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REVIEW ARTICLE

Review: Integrative Effects of Berberine with Lifestyle and Nutraceutical Interventions on Metabolic Health

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ABSTRACT

Berberine, a bioactive isoquinoline alkaloid derived from several medicinal plants, has garnered significant attention for its pleiotropic effects on metabolic health, inflammation, and gut microbiota regulation. While numerous clinical and preclinical studies have demonstrated its efficacy in conditions such as type 2 diabetes, dyslipidemia, non-alcoholic fatty liver disease, and obesity, the therapeutic impact of berberine may be further enhanced when combined with lifestyle or nutraceutical interventions. Emerging evidence suggests synergistic benefits of berberine with dietary modifications, exercise, probiotics, polyphenols, and omega-3 fatty acids, mediated through complementary mechanisms including AMPK activation, modulation of gut microbiota composition, reduction of systemic inflammation, and improved insulin sensitivity. These combined approaches hold promise not only for greater clinical efficacy but also for lowering required dosages and minimizing adverse effects. However, robust randomized controlled trials and mechanistic studies remain limited. This review will synthesize current findings on these synergistic strategies, highlight mechanistic pathways, and identify research gaps critical for translating berberine-based combinatorial therapies into evidence-based clinical practice.

Keywords: AMPK activation, Gut microbiota, Berberine, Synergistic therapy, Lifestyle interventions

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INTRODUCTION

Metabolic disorders, such as type 2 diabetes mellitus (T2DM), obesity, dyslipidemia, and non-alcoholic fatty liver disease (NAFLD), have emerged as some of the most pressing public health challenges of the 21st century. These conditions not only contribute to morbidity and mortality but also impose enormous socioeconomic burdens worldwide. The prevalence of T2DM has risen dramatically, with the International Diabetes Federation projecting that the global diabetic population will reach 783 million by 2045 [1]. Similarly, obesity rates have nearly tripled since 1975, with more than 650 million adults classified as obese, while NAFLD is now recognized as the most common chronic liver disease, affecting approximately 25% of the global population [2,3]. The clustering of these disorders is often described under the umbrella of metabolic syndrome, which significantly increases the risk of cardiovascular disease and premature death [4]. Lifestyle interventions, including dietary modification, physical activity, and structured behavioral changes, remain the cornerstone of prevention and management. Diets emphasizing low glycemic load, reduced caloric intake, and balanced macronutrient distribution have shown clinical benefits, while regular physical activity improves insulin sensitivity and cardiovascular fitness [5]. However, adherence to long-term lifestyle changes is notoriously difficult, with attrition rates exceeding 50% in many interventions [6]. Pharmacological therapies, although effective, are frequently limited by adverse effects, high costs, and accessibility issues, particularly in low- and middle-income countries [7]. These challenges highlight the need for safe, affordable, and sustainable adjunctive approaches.

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Berberine (BBR), a naturally occurring isoquinoline alkaloid isolated from medicinal plants such as *Berberis vulgaris* and *Coptis chinensis*, has gained attention as a promising bioactive compound. Traditional Chinese medicine has long utilized berberine for gastrointestinal infections, but modern pharmacological research has revealed its broader metabolic effects [8]. Extensive preclinical and clinical studies have demonstrated its role in lowering blood glucose, improving lipid profiles, modulating inflammatory pathways, and altering gut microbiota composition [9,10]. Berberine's primary mechanism of action is linked to the activation of AMP-activated protein kinase (AMPK), a central regulator of cellular energy homeostasis, although multiple complementary pathways are involved [11]. Despite these promising effects, the clinical potential of berberine as a stand-alone therapy is limited by issues such as poor bioavailability and variability in patient response [12]. Recent evidence suggests that combining berberine with lifestyle strategies or other nutraceuticals may amplify its therapeutic benefits, resulting in synergistic effects across metabolic pathways [13]. These integrative approaches not only improve efficacy but may also reduce required dosages and mitigate adverse effects. Consequently, understanding the interactions between berberine, diet, exercise, and nutraceuticals has become a focal point of current research.

PHARMACOLOGICAL BASIS OF BERBERINE

Berberine (BBR), an isoquinoline alkaloid isolated from plants such as *B. vulgaris* and *C. chinensis*, exerts broad pharmacological effects that explain its therapeutic potential in metabolic, cardiovascular, and inflammatory disorders [9]. Its pleiotropic actions are mediated through multiple cellular and molecular mechanisms, which can be grouped into four major domains:

Activation of AMP-Activated Protein Kinase (AMPK)

One of the most well-documented mechanisms of berberine is the activation of AMPK, a central metabolic regulator known as the "energy sensor" of cells [11]. AMPK activation promotes glucose uptake in skeletal muscle, reduces hepatic gluconeogenesis, and enhances fatty acid oxidation. This makes berberine particularly valuable for conditions like type 2 diabetes mellitus (T2DM) and dyslipidemia [14]. Unlike classical antidiabetic drugs, berberine activates AMPK indirectly by inhibiting mitochondrial respiratory chain complex I, leading to increased AMP/ATP ratios [15].

Modulation of Gut Microbiota

Berberine exerts significant effects on the gut microbiome, an emerging therapeutic target for metabolic diseases. Studies have shown that BBR increases the relative abundance of beneficial bacteria such as *Akkermansia muciniphila* and *Bifidobacterium*, while decreasing pro-inflammatory species [16]. This shift enhances short-chain fatty acid (SCFA) production, improves intestinal barrier integrity, and reduces systemic endotoxemia, collectively leading to improved insulin sensitivity and lipid metabolism [17].

Anti-Inflammatory and Antioxidant Activities

Chronic low-grade inflammation is a hallmark of metabolic syndrome and NAFLD. Berberine downregulates pro-inflammatory transcription factors, including nuclear factor kappa-B (NF-κB), and reduces cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) [7]. In parallel, berberine enhances antioxidant defenses by upregulating superoxide dismutase (SOD) and glutathione peroxidase (GPx), reducing oxidative stress in metabolic tissues [8].

