protection effects of berberine

The effects of berberine on vasodilation of vessels has been shown in different rat models.^{44,45} Berberine affects both endothelium and vascular smooth muscle. The vasorelaxant effect of berberine is endothelium dependent at low concen-

trations ($<1 \times 10^6$ M), but endothelium independent at higher concentrations.^{46,47} Barberry juice contains some vasodilator factors such as berberine, this substance effects on the central nervous system and reduce blood pressure.⁴³ Regarding the possible mechanism of barberry on blood pressure, it is suggested that barberry may induce the production of nitric oxide and, thus, vasodilatation.⁴⁸ Berberine enhances the expression of endothelial nitric oxide synthase mRNA and suppresses the expression of inducible nitric oxide synthase mRNA in gastric tissue⁴⁹ and inhibits angiotensin converting enzyme.⁵⁰

Berberine-induced endothelium-independent relaxation appears to occur by the activation of tetrapentylammonium-4-aminopyridine- and Ba(2+)-sensitive K(+) channels, inhibition of intracellular Ca(2+) release from caffeine-sensitive pools or as a direct relaxant effect.⁴⁶

In rat models, the nephroprotective effect of berberine was shown to reduce hypertension.⁴⁰ Berberine preserved endothelial functions by maintaining the reactive and elastic features of vessels. In this connection, berberine suppresses platelet-derived growth factor (PDGF)-induced vascular smooth muscle cell growth by activating AMPK/p53/p21

Table 2 Clinical efficacy of barberry

Author (publication year) Country	Patient (number)	Study design	Intervention	Duration	Results Significant reduction ($P < 0.05$)
Lazavi et al (2018) ⁴³ Iran	Patients with type 2 diabetes (n=45)	Randomized clinical trial	200 mL of barberry juice/day	8 weeks	FBG, TC, blood pressure: both systolic and diastolic, TGs
Zilaei et al (2015) ⁴⁸ Iran	Subjects with metabolic syndrome (n=106)	Double-blind controlled trial	200 mg (capsule) three times per day	6 weeks	FBG, BMI, blood pressure: both systolic and diastolic
Ilooni Kashkooli et al (2015) ⁵⁴ Iran	Patients with NAFLD (n=80), including 32 males and 48 females	Case and control	Case group received two capsules (750 mg) every day	3 months	Weight, TGs and TC
Li et al (2015) ⁵⁵ China	Rat model of metabolic syndrome (n=20)	Randomized clinical trial	Case group received 50 mg/kg/day berberine	16 weeks	p38 MAPK, ATF-2 and MMP-2
Moazezi and Qujeq (2014) ⁵⁶ Iran	Patients with type 2 diabetes (n=30)	Double-blind controlled trial	1 mg barberry extracts (capsule) two times per day	8 weeks	FBG, HbA1c
Pérez-Rubio et al (2013) ⁵⁷ USA	Patients with a diagnosis of metabolic syndrome (n=24)	Double-blind controlled clinical trial	Twelve patients received 500 mg berberine three times daily and 12 patients received placebo	3 months	Waist circumference, SBP, TGs and total insulin secretion
di Pierro et al (2012) ¹⁸ Italy	Patients with suboptimal glycemic control (n=22)	Pilot clinical trial	An oral tablet containing 588 mg of <i>Berberis aristata</i> extract titrated as 85% berberine and 105 mg of <i>Silybum marianum</i> extract titrated as 60% flavonolignans	90 days	HbA1c, TC, LDL-C, TGs, basal insulin, HOMA-R
Hu and Davies (2010) ²⁶ USA	Nine-week-old C57BL/6J male mice (n=36)	Randomized clinical trial	Group 1: normal diet with 3 mg/kg/day berberine Group 2: subgroup 1: high-fat diet; subgroups 2–4: high-fat diet mice treated with 0.75, 1.5, 3 mg/kg/day berberine, respectively	36 days	Weight gain and food intake, serum glucose, TG and TC. Also, downregulation of PPAR- γ expression and upregulation of GATA-3 expression
Ebrahimi-Mamaghani et al (2009) ⁵⁸ Iran	Patients with type 2 diabetes (n=57)	Randomized controlled clinical trial	–	8 weeks	LDL-c and TC/HDL-c ratio
Yin et al (2009) ³⁴ China	Patients with type 2 diabetes (n=36)	Randomized clinical trial	500 mg berberine three times daily	3 months	HbA1c, FBG, postprandial blood glucose and TGs

Abbreviations: ATF-2, activating transcription factor 2; BMI, body mass index; FBG, fasting blood glucose; HbA1c, hemoglobin A1c; HDL-c, high-density lipoprotein-cholesterol; HOMA-R: homeostatic model assessment-insulin resistance; LDL-c, low-density lipoprotein-cholesterol; MMP-2, matrix metalloproteinase 2; NAFLD, nonalcoholic fatty liver disease; TC, total cholesterol; TGs, triglycerides.

(Cip1) signaling and Ras/Rac1/Cyclin D/Cdks and inhibiting PDGF-stimulated migration by Rac1 and also inhibiting Cdc42, resulting in antiproliferative and antimigratory activity.⁵¹ Berberine suppresses the synthesis of fibronectin and collagen by p38 MAPK pathway⁴⁰ and prevents the migration and regrowth of smooth muscle cells via inactivating mitogen-activated protein kinase/extracellular signal regulated kinase/early growth response gene 1 (MEK1/2/ERK/Egr1 signaling pathway) and decreasing Erg1, cFos, cyclin-D and PDGF-A levels.⁵² Lysophosphatidylcholine-stimulated vascular smooth muscle cell proliferation and migration is inhibited by activation of ERK1/2 pathway (one of the three MAPK groups).⁵³

In Table 2, some human and animal studies related to the effect of berberine and barberry in obesity and MetS are summarized. Some clinical trials used berberine and some used barberry juice. Most of the studies that explained the molecular mechanisms were conducted in animal models and the molecular mechanisms in humans are not explained.

Conclusion

According to this study, berberine as a major antioxidant component of *B. vulgaris*, suppresses adipocyte differentiation and decreases obesity. Also, it regulates glucose metabolism via decreasing insulin resistance and increasing insulin secretion. Berberine also has antihyperlipidemic and antihypertensive effects and protects the endothelium, thereby reducing the risk factors of MetS. In conclusion, *B. vulgaris* may be effective in treatment of obesity and MetS, but more human clinical trials are needed to judge about its effectiveness in this issue because most of the studies explaining the molecular mechanisms were conducted in animal models. Also, some clinical trials used berberine and some others used barberry juice, so we suggest that studies should be conducted to compare the efficacy of berberine and barberry juice. We do not know whether these effects of berberine are dose dependent or not; therefore, to clarify the effective doses, more studies are needed.

The perspective studies work on the isolation or neo-synthesis of berberine analogs with a higher bioavailability. The scientist can then clarify the mechanism of action of berberine on glucose and lipid metabolism. The possible action of berberine is as a modulator of a gene involved in more processes or as a gene regulator (eg, the upstream stimulatory factors). Anyway, the effect of berberine on PCSK9 modulation is another potential therapeutic target, because berberine strengthens the effects of available antihyperlipidemic drugs. The antihyperlipidemic and antidiabetic effects of berberine

are studied through improvement in organ damage in humans (ie, by evaluating their effect on microalbuminuria or arterial stiffness).

Disclosure

The authors report no conflicts of interest in this work.

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