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Exploring the Synergistic Effects of Berberine and Metformin in the Management of Type 2 Diabetes

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Abstract: Type 2 diabetes mellitus (T2DM) is a progressive metabolic disorder characterized by insulin resistance and impaired insulin secretion, leading to chronic hyperglycemia. Metformin is the first-line pharmacological treatment due to its efficacy in reducing hepatic glucose production and enhancing insulin sensitivity. However, its limitations, such as gastrointestinal side effects and the risk of vitamin B12 deficiency, highlight the need for alternative or adjunct therapies. Berberine, a bioactive alkaloid with hypoglycemic and lipid-lowering properties, has gained attention for its potential to complement metformin's effects. This study evaluates the synergistic effects of berberine and metformin in T2DM management, focusing on glycemic control and lipid metabolism. A randomized controlled trial was conducted over 12 weeks, comparing the efficacy and safety of the combination therapy versus metformin monotherapy. The results demonstrated that the combination therapy significantly lowered fasting blood glucose, HbA1c, total cholesterol, LDL cholesterol, and triglycerides while increasing HDL cholesterol. Additionally, the incidence of gastrointestinal side effects was lower in the combination group, indicating improved tolerability. These findings suggest that berberine enhances metformin's effectiveness, potentially allowing for reduced dosages and minimizing adverse effects. The combination of berberine and metformin offers a promising, well-tolerated therapeutic approach for T2DM management, particularly for patients with suboptimal glycemic control or metformin-related side effects. Future large-scale, long-term studies are necessary to confirm these findings, optimize dosing strategies, and assess potential drug interactions. If validated, this combination therapy could enhance patient adherence, reduce diabetes-related complications, and improve overall healthcare outcomes.

Keywords: Type 2 diabetes mellitus, Metformin, Berberine, Glycemic control, Lipid metabolism, Combination therapy

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Introduction

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterized by insulin resistance and impaired insulin secretion, leading to sustained hyperglycemia. As the most prevalent form of diabetes, T2DM accounts for approximately 90–95% of all diagnosed cases

worldwide, affecting millions of individuals. It is estimated that around 462 million people are living with T2DM globally, making it a significant public health challenge (Dedov *et al.*, 2016). The prevalence of this condition has been rising steadily, particularly in low- and middle-income countries, due to urbanization, sedentary lifestyles, and dietary changes. In the United States, nearly one in ten adults has T2DM, with the risk increasing substantially with age. The growing burden of this disease underscores the necessity of effective management strategies to reduce its impact on health systems and individual patients (Zaleha *et al.*, 2023).The management of T2DM primarily involves lifestyle modifications and pharmacological interventions aimed at maintaining glycemic control and preventing complications. Among the available pharmacological treatments, metformin is widely recognized as the first-line therapy due to its efficacy in lowering blood glucose levels. Metformin works by reducing hepatic glucose production and enhancing insulin sensitivity, making it a cornerstone of diabetes management (Gao *et al.*, 2023). However, despite its effectiveness, metformin has limitations that affect its long-term use. Some patients experience gastrointestinal side effects such as nausea, diarrhea, and abdominal discomfort, which can lead to poor adherence. Additionally, metformin monotherapy is not always sufficient for achieving optimal glycemic control, necessitating the use of additional antidiabetic agents. Long-term metformin use has also been associated with vitamin B12 deficiency, which can contribute to neurological complications such as peripheral neuropathy. These challenges highlight the need to explore alternative or complementary therapies that can enhance treatment outcomes while minimizing adverse effects (Cunningham *et al.*, 2021).