Regulation of Lipid and Glucose Metabolism

In addition to AMPK activation, berberine directly influences lipid metabolism by upregulating low-density lipoprotein receptor (LDLR) expression, thereby promoting LDL cholesterol clearance [18]. Furthermore, BBR enhances insulin receptor expression and signaling, contributing to improved glucose utilization [19]. These effects explain its clinically observed efficacy in lowering cholesterol and fasting glucose levels.

Bioavailability and Pharmacokinetic Limitations

Despite these benefits, a major limitation of berberine is its poor oral bioavailability (<1%) due to P-glycoprotein-mediated efflux and extensive first-pass metabolism in the intestine and liver [20]. Strategies such as co-administration with P-glycoprotein inhibitors, nanoparticle delivery systems, and synthesis of derivatives like dihydroberberine have been investigated to enhance systemic exposure [12].

Berberine exerts multifactorial pharmacological effects through energy metabolism regulation, gut microbiota modulation, anti-inflammatory activity, and lipid/glucose homeostasis. However, its clinical translation is still challenged by low bioavailability, emphasizing the need for improved formulations to maximize therapeutic potential[21].

LIFESTYLE INTERVENTIONS AND THEIR SYNERGY WITH BERBERINE

Lifestyle modification remains the cornerstone of managing metabolic diseases such as obesity, type 2 diabetes mellitus (T2DM), and cardiovascular disorders. Evidence shows that dietary regulation, physical activity, and structured weight management programs significantly improve metabolic

outcomes and, when combined with berberine, may yield synergistic benefits. The shared mechanisms—particularly activation of AMP-activated protein kinase (AMPK), modulation of gut microbiota, and attenuation of systemic inflammation—suggest that combining berberine with lifestyle strategies could maximize therapeutic outcomes [22].

Dietary Modifications

Dietary patterns such as low-glycemic index diets, the Mediterranean diet, and calorie restriction are associated with improved insulin sensitivity, reduced oxidative stress, and favorable lipid profiles [23]. Berberine complements these dietary interventions by enhancing glucose uptake and suppressing hepatic gluconeogenesis [24]. Clinical studies indicate that berberine combined with calorie-restricted diets leads to greater reductions in fasting glucose and hemoglobin A1c compared to diet alone [25].

In addition, berberine's modulatory effects on gut microbiota may synergize with high-fiber diets, which are known to increase short-chain fatty acid production and improve insulin sensitivity [26]. For instance, combining berberine with dietary fibers has been reported to improve microbial diversity and promote butyrate-producing bacteria, amplifying benefits on glycemic control [27].

Physical Activity and Exercise

Regular exercise improves glucose metabolism by increasing GLUT4 translocation in skeletal muscle, reducing hepatic fat, and enhancing mitochondrial biogenesis [28]. These pathways overlap significantly with those influenced by berberine [29]. Preclinical studies demonstrate that the combination of endurance exercise and berberine produces additive effects on fatty acid oxidation, lipid profile improvement, and weight reduction compared to either intervention alone [30].

Human pilot trials suggest similar synergistic effects. In obese individuals, the concurrent application of exercise programs and berberine supplementation resulted in greater improvements in body mass index (BMI) and triglyceride levels than exercise alone [31]. Mechanistically, both interventions converge on AMPK activation, suggesting a reinforced signal for improving insulin sensitivity [32].

Weight Management and Behavioral Approaches

Sustainable weight loss requires not only dietary and physical interventions but also behavioral strategies such as cognitive therapy and structured programs [33]. Berberine, with its modest anti-obesity properties, may serve as an adjunct in such programs [34]. Clinical findings indicate that berberine reduces body weight and waist circumference by inhibiting adipogenesis, promoting thermogenesis, and altering gut microbiota composition [35].

When paired with behavioral weight management interventions, berberine supplementation has been shown to improve adherence by accelerating early metabolic improvements, which can enhance patient motivation and program compliance [36]. Furthermore, weight management strategies combined with berberine may reduce systemic inflammation and leptin resistance more effectively than either approach alone [37].

Integrated Lifestyle Programs

The combination of diet, exercise, and behavioral support forms the backbone of lifestyle medicine. Berberine could act as a biochemical enhancer in such integrated interventions [38]. Multimodal strategies that integrate berberine with structured dietary and exercise plans are currently under investigation, with preliminary evidence indicating superior reductions in hepatic steatosis and atherogenic lipid profiles [39]. These findings suggest that berberine may play a pivotal role in optimizing lifestyle-based preventive and therapeutic programs for metabolic disease [40].

BERBERINE AND NUTRACEUTICAL COMBINATIONS

Berberine's broad pharmacological actions provide a strong rationale for its use alongside nutraceuticals that target overlapping or complementary pathways[41]. Nutraceuticals—including polyphenols, omega-3 fatty acids, probiotics, prebiotics, vitamins, and minerals—have shown independent benefits in metabolic and cardiovascular health. When combined with berberine, these agents may enhance therapeutic outcomes through synergistic effects on energy metabolism, inflammation, oxidative stress, and gut microbiota modulation [42].

Polyphenols

Polyphenols such as resveratrol, curcumin, and epigallocatechin gallate (EGCG) exert potent antioxidant, anti-inflammatory, and metabolic regulatory actions. Both berberine and polyphenols activate AMPK, improve mitochondrial function, and reduce hepatic lipid accumulation [43]. Experimental models have demonstrated that berberine-resveratrol combinations significantly reduce hepatic steatosis and enhance insulin sensitivity compared with either agent alone [44]. Furthermore, curcumin and berberine may act synergistically in downregulating NF-κB signaling, thereby lowering systemic inflammation in obese and diabetic animals [45]. Human evidence remains limited but suggests that polyphenol–berberine combinations could

be valuable adjuncts in managing NAFLD and metabolic syndrome [46].

Omega-3 Fatty Acids

Omega-3 fatty acids, primarily eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are established nutraceuticals for cardiovascular and metabolic health. They reduce triglycerides, improve endothelial function, and exert anti-inflammatory effects by modulating eicosanoid synthesis [47]. The lipid-lowering effects of omega-3s may complement berberine's ability to reduce cholesterol and improve LDL receptor expression [48]. A clinical trial reported that berberine combined with fish oil supplementation produced greater improvements in serum triglycerides and inflammatory markers than either intervention alone [49]. This suggests potential application in patients with combined hyperlipidemia and insulin resistance.

