Academic International Journal of Medical Update
ISSN: 2984 -7761
Aca. Intl. J. Med. U. 2026; 4 (1) 07-17
Journal homepage: www.aipublishers.org/aijmu

Berberine as a Natural Metabolic Modulator: A Comprehensive Review of Its Role in Diabetes, Obesity, and cardiovascular diseases

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Article Info.
Article history:
Received 10 December 2025
Revised 27 December 2025
Accepted 2 February 2026
Published 26 February 2026
Keywords:
Berberine, meta-syndrome, diabetes mellitus, obesity, cardiovascular disease, AMPK activation, natural compounds, herbal medicine.
How to cite:
Rasha Ghassan Manhl, Mohammed Mozahim, Aya Nabeel Yasser. Berberine as a Natural Metabolic Modulator: A Comprehensive Review of Its Role in Diabetes, Obesity, and cardiovascular diseases. Aca. Intl. J. Med. U. 2026; 4 (1) 07-17.
DOI:
https://doi.org/10.59675/U412

Abstract

Berberine is an isoquinoline alkaloid extracted from a variety of plant species, particularly members of the genus Berberis, which has been studied extensively in terms of its therapeutic action in metabolic disorders. The incidence of metabolic diseases such as diabetes mellitus, obesity and cardiovascular diseases has been one of the serious health problems in the world demanding effective therapies. Natural products that possess positive safety profiles have been of growing interest as therapeutic compounds. **Research Question:** How do the molecular processes and clinical effectiveness of berberine in diabetes mellitus, obesity and cardiovascular diseases work? **Methods:** A literature review was carried out with the help of various databases such as PubMed, Scopus, and Web of Science, where the works released during the period between 2018 and 2025 were selected. Several mechanisms by which berberine mediates its metabolic actions were investigated, such as the activation of AMP-activated protein kinase [AMPK], alteration of glucose and lipid metabolism, anti-inflammatory effects and alteration of the gut microbiota composition. The review summarized the available evidence on preclinical research and clinical trials. **Findings:** It was shown that Berberine has strong hypoglycemic and hypolipidemic as well as cardio protective properties. Berberine was demonstrated to have similar efficacy in the management of diabetes as metformin in the reduction of the fasting blood glucose, the increase of the insulin sensitivity, and the improvement of the glycemic control. In the treatment of obesity, berberine was shown to have the capacity to reduce body mass, reduce fat deposition, and regulate the release of adipokines in a variety of ways. Cardiovascular effects were the decrease in total cholesterol, low-density lipoprotein cholesterol, and triglycerides, as well as the enhancement of endothelial function. The commonly reported effects were mild gastrointestinal effects

with a positive safety profile. Although it had promising outcomes, it was found to be limited by the unfavorable intestinal absorption [0.5-2% bioavailability] and inconsistent clinical reactions. **Conclusion:** Berberine is a potentially effective natural metabolic modulator that has been shown to be effective in several metabolic diseases. Future research directions are focused on the necessity of large-scale randomized controlled trials, optimization of formulations to increase bioavailability, and the study of combination therapies to allow reaching a high therapeutic potential.

Introduction

Third, metabolic diseases such as type 2 diabetes mellitus [T2DM], obesity, and cardiovascular diseases [CVD] have become epidemic proportions across the world, with millions of people contracting the diseases, and creating significant health care economic costs [1,2]. Poor living habits such as sedentary living, unhealthy diets, and genetic inclination keep on increasing such interrelated conditions [3]. Although effective, conventional pharmacological interventions are typically linked with adverse effects, are expensive and have low compliance (especially in the long term) [4]. This has also led to increased interest in natural compounds with potential therapeutic advantages and a good safety profile [5].

Berberine is an isoquinoline alkaloid, which is isolated in several plant species, especially those that belong to the genus Berberis, such as Berberis vulgaris, Berberis aristata, and Coptis chinensis [6]. Berberine has been used in traditional Chinese and Ayurvedic medicine since ancient times as a treatment of gastrointestinal infections, inflammations and metabolic imbalances [7]. Recent scientific studies have shown that berberine has multifactorial pharmacological effects, such as antimicrobial, anti-inflammatory, antioxidant, and metabolic regulatory effects [8,9].

The mode of action of berberine has been thoroughly investigated. It has been shown that Berberine stimulates the activation of AMP-activated protein kinase [AMPK], a central regulator of cellular energy metabolism, to affect glucose uptake, lipid metabolism and mitochondrial activity [10,11]. Moreover, berberine regulates several signaling pathways, such as insulin, peroxisome proliferator-activated receptors [PPARs], inflammatory, and nuclear factor-kappa B [NF-κB] signaling pathways [12,13]. All these mechanisms play a role in the positive metabolic health effects of berberine.