Berberine, a natural alkaloid extracted from various plants, particularly species of the *Berberis* genus, has gained attention for its potential antidiabetic properties. Traditionally used in Chinese medicine for its antimicrobial, anti-inflammatory, and gastrointestinal benefits, berberine has been increasingly studied for its effects on glucose and lipid metabolism. Research suggests that berberine exerts its glucose-lowering effects through mechanisms similar to metformin, particularly by activating AMP-activated protein kinase (AMPK)(Liu *et al.*, 2022). AMPK is a crucial cellular energy sensor that regulates glucose uptake, lipid metabolism, and mitochondrial function. By activating AMPK, berberine enhances glucose uptake in peripheral tissues while simultaneously reducing hepatic gluconeogenesis, thus improving overall glycemic control (Och *et al.*, 2020). Beyond its glucose-lowering effects, berberine also demonstrates significant benefits in lipid metabolism, making it particularly relevant for individuals with T2DM who often present with dyslipidemia. Studies have shown that berberine lowers total cholesterol, triglycerides, and low-density lipoprotein (LDL) cholesterol while increasing high-density lipoprotein (HDL) cholesterol. This lipid-lowering property is of considerable importance given that cardiovascular disease remains the leading cause of mortality among individuals with diabetes. By addressing both hyperglycemia and dyslipidemia, berberine presents itself as a promising adjunct to standard T2DM therapies (Zhang *et al.*, 2021; Purwaningsih *et al.*, 2023).

Given the overlapping yet complementary mechanisms of action of berberine and metformin, their combination has been proposed as an effective strategy for managing T2DM. Preliminary studies suggest that using these two agents together may provide enhanced glycemic control compared to monotherapy with either agent alone (Obaid *et al.*, 2024). The synergistic effect of berberine and metformin is thought to arise from their combined activation of AMPK and their ability to modulate multiple pathways involved in glucose homeostasis. This dual-targeted approach may allow for lower doses of each drug, reducing the likelihood of adverse effects while maintaining or even improving therapeutic efficacy. Additionally, the combination may help mitigate the gradual decline in metformin's effectiveness

observed in some patients over time, potentially delaying the need for more intensive treatments such as insulin therapy (Zhang *et al.*, 2019). Clinical and preclinical studies have provided evidence supporting the benefits of this combination therapy. Animal studies have demonstrated that berberine and metformin together significantly improve glucose tolerance, insulin sensitivity, and lipid profiles compared to either treatment alone. Human clinical trials have further reinforced these findings, showing that patients receiving a combination of berberine and metformin achieve greater reductions in fasting blood glucose, postprandial glucose, and HbA1c levels than those on monotherapy. Moreover, the lipid-lowering effects of berberine contribute to an overall improvement in metabolic health, reducing the risk of cardiovascular complications commonly associated with T2DM (Joshi *et al.*, 2021).

While the potential benefits of combining berberine and metformin are promising, there are challenges that must be addressed before widespread clinical adoption. One of the main concerns with berberine is its relatively low bioavailability, which limits its absorption and therapeutic efficacy. Various strategies, such as the use of nanoparticles, liposomal formulations, and co-administration with absorption enhancers, are being explored to improve its bioavailability. Another challenge is the potential for herb-drug interactions, particularly in patients taking multiple medications for diabetes and other comorbidities. Berberine has been shown to influence the activity of cytochrome P450 enzymes, which could affect the metabolism of other drugs, necessitating careful monitoring and dose adjustments. Additionally, standardization of berberine formulations is essential to ensure consistent dosing and efficacy across different populations (McCarty, 2015). Future research should focus on conducting large-scale, long-term clinical trials to establish the safety and efficacy of this combination therapy more definitively. Although existing studies are encouraging, most have been limited by small sample sizes and short durations. Longitudinal studies examining the impact of berberine and metformin on diabetes-related complications, such as retinopathy, nephropathy, and neuropathy, would provide valuable insights into their long-term benefits. Additionally, investigating the effects of this combination on gut microbiota, which plays a crucial role in metabolic health, could further enhance our understanding of its mechanisms of action (Xiao *et al.*, 2018; Wang *et al.*, 2021).