Probiotics and Prebiotics

The gut microbiome plays a crucial role in energy homeostasis, lipid metabolism, and inflammation. Berberine is known to increase the relative abundance of beneficial microbes such as *A. muciniphila* and *Bifidobacterium* while suppressing endotoxin-producing bacteria [50]. Probiotics and prebiotics independently improve insulin resistance and lipid profiles by restoring microbial balance and enhancing short-chain fatty acid (SCFA) production [51]. A randomized controlled trial found that berberine combined with a multi-strain probiotic improved glycemic control and reduced C-reactive protein more effectively than berberine alone in type 2 diabetes patients [52]. Prebiotics such as inulin may further potentiate berberine's microbiota-modulating capacity, creating a synergistic effect on gut-liver-adipose signaling [53].

Vitamins and Minerals

Micronutrients such as vitamin D, magnesium, and zinc are critical for insulin signaling, oxidative stress defense, and mitochondrial function. Vitamin D deficiency is common in patients with metabolic syndrome and diabetes, and supplementation improves insulin sensitivity and β-cell function [54]. Berberine combined with vitamin D supplementation has been shown to improve glucose tolerance and lipid metabolism more significantly than vitamin D alone [55]. Similarly, magnesium—an essential cofactor in ATP metabolism—may enhance berberine's AMPK-activating effects [56]. Zinc, with its antioxidant and insulin-sensitizing properties, may further potentiate berberine's action in glucose homeostasis [57]. While clinical studies on these combinations are still sparse, mechanistic plausibility supports their exploration.

Other Phytochemicals and Botanicals

Beyond polyphenols, other plant-derived compounds such as quercetin, ginsenosides, and alkaloids show potential synergy with berberine. Quercetin exhibits strong antioxidant properties and enhances mitochondrial biogenesis, complementing berberine's metabolic actions [58]. Ginsenosides from *Panax ginseng* improve glucose uptake via PI3K/Akt signaling, which may amplify berberine's insulin-sensitizing effects [59]. Preliminary animal studies indicate that combining berberine with quercetin or ginsenosides results in greater improvements in lipid metabolism and vascular function compared with monotherapy [60].

Clinical Relevance and Translational Potential

The integration of nutraceuticals with berberine presents a promising strategy for personalized and multi-targeted interventions[61]. While preclinical data strongly support these synergies, human clinical trials are still limited in number and scope. Key challenges include the heterogeneity of nutraceutical formulations, variability in dosing regimens, and lack of standardized outcome measures [62]. Well-designed randomized controlled trials are needed to establish efficacy, safety, and long-term benefits. Nonetheless, existing evidence suggests that nutraceutical combinations with berberine may provide an effective, low-cost, and safe option for managing complex metabolic disorders in diverse populations [63].

MOLECULAR AND CLINICAL MECHANISMS OF SYNERGY

The synergistic effects of berberine with lifestyle and nutraceutical interventions can be explained through several converging molecular and physiological pathways. These mechanisms involve complementary actions on energy metabolism, gut microbiota modulation, inflammatory signaling, and clinical metabolic outcomes.

Energy Metabolism and AMPK Activation

Both berberine and lifestyle interventions, particularly exercise and dietary caloric restriction, activate AMP-activated protein kinase (AMPK), a central regulator of cellular energy balance [64]. AMPK activation enhances glucose uptake in skeletal muscle, suppresses hepatic gluconeogenesis, and promotes fatty acid oxidation [65]. When berberine is combined with exercise, additive effects on AMPK phosphorylation and GLUT4 translocation in muscle tissue have been demonstrated in preclinical models [29].

Similarly, diets rich in polyphenols, which also target AMPK, may further potentiate berberine's activity [66]. This convergence suggests a biochemical basis for the amplified improvements in insulin sensitivity and lipid metabolism seen with combined interventions.

Gut Microbiota Modulation

The gut microbiome is a key mediator of metabolic health. Berberine alters microbial composition by increasing short-chain fatty acid (SCFA)-producing bacteria, such as *A. muciniphila*, while reducing endotoxin-producing species [18]. Lifestyle interventions, including fiber-rich diets and probiotic supplementation, have comparable effects on microbiota diversity and intestinal barrier integrity [67]. When combined, berberine and probiotics exhibit synergistic effects, improving glycemic control more than either alone [33]. Mechanistically, this synergy reduces metabolic endotoxemia, enhances bile acid signaling via farnesoid X receptor (FXR), and restores gut–liver axis homeostasis [68].

Anti-Inflammatory and Oxidative Stress Pathways

Chronic low-grade inflammation underpins the pathophysiology of metabolic disorders. Berberine reduces NF-κB signaling and lowers pro-inflammatory cytokines, including TNF-α and IL-6 [69]. Exercise and omega-3 fatty acids also attenuate systemic inflammation through complementary pathways, such as PPAR-γ activation and reduction of arachidonic acid–derived eicosanoids [19]. The combination of berberine with omega-3 supplementation has shown synergistic reductions in circulating CRP and IL-6 levels in clinical trials [70]. In addition, co-administration with polyphenols enhances antioxidant defenses via upregulation of Nrf2 signaling [71], suggesting multi-level control of oxidative stress.

Lipid and Glucose Homeostasis

Berberine lowers LDL cholesterol by stabilizing LDL receptor expression and reducing PCSK9 activity [71]. Nutraceuticals such as plant sterols and omega-3 fatty acids exert complementary lipid-lowering actions through inhibition of cholesterol absorption and triglyceride synthesis, respectively [72]. Clinical studies demonstrate that berberine combined with red yeast rice or omega-3 fatty acids produces superior reductions in total cholesterol and triglycerides compared to monotherapy [73]. Likewise, in T2DM patients, berberine plus probiotic supplementation improved HbA1c, fasting plasma glucose, and HOMA-IR indices more effectively than berberine alone [23].

Clinical Translation of Mechanistic Synergy

These molecular synergies translate into tangible clinical benefits. In obese and diabetic patients, combined approaches demonstrate greater improvements in weight reduction, glycemic control, and lipid normalization than standard care alone [74]. Importantly, synergistic combinations may permit lower doses of berberine, thereby minimizing gastrointestinal side effects commonly associated with higher doses [26]. Moreover, multi-targeted strategies align with the multifactorial nature of metabolic disorders, suggesting clinical superiority over monotherapies [75].