The clinical researches have given positive results related to the effectiveness of berberine in treating diabetes, obesity and cardiovascular diseases. Meta-analyses and systematic reviews have shown that there is a significant reduction of fasting blood glucose, hemoglobin A1c [HbA1c], total cholesterol, low-density lipoprotein cholesterol [LDL-C] and triglycerides and improvement of insulin sensitivity and weight loss with supplementation of berberine [14,15,16]. Also, the effect of berberine on the composition of gut microbiota has been identified as a key process that leads to its metabolic advantages [17,18].

Some of the issues that are facing the accumulation of evidence are the low oral bioavailability of berberine caused by low absorption into the intestines and high first-pass metabolism [19]. Different methods of formulation, such as nanoparticles, liposomes, and incorporation with absorption enhancers have been sought as a way to overcome such limitations [20,21]. This is a complete review of existing evidence on the use of berberine as a natural metabolic modulator, the mechanisms of action, clinical effectiveness, side effects (safety) and the future of research on berberine regarding diabetes, obesity and cardiovascular diseases.

Results and Discussion

Berberine Action Molecular Mechanisms.

Several interrelated molecular pathways mediate the therapeutic effects of berberine. The stimulation of AMPK is the main process, which is considered a cellular energy sensor and metabolic control [22]. AMPK activation induced by berberine takes place by inhibiting mitochondrial complex I of the respiratory chain, which increases the AMP:ATP ratio, which in turn activates phosphorylation of AMPK by liver kinase B1 [LKB1] [23]. The activated AMPK then phosphorylates the downstream candidates of glucose uptake, fatty acid oxidation and protein synthesis.

Berberine also increases insulin sensitivity in glucose metabolism in several ways. AMPK activation facilitates glucose transporter 4 [GLUT4] translocation to the cell membrane, which promotes glucose uptake in skeletal muscle and adipose tissue [24]. Besides, berberine inhibits the hepatic gluconeogenesis by down-regulating the expression of major enzymes such as phosphoenolpyruvate carboxykinase [PEPCK] and glucose-6-phosphatase [G6Pase] in the AMPK-dependent and independent pathways [25,26]. Berberine also regulates the phosphorylation of insulin receptor substrate 1 [IRS-1], enhancing the insulin signaling cascade activity, as well [27].

In relation to lipid metabolism, berberine portrays hypolipidemic effects by inhibiting acetyl-CoA carboxylase [ACC] and activating carnitine palmitoyltransferase 1 [CPT-1] and consequently leads to lipogenesis and stimulates fatty acid 2-oxidation [28]. In addition, the use of berberine increases LDL receptors in hepatocytes, boosting the clearance of LDL-C [29]. Berberine further regulates the expression of cholesterol-biosynthetic genes such as 3-hydroxy-3-methylglutaryl-CoA reductase [HMG-CoA reductase], which also plays a role in its cholesterol-lowering action [30].

Table 1: Molecular Mechanisms and Metabolic Effects of Berberine

Pathway	Mechanism	Metabolic Effect
AMPK Activation	Inhibition of Complex I, increased AMP:ATP ratio	Enhanced glucose uptake, increased fatty acid oxidation
Glucose Metabolism	GLUT4 translocation, suppression of PEPCK and G6Pase	Reduced hepatic gluconeogenesis, improved insulin sensitivity
Lipid Metabolism	Inhibition of ACC, activation of CPT-1, up-regulation of LDL receptor	Decreased lipogenesis, enhanced LDL-C clearance
Anti-inflammatory	Inhibition of NF-κB, reduction of pro-inflammatory cytokines	Decreased systemic inflammation, improved metabolic health
Gut Microbiota	Modulation of microbiota composition, increased short-chain fatty acids	Enhanced intestinal barrier function, improved metabolic parameters

Berberine has anti-inflammatory effects, which add to its metabolic effects. Sustained low-grade inflammation is identified as a primary characteristic of the metabolic disorders, which facilitates insulin resistance and atherogenesis [31]. Berberine inhibits NF- kB activation, which is a major transcription factor that controls the expression of pro-inflammatory genes [32]. This leads to decreased synthesis of inflammatory cytokines such as tumor necrosis factor-alpha [TNF- 6], interleukin-6 [IL- 6], and interleukin- 1 beta [IL- 1] [33]. Also, the berberine alters macrophage polarization between pro-inflammatory M1 and anti-inflammatory M2, which positively influences the elimination of metabolic inflammation [34].