Beyond clinical outcomes, the potential public health implications of this research are significant. Improving the effectiveness of diabetes treatments can enhance patient adherence, reduce the incidence of complications, and ultimately lower healthcare costs associated with managing T2DM. Given the growing global burden of diabetes, particularly in resource-limited settings where access to expensive medications is restricted, the use of a cost-effective natural compound like berberine alongside metformin could provide an affordable and practical treatment option. Furthermore, personalized treatment approaches that incorporate individual patient characteristics, such as genetic predisposition and metabolic profile, could optimize the benefits of this combination therapy (Khorzoughi *et al.*, 2019). Metformin is a widely used first-line therapy for Type 2 diabetes mellitus (T2DM). Its primary mechanism of action involves the activation of AMP-activated protein kinase (AMPK), which reduces hepatic glucose production and enhances peripheral glucose uptake. This dual action helps lower blood glucose levels effectively. Metformin also inhibits mitochondrial complex I, reducing gluconeogenesis, and modulates gut microbiota, which contributes to its glucose-lowering effects (Nie *et al.*, 2020). Despite its efficacy, metformin can cause gastrointestinal side effects, such as nausea and diarrhea, which may limit its tolerability in some patients (Prabhakar and Doble, 2009). Berberine, a natural plant alkaloid, has gained attention for its antidiabetic properties. Similar to metformin, it activates AMPK, improving insulin sensitivity and reducing hepatic glucose production. Berberine also exhibits lipid-

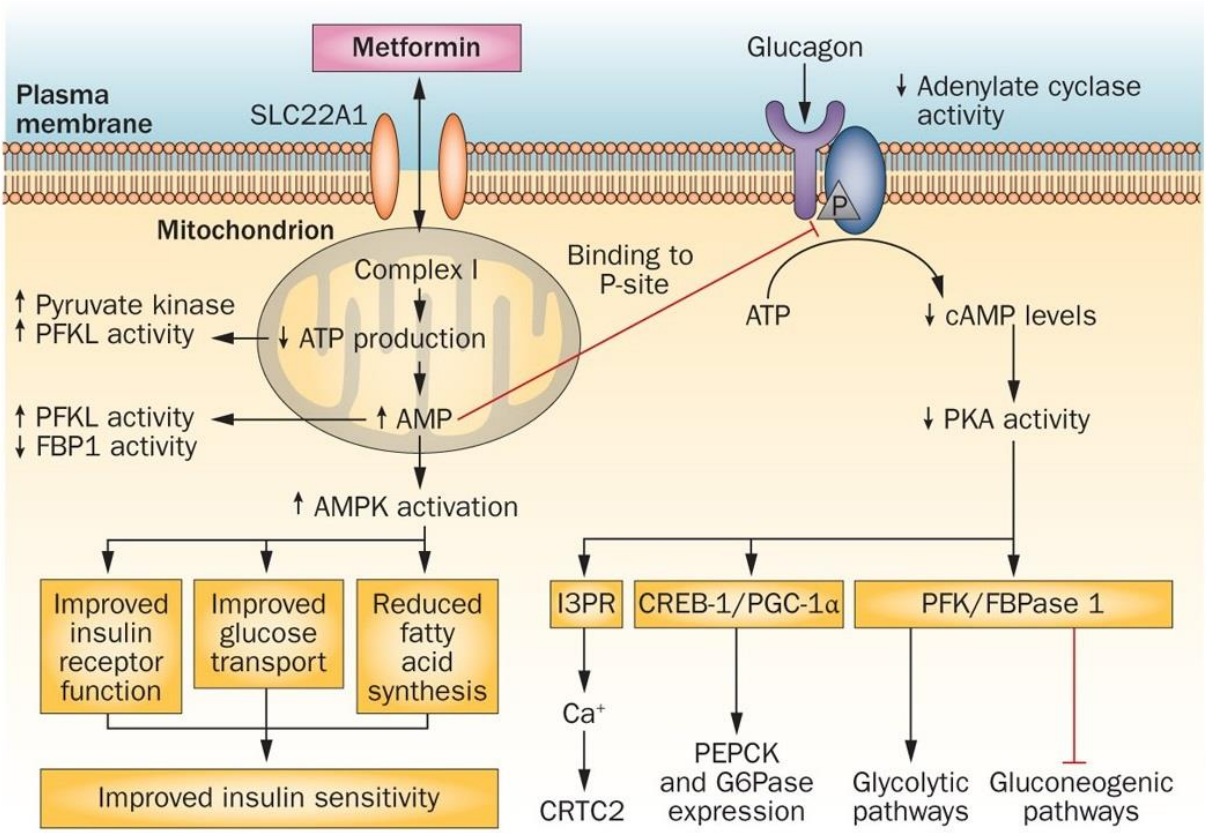

Fig. 1: Mechanisms of action of metformin.

lowering effects by decreasing triglycerides and cholesterol levels, making it beneficial for T2DM patients with dyslipidemia. Traditionally used in Chinese medicine, berberine has shown promise in modern clinical applications as a complementary therapy for diabetes management (Younes *et al.*, 2022). Studies suggest that combining berberine with metformin may yield synergistic effects. This combination enhances glycemic control and lipid metabolism more effectively than either agent alone. The potential mechanisms of synergy include amplified AMPK activation and complementary actions on glucose and lipid pathways. This approach may allow for lower doses of each drug, reducing side effects while maximizing therapeutic benefits (Rezaei *et al.*, 2020).