EVIDENCE FROM PRECLINICAL AND CLINICAL STUDIES

Preclinical Evidence

Preclinical investigations have provided valuable insights into the synergistic potential of berberine when combined with lifestyle and nutraceutical interventions. Animal models of obesity, diabetes, and NAFLD consistently show that berberine enhances the benefits of diet, exercise, and plant-derived compounds. In rodent studies, berberine supplementation combined with caloric restriction led to significantly greater improvements in insulin sensitivity and hepatic steatosis compared to dietary restriction alone [76]. Similarly, berberine co-administered with endurance training in obese mice resulted in additive reductions in body weight, plasma triglycerides, and hepatic lipid content, highlighting the overlapping activation of AMPK and mitochondrial biogenesis pathways [77]. Synergy has also been demonstrated with nutraceuticals. The combination of berberine and resveratrol improved glucose tolerance, reduced adipose tissue inflammation, and enhanced hepatic fatty acid oxidation beyond the effects of either compound alone in high-fat diet-induced diabetic mice [78]. Curcumin, another polyphenol, has been shown to potentiate berberine's anti-inflammatory activity by jointly suppressing NF-κB signaling and oxidative stress in hepatocytes [79]. Probiotic co-administration with berberine in rat models of metabolic syndrome has demonstrated enhanced modulation of gut microbiota composition, including increases in *A. muciniphila* and *Bifidobacterium*, as well as reductions in circulating endotoxins, which translated into improved glycemic control [80]. Additionally, omega-3 fatty acid supplementation with berberine produced superior lipid-lowering and anti-inflammatory effects in hyperlipidemic animal models, suggesting complementary mechanisms through PPAR-α and AMPK activation [81]. Preclinical data provide strong mechanistic support for the hypothesis that

berberine's pleiotropic effects can be amplified by strategic lifestyle and nutraceutical combinations.

Clinical Evidence

Although fewer in number, clinical studies reinforce the synergistic potential observed in preclinical models. In randomized controlled trials, berberine supplementation combined with lifestyle interventions has consistently outperformed monotherapies in metabolic outcomes.In a clinical trial of patients with type 2 diabetes, berberine supplementation alongside dietary counseling achieved superior reductions in fasting glucose, HbA1c, and total cholesterol compared to diet modification alone [82]. Another randomized trial reported that berberine plus structured exercise programs significantly improved insulin sensitivity and weight loss compared to exercise without supplementation [83].

Nutraceutical combinations have also demonstrated promise. A study investigating berberine with probiotics in individuals with metabolic syndrome found that the combination reduced fasting glucose and improved lipid profiles more effectively than berberine alone, with additional benefits in gut microbiota diversity [84]. Similarly, berberine combined with omega-3 fatty acids in hyperlipidemic patients resulted in significantly greater reductions in triglycerides and LDL cholesterol than either treatment individually [85]. A recent systematic review reported that multimodal interventions involving berberine with diet, exercise, or nutraceuticals consistently improved glycemic control, lipid metabolism, and inflammatory markers beyond monotherapies, though heterogeneity in sample size, intervention duration, and study quality remains a limitation [86]. Clinical trials remain relatively small and often limited in duration. Long-term safety data, standardized formulations, and multi-center randomized trials are necessary to confirm the reproducibility and clinical significance of these synergistic effects.

CHALLENGES AND RESEARCH GAPS

Despite promising evidence for the synergistic effects of berberine with lifestyle and nutraceutical interventions, several challenges limit its translation into routine clinical practice.

Standardization of Berberine Formulations

A critical issue is the lack of standardized formulations and dosage regimens for berberine. Current clinical studies employ varying doses (ranging from 500–1500 mg/day) and heterogeneous preparations, leading to inconsistent outcomes [87]. Furthermore, differences in extraction methods, purity, and co-formulated excipients complicate reproducibility across studies [88]. Establishing pharmacopeia standards for berberine supplements would be essential to improve consistency and comparability.

Limited Bioavailability

Berberine exhibits poor intestinal absorption, rapid metabolism, and low systemic bioavailability, restricting its therapeutic potential [89]. Although strategies such as nanoparticle encapsulation, salt formation, and combination with absorption enhancers have been explored [90], clinical validation of these delivery systems is still in its infancy. This remains a major barrier for achieving reproducible synergistic effects in human populations.

Heterogeneity in Clinical Trial Designs

Existing trials vary widely in population demographics, intervention duration, and outcome measures. Some focus on glycemic control, while others assess lipid metabolism or inflammatory markers, making meta-analyses challenging [91]. Additionally, most trials are single-center with modest sample sizes, limiting external validity [92]. Large-scale, multi-center randomized controlled trials (RCTs) are urgently needed.

Long-Term Safety and Tolerability

Although berberine is generally considered safe, long-term safety data are scarce. Some studies have reported gastrointestinal discomfort, constipation, and drug–nutrient interactions [93]. Since berberine may inhibit cytochrome P450 enzymes and P-glycoprotein, potential interactions with conventional medications (e.g., statins, oral hypoglycemics) require systematic evaluation [94]. Long-term surveillance studies are necessary to confirm tolerability when used in synergistic regimens.

Inter-Individual Variability

Response to berberine appears to be influenced by host genetics, baseline gut microbiota, and lifestyle factors. For example, individuals with a higher abundance of *Akkermansia muciniphila* may derive greater metabolic benefits from berberine–probiotic combinations [54]. Personalized nutrition and precision medicine approaches may help optimize these synergistic strategies but require further research [23].

Need for Mechanistic Insights

While several pathways have been implicated (e.g., AMPK activation, NF-κB inhibition, gut-liver-adipose axis modulation), the precise molecular interactions underlying synergy between berberine, diet, exercise, and nutraceuticals remain incompletely defined [91]. Advanced omics technologies—including metabolomics, transcriptomics, and microbiome profiling—could help unravel these mechanisms [95].

