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Berberine from Medicinal Plants as a Potential Therapeutic Agent for Type 2 Diabetes Mellitus: Pharmacological Mechanisms, Clinical Efficacy, and Safety

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ABSTRACT: Type 2 diabetes mellitus (T2DM) is a major metabolic disorder characterized by hyperglycemia, insulin resistance, and impaired glucose and lipid metabolism. Increasing interest in natural therapeutic agents has highlighted berberine, a bioactive is quinoline alkaloid found in several medicinal plants, because of its potential antidiabetic and metabolic effects. **Objective**: This review aims to evaluate the potential of berberine derived from medicinal plants as a therapeutic agent for T2DM, focusing on its pharmacological mechanisms, clinical efficacy, and safety. Methods: Relevant experimental studies randomized clinical trials, systematic reviews, and meta-analyses were reviewed, with emphasis on the effects of berberine on glycemic control, insulin sensitivity, lipid metabolism, inflammation, oxidative stress, and related molecular pathways, Results: Evidence suggests that berberine exerts multiple antidiabetic effects through mechanisms including activation of adenosine monophosphate-activated protein kinase (AMPK), improvement of insulin signaling, inhibition of hepatic gluconeogenesis, enhancement of glucose uptake, and regulation of lipid metabolism. Conclusion: Berberine appears to be a promising natural therapeutic candidate for T2DM due to its diverse pharmacological actions and potential benefits in glycemic and metabolic control. However, further high-quality, long-term clinical trials are needed to establish optimal dosage, formulation, efficacy, and long-term safety.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a complex and progressive metabolic disorder characterized primarily by insulin resistance, impaired pancreatic β-cell function, and persistent hyperglycemia. It is associated with abnormalities in glucose and lipid metabolism and represents a major global health challenge because of its increasing prevalence and the development of long-term microvascular and macrovascular complications. Although several effective pharmacological therapies are currently available, limitations related to adverse effects, treatment response, cost, and the progressive nature of the disease have increased interest in complementary and naturally derived therapeutic agents (Xie et al. 2022).

Berberine is a naturally occurring quinoline alkaloid found in several medicinal plants, particularly species belonging to the genera Berberis and Coptis **(Figure 1).** It has traditionally been used in various systems of medicine and has attracted considerable scientific interest because of its broad pharmacological activities. Experimental and clinical studies have demonstrated that berberine may influence glucose and lipid metabolism, insulin sensitivity, inflammation, oxidative stress, and

intestinal microbial composition, suggesting that its effects may extend beyond simple glucose lowering (Khoshandam et al. 2022; Dong et al. 2012).

Several molecular mechanisms have been proposed to explain the antidiabetic effects of berberine. These include activation of adenosine monophosphate-activated protein kinase (AMPK), modulation of insulin-signaling pathways, inhibition of hepatic gluconeogenesis, enhancement of glucose utilization, and regulation of lipid metabolism. Such multiple mechanisms are particularly relevant to T2DM, which involves several interconnected metabolic abnormalities rather than a single pathological pathway (Bray et al. 2021).

BERBERINE POWDER

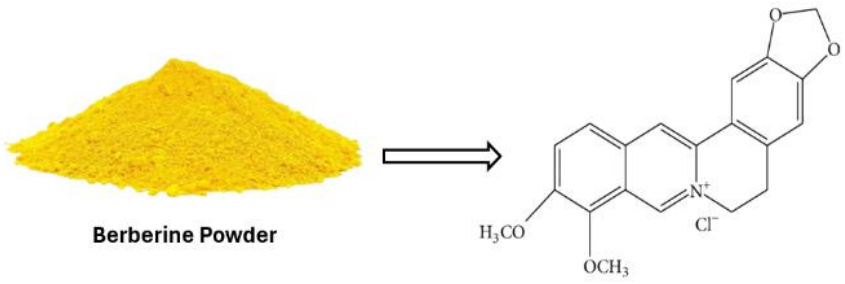

Figure 1. Berberine Powder: Chemical Form and Molecular Structure. The figure shows berberine in powder form and its corresponding chemical structure.