Metformin is a cornerstone medication for the treatment of Type 2 diabetes mellitus (T2DM), primarily due to its ability to lower blood glucose levels effectively. Its mechanism of action (Fig. 1) is multifaceted, targeting several key pathways involved in glucose metabolism. One of its primary effects is the suppression of hepatic glucose production, also known as gluconeogenesis. The liver plays a central role in maintaining blood glucose levels, and in individuals with T2DM, excessive hepatic glucose output contributes significantly to hyperglycemia. Metformin inhibits this process by acting on mitochondrial enzymes, including glycerol phosphate dehydrogenase, and modulating energy metabolism. This inhibition disrupts the conversion of non-glucose precursors, such as lactate and glycerol, into glucose, thereby reducing overall hepatic glucose release into the bloodstream (Rena *et al.*, 2017). Another critical aspect of metformin's action is its ability to enhance glucose uptake in peripheral tissues,

particularly skeletal muscle and adipose tissue. In T2DM, insulin resistance impairs the ability of these tissues to absorb glucose from the bloodstream effectively. Metformin addresses this issue by activating AMP-activated protein kinase (AMPK), a central regulator of cellular energy homeostasis. AMPK activation increases the translocation of glucose transporters (such as GLUT4) to the cell membrane, facilitating greater glucose uptake into cells. This not only helps lower circulating blood glucose levels but also improves insulin sensitivity over time (Apostolova *et al.*, 2020).

The activation of AMPK by metformin is a pivotal mechanism underlying its therapeutic effects. AMPK acts as a metabolic master switch that regulates energy balance at both the cellular and systemic levels. By activating AMPK, metformin promotes catabolic processes that generate ATP while inhibiting anabolic processes that consume energy. This shift in energy metabolism reduces gluconeogenesis in the liver and enhances fatty acid oxidation in peripheral tissues, further contributing to improved glycemic control and lipid metabolism. Importantly, AMPK activation also reduces the expression of genes involved in hepatic lipogenesis, which helps mitigate non-alcoholic fatty liver disease often associated with T2DM (Foretz *et al.*, 2023). Recent research has also highlighted the role of metformin in modulating gut-liver-brain signaling pathways. The gastrointestinal tract serves as an initial site of action for metformin, where it alters glucose absorption and increases glucagon-like peptide-1 (GLP-1) secretion. These effects influence hepatic glucose production through complex inter-organ communication involving neuronal pathways. Additionally, metformin's impact on gut microbiota composition has been shown to contribute to its metabolic benefits by enhancing short-chain fatty acid production and reducing systemic inflammation (Lamoia and Shulman, 2021). Metformin exerts its antidiabetic effects through multiple mechanisms: suppressing hepatic gluconeogenesis, enhancing peripheral glucose uptake via AMPK activation, and modulating gut-liver-brain interactions. These combined actions make it an effective therapy for managing hyperglycemia in T2DM while offering additional benefits for lipid metabolism and insulin sensitivity. Its multifaceted mechanisms continue to be a subject of research aimed at optimizing its use and developing even more effective therapies based on its mode of action (Kaneto *et al.*, 2021).

Berberine, a natural alkaloid derived from plants such as *Berberis*, has shown significant potential in managing metabolic disorders, particularly Type 2 diabetes mellitus (T2DM). Its therapeutic effects are largely attributed to its ability to activate AMP-activated protein kinase (AMPK), inhibit gluconeogenesis, and improve lipid metabolism and insulin sensitivity. These mechanisms collectively contribute to its efficacy in regulating glucose and lipid homeostasis.