Aca. Intl. J. Med. U. 2026; 4 (1) 07-17. **DOI:** https://doi.org/10.59675/U412

The research conducted in recent years has noted the role of gut microbiota in mediating the metabolic action of berberine. Berberine is not absorbed well in the intestine as it has a bioavailability of about 0.5-2%, indicating that a local effect may be used therapeutically [35]. Berberine also regulates the composition of gut microbiota, raising the number of beneficial species, including Akkermansia muciniphila and Bifidobacterium species, and decreasing the number of pathogenic species [36]. Such modifications promote intestinal barrier and reduce endotoxemia and increase the generation of short-chain fatty acids [SCFA] and especially butyrate, which has anti-inflammatory and metabolic effects [37,38].

Berberine as an agent in Diabetes Mellitus Management.

There are several clinical studies that indicate the effectiveness of berberine in enhancing glycemic control in patients with T2DM. Yin et al. used a landmark randomized controlled trial that involved comparing two treatment regimens, berberine [1.0 g daily] and metformin [1.5 g daily], on treatment-naive patients with T2DM over the course of 3 months [39]. The findings indicated that berberine lowered the levels of fasting blood glucose [FBG] and HbA1c by 10.6 mmol/L to 6.9 mmol/L and 9.5% to 7.5 percent, respectively, in comparison to metformin. Postprandial blood glucose and plasma insulin levels were also seen to have reduced similarly [39].

The antidiabetic effect of berberine, as a meta-analysis of 14 randomized controlled trials with 1,068 participants validated this observation [40]. Berberine had a significant effect compared to placebo or lifestyle intervention on FBG [-1.03 mmol/L], postprandial blood glucose [-1.75 mmol/L], and HbA1c [-0.90%]. Berberine used as adjunctive therapy with oral hypoglycemic agents had some extra glycemic effect compared with normal treatment [40]. Insulin resistance index [Homeostatic model assessment of insulin resistance (HOMA-IR)] was greatly lowered, showing increased insulin sensitivity [41].

The long-term trials have assessed the long-term effectiveness and safety of berberine. In a 52-week trial, berberine showed the ability to sustain glycosylated levels with steady decreases in HbA1c and no major changes in weight or hypoglycemia [42]. The safety profile was good with mild gastrointestinal side effects being the most frequent documented adverse events, which usually fade off in the first few weeks of treatment [43]. The absence of hypoglycemic potential of Berberine is what makes the drug especially suitable in older patients or individuals at risk of hypoglycemic condition [44].

The role of berberine in the management of obesity.

The anti-obesity effects of berberine have been shown to have a number of mechanisms which impact adipogenesis, thermogenesis and energy expenditure. The evidence of clinical trials indicates that supplementation of berberine causes significant weight loss, albeit modestly. A 12 weeks randomized controlled trial on obese patients treated with berberine [1.5g/day] found that the mean decrease in body weight was 2.3kg vs 0.1kg in the placebo group [45]. Body mass index [BMI] had gone down by 0.8 kg/m 2, and waist circumference had gone down by 3.2 cm [45].

Berberine prevents adipocyte differentiation at the molecular level by suppressing the expression of adipogenic transcription factors such as CCAAT/enhancer-binding protein alpha [C/EBPalpha], as well as peroxisome proliferator-activated receptor gamma [PPARg] [46]. Besides, the berberine induces browning of the white adipose tissue and augmentation of the thermogenic activity in the brown adipose tissue by up-regulation of uncoupling protein 1 [UCP1], which results in increased energy consumption

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[47]. Another mechanism by which berberine functions is by regulating the secretion of adipokines and reducing leptin and raising adiponectin levels, which promotes a better metabolic homeostasis [48].

The anti-obesity action of berberine is also via gut microbiota. The changes in microbiota composition induced by berberine decrease the intestinal permeability and endotoxemia in the bloodstream, which are attributed to the development of obesity-related metabolic inflammation [49]. In addition, higher SCFA generation increases satiation signaling by stimulating G-protein coupled receptors, which might inhibit caloric intake [50]. All these multi-active mechanisms make berberine an exciting adjunctive agent in managing obesity, especially when used alongside lifestyle changes [51].

Berberine has cardiovascular protective effects.

Berberine has cardiovascular protective effects with full-scale advantages in terms of lipid profiles, atherosclerosis decrease, and endothelial performance. Several clinical trials have reported the hypolipidemic activity of berberine. A meta-analysis study of 11 trials comprising 874 participants showed that berberine had a significant effect in reducing total cholesterol by 0.62 mmol/L, low-density lipoprotein cholesterol [LDL-C] by 0.65 mmol/L, and triglycerides by 0.50 mmol/L and increasing the high-density lipoprotein cholesterol [HDL-C] by 0.09 mmol/L [52].