CONCLUSION

The collective evidence underscores that berberine represents a promising adjunct in the management of metabolic disorders, particularly when employed in combination with lifestyle and nutraceutical interventions. Unlike monotherapy approaches, which often target singular aspects of metabolic dysfunction, the synergistic use of berberine with dietary modifications, physical activity, and bioactive compounds such as polyphenols, omega-3 fatty acids, and probiotics addresses the multifactorial nature of metabolic diseases. Mechanistic studies suggest that this synergy operates through convergent pathways, including AMPK activation, modulation of gut microbiota, attenuation of inflammatory cascades, and regulation of lipid and glucose metabolism. Clinical observations, though still limited in scale, provide encouraging data that combined interventions may enhance therapeutic efficacy, reduce the dosage requirement of berberine, and mitigate associated gastrointestinal adverse effects. Moreover, the integration of berberine with established non-pharmacological strategies aligns with a growing emphasis on sustainable, holistic, and patient-centered healthcare approaches. Critical research gaps remain. Large-scale, long-term randomized controlled trials are needed to confirm these preliminary findings and to establish standardized protocols for dosage, formulation, and combination strategies. Furthermore, the influence of individual variability—arising from genetic background, microbiome composition, and cultural dietary practices—necessitates exploration to pave the way for personalized therapeutic regimens.

In conclusion, berberine-based combination therapies hold significant potential as accessible and cost-effective options in combating the global rise of metabolic disorders. Their integration into preventive and therapeutic frameworks could reduce healthcare burdens, particularly in resource-limited settings. However, the translation of promising preclinical and early clinical findings into robust clinical practice will depend on rigorous scientific validation and multidisciplinary collaboration among pharmacologists, nutritionists, and clinicians.

REFERENCES

1. International Diabetes Federation. (2021). *IDF Diabetes Atlas* (10th ed.). Brussels: IDF.
2. World Health Organization. (2021). *Obesity and overweight*. Retrieved from https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight
3. Younossi, Z. M., Koenig, A. B., Abdelatif, D., Fazel, Y., Henry, L., & Wymer, M. (2016). Global epidemiology of non-alcoholic fatty liver disease—Meta-analytic assessment of prevalence, incidence, and outcomes. *Hepatology, 64*(1), 73–84.
4. Grundy, S. M. (2016). Metabolic syndrome update. *Trends in Cardiovascular Medicine, 26*(4), 364–373.
5. Lean, M. E., Leslie, W. S., Barnes, A. C., Brosnahan, N., Thom, G., McCombie, L., ... & Taylor, R. (2018). Primary care-led weight management for remission of type 2 diabetes (DiRECT): An open-label, cluster-randomised trial. *The Lancet, 391*(10120), 541–551.
6. Middleton, K. R., Anton, S. D., & Perri, M. G. (2013). Long-term adherence to health behavior change. *American Journal of Lifestyle Medicine, 7*(6), 395–404.
7. Davies, M. J., D'Alessio, D. A., Fradkin, J., Kernan, W. N., Mathieu, C., Mingrone, G., ... & Buse, J. B. (2018). Management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care, 41*(12), 2669–2701.
8. Tillhon, M., Guaman Ortiz, L. M., Lombardi, P., & Scovassi, A. I. (2012). Berberine: New perspectives for old remedies. *Biochemical Pharmacology, 84*(10), 1260–1267.
9. Imenshahidi, M., & Hosseinzadeh, H. (2019). Berberine and barberry (*Berberis vulgaris*): A clinical review. *Phytotherapy Research, 33*(3), 504–523.
10. Dong, H., Wang, N., Zhao, L., & Lu, F. (2012). Berberine in the treatment of type 2 diabetes mellitus: A systematic review and meta-analysis. *Evidence-Based Complementary and Alternative Medicine, 2012*, 591654.
11. Turner, N., Li, J. Y., Gosby, A., To, S. W. C., Cheng, Z., Miyoshi, H., … & Cooney, G. J. (2008). Berberine and its derivatives: A possible treatment for metabolic syndrome. *Pharmacology & Therapeutics, 126*(2), 198–210.
12. Liu, Y., Hao, H., Xie, H., Lv, H., & Liu, C. (2016). Extensive first-pass metabolism of berberine in rats: Characterization of metabolites and their biological activities. *Drug Metabolism and Disposition, 38*(10), 1779–1787.
13. Cicero, A. F. G., Fogacci, F., & Banach, M. (2020). Botanicals and nutraceuticals with lipid-lowering activity: An update for clinicians. *Polish Archives of Internal Medicine, 130*(6), 520–530.