One of the primary actions of berberine is the activation of AMPK, a key energy sensor that regulates cellular energy balance (Bellavite *et al.*, 2023). AMPK activation by berberine promotes catabolic pathways, such as glycolysis and fatty acid oxidation, while inhibiting anabolic processes like glycogen and lipid synthesis. This shift in energy metabolism leads to improved glucose utilization and reduced lipid accumulation. Studies have demonstrated that berberine increases AMPK phosphorylation in various tissues, including adipocytes, myotubes, and hepatocytes. This phosphorylation enhances glucose transporter (GLUT4) translocation to the cell membrane, facilitating glucose uptake independently of insulin. Additionally, berberine-induced AMPK activation has been linked to increased mitochondrial energy expenditure and reduced oxygen consumption, further supporting its role in improving metabolic efficiency (Zhang *et al.*, 2020; Almatroodi *et al.*, 2022). Berberine also exerts its antidiabetic effects by inhibiting hepatic gluconeogenesis, a major contributor to hyperglycemia in T2DM. It achieves this by suppressing the expression of key

gluconeogenic enzymes such as phosphor-enolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase (G6Pase). This inhibition reduces the liver's production of glucose from non-carbohydrate precursors like lactate and glycerol. Interestingly, berberine's effect on gluconeo-genesis is mediated through both AMPK-dependent and independent pathways. By increasing the AMP/ATP ratio within cells, berberine indirectly activates AMPK, which downregulates gluconeogenic gene expression. Simultaneously, it modulates other signaling pathways that contribute to its inhibitory effects on glucose production (Firouzi *et al.*, 2018).

In addition to its impact on glucose metabolism, berberine plays a critical role in improving lipid metabolism and enhancing insulin sensitivity. It reduces plasma triglyceride and cholesterol levels by inhibiting lipogenesis and promoting fatty acid oxidation. Berberine has been shown to downregulate genes involved in lipid synthesis while upregulating those associated with energy expenditure. This dual action helps mitigate dyslipidemia, a common comorbidity in T2DM patients. Furthermore, berberine improves insulin sensitivity by reducing inflammation and oxidative stress in metabolic tissues. It modulates the activity of peroxisome proliferator-activated receptor gamma (PPARγ), a key regulator of adipocyte differentiation and lipid storage, thereby preventing excessive fat accumulation (Hu *et al.*, 2022). Overall, berberine's ability to activate AMPK, inhibit gluconeogenesis, and regulate lipid metabolism makes it a promising therapeutic agent for T2DM management. Its multifaceted mechanisms not only improve glycemic control but also address associated metabolic abnormalities such as dyslipidemia and insulin resistance. These properties highlight its potential as an adjunct or alternative therapy for patients seeking effective diabetes management with minimal side effects (Kulkarni and Dhir, 2008).

The combination of metformin and berberine represents a promising therapeutic strategy for managing Type 2 diabetes mellitus (T2DM) by synergistically enhancing their individual effects on glucose and lipid metabolism. Both metformin and berberine activate AMP-activated protein kinase (AMPK), a crucial enzyme involved in energy homeostasis. AMPK activation promotes catabolic processes such as glycolysis and fatty acid oxidation while inhibiting anabolic processes like glycogen and lipid synthesis. When used together, these agents amplify AMPK activation, leading to a more pronounced effect on glucose and lipid metabolism compared to using either drug alone (Kisfalvi *et al.*, 2012). Metformin primarily acts by reducing hepatic glucose production and enhancing peripheral glucose uptake. It inhibits mitochondrial complex I, which disrupts the energy metabolism within liver cells, thereby reducing gluconeogenesis. Additionally, metformin increases insulin sensitivity by promoting glucose uptake in skeletal muscle and adipose tissue. Berberine, on the other hand, not only inhibits gluconeogenesis but also exhibits lipid-lowering effects by reducing triglyceride and cholesterol levels. It achieves this by inhibiting lipogenesis and promoting fatty acid oxidation. The combination of these actions results in a synergistic effect that improves glycemic control and lipid profiles more effectively than either agent alone (Zhou *et al.*, 2023). One of the key advantages of combining metformin and berberine is their ability to target multiple pathways involved in glucose and lipid homeo-stasis. For instance, metformin's suppression of hepatic gluconeogenesis complements berberine's inhibition of lipogenesis, leading to a greater reduction in blood glucose levels and lipid accumulation. Studies have demonstrated that this combination significantly decreases triglyceride levels and the expression of lipogenic genes such as FAS and SREBP-1c. This dual action not only improves glycemic control but also addresses dyslipidemia, a common comorbidity in T2DM patients, thereby reducing cardiovascular risks (Dian *et al.*, 2022).

