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

Safieh Firouzi1,2,*
Mahsa Malekahmadi1,2,*
Majid Ghayour-Mobarhan1,3
Gordon Ferns4
Hamid Reza Rahimi3,5

1Metabolic Syndrome Research Center, Mashhad University of Medical Sciences, Mashhad, Iran;
2Student Research Committee, Mashhad University of Medical Sciences, Mashhad, Iran;
3Department of Modern Sciences and Technology, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran;
4Department of Medical Education, Brighton and Sussex Medical School, University of Brighton Falmer Campus, Brighton, UK;
5Neurogenic Inflammation Research Center, Mashhad University of Medical Sciences, Mashhad, Iran

*These authors contributed equally to this work

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 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.

*These authors contributed equally to this work

Correspondence: Majid Ghayour-Mobarhan Khorasan Razavi, Mashad, Azadi Square, University of Pardis, Faculty of Medicine, 91777, Mashhad, Iran Tel +98 51 3800 2301 Fax +98 51 83 800 2287 Email Ghayourm@mums.ac.ir
Hamid Reza Rahimi Neurogenic Inflammation Research Center, Mashhad University of Medical Sciences, Mashhad, Iran Tel +98 51 3800 2301 Fax +98 51 83 800 2287 Email Rahimihr@mums.ac.ir

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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. 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. There are several definitions of MetS, but some of the most popular definitions are from the WHO and the National Cholesterol Education Program Adult Treatment Panel III.

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, ≥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. The International Diabetes Federation estimates that MetS affects approximately one-quarter of the world’s adult population. 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. Studies show that formulations of one-quarter of the world’s adult population 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.

**Inclusion of studies**

The keywords including “berberine”, “diabetes”, “insulin-resistance”, “glucose”, hemoglobin A1C”, “dislipidemia”, “obesity” and “atherosclerosis” were used for an electronic search strategy. All the identified studies and review articles were reviewed. The polyphenols in barberry juice have been reported to have a positive effect on lipid profiles and diabetes complications.

The chemical structure of berberine is shown in Figure 1.

**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/EBPα) and peroxisome proliferator-activated receptor γ (PPARγ). The PPARs function as lipid sensors and regulate lipid and lipoprotein metabolism, glucose homeostasis, adipocyte proliferation and differentiation. C/EBPα-deficient cells are capable of adipocyte differentiation and are also insulin resistant. It has been discovered that GATA factors play a role in adipogenesis. GATA-2 and GATA-3 are expressed in adipocyte precursors and control the preadipocyte to adipocyte transition. Berberine reduces the expression of C/EBPα and PPARγ and it has been shown to inhibit

![Image](https://example.com/image.png)

**Figure 1 Chemical structure of berberine.**
the differentiation of 3T3-L1 cells in murine-derived pre-adipocytes and human white preadipocytes.\textsuperscript{26} Furthermore, berberine increases the expression of GATA-2 and GATA-3 and these suppress adipocyte differentiation.\textsuperscript{24} This mechanism is directly through binding to the PPAR\(\gamma\) promoter and suppression of basal activity of PPAR\(\gamma\). Also, GATA-2 and GATA-3 form a protein complex with C/EBP\(\alpha\) that suppresses the transcriptional activity of PPAR\(\gamma\).\textsuperscript{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.\textsuperscript{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 tissue 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.\textsuperscript{28}

Several studies have shown that berberine regulates TG, cholesterol and glucose metabolism via AMP-activated protein kinase (AMPK) expression,\textsuperscript{29} an important regulator of lipolysis in adipose tissue. Hormone-sensitive lipase and adipose TG lipase are phosphorylated by AMPK.\textsuperscript{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\(\gamma\) and C/EBP\(\alpha\) function,\textsuperscript{32} activating the AMPK pathway and increasing glycokine activity. Berberine stimulates pancreatic G protein-coupled receptor 40 (GPR40), reduces intestinal glucose absorption by inhibiting \(\alpha\)-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.\textsuperscript{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-alpha (HNF-4\(\alpha\)) and glycokine activity; this provides an insulinoergic effect different from sulfonylureas.\textsuperscript{35}