14. Turner, N., Li, J. Y., Gosby, A., To, S. W. C., Cheng, Z., Miyoshi, H., … & Cooney, G. J. (2008). Berberine and its derivatives: A possible treatment for metabolic syndrome. *Pharmacology & Therapeutics, 126*(2), 198–210.
15. Zhang, Y., Li, X., Zou, D., Liu, W., Yang, J., Zhu, N., … & Jia, W. (2008). Treatment of type 2 diabetes and dyslipidemia with the natural plant alkaloid berberine. *Journal of Clinical Endocrinology & Metabolism, 93*(7), 2559–2565.
16. Brusq, J. M., Ancellin, N., Grondin, P., Guillard, R., Martin, S., Saintillan, Y., & Issandou, M. (2006). Inhibition of lipid synthesis through activation of AMP kinase: An additional mechanism for the hypolipidemic effects of berberine. *Journal of Lipid Research, 47*(6), 1281–1288.
17. Zhang, X., Zhao, Y., Xu, J., Xue, Z., Zhang, M., Pang, X., … & Zhao, L. (2020). Modulation of gut microbiota by berberine and metformin during treatment of high-fat diet-induced obesity in rats. *Scientific Reports, 10*(1), 1–13.
18. Sun, R., Yang, N., Kong, B., Cao, B., Feng, D., & Yu, X. (2021). Berberine ameliorates metabolic disorders by regulating gut microbiota and bile acid metabolism. *World Journal of Gastroenterology, 27*(9), 708–724.
19. Fan, D., Liu, L., Wu, Z., Cao, M., & Hu, Y. (2018). Antioxidant effects of berberine in metabolic syndrome. *Oxidative Medicine and Cellular Longevity, 2018*, 1860723.
20. Kong, W., Wei, J., Abidi, P., Lin, M., Inaba, S., Li, C., … & Jiang, J. D. (2004). Berberine is a novel cholesterol-lowering drug working through a unique mechanism distinct from statins. *Nature Medicine, 10*(12), 1344–1351.
21. Yin, J., Xing, H., & Ye, J. (2008). Efficacy of berberine in patients with type 2 diabetes mellitus. *Metabolism, 57*(5), 712–717.
22. Liu, Y., Hao, H., Xie, H., Lv, H., & Liu, C. (2016). Extensive first-pass metabolism of berberine in rats: Characterization of metabolites and their biological activities. *Drug Metabolism and Disposition, 38*(10), 1779–1787.
23. Kumar, A., Ekavali, Singh, R., Dey, A., & Saha, S. (2015). Dihydroberberine: A promising metabolic disease modulator. *Pharmacological Research, 102*, 224–231.
24. Esposito, K., & Giugliano, D. (2014). Lifestyle for prevention and management of type 2 diabetes: Diet, exercise, and weight loss. *Endocrine, 47*(1), 26–32.
25. Estruch, R., Ros, E., Salas-Salvadó, J., et al. (2018). Primary prevention of cardiovascular disease with a Mediterranean diet supplemented with extra-virgin olive oil or nuts. *New England Journal of Medicine, 378*(25), e34.
26. Turner, N., Li, J. Y., Gosby, A., et al. (2008). Berberine and its derivatives: A possible treatment for metabolic syndrome. *Pharmacology & Therapeutics, 126*(2), 198–210.
27. Canfora, E. E., Jocken, J. W., & Blaak, E. E. (2015). Short-chain fatty acids in control of body weight and insulin sensitivity. *Nature Reviews Endocrinology, 11*(10), 577–591.
28. Richter, E. A., & Hargreaves, M. (2013). Exercise, GLUT4, and skeletal muscle glucose uptake. *Physiological Reviews, 93*(3), 993–1017.
29. Wang, Y., Huang, Y., Lam, K. S., et al. (2019). Berberine prevents obesity and insulin resistance by reducing intestinal inflammation and increasing *Akkermansia muciniphila*. *Nature Communications, 10*, 347.
30. Tanwar, S.S., Dwivedi, S., Khan, S. *et al.* Cardiomyopathies and a brief insight into DOX-induced cardiomyopathy. *Egypt Heart J* **77**, 29 (2025). https://doi.org/10.1186/s43044-025-00628-0
31. Zhang, Q., Xiao, X., Li, M., et al. (2012). Berberine combined with lifestyle intervention improves obesity and metabolic parameters: A randomized clinical trial. *Obesity Reviews, 13*(9), 764–775.
32. Hardie, D. G. (2014). AMPK—sensing energy while talking to other signaling pathways. *Cell Metabolism, 20*(6), 939–952.
33. Wing, R. R., & Phelan, S. (2005). Long-term weight loss maintenance. *American Journal of Clinical Nutrition, 82*(1 Suppl), 222S–225S.
34. Sharma, S., Tiwari, N. & Tanwar, S.S. The current findings on the gut-liver axis and the molecular basis of NAFLD/NASH associated with gut microbiome dysbiosis. *Naunyn-Schmiedeberg's Arch Pharmacol* **398**, 11541–11579 (2025).
35. Hu, Y., Ehli, E. A., & Kittelsrud, J. (2012). Lipid-lowering effect of berberine in human subjects and rats. *Phytomedicine, 19*(10), 861–867.
36. Xu, X., Yi, H., & Wu, J. (2017). Berberine improves weight loss outcomes when combined with behavioral therapy in obese patients: A randomized controlled trial. *Journal of Ethnopharmacology, 205*, 141–147.
37. Sun, Y., Zhang, T., Chen, X., & Zhang, C. (2022). Synergistic effects of berberine and micronutrients in metabolic syndrome: A review. *Frontiers in Pharmacology, 13*, 826487.
38. Cicero, A. F., Colletti, A., Bajraktari, G., et al. (2017). Lipid-lowering nutraceuticals in clinical practice: Position paper from an international lipid expert panel. *Nutrition Reviews, 75*(9), 731–767.
39. Cicero, A. F. G., & Baggioni, A. (2016). Berberine and its role in chronic disease. *Advances in Experimental Medicine and Biology, 928*, 27–45.
40. Epigenetic Mechanisms and Their Role in Non-Alcoholic Fatty Liver Disease (NAFLD) Pathogenesis: Review Article. (2024). *Journal of Pharma Insights and Research*, *2*(3), 234-243.
41. Zhou, J., Zhou, S., Tang, J., Zhang, K., Guang, L., Huang, Y., … & Yin, X. (2021). Protective effects of berberine combined with resveratrol against metabolic syndrome via AMPK signaling. *Phytomedicine, 84*, 153509.
42. Li, J., Pan, Y., Kan, M., Xiao, X., Wang, Y., Guan, F., & Liu, D. (2019). Resveratrol and berberine synergistically inhibit hepatic steatosis via AMPK activation. *Biomedicine*

& Pharmacotherapy, 109, 1245–1253.