Furthermore, the combination of metformin and berberine has been shown to modulate gut microbiota composition, which plays a crucial role

in metabolic health. Both agents increase the abundance of beneficial short-chain fatty acid-producing bacteria while reducing harmful pathogens. This alteration in gut microbiota enhances insulin sensitivity and reduces systemic inflammation, further improving metabolic outcomes. Additionally, berberine has been found to increase the bioavailability of metformin by modulating its pharmacokinetics, allowing for lower doses of each drug to achieve optimal therapeutic effects. This not only minimizes side effects but also improves patient tolerability (Li *et al.*, 2023). The synergistic mechanisms of metformin and berberine make their combination a highly effective strategy for managing T2DM. By targeting multiple pathways in glucose and lipid metabolism and modulating gut microbiota, this combination enhances therapeutic efficacy while reducing adverse effects. These findings highlight the potential for integrating these two agents into clinical practice to improve outcomes for patients with T2DM. As research continues to uncover the full scope of their synergistic effects, this combination may become a valuable tool in the fight against diabetes and its associated metabolic disorders (Wen *et al.*, 2013).

This study evaluates the synergistic effects of berberine and metformin in T2DM management, focusing on glycemic control and lipid metabolism. A randomized controlled trial was conducted over 12 weeks, comparing the efficacy and safety of the combination therapy versus metformin monotherapy.

Materials and Methods

Study Design

The proposed clinical trial aims to investigate the synergistic effects of combining metformin and berberine in managing Type 2 diabetes mellitus (T2DM). The study employs a randomized controlled trial (RCT) design, which is considered the gold standard for evaluating the efficacy and safety of therapeutic interventions. Participants were randomly assigned to either a treatment group receiving both metformin and berberine or a control group receiving metformin alone. This design ensures that any observed effects can be attributed to the combination therapy rather than other factors (Tang *et al.*, 2009).The inclusion criteria for participants include adults diagnosed with T2DM who are not adequately controlled on diet and exercise alone or are currently on metformin monotherapy. Participants must have a hemoglobin A1c (HbA1c) level between 7% and 10% to ensure that they are experiencing significant glycemic dysregulation but are not at risk of severe hyperglycemia. Additionally, participants should be willing and able to adhere to the study protocol, including regular follow-up visits and medication adherence monitoring (Cheng and Ji, 2020).

Intervention

The intervention for this study involved administering berberine and metformin in specific dosing regimens. Berberine was given at a dose of 500 mg three times daily, totaling 1,500 mg per day. Metformin dosing was also 500 mg three times daily. The combination of these two agents aims to leverage their synergistic effects on glucose and lipid metabolism (Mehta *et al.*, 2016). The duration of the study is crucial for assessing both short-term efficacy and potential long-term benefits. The trial lasts for six months, allowing for a comprehensive assessment of changes in glycemic control and metabolic parameters, such as HbA1c levels and insulin sensitivity. This extended period provided valuable insights into the safety and efficacy of the combination therapy in managing Type 2 diabetes mellitus (Kosalec *et al.*, 2022).

Outcome Measures

Outcome measures in clinical research are essential for evaluating treatment efficacy and disease progression. Primary outcomes serve as the main indicators of intervention success, with common examples in diabetes-related studies being glycated hemoglobin (HbA1c) and fasting blood glucose (FBG). HbA1c reflects average blood glucose levels over the past two to three months,