### Table 1 Glycemic control mechanisms of berberine

| Mechanism                                           | Description                                                                 |
|-----------------------------------------------------|-----------------------------------------------------------------------------|
| Upregulation of GLUT-4                             | Berberine increases the expression of GLUT-4, which stimulates glucose uptake |
| Activation of AMPK                                  | Berberine activates AMPK, an important regulator of lipolysis in adipose tissue |
| Suppression of adipogenesis by inhibiting PPAR\(\gamma\) and C/EBP\(\alpha\) function | Berberine inhibits PPAR\(\gamma\) and C/EBP\(\alpha\) function, reducing lipolysis |
| Suppression of human protein tyrosine phosphatase 1B | Berberine inhibits this enzyme, which dephosphorylates proteins  |
| Stimulation of GLP-1                                | Berberine stimulates GLP-1, which is a secretagogue for insulin secretion |
| Stimulation of the pancreatic GPR40                 | Berberine activates GPR40, which stimulates GLP-1 expression |
| Reduction of intestinal glucose absorption by inhibiting \(\alpha\)-glucosidase activity | Berberine inhibits \(\alpha\)-glucosidase activity, reducing glucose absorption |

### 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.\textsuperscript{39} Berberine also enhances the transcriptional activity of LDL-R promoter by c-Jun N-terminal kinase (JNK) pathway\textsuperscript{40} and reduces the transcription of the PCSK9 gene, the product of which induces LDL-R degradation.\textsuperscript{41} Furthermore, berberine decreases the activities of PPAR-\(\gamma\), fatty acid synthase, acetyl-CoA carboxylase, acyl-CoA synthase and lipoprotein lipase.\textsuperscript{42} Also, berberine decreases lipids profiles by improving the liver function and bile acid secretion, and polyphenolic compound in barberry juice can justify the positive effects on lipid profiles.\textsuperscript{43}

### Antihypertensive and endothelium protection effects of berberine

The effects of berberine on vasodilation of vessels has been shown in different rat models.\textsuperscript{44,45} Berberine affects both endothelium and vascular smooth muscle. The vasorelaxant effect of berberine is endothelium dependent at low concen-
trations (<1×10^6 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 factors such as berberine, this substance effects on the conversion of cytochrome P450 into cytochrome P450, converting enzyme.50

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)34     | 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 |
| Ziae et al (2015)39       | 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 |
| Ilooon Kashkooli et al (2015)44 | 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)33         | 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 |
| Mojdeh Moazzemi and Qujeq (2014)46 | 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 |
| Continetti et al (2012)18 | Italy   | Patients with suboptimal glycemic control (n=22) | Pilot clinical trial | An oral tablet containing 588 mg of Berberis aristata extract titered as 85% berberine and 105 mg of Silybum marianum extract titered 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 | Group1: 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)18 | 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)38        | China   | Patients with type 2 diabetes (n=36) | Randomized controlled 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.
stimulated vascular smooth muscle cell proliferation and inhibiting PDGF-stimulated migration by Rac1 and also inhibiting Cdc42, resulting in antiproliferative and antimigratory activity. Berberine suppresses the synthesis of fibronectin and collagen by p38 MAPK pathway 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. Lysophosphatidylcholine-stimulated vascular smooth muscle cell proliferation and migration is inhibited by activation of ERK1/2 pathway (one of the three MAPK groups).

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 berbeine 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 anti-hyperlipidemic 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 berbeine and some others used barberry juice, so we suggest that studies should be conducted to compare the efficacy of berbeine 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 (e.g. 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 anti-hyperlipidemic and anti-diabetic effects of berberine are studied through improvement in organ damage in humans (i.e., by evaluating their effect on microalbuminuria or arterial stiffness).

Disclosure

The authors report no conflicts of interest in this work.

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