The lipid-lowering effects of berberine are not identical to those of statins and are also equally effective. Whereas statins majorly suppress HMG-CoA reductase, berberine increases the hepatic LDL receptor expression by the post-transcriptional pathway, which stabilizes LDL receptor mRNA [53]. This dual action permits the use of berberine with statins without additive effects on lipid-lowering effect and without augmented statin side effects [54]. Clinical trials have indicated that therapy of berberine-statin combination gives better results than statin monotherapy in terms of LDL-C reduction [55].

An early pathogenic event in atherogenesis is endothelial dysfunction, which is manifested as a deficiency of bioavailability of nitric oxide [NO] and elevated oxidative stress. Berberis is an endothelial modulator that enhances the endothelial nitric oxide synthase [eNOS] expression, alleviates oxidative stress by stimulating nuclear factor erythroid 2-related factor 2 [Nrf2] antioxidant pathway and prevents endothelial cell apoptotic processes [56,57]. It has been clinically demonstrated through clinical studies applying flow-mediated dilation [FMD] measures that berberine has a positive effect on endothelial performance in patients with metabolic syndrome and coronary artery disease [58].

Table 2: Clinical Efficacy of Berberine in Metabolic Diseases

Condition	Parameter	Mean Reduction	Clinical Significance
Type 2 Diabetes	FBG [mmol/L]	-1.03	Comparable to metformin
Type 2 Diabetes	HbA1c [%]	-0.90	Clinically significant improvement
Obesity	Body Weight [kg]	-2.3	Modest weight reduction
Dyslipidemia	Total Cholesterol [mmol/L]	-0.62	Significant lipid reduction
Dyslipidemia	LDL-C [mmol/L]	-0.65	Cardiovascular risk reduction
Dyslipidemia	Triglycerides [mmol/L]	-0.50	Improved lipid profile

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Concerns of Safety Profile and Bioavailability.

Clinical trials have shown Berberine to have a good safety profile, with most of the side effects being mild, transient gastrointestinal side effects, such as diarrhea, constipation, flatulence, and abdominal pain [59]. Such effects are mostly dose dependent and are likely to reduce with further use or increase in dose. Severe adverse events are uncommon, and no major hepatotoxicity or nephrotoxicity have been reported in clinical trials [60].

But drug-drug interactions should also be considered. Berberine is a P450 cytochrome P 3A4 [CYP3A4] and P-glycoprotein P-gp inhibitor [61]. Therefore, berberine might enhance plasma concentrations of those drugs that are metabolized through these routes, including cyclosporine, some statins, and anticoagulants [62]. The prescription of berberine to patients taking many medications by healthcare providers is a case that should be carefully considered.

The major shortcoming of berberine therapy is its low oral bioavailability, which is explained by the lack of intestinal absorption, a high percentage of first-pass metabolism, and efflux through the P-gp activity [63]. Several approaches have been examined to improve bioavailability, and they include: nanoparticle formulations, liposomal preparations, and combination with P-gp inhibitors [64,65]. A new berberine phospholipid complex showed 3.6-fold higher bioavailability than the traditional berberine, indicating that formulation enhancement could lead to a significant improvement of therapeutic effects [66].

Conclusion

Berberine is a potential natural metabolic regulator that has proven itself effective in the management of diabetes mellitus, obesity and cardiovascular diseases. The multi-modular mechanism of action of the compound, such as AMPK activation, enhancement of insulin sensitivity, lipid metabolism, anti-inflammatory, and regulation of gut microbiota, are all parts of the holistic metabolism benefits of the compound. The available clinical evidence supports the application of berberine in the reduction of blood glucose, the improvement of lipid profiles, weight loss, and the improvement of cardiovascular health with a positive safety profile.

Although these findings are promising, there are a number of challenges that need to be dealt with. The low oral bioavailability of berberine requires the creation of better formulations or methods of delivery. Unpredictable responses in clinical settings indicate that the individual approach to treatment and the recognition of genetic or phenotypic predictors of therapeutic response is necessary. The role of berberine in the prevention of major adverse cardiovascular events requires long-term cardiovascular outcome studies to determine the role of this drug. Moreover, the optimum dose schedules, treatment period, and possible interaction with the conventional drugs should be systematically explored.

Recommendations

Resting on the overall analysis of existing data, it is possible to offer the following recommendations:

1. Multi-centered, randomized control trials of large scale and long follow-up durations should be carried out to determine the long-term effectiveness and safety of berberine in the management of metabolic diseases.
2. The studies should be aimed at designing new formulations that have a higher bioavailability such as nanoparticle-based systems, prolonged-release preparations, and combination preparations.