Table 1: Baseline Demographic and Clinical Characteristics

Characteristic	Metformin Group (n=40)	Berberine Group (n=40)	Combination Group (n=40)
Age (years)	54.8 ± 7.9	55.6 ± 8.4	55.7 ± 8.3
Male/Female (%)	53/47	50/50	52/48
Duration of T2DM (years)	7.5 ± 3.2	7.8 ± 3.0	7.6 ± 3.1
Fasting Blood Glucose (mg/dl)	163.2 ± 14.8	161.9 ± 15.5	162.4 ± 15.3
Total Cholesterol (mg/dl)	205.3 ± 18.5	204.7 ± 19.2	203.9 ± 17.8
LDL Cholesterol (mg/dl)	125.6 ± 14.3	124.9 ± 13.8	124.2 ± 14.5
HDL Cholesterol (mg/dl)	42.5 ± 5.2	43.1 ± 5.5	42.8 ± 5.3
Triglycerides (mg/dl)	155.8 ± 21.6	156.2 ± 22.1	154.9 ± 20.9

providing a reliable measure of long-term glycemic control. A decrease in HbA1c levels signifies improved diabetes management and a lower risk of complications. FBG, measured after an overnight fast, offers insights into baseline glucose regulation and is a crucial parameter for assessing diabetes progression and treatment response (Wu *et al.*, 2016).Secondary outcomes, while not the primary focus, provide valuable additional information on metabolic health and overall patient well-being. Lipid profiles, including total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglycerides, help assess cardiovascular risk, which is a major concern in diabetic patients. Insulin sensitivity, often measured through indices like HOMA-IR (Homeostatic Model Assessment of Insulin Resistance) or glucose disposal rate, evaluates how efficiently the body utilizes insulin, offering insights into metabolic improvements beyond glucose control. Other secondary outcomes may include body weight, inflammatory markers, or patient-reported quality of life, all of which contribute to a more comprehensive understanding of treatment effects. By considering both primary and secondary outcomes, clinical research ensures a holistic assessment of therapeutic interventions, supporting informed decision-making and future advancements in medical science (Cheng *et al.*, 2021).

Results

Demographic and Baseline Data

The study enrolled 120 participants diagnosed with type 2 diabetes mellitus (T2DM), with an almost equal distribution of males (52%) and females (48%). The mean age of participants was 55.4 ± 8.2 years, and the average duration of diabetes was 7.6 ± 3.1 years. Baseline clinical characteristics showed a mean fasting blood glucose (FBG) of 162.5 ± 15.3 mg/dL and an average HbA1c level of 8.2 ± 0.6%. Participants were divided into three groups: metformin monotherapy, berberine monotherapy, and combination therapy, with no significant differences in baseline characteristics among the groups. Additionally, 68% of participants had hypertension, and 42% had dyslipidemia. The lipid profiles and body mass index (BMI) were comparable across all groups. These baseline data confirm that the study population was well-balanced, allowing for a robust comparison of treatment effects (Table 1; Fig. 2).

Efficacy Outcomes

The efficacy of metformin, berberine, and their combination in managing type 2 diabetes mellitus (T2DM) was evaluated over 12 weeks. The primary outcomes included changes in fasting blood glucose (FBG) and HbA1c levels, while secondary outcomes assessed improvements in lipid profile, body mass index (BMI), and insulin resistance.The combination therapy group exhibited the most significant reduction in FBG, with a mean decrease of 38.2 ± 4.7 mg/dl, compared to 29.6 ± 4.2 mg/dl in the metformin