Clinical evidence has increasingly supported the potential therapeutic value of berberine. A systematic review and meta-analysis of 37 randomized controlled trials involving 3,048 patients found that berberine significantly reduced fasting plasma glucose, glycated hemoglobin (HbA1c), and 2-hour postprandial blood glucose. The analysis also found no significant increase in the risk of hypoglycemia. More recently, a 2024 systematic review and meta-analysis evaluated randomized controlled trials of berberine administered alone or in combination with other interventions, providing further evidence regarding its potential efficacy and safety in T2DM (Wang et al. 2024).

Despite these encouraging findings, important questions remain regarding the variability of berberine preparations, optimal dosage, bioavailability, duration of treatment, long-term safety, and its position relative to established antidiabetic therapies. Therefore, a comprehensive evaluation of the available evidence is necessary to clarify the therapeutic potential of berberine derived from medicinal plants. Accordingly, this review aims to examine the pharmacological mechanisms, clinical efficacy, and safety of berberine in the management of T2DM, while highlighting current evidence, limitations, and future research directions.

BERBERINE FROM MEDICINAL PLANTS

Berberine is a naturally occurring quinoline alkaloid that is widely distributed among several medicinal plants. It is particularly abundant in plants belonging to the families Burseraceae, Ranunculaceae, and Papaveraceae. Important botanical sources include Berberis vulgaris, Berberis aristata, Coptic chinensis, and Philodendrons ameens. Among these, species of the genus Berberis and Coptic are considered important natural sources of berberine and have a long history of use in traditional medicine (Khoshandam et al. 2022).

Berberis vulgaris (barberry) **(Figure 2),** is one of the best-known medicinal plants containing berberine. Its roots, bark, and other plant parts contain several alkaloids, with berberine representing an important bioactive constituent. Traditional preparations of B. vulgaris have been used for various metabolic and inflammatory conditions. Recent reviews have also documented the antioxidant, anti-inflammatory, and immunomodulatory properties of both B. vulgaris and its constituent berberine (Shakeri et al. 2024; Fan et al. 2025).

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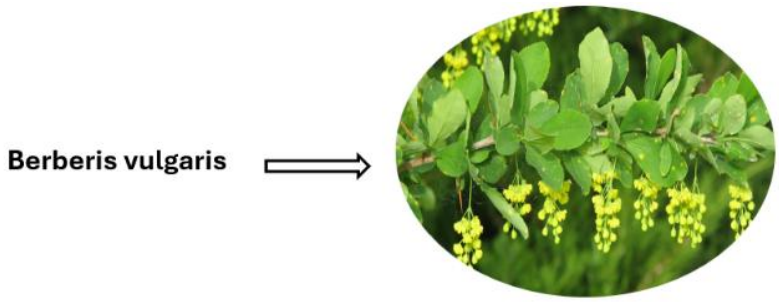

Figure 2. Berberis vulgaris (barberry), a medicinal plant containing berberine. The plant is characterized by its green leaves and yellow flowers, while its roots and bark are important sources of bioactive alkaloids, including berberine.

Another important source is Coptic chinensis, commonly known as Chinese goldthread. The rhizome of this plant is traditionally used in Chinese medicine and contains several protoberberine alkaloids, including berberine. The pharmacological activity of C. chinensis and its alkaloid constituents has contributed to increasing scientific interest in their potential applications in metabolic disorders. Chemically, berberine is a quaternary ammonium is quinoline alkaloid with a characteristic yellow color. Its chemical structure contributes to its diverse biological activities, while its physicochemical properties also influence its absorption and pharmacokinetic behavior. Despite its promising pharmacological effects, berberine has relatively low oral bioavailability, which is considered an important limitation for its therapeutic application. Recent research has therefore investigated different formulations and delivery systems to improve their absorption and biological availability (Sobhani et al. 2021; Alam et al. 2023).