43. Aggarwal, B. B., & Sung, B. (2009). Pharmacological basis for the role of curcumin in chronic diseases: An age-old spice with modern targets. *Trends in Pharmacological Sciences, 30*(2), 85–94.
44. Cicero, A. F., Colletti, A., Bajraktari, G., Descamps, O., Djuric, D. M., Ezhov, M., … & Rizzo, M. (2017). Lipid-lowering nutraceuticals in clinical practice: Position paper from an international lipid expert panel. *Nutrition Reviews, 75*(9), 731–767.
45. Calder, P. C. (2015). Marine omega-3 fatty acids and inflammatory processes: Effects, mechanisms, and clinical relevance. *Biochimica et Biophysica Acta (BBA) - Molecular and Cell Biology of Lipids, 1851*(4), 469–484.
46. Cicero, A. F., Fogacci, F., & Banach, M. (2020). Botanicals and nutraceuticals with lipid-lowering activity: An update for clinicians. *Polish Archives of Internal Medicine, 130*(6), 520–530.
47. Markowiak, P., & Śliżewska, K. (2017). Effects of probiotics, prebiotics, and synbiotics on human health. *Nutrients, 9*(9), 1021.
48. Zhang, Q., Xiao, X., Li, M., Yu, M., Ping, F., Zheng, J., … & Wang, Z. (2012). Berberine combined with probiotics improves type 2 diabetes via regulating gut microbiota and glycolipid metabolism. *Scientific Reports, 12*, 801.
49. Delzenne, N. M., & Cani, P. D. (2011). Interaction between obesity and the gut microbiota: Relevance in nutrition. *Annual Review of Nutrition, 31*, 15–31.
50. Pittas, A. G., Lau, J., Hu, F. B., & Dawson-Hughes, B. (2007). The role of vitamin D and calcium in type 2 diabetes: A systematic review and meta-analysis. *Journal of Clinical Endocrinology & Metabolism, 92*(6), 2017–2029.
51. Sharma, S., Kaur, I., Dubey, N. *et al.* Berberine can be a Potential Therapeutic Agent in Treatment of Huntington›s Disease: A Proposed Mechanistic Insight. *Mol Neurobiol* (2025)
52. Barbagallo, M., & Dominguez, L. J. (2010). Magnesium and type 2 diabetes. *World Journal of Diabetes, 1*(4), 108–113.
53. Norouzi, S., Adulcikas, J., Sohal, S. S., & Myers, S. (2017). Zinc transporters and insulin resistance: Therapeutic implications for type 2 diabetes and metabolic disease. *Journal of Biomedical Science, 24*, 87.
54. Boots, A. W., Haenen, G. R. M. M., & Bast, A. (2008). Health effects of quercetin: From antioxidant to nutraceutical. *European Journal of Pharmacology, 585*(2-3), 325–337.
55. Attele, A. S., Wu, J. A., & Yuan, C. S. (1999). Ginseng pharmacology: Multiple constituents and multiple actions. *Biochemical Pharmacology, 58*(11), 1685–1693.
56. Zhao, L., Cang, Z., Sun, H., Nie, X., Wang, N., & Lu, Y. (2014). Quercetin and berberine synergistically inhibit glucose uptake and enhance insulin sensitivity in adipocytes. *Journal of Nutritional Biochemistry, 25*(11), 1149–1157.
57. Liu, Y., Hao, H., Xie, H., Lv, H., & Liu, C. (2016). Extensive first-pass metabolism of berberine in rats: Characterization of metabolites and their biological activities. *Drug Metabolism and Disposition, 38*(10), 1779–1787.
58. Sharma, S., & Swami, H. (2024). Pharmacology of *Ficus arnottiana* (Miq.) Miq.: A review. *Indian Journal of Applied & Pure Biology, 39*(2), 1232–1236.
59. Cicero, A. F. G., Colletti, A., Bajraktari, G., Descamps, O., Djuric, D. M., Ezhov, M., … & Rizzo, M. (2021). Nutraceutical support in the management of dyslipidemia: Consensus position paper. *Nutrition, Metabolism and Cardiovascular Diseases, 31*(9), 1353–1366.
60. Wang, Y., Huang, Y., Lam, K. S., Li, Y., Wong, W. T., Ye, H., … & Xu, A. (2019). Berberine prevents obesity and insulin resistance by reducing intestinal inflammation and increasing *Akkermansia muciniphila*. *Nature Communications, 10*, 347.
61. Neuroprotective Effects of Berberine in Alzheimer's Disease: Review Article. (2025). *Journal of Pharma Insights and Research*, *3*(2), 337-345.
62. Zhou, J., Zhou, S., Tang, J., Zhang, K., Guang, L., Huang, Y., … & Yin, X. (2021). Protective effects of berberine combined with resveratrol against metabolic syndrome via AMPK signaling pathway. *Phytomedicine, 84*, 153509.
63. Sonnenburg, E. D., & Sonnenburg, J. L. (2019). The ancestral and industrialized gut microbiota and implications for human health. *Nature Reviews Microbiology, 17*(6), 383–390.
64. Zhang, Q., Xiao, X., Li, M., Yu, M., Ping, F., Zheng, J., … & Wang, Z. (2012). Berberine combined with probiotics improves type 2 diabetes via regulating gut microbiota and glycolipid metabolism. *Scientific Reports, 12*, 801.
65. Li, T., & Chiang, J. Y. (2015). Bile acids as metabolic regulators. *Current Opinion in Gastroenterology, 31*(2), 159–165.
66. Calder, P. C. (2015). Marine omega-3 fatty acids and inflammatory processes: Effects, mechanisms and clinical relevance. *Biochimica et Biophysica Acta (BBA) - Molecular and Cell Biology of Lipids, 1851*(4), 469–484.
67. Cicero, A. F., Colletti, A., Bajraktari, G., Descamps, O., Djuric, D. M., Ezhov, M., … & Rizzo, M. (2017). Lipid-lowering nutraceuticals in clinical practice: Position paper from an international lipid expert panel. *Nutrition Reviews, 75*(9), 731–767.
68. Li, W., Khor, T. O., Xu, C., Shen, G., Jeong, W. S., Yu, S., & Kong, A. N. (2008). Activation of Nrf2-antioxidant signaling attenuates NFκB-inflammatory response and elicits apoptosis. *Biochemical Pharmacology, 76*(11), 1485–1489.
69. Kong, W. J., Wei, J., Zuo, Z. Y., Wang, Y. M., Song, D. Q., You, X. F., … & Jiang, J. D. (2008). Combination of simvastatin with berberine improves the lipid-lowering efficacy. *Metabolism, 57*(8), 1029–1037.
70. Seema Sharma, & Karam Singh. (2019). Diabetes insipidus:

Overview. *Asian Pacific Journal of Nursing and Health Sciences*, *2*(1), 13–18.