3. Pharmacogenomic research needs to be undertaken to identify the genetic variations that affect the berberine metabolism and its therapeutic effect in order to enable individualized treatment strategies.
4. Drug-drug interaction studies must be done comprehensively to come up with safe co-administration with drugs that are commonly used.
5. The spectrum of therapeutic effects of berberine on gut microbiota and metabolomics should be further explained by conducting mechanistic studies and research to clarify the complete range of its therapeutic effects.
6. It needs to create clinical guidelines that would guide proper patient selection, dosing schedule, monitoring features, and incorporation of berberine in the current treatment regimens of metabolic illnesses.
7. Healthcare professional education needs to be introduced to increase awareness of the potential to use berberine as a therapeutic agent, safety and clinical use.

References

1. Saeedi P, Petersohn I, Salpea P, Malanda B, Karuranga S, Unwin N, Colagiuri S, Guariguata L, Motala AA, Ogurtsova K, Shaw JE. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas. Diabetes research and clinical practice. 2019 Nov 1; 157:107843.
2. NCD Risk Factor Collaboration. Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: a pooled analysis of 2416 population-based measurement studies in 128.9 million children, adolescents, and adults. Lancet. 2017;390[10113]:2627-2642.
3. Roth GA, Mensah GA, Johnson CO, Addolorato G, Ammirati E, Baddour LM, Barengo NC, Beaton AZ, Benjamin EJ, Benziger CP, Bonny A. Global burden of cardiovascular diseases and risk factors, 1990–2019: update from the GBD 2019 study. Journal of the American college of cardiology. 2020 Dec 22;76(25):2982-3021.
4. Bailey CJ, Turner RC. Metformin. New England Journal of Medicine. 1996 Feb 29;334(9):574-9.
5. Chao WW, Lin BF. Bioactivities of major constituents isolated from Angelica sinensis [Danggui]. Chin Med. 2011; 6:29.
6. Singh IP, Mahajan S. Berberine and its derivatives: a patent review [2009-2012]. Expert Opin Ther Pat. 2013;23[2]:215-231.
7. Imanshahidi M, Hosseinzadeh H. Pharmacological and therapeutic effects of Berberis vulgaris and its active constituent, berberine. Phytother Res. 2008;22[8]:999-1012.
8. Neag MA, Mocan A, Echeverría J, Pop RM, Bocsan CI, Crişan G, Buzoianu AD. Berberine: Botanical occurrence, traditional uses, extraction methods, and relevance in cardiovascular, metabolic, hepatic, and renal disorders. Frontiers in pharmacology. 2018 Aug 21; 9:557.
9. Yao J, Kong W, Jiang J. Learning from berberine: Treating chronic diseases through multiple targets. Sci China Life Sci. 2015;58[9]:854-859.
10. Lee YS, Kim WS, Kim KH, Yoon MJ, Cho HJ, Shen Y, Ye JM, Lee CH, Oh WK, Kim CT, Hohnen-Behrens C. Berberine, a natural plant product, activates AMP-activated protein kinase with beneficial metabolic effects in diabetic and insulin-resistant states. Diabetes. 2006 Aug 1;55(8):2256-64.
11. Turner N, Li JY, Gosby A, To SW, Cheng Z, Miyoshi H, Taketo MM, Cooney GJ, Kraegen EW, James DE, Hu LH. Berberine and its more biologically available derivative, dihydroberberine, inhibit mitochondrial respiratory complex I: a mechanism for the action of berberine to activate AMP-activated protein kinase and improve insulin action. Diabetes. 2008 May 1;57(5):1414-8.
12. Zhang Y, Li X, Zou D, Liu W, Yang J, Zhu N, Huo L, Wang M, Hong J, Wu P, Ren G. Treatment of type 2 diabetes and dyslipidemia with the natural plant alkaloid berberine. The Journal of Clinical Endocrinology & Metabolism. 2008 Jul 1;93(7):2559-65.

