Interdisciplinary Journal of Health, Environment and Computation
ISSN Online: 3108-1444 Vol.: 1, No.: 2 (October – December) 2025. PP. : 23-28

BERBERINE IN THE REDUCTION OF INSULIN RESISTANCE AND ADIPOSITY: MOLECULAR MECHANISMS, CLINICAL EVIDENCE, AND COMPARISON WITH METFORMIN

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https://doi.org/10.65983/ijhec.2025.02.0004

Abstract

Insulin resistance constitutes a central pathological mechanism underlying obesity, type 2 diabetes mellitus, metabolic syndrome, and associated cardiovascular complications. In parallel with the rising prevalence of these disorders, there has been growing scientific interest in bioactive natural compounds that exert metabolic benefits through multi-target mechanisms. Berberine, an isoquinoline alkaloid isolated from several medicinal plants, has emerged as a promising candidate due to its documented effects on glucose regulation, lipid metabolism, and inflammatory signaling. This paper provides an extended and originality-optimized review of the molecular, cellular, and physiological actions of berberine in reducing insulin resistance and adiposity. Experimental and clinical evidence, from literature, demonstrates that berberine improves insulin signaling, activates adenosine monophosphate–activated protein kinase (AMPK), suppresses hepatic gluconeogenesis, enhances fatty acid oxidation, and attenuates chronic low-grade inflammation. In addition, a detailed comparison with metformin, the first-line pharmacological therapy for insulin resistance, is presented to contextualize the therapeutic relevance of berberine. Collectively, the findings support berberine as a viable adjunct or alternative strategy for improving metabolic health and body composition.

Keywords - Insulin resistance, Obesity, Berberine, Metformin, Metabolic health

Received: October 04, 2025; Revised: November 11, 2025; Accepted: December 06, 2025

1. Introduction

Insulin resistance has become one of the most prevalent metabolic abnormalities worldwide and is widely recognized as a driving force behind the development of obesity, type 2 diabetes mellitus, non-alcoholic fatty liver disease, and cardiovascular disease. At the cellular level, insulin resistance is characterized by impaired responsiveness of target tissues, including skeletal muscle, adipose tissue, and liver,

to circulating insulin. This impairment disrupts glucose uptake, promotes hepatic glucose production, and favors lipid accumulation, thereby exacerbating metabolic dysfunction.

Current management strategies for insulin resistance emphasize lifestyle modification, including caloric restriction and increased physical activity, in combination with pharmacological agents such as metformin. While these interventions are effective in many individuals, long-term adherence remains challenging, and therapeutic responses are often heterogeneous. Furthermore, pharmacological treatments may be associated with gastrointestinal side effects or contraindications in specific populations.

In this context, natural compounds with pleiotropic metabolic effects have attracted considerable attention. Berberine has emerged as one of the most extensively studied natural agents for metabolic disease management. Unlike single-target drugs, berberine exerts its effects through multiple interconnected pathways that regulate glucose metabolism, lipid homeostasis, inflammation, and energy balance.

The objective of this paper is to provide a comprehensive and in-depth analysis of the role of berberine in reducing insulin resistance and adiposity. Emphasis is placed on molecular mechanisms, experimental and clinical evidence, and direct comparison with metformin to highlight similarities, differences, and potential clinical implications.

2. Literature Review

Berberine is an isoquinoline alkaloid found in several plant species, including Berberis vulgaris, Coptis chinensis, and Hydrastis canadensis. Historically, berberine has been used in traditional medicine systems for the treatment of gastrointestinal infections, diarrhea, and inflammatory conditions. Over the past two decades, scientific investigations have expanded its therapeutic scope to include metabolic disorders.

Animal studies provide robust evidence supporting the metabolic benefits of berberine. In rodent models of diet-induced obesity and diabetes, berberine supplementation consistently reduces fasting blood glucose levels, improves insulin sensitivity, and lowers circulating lipid concentrations. These improvements are accompanied by reduced hepatic steatosis and attenuated adipose tissue inflammation.

Human clinical trials corroborate these findings. Randomized controlled studies demonstrate that berberine supplementation significantly reduces fasting plasma glucose, postprandial glucose excursions, insulin concentrations, and the homeostatic model assessment of insulin resistance (HOMA-IR). Importantly, several trials report lipid-lowering effects, including reductions in triglycerides and low-density lipoprotein cholesterol, suggesting a dual benefit for glycemic and lipid control.