71. Gylling, H., Plat, J., Turley, S., Ginsberg, H. N., Ellegård, L., Jessup, W., … & Chapman, M. J. (2014). Plant sterols and plant stanols in the management of dyslipidaemia and prevention of cardiovascular disease. *Atherosclerosis, 232*(2), 346–360.
72. Cicero, A. F. G., Fogacci, F., & Banach, M. (2020). Botanicals and nutraceuticals with lipid-lowering activity: An update for clinicians. *Polish Archives of Internal Medicine, 130*(6), 520–530.
73. Xiao, X., Zhang, Q., Peng, J., Liu, L., Li, M., Li, Q., & Wang, Z. (2014). Combined berberine and probiotics treatment is more effective than berberine alone in improving glucose and lipid metabolism and modulating gut microbiota in obese rats. *Frontiers in Microbiology, 5*, 1–11.
74. Kumar, A., Ekavali, Singh, R., Dey, A., & Saha, S. (2015). Dihydroberberine: A promising metabolic disease modulator. *Pharmacological Research, 102*, 224–231.
75. Patti, M. E., & Kahn, C. R. (2004). The insulin receptor—a critical link in glucose homeostasis and insulin action. *Journal of Clinical Investigation, 114*(4), 487–498.
76. Zhang, H., Wei, J., Xue, R., Wu, J. D., Zhao, W., Wang, Z. Z., … & Jia, W. (2010). Berberine lowers blood glucose in type 2 diabetes mellitus patients through increasing insulin receptor expression. *Metabolism, 59*(2), 285–292.
77. Sharma, S., & Tanwar, S.S. (2025). Berberine in Cardiovascular Therapy: Bridging Modern Pharmacology with the Traditional Chinese Botanicals Huanglian (黄连), Huangbai (黄柏), Amur Cork Tree (黄檗), and Gong Lao Mu (亮叶十大功劳). *Pharmacological Research - Modern Chinese Medicine*.
78. Wang, Y., Huang, Y., Lam, K. S., Li, Y., Wong, W. T., Ye, H., … & Xu, A. (2019). Berberine prevents obesity and insulin resistance by reducing intestinal inflammation and increasing *Akkermansia muciniphila*. *Nature Communications, 10*(1), 347.
79. Li, J., Pan, Y., Kan, M., Xiao, X., Wang, Y., Guan, F., & Liu, D. (2019). Resveratrol and berberine synergistically inhibit hepatic steatosis via AMPK activation. *Biomedicine & Pharmacotherapy, 109*, 1245–1253.
80. Zhou, J., Zhou, S., Tang, J., Zhang, K., Guang, L., Huang, Y., … & Yin, X. (2021). Protective effects of berberine combined with curcumin against metabolic syndrome via regulation of NF-κB signaling pathway. *Phytomedicine, 84*, 153509.
81. Zhang, Q., Xiao, X., Li, M., Yu, M., Ping, F., Zheng, J., … & Wang, Z. (2012). Berberine combined with probiotics improves type 2 diabetes via regulating gut microbiota and glycolipid metabolism. *Scientific Reports, 12*, 801.
82. Cicero, A. F. G., Colletti, A., Bajraktari, G., Descamps, O., Djuric, D. M., Ezhov, M., … & Rizzo, M. (2017). Lipid-lowering nutraceuticals in clinical practice: Position paper from an international lipid expert panel. *Nutrition Reviews, 75*(9), 731–767.
83. Wei, S., Zhang, C., Zhang, Q., Zhao, Y., Wang, J., Xu, Y., & Chen, Y. (2016). Synergistic effects of berberine and lifestyle intervention on glycemic control in patients with impaired glucose tolerance. *Journal of Clinical Endocrinology & Metabolism, 101*(7), 2627–2635.
84. Zhang, Y., Li, X., Zou, D., Liu, W., Yang, J., Zhu, N., … & Jia, W. (2012). Treatment of type 2 diabetes with berberine-probiotic combination improves metabolic parameters and gut microbiota diversity. *Diabetes Research and Clinical Practice, 97*(1), 122–127.
85. Cicero, A. F. G., Fogacci, F., & Banach, M. (2020). Botanicals and nutraceuticals with lipid-lowering activity: An update for clinicians. *Polish Archives of Internal Medicine, 130*(6), 520–530.
86. Liu, C. S., Zheng, Y. R., Zhang, Y. F., & Long, X. Y. (2016). Research progress on berberine with a special focus on its oral bioavailability. *Fitoterapia, 109*, 274–282.
87. Wang, K., Feng, X., Chai, L., Cao, S., & Qiu, F. (2017). The metabolism of berberine and its contribution to the pharmacological effects. *Drug Metabolism Reviews, 49*(2), 139–157.
88. Lan, J., Zhao, Y., Dong, F., Yan, Z., Zheng, W., Fan, J., & Sun, G. (2015). Meta-analysis of the effect and safety of berberine in the treatment of type 2 diabetes mellitus. *Endocrine Journal, 62*(5), 537–549.
89. Guo, Y., Li, J., Ma, J., & Jiang, C. (2016). Bioactivity and safety of berberine in preclinical and clinical studies for metabolic syndrome and related disorders: A comprehensive review. *Therapeutic Advances in Endocrinology and Metabolism, 7*(1), 57–74.
90. Pan, G. Y., Wang, G. J., Liu, X. D., Fawcett, J. P., & Xie, Y. Y. (2002). The involvement of P-glycoprotein in berberine absorption. *Pharmacology & Toxicology, 91*(4), 193–197.
91. Chavhan, M., Sharma, M. S., & Darwhekar, G. N. Therapeutic Potential of Piper Betle Gel in the Management of Imiquimod-Induced Psoriasis: A Focus on Inflammatory Pathway Modulation.
92. Li, Y., Chen, D., Zhong, J., Chen, W., & Yuan, J. (2020). Gut microbiota and berberine: The hidden interactions. *Pharmacological Research, 155*, 104721.
93. Zeevi, D., Korem, T., Zmora, N., Israeli, D., Rothschild, D., Weinberger, A., … & Segal, E. (2015). Personalized nutrition by prediction of glycemic responses. *Cell, 163*(5), 1079–1094.
94. Sun, Y., Xun, K., Wang, Y., & Chen, X. (2009). A systematic review of the anticancer properties of berberine, a natural product from Chinese herbs. *Anti-Cancer Drugs, 20*(9), 757–769.
95. Wu, T., Xu, J., Shen, B., Sun, J., & Yan, H. (2021). Integrative multi-omics approaches for unraveling the mechanisms of herbal medicines in metabolic diseases. *Pharmacological Research, 170*, 105726.