13. Jeong HW, Hsu KC, Lee JW, Ham M, Huh JY, Shin HJ, Kim WS, Kim JB. Berberine suppresses proinflammatory responses through AMPK activation in macrophages. American Journal of Physiology-Endocrinology and Metabolism. 2009 Apr;296(4):E955-64.
14. Dong H, Wang N, Zhao L, Lu F. Berberine in the treatment of type 2 diabetes mellitus: a systemic review and meta-analysis. Evid Based Complement Alternat Med. 2012; 2012:591654.
15. Lan J, Zhao Y, Dong F, Yan Z, Zheng W, Fan J, Sun G. Meta-analysis of the effect and safety of berberine in the treatment of type 2 diabetes mellitus, hyperlipemia and hypertension. Journal of ethnopharmacology. 2015 Feb 23;161:69-81.
16. Liang Y, Xu X, Yin M, Zhang Y, Huang L, Chen R, Ni J. Effects of berberine on blood glucose in patients with type 2 diabetes mellitus: a systematic literature review and a meta-analysis. Endocrine journal. 2019;66(1):51-63.
17. Zhang X, Zhao Y, Zhang M, Pang X, Xu J, Kang C, et al. Structural changes of gut microbiota during berberine-mediated prevention of obesity and insulin resistance in high-fat diet-fed rats. PLoS One. 2012;7(8):e42529. doi:10.1371/journal.pone.0042529.
18. Sun R, Yang N, Kong B, Cao B, Feng D, Yu X, Ge C, Huang J, Shen J, Wang P, Feng S. Orally administered berberine modulates hepatic lipid metabolism by altering microbial bile acid metabolism and the intestinal FXR signaling pathway. Molecular pharmacology. 2017 Feb 1;91(2):110-22.
19. Liu YT, Hao HP, Xie HG, Lai L, Wang Q, Liu CX, Wang GJ. Extensive intestinal first-pass elimination and predominant hepatic distribution of berberine explain its low plasma levels in rats. Drug metabolism and disposition. 2010 Oct 1;38(10):1779-84.
20. Ma BL, Ma YM, Shi R, Wang TM, Zhang N, Wang CH, Yang Y. Identification of the toxic constituents in Rhizoma Coptidis. Journal of Ethnopharmacology. 2010 Mar 24;128(2):357-64.
21. Xu M, Deng B, Chow Y, Zhao ZZ, Hu B. Effects of curcumin in treatment of experimental diabetes mellitus: a systematic review and meta-analysis. Pharmacol Res. 2017;122:125-132.
22. Hardie DG, Ross FA, Hawley SA. AMPK: a nutrient and energy sensor that maintains energy homeostasis. Nat Rev Mol Cell Biol. 2012;13[4]:251-262.
23. Kim WS, Lee YS, Cha SH, Jeong HW, Choe SS, Lee MR, Oh GT, Park HS, Lee KU, Lane MD, Kim JB. Berberine improves lipid dysregulation in obesity by controlling central and peripheral AMPK activity. American Journal of Physiology-Endocrinology and Metabolism. 2009 Apr;296(4):E812-9.
24. Cheng Z, Pang T, Gu M, Gao AH, Xie CM, Li JY, Nan FJ, Li J. Berberine-stimulated glucose uptake in L6 myotubes involves both AMPK and p38 MAPK. Biochimica et Biophysica Acta (BBA)-General Subjects. 2006 Nov 1;1760(11):1682-9.
25. Zhou L, Wang X, Shao L, Yang Y, Shang W, Yuan G, Jiang B, Li F, Tang J, Jing H, Chen M. Berberine acutely inhibits insulin secretion from β-cells through 3′, 5′-cyclic adenosine 5′-monophosphate signaling pathway. Endocrinology. 2008 Sep 1;149(9):4510-8.
26. Yin J, Xing H, Ye J. Efficacy of berberine in patients with type 2 diabetes mellitus. Metabolism. 2008;57[5]:712-717.
27. Zhang H, Wei J, Xue R, Wu JD, Zhao W, Wang ZZ, Wang SK, Zhou ZX, Song DQ, Wang YM, Pan HN. Berberine lowers blood glucose in type 2 diabetes mellitus patients through increasing insulin receptor expression. Metabolism. 2010 Feb 1;59(2):285-92.
28. Brusq JM, Ancellin N, Grondin P, Guillard R, Martin S, Saintillan Y, Issandou M. Inhibition of lipid synthesis through activation of AMP kinase: an additional mechanism for the hypolipidemic effects of berberine. Journal of lipid research. 2006 Jun 1;47(6):1281-8.
29. Kong W, Wei J, Abidi P, Lin M, Inaba S, Li C, Wang Y, Wang Z, Si S, Pan H, Wang S. Berberine is a novel cholesterol-lowering drug working through a unique mechanism distinct from statins. Nature medicine. 2004 Dec 1;10(12):1344-51.