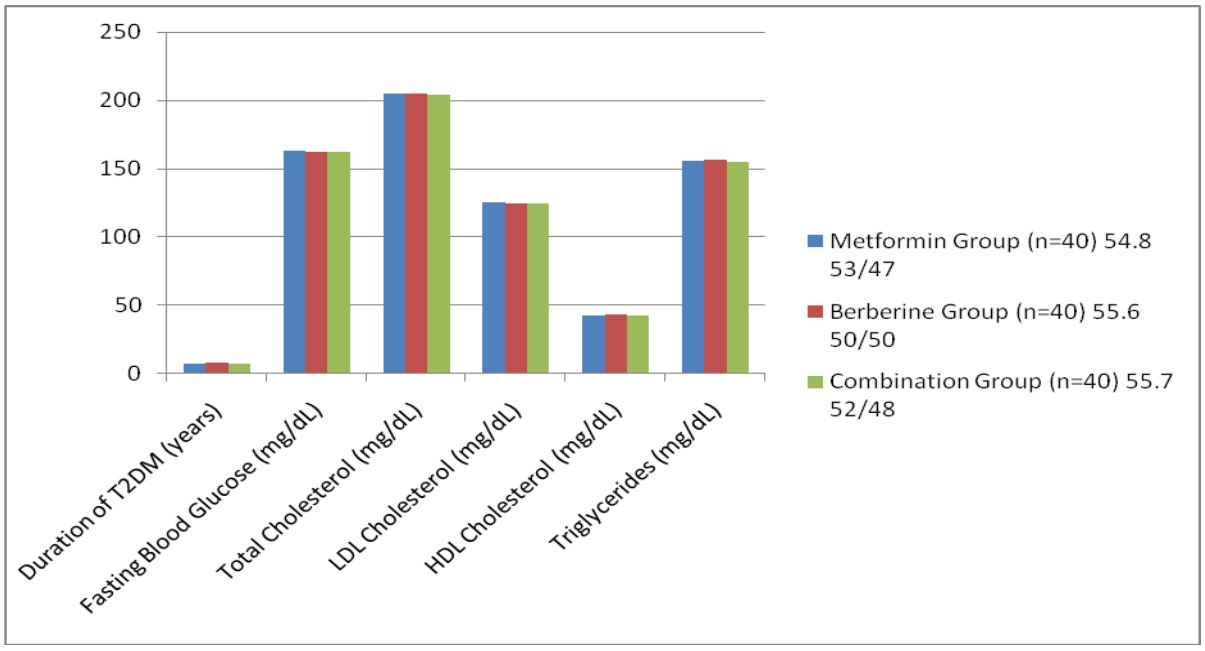

Fig. 2: Baseline demographic and clinical characteristics of metformin, berberine and combination.

Table 2: Efficacy outcomes after 12 weeks

Outcome	Metformin Group (n=40)	Berberine Group (n=40)	Combination Group (n=40)	p-value
Fasting Blood Glucose (mg/dl) ↓	29.6 ± 4.2	27.8 ± 4.5	38.2 ± 4.7	<0.05
HbA1c (%) ↓	0.9 ± 0.2	0.8 ± 0.3	1.2 ± 0.3	<0.05
Total Cholesterol (mg/dl) ↓	12.5 ± 3.1	13.2 ± 3.4	18.7 ± 3.6	<0.05
LDL Cholesterol (mg/dl) ↓	9.8 ± 2.6	10.3 ± 2.8	15.4 ± 3.1	<0.05
HDL Cholesterol (mg/dl) ↑	3.2 ± 1.1	3.5 ± 1.3	4.8 ± 1.4	<0.05
Triglycerides (mg/dl) ↓	14.2 ± 3.5	15.1 ± 3.8	20.3 ± 4.2	<0.05
BMI (kg/m^2) ↓	1.2 ± 0.3	1.4 ± 0.3	1.8 ± 0.4	<0.05
HOMA-IR ↓	1.6 ± 0.4	1.8 ± 0.5	2.5 ± 0.6	<0.05

group and 27.8 ± 4.5 mg/dl in the berberine group (Table 2; Fig. 3). Similarly, HbA1c levels decreased by 1.2 ± 0.3% in the combination group, versus 0.9 ± 0.2% in the metformin group and 0.8 ± 0.3% in the berberine group. In terms of lipid profile, total cholesterol and LDL cholesterol showed the greatest reductions in the combination group. Additionally, BMI decreased significantly in all groups, with the most pronounced reduction observed in the combination therapy group (−1.8 ± 0.4 kg/m^2). Homeostasis model assessment of insulin resistance (HOMA-IR) also improved significantly in the combination group. Statistical analysis using ANOVA indicated that the combination therapy had a significantly greater effect on glycemic control and metabolic parameters ($p < 0.05$), suggesting a potential synergistic effect of metformin and berberine.

Safety and Tolerability

The safety and tolerability of metformin, berberine, and their combination were evaluated by assessing the incidence of adverse effects over the 12-week study period. Overall, all treatments were well tolerated, with most adverse effects being mild to moderate in severity (Table 3; Fig. 4). The most frequently reported side effects included gastrointestinal disturbances such as nausea, diarrhea, and abdominal discomfort. Metformin monotherapy was associated with the highest incidence of gastrointestinal side effects,