The traditional use of berberine-containing medicinal plants provides an important foundation for modern pharmacological research. However, the therapeutic effects observed with purified berberine should be distinguished from those of whole-plant preparations because medicinal plants contain multiple bioactive compounds that may contribute to their overall pharmacological activity. This distinction is particularly important when evaluating clinical evidence and considering the development of standardized berberine-based therapeutic preparations.

Pharmacological Mechanisms of Berberine in Type 2 Diabetes Mellitus:

Berberine exerts its antidiabetic effects through multiple interconnected molecular and cellular pathways rather than through a single mechanism. Current evidence indicates that its actions involve the regulation of glucose metabolism, insulin sensitivity, lipid metabolism, inflammation, oxidative stress, and intestinal microbiota (Sun et al. 2024).

Activation of AMPK:

One of the most important mechanisms associated with the metabolic effects of berberine is the activation of adenosine monophosphate-activated protein kinase (AMPK), a major cellular energy sensor. Activation of AMPK promotes glucose utilization and fatty-acid oxidation while reducing hepatic glucose production and lipid synthesis. Through these effects, Berberine may improve metabolic homeostasis and insulin sensitivity in patients with T2DM (Khezri et al. 2024).

Improvement of Insulin Signaling and Glucose Uptake:

Berberine may improve insulin sensitivity by modulating intracellular signaling pathways involved in glucose metabolism, particularly the PI3K/Akt pathway. Activation of these pathways facilitates glucose uptake and utilization in peripheral tissues and may contribute to improved glycemic control. Berberine has also been associated with regulation of glucose transporter proteins, including GLUT4, which are important for glucose uptake in skeletal muscle and adipose tissue (Araj et al. 2024).

Inhibition of Hepatic Gluconeogenesis:

Excessive hepatic gluconeogenesis is an important contributor to fasting hyperglycemia in T2DM. Experimental evidence suggests that berberine can suppress hepatic gluconeogenesis by affecting key regulatory pathways and enzymes involved in glucose production. This includes modulation of transcriptional regulators such as FoxO1 and gluconeogenic enzymes, including phosphoenolpyruvate carboxin's and glucose-6-phosphatase (Fan et al. 2025).

Regulation of Glucose and Lipid Metabolism:

In addition to lowering blood glucose, Berberine appears to influence lipid metabolism. Its activation of AMPK and related metabolic pathways may reduce lipid synthesis and promote fatty-acid oxidation. These effects are particularly relevant because dyslipidemia and insulin resistance frequently coexist in T2DM and contribute to cardiovascular risk. Clinical evidence from systematic reviews also indicates beneficial effects of berberine on several glucose- and lipid-related metabolic parameters (Wang et al. 2024).

Effects on Gut Microbiota and GLP-1:

Increasing evidence suggests that gut microbiota may contribute to the metabolic effects of berberine. Berberine can alter intestinal microbial composition and may influence the production of metabolites involved in glucose regulation. In addition, evidence suggests that berberine may enhance glucagon-like peptide-1 (GLP-1)-related pathways, which can affect insulin secretion, glucose homeostasis, and intestinal metabolic signaling (Khezri et al. 2024).

Anti-inflammatory and Antioxidant Effects:

Chronic low-grade inflammation and oxidative stress are closely associated with insulin resistance and the progression of T2DM. Berberine has demonstrated anti-inflammatory and antioxidant activities that may help reduce cellular stress and improve metabolic function. These properties may provide additional benefits beyond its direct glucose-lowering effects and contribute to its potential role in preventing or reducing diabetes-associated complications (Sun et al. 2024).

Overall, the pharmacological activity of berberine appears to result from a multi-target and multi-pathway mechanism, involving AMPK, PI3K/Akt, GLUTs, hepatic gluconeogenesis, lipid metabolism, inflammatory pathways, and gut microbiota. This broad mechanism of action may explain its potential therapeutic value in a complex metabolic disease such as T2DM.