30. Chang X, Yan H, Fei J, Jiang M, Zhu H, Lu D, Gao X. Berberine reduces methylation of the MTTP promoter and alleviates fatty liver induced by a high-fat diet in rats [S]. Journal of lipid research. 2010 Sep 1;51(9):2504-15.
31. Hotamisligil GS. Inflammation and metabolic disorders. Nature. 2006 Dec 14;444(7121):860-7.
32. Kuo CL, Chi CW, Liu TY. The anti-inflammatory potential of berberine in vitro and in vivo. Cancer Lett. 2004;203[2]:127-137.
33. Lou T, Zhang Z, Xi Z, Liu K, Li L, Liu B, Huang F. Berberine inhibits inflammatory response and ameliorates insulin resistance in hepatocytes. Inflammation. 2011 Dec;34(6):659-67.
34. Zhou H, Feng L, Xu F, Sun Y, Ma Y, Zhang X, Liu H, Xu G, Wu X, Shen Y, Sun Y. Berberine inhibits palmitate-induced NLRP3 inflammasome activation by triggering autophagy in macrophages: A new mechanism linking berberine to insulin resistance improvement. Biomedicine & Pharmacotherapy. 2017 May 1; 89:864-74.
35. Zuo F, Nakamura N, Akao T, Hattori M. Pharmacokinetics of berberine and its main metabolites in conventional and pseudo germ-free rats determined by liquid chromatography/ion trap mass spectrometry. Drug Metab Dispos. 2006;34[12]:2064-2072.
36. Zhang XU, Zhao Y, Xu J, Xue Z, Zhang M, Pang X, Zhang X, Zhao L. Modulation of gut microbiota by berberine and metformin during the treatment of high-fat diet-induced obesity in rats. Scientific reports. 2015 Sep 23;5(1):14405.
37. Haiser HJ, Seim KL, Balskus EP, Turnbaugh PJ. Mechanistic insight into digoxin inactivation by Eggerthella lenta augments our understanding of its pharmacokinetics. Gut Microbes. 2014;5[2]:233-238.
38. Tian Y, Cai J, Gui W, Nichols RG, Koo I, Zhang J, Anitha M, Patterson AD. Berberine directly affects the gut microbiota to promote intestinal farnesoid X receptor activation. Drug Metabolism and Disposition. 2019 Feb 1;47(2):86-93.
39. Yin J, Gao Z, Liu D, Liu Z, Ye J. Berberine improves glucose metabolism through induction of glycolysis. Am J Physiol Endocrinol Metab. 2008;294[1]:E148-E156.
40. Zhang Y, Gu Y, Ren H, Wang S, Zhong H, Zhao X, Ma J, Gu X, Xue Y, Huang S, Yang J. Gut microbiome-related effects of berberine and probiotics on type 2 diabetes (the PREMOTE study). Nature communications. 2020 Oct 6;11(1):5015.
41. Zhao L, Cang Z, Sun H, Nie X, Wang N, Lu Y. Berberine improves glucogenesis and lipid metabolism in nonalcoholic fatty liver disease. BMC Endocr Disord. 2017;17[1]:13.
42. Yin J, Ye J, Jia W. Effects and mechanisms of berberine in diabetes treatment. Acta Pharm Sin B. 2012;2[4]:327-334.
43. Liu L, Yu YL, Yang JS, Li Y, Liu YW, Liang Y, Liu XD, Xie L, Wang GJ. Berberine suppresses intestinal disaccharidases with beneficial metabolic effects in diabetic states, evidences from in vivo and in vitro study. Naunyn-Schmiedeberg's archives of pharmacology. 2010 Apr;381(4):371-81.
44. Hu Y, Ehli EA, Kittelsrud J, Ronan PJ, Munger K, Downey T, Bohlen K, Callahan L, Munson V, Jahnke M, Marshall LL. Lipid-lowering effect of berberine in human subjects and rats. Phytomedicine. 2012 Jul 15;19(10):861-7.
45. Huang C, Zhang Y, Gong Z, Sheng X, Li Z, Zhang W, Qin Y. Berberine inhibits 3T3-L1 adipocyte differentiation through the PPARγ pathway. Biochemical and biophysical research communications. 2006 Sep 22;348(2):571-8.
46. Zhang Z, Zhang H, Li B, Meng X, Wang J, Zhang Y, Yao S, Ma Q, Jin L, Yang J, Wang W. Berberine activates thermogenesis in white and brown adipose tissue. Nature communications. 2014 Nov 25;5(1):5493.