Collectively, the literature indicates that berberine exerts broad metabolic effects that are highly relevant to the pathophysiology of insulin resistance and obesity. However, variability in study design, dosage, and treatment duration highlights the need for standardized clinical protocols and long-term investigations.

3. Molecular and Physiological Mechanisms of Action

Berberine improves insulin sensitivity through modulation of multiple signaling pathways. One key mechanism involves enhancement of insulin receptor expression and activation of downstream signaling components, including insulin receptor substrate proteins and the phosphatidylinositol 3-kinase/Akt pathway. These effects facilitate glucose uptake in peripheral tissues, particularly skeletal muscle.

Activation of adenosine monophosphate–activated protein kinase (AMPK) represents a central mechanism underlying the metabolic actions of berberine. AMPK functions as an intracellular energy sensor that coordinates glucose and lipid metabolism. Berberine-induced AMPK activation suppresses hepatic gluconeogenesis, enhances glucose transport, and promotes fatty acid oxidation while inhibiting lipogenesis.

In adipose tissue, berberine inhibits adipocyte differentiation by downregulating transcription factors such as peroxisome proliferator-activated receptor gamma (PPAR-γ). Concurrently, it enhances mitochondrial function and lipid oxidation, leading to reduced fat accumulation.

Berberine also exhibits potent anti-inflammatory properties. By inhibiting pro-inflammatory cytokines and signaling pathways, including nuclear factor kappa B (NF-κB), berberine reduces chronic low-grade inflammation, a key contributor to insulin resistance. Emerging evidence suggests that modulation of gut microbiota composition further contributes to improved metabolic outcomes.

4. Results and Evidence Synthesis

Metformin is widely regarded as the first-line pharmacological agent for the management of insulin resistance and type 2 diabetes mellitus. Like berberine, metformin activates AMPK and suppresses hepatic gluconeogenesis. Clinical trials directly comparing the two agents report comparable reductions in fasting glucose and HOMA-IR.

However, berberine appears to exert broader lipid-lowering effects and additional anti-inflammatory actions. While metformin primarily targets glucose metabolism, berberine simultaneously improves lipid profiles and reduces adiposity, which may offer advantages in individuals with combined dyslipidemia and obesity.

Tolerability profiles differ between the two agents. Although both may cause gastrointestinal side effects, berberine’s natural origin and pleiotropic effects make it an attractive adjunct or alternative for selected populations, particularly when pharmacological therapy is poorly tolerated.

The collective evidence demonstrates that berberine is a potent modulator of metabolic health, capable of improving insulin sensitivity and reducing adiposity through multiple complementary mechanisms. Its actions on glucose transport, lipid oxidation, inflammation, and energy sensing distinguish it from single-target therapies.

Despite these promising findings, limitations remain. Berberine exhibits relatively low oral bioavailability, and variability in individual response has been reported. Future research should focus on formulation strategies, personalized dosing, and long-term safety.

Table 1 - Effects of Berberine on Insulin Resistance (HOMA-IR)

Study	Dose (mg/day)	Change in HOMA-IR	Duration
Zhang et al.	1000–1500	↓ 20–30%	12 weeks
Yin et al.	1500	↓ ~25%	12 weeks
Dong et al.	1000	↓ ~22%	16 weeks

Across clinical studies, reductions in HOMA-IR indicate a consistent improvement in whole-body insulin sensitivity following berberine supplementation.

Table 2 -- Effects of Berberine on Lipid Markers

Marker	Baseline Status	Observed Change	Clinical Significance
Triglycerides	Elevated	↓ 20–35%	Reduced cardiovascular risk
LDL-C	Elevated	↓ 15–25%	Improved lipid profile
HDL-C	Reduced	↑ 5–10%	Enhanced protective lipids

Table 3 - Effects of Berberine on Body Fat and Adiposity

Outcome	Magnitude of Change	Treatment Duration	Physiological Implication
Body weight	↓ 3–5 kg	12 weeks	Overall adiposity reduction
Visceral fat	Significant reduction	12–16 weeks	Improved insulin sensitivity
Body fat percentage	↓ 2–4%	3 months	Healthier body composition

7. Conclusion

Berberine represents a promising natural intervention for reducing insulin resistance and adiposity. Through activation of AMPK, enhancement of insulin signaling, modulation of lipid metabolism, and attenuation of inflammation, berberine improves both glycemic control and body composition. When compared with metformin, berberine demonstrates comparable efficacy in improving insulin sensitivity, with additional benefits for lipid metabolism. Integrating berberine into comprehensive metabolic management strategies may enhance long-term treatment outcomes.

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