Clinical Efficacy of Berberine in Type 2 Diabetes Mellitus:

The clinical efficacy of berberine in T2DM has been investigated in numerous randomized controlled trials and systematic reviews. Overall, the available evidence suggests that berberine may improve glycemic control and several metabolic parameters, either when used alone or in combination with conventional antidiabetic therapy (Xie et al. 2022).

Effects on Glycemic Control:

A systematic review and meta-analysis of 37 randomized controlled trials involving 3,048 patients found that berberine significantly reduced fasting plasma glucose, HbA1c, and 2-hour postprandial glucose. More recent evidence has also supported its potential glucose-lowering effects (Liu et al. 2025).

Effects on Insulin Resistance and Lipid Metabolism:

Berberine may improve insulin sensitivity through AMPK activation and modulation of insulin-signaling pathways. It may also improve lipid parameters, including total cholesterol, LDL cholesterol, and triglycerides, potentially providing additional metabolic benefits in patients with T2DM (Wang et al. 2024).

Adjunctive Use and Overall Evidence:

Evidence suggests that Berberine may provide additional benefits when combined with conventional antidiabetic therapies. However, differences in dosage, formulations, treatment duration, and study quality limit direct comparisons. Overall, Berberine appears to be a promising adjunctive treatment for T2DM, but larger and longer-term clinical trials using standardized preparations are needed to confirm its efficacy and establish its appropriate clinical role (Alam et al. 2023).

Safety, Adverse Effects, and Tolerability of Berberine:

Although berberine has demonstrated promising antidiabetic effects, its safety profile is an important consideration when evaluating its potential therapeutic use. Available clinical evidence generally suggests that berberine is well tolerated, particularly during short-term treatment. However, adverse effects, drug interactions, differences in formulations, and limited long-term safety data should be considered. The adverse effects most frequently reported with berberine are primarily gastrointestinal, including constipation, diarrhea, abdominal discomfort, nausea, and flatulence. These effects are generally mild and may be related to the relatively low oral bioavailability of berberine and its interaction with the gastrointestinal tract. Nevertheless,

caution may be required when berberine is combined with other glucose-lowering medications because the combined effects may increase the potential for excessive reductions in blood glucose. (Wang et al. 2024).

Drug Interactions and Precautions:

Despite its generally favorable short-term tolerability, Berberine should not be considered completely free of safety concerns. Berberine can interact with drug-metabolizing enzymes and transporters, potentially altering the pharmacokinetics of concomitantly administered medications. Therefore, patients receiving multiple medications may require appropriate clinical monitoring. Furthermore, differences in berberine preparations and doses make it difficult to generalize safety findings from one formulation to another. This is particularly relevant because newer formulations, such as berberine Urso deoxycholate, may have different pharmacokinetic and pharmacodynamic characteristics from conventional berberine preparations (Mansour et al. 2025).

Long Term Safety:

One of the major limitations of the current evidence is the relatively short duration of many clinical studies. Most randomized trials have evaluated berberine over several weeks or months, whereas T2DM is a chronic disease requiring long-term treatment. Consequently, additional long-term randomized controlled trials are needed to determine the sustained safety of berberine, particularly regarding hepatic, renal, cardiovascular, and drug-interaction outcomes (Ji L et al. 2025; Alam et al. 2023).

Overall, current evidence indicates that Berberine has a generally acceptable short-term safety and tolerability profile, with gastrointestinal symptoms representing the most reported adverse effects. However, its long-term safety and appropriate use in combination with conventional antidiabetic medications require further investigation.