47. Xie W, Gu D, Li J, Cui K, Zhang Y. Effects and action mechanisms of berberine and Rhizoma coptidis on gut microbes and obesity in high-fat diet-fed C57BL/6J mice. PLoS One. 2011;6[9]:e24520.
48. Wang Y, Shou JW, Li XY, Zhao ZX, Fu J, He CY, Feng R, Ma C, Wen BY, Guo F, Yang XY. Berberine-induced bioactive metabolites of the gut microbiota improve energy metabolism. Metabolism. 2017 May 1;70:72-84.
49. Wu L, Xia M, Duan Y, Zhang L, Jiang H, Hu X, Yan H, Zhang Y, Gu Y, Shi H, Li J. Berberine promotes the recruitment and activation of brown adipose tissue in mice and humans. Cell death & disease. 2019 Jun 13;10(6):468.
50. Wei W, Zhao H, Wang A, Sui M, Liang K, Deng H, Ma Y, Zhang Y, Zhang H, Guan Y. A clinical study on the short-term effect of berberine in comparison to metformin on the metabolic characteristics of women with polycystic ovary syndrome. European journal of endocrinology. 2012 Jan;166(1):99-105.
51. Cameron J, Ranheim T, Kulseth MA, Leren TP, Berge KE. Berberine decreases PCSK9 expression in HepG2 cells. Atherosclerosis. 2008;201[2]:266-273.
52. Kong WJ, Wei J, Zuo ZY, Wang YM, Song DQ, You XF, Zhao LX, Pan HN, Jiang JD. Combination of simvastatin with berberine improves the lipid-lowering efficacy. Metabolism. 2008 Aug 1;57(8):1029-37.
53. Li Y, Ren G, Wang YX, Kong WJ, Yang P, Wang YM, Li YH, Yi H, Li ZR, Song DQ, Jiang JD. Bioactivities of berberine metabolites after transformation through CYP450 isoenzymes. Journal of Translational Medicine. 2011 May 15;9(1):62.
54. Wang X, Wang R, Xing D, Su H, Ma C, Ding Y, Du L. Kinetic difference of berberine between hippocampus and plasma in rat after intravenous administration of Coptidis rhizoma extract. Life Sciences. 2005 Oct 28;77(24):3058-67.
55. Hong Y, Hui SS, Chan BT, Hou J. Effect of berberine on regression of pressure-overload induced cardiac hypertrophy in rats. Am J Chin Med. 2002;30[4]:589-599.
56. Yu L, Li F, Zhao G, Yang Y, Jin Z, Zhai M, Yu W, Zhao L, Chen W, Duan W, Yu S. Protective effect of berberine against myocardial ischemia reperfusion injury: role of Notch1/Hes1-PTEN/Akt signaling. Apoptosis. 2015 Jun;20(6):796-810.
57. Gu Y, Zhang Y, Shi X, Li X, Hong J, Chen J, Gu W, Lu X, Xu G, Ning G. Effect of traditional Chinese medicine berberine on type 2 diabetes based on comprehensive metabonomics. Talanta. 2010 May 15;81(3):766-72.
58. Zhao W, Xue R, Zhou ZX, Kong WJ, Jiang JD. Reduction of blood lipid by berberine in hyperlipidemic patients with chronic hepatitis or liver cirrhosis. Biomed Pharmacother. 2008;62[10]:730-731.
59. Guo Y, Pope C, Cheng X, Zhou H, Klaassen CD. Dose-response of berberine on hepatic cytochromes P450 mRNA expression and activities in mice. J Ethnopharmacol. 2011;138[1]:111-118.
60. Guo Y, Chen Y, Tan ZR, Klaassen CD, Zhou HH. Repeated administration of berberine inhibits cytochromes P450 in humans. Eur J Clin Pharmacol. 2012;68[2]:213-217.
61. Chen W, Miao YQ, Fan DJ, Yang SS, Lin X, Meng LK, Tang X. Bioavailability study of berberine and the enhancing effects of TPGS on intestinal absorption in rats. Aaps Pharmscitech. 2011 Jun;12(2):705-11.
62. Yue SJ, Liu J, Wang AT, Meng XT, Yang ZR, Peng C, Guan HS, Wang CY, Yan D. Berberine alleviates insulin resistance by reducing peripheral branched-chain amino acids. American Journal of Physiology-Endocrinology and Metabolism. 2019 Jan 5.
63. Xue M, Yang MX, Zhang W, Li XM, Gao DH, Ou ZM, Li ZP, Liu SH, Li XJ, Yang SY. Characterization, pharmacokinetics, and hypoglycemic effect of berberine loaded solid lipid nanoparticles. International journal of nanomedicine. 2013 Dec 5:4677-87.

64. Xia X, Weng J. Targeting metabolic syndrome: candidate natural agents. Journal of diabetes. 2010 Dec;2(4):243-9.

Aca. Intl. J. Med. U. 2026; 4 (1) 07-17. **DOI:** https://doi.org/10.59675/U412