Several limitations:

Despite the promising pharmacological and clinical evidence, several limitations currently restrict the widespread clinical application of berberine in T2DM. One major limitation is its low oral bioavailability, which may affect the consistency of its therapeutic effects. Differences in berberine formulations, doses, treatment duration, and patient characteristics also contribute to substantial heterogeneity among clinical studies. Another important limitation is the relatively short duration and small sample size of many randomized controlled trials. Although existing meta-analyses generally support beneficial effects on glycemic and metabolic parameters, long-term evidence regarding cardiovascular outcomes, diabetes-related complications, and sustained safety remains limited. Furthermore, the mechanisms underlying berberine's effects are complex and involve multiple pathways, including AMPK, insulin signaling, lipid metabolism, inflammation, and gut microbiota. More studies are needed to clarify the relative contribution of these mechanisms and determine whether specific patient populations may benefit more than others.

Future research should therefore focus on large, multicenter, long-term randomized controlled trials using standardized berberine preparations. Studies should also establish optimal doses, treatment duration, bioavailability, drug interactions, and long-term safety. Comparative studies against established antidiabetic medications would further clarify the appropriate clinical role of berberine.

Recommendations:

The following recommendations are proposed:

- Conduct large, multicenter, long-term randomized controlled trials to confirm the efficacy and safety of berberine in patients with T2DM.
- Standardize berberine formulations, dosage, and treatment duration to improve comparability among clinical studies and establish optimal therapeutic regimens.
- Develop improved formulations and delivery systems to overcome the low oral bioavailability of berberine and enhance its therapeutic effectiveness.
- Investigate potential drug interactions between berberine and conventional antidiabetic medications to ensure safe combined use.
- Evaluate long term safety and clinical outcomes, particularly cardiovascular events, diabetes-related complications, and effects on hepatic and renal function.

- Conduct comparative clinical studies between berberine and established antidiabetic therapies to determine its appropriate role as an adjunctive or alternative treatment.
- Explore personalized therapeutic approaches to identify patient populations that may obtain the greatest benefit from berberine treatment.

CONCLUSION

Berberine derived from medicinal plants has emerged as a promising natural compound with potential therapeutic value in the management of type 2 diabetes mellitus. Current evidence indicates that its antidiabetic effects involve multiple mechanisms, including AMPK activation, improvement of insulin sensitivity, inhibition of hepatic gluconeogenesis, regulation of lipid metabolism, and modulation of inflammation and gut microbiota. Clinical studies and meta-analyses suggest that berberine may improve fasting plasma glucose, HbA1c, postprandial glucose, and several metabolic parameters, with a generally acceptable short-term safety profile. However, variations in formulations, dosage, bioavailability, study duration, and methodological quality limit definitive conclusions regarding its long-term therapeutic effectiveness.

Therefore, berberine may represent a promising adjunctive therapeutic option for T2DM, but it should not currently be considered a replacement for established antidiabetic therapies. Further large-scale, standardized, and long-term clinical trials are required to confirm its efficacy, establish optimal dosing and formulations, evaluate long-term safety, and determine its appropriate role in contemporary diabetes management.

REFERENCES

[1] Alam S. D., et al. (2023). Facile extraction of berberine from different plants, separation, and identification by thin-layer chromatography, high-performance liquid chromatography, and biological evaluation against leishmaniosis. J. Sep. Sci. 46.

[2] Araj-Khodaei M., Ayati M. H., Azizi Zeinalhajlou A., Novinbahador T., Yousefi M., Shiri M., et al. (2024). Berberine-induced glucagon-like peptide-1 and its mechanism for controlling type 2 diabetes mellitus: A comprehensive pathway review. Arch. Physiol. Biochem. 130 (6), 678–685.

[3] Bray J. J. H., Foster-Davies H., Salem A., Hoole A. L., Obaid D. R., Halcox J. P. J., et al. (2021). Glucagon-like peptide-1 receptor agonists improve biomarkers of inflammation and oxidative stress: A systematic review and meta-analysis of randomised controlled trials. Diabetes Obes. Metab. 23 (8), 1806–1822.

[4] Chang W., Chen L., Hatch G. M. (2015). Berberine as a therapy for type 2 diabetes and its complications: From mechanism of action to clinical studies. Biochem. Cell Biol. 93 (5), 479–486.

[5] Chang Y. C., Lin C. J., Hsiao Y. H., Chang Y. H., Liu S. J., Hsu H. Y. (2020). Therapeutic effects of bcg vaccination on type 1 diabetes mellitus: A systematic review and meta-analysis of randomized controlled trials. J. Diabetes Res. 2020, 8954125.

[6] Dong H., Wang N., Zhao L., Lu F. (2012). Berberine in the treatment of type 2 diabetes mellitus: A systematic review and meta-analysis. Evid. Based Complement. Alternat. Med. 2012, 591654.

[7] Fan K. Q., Zhang L., Song F., Zhang Y. H., Chen T., Cheng X., et al. (2025). Pharmacological properties and therapeutic potential of berberine: A comprehensive review. Front. Pharmacol. 16, 1604071.

[8] Ji L., Ma J., Ma Y., Cheng Z., Gan S., Yuan G., Liu D., Li S., Liu Y., Xue X., Bai J., Wang K., Cai H., Li S., Liu K., Yu M., Liu L. (2025). Berberine ursodeoxycholate for the treatment of type 2 diabetes: A randomized clinical trial. JAMA Netw. Open 8 (3), e2462185.

[9] Khezri M. R., Mohammadipanah S., Ghasemnejad-Berenji M. (2024). The pharmacological effects of Berberine and its therapeutic potential in different diseases: Role of the phosphatidylinositol 3-kinase/AKT signaling pathway. Phytother. Res. 38 (1), 349–367.

[10] Khoshandam A., Imenshahidi M., Hosseinzadeh H. (2022). Pharmacokinetic of berberine, the main constituent of Berberis vulgaris L.: A comprehensive review. Phytother. Res. 36 (11), 4063–4079.

[11] Liu D., Zhao H., Zhang Y., Hu J., Xu H. (2025). Efficacy and safety of berberine on the components of metabolic syndrome: A systematic review and meta-analysis of randomized placebo-controlled trials. Front. Pharmacol. 16, 1572197.

[12] Mansour A., Sajjadi-Jazi S. M., Gerami H., Khorasanian A. S., Moalemzadeh B., Karimi S., Mohamadi Afrakoti N., Mofid V., Mohajeri-Tehrani M. R., Hekmatdoost A. (2025). The efficacy and safety of berberine in combination with cinnamon supplementation in patients with type 2 diabetes: A randomized clinical trial. Eur. J. Nutr. 64 (2), 102.

[13] Shakeri F., Kiani S., Rahimi G., Boskabady M. H. (2024). Anti-inflammatory, antioxidant, and immunomodulatory effects of Berberis vulgaris and its constituent berberine, experimental and clinical, a review. Phytother. Res. 38 (4), 1882–1902.

[14] Sobhani Z., Akaberi M., Amiri M. S., Ramezani M., Emami S. A., Sahebkar A. (2021). Medicinal species of the genus Berberis: A review of their traditional and ethnomedicinal uses, phytochemistry and pharmacology. Adv. Exp. Med. Biol. 1308, 547–577.

[15] Sun A., Yang H., Li T., Luo J., Zhou L., Chen R., Han L., Lin Y. (2024). Molecular mechanisms, targets and clinical potential of berberine in regulating metabolism: A review focussing on databases and molecular docking studies. Front. Pharmacol. 15, 1368950

[16] Wang J., Bi C., Xi H., Wei F. (2024). Effects of administering berberine alone or in combination on type 2 diabetes mellitus: A systematic review and meta-analysis. Front. Pharmacol. 15, 1455534.

[17] Xie W., Su F., Wang G., Peng Z., Xu Y., Zhang Y., et al. (2022). Glucose-lowering effect of berberine on type 2 diabetes: A systematic review and meta-analysis. Front. Pharmacol. 13, 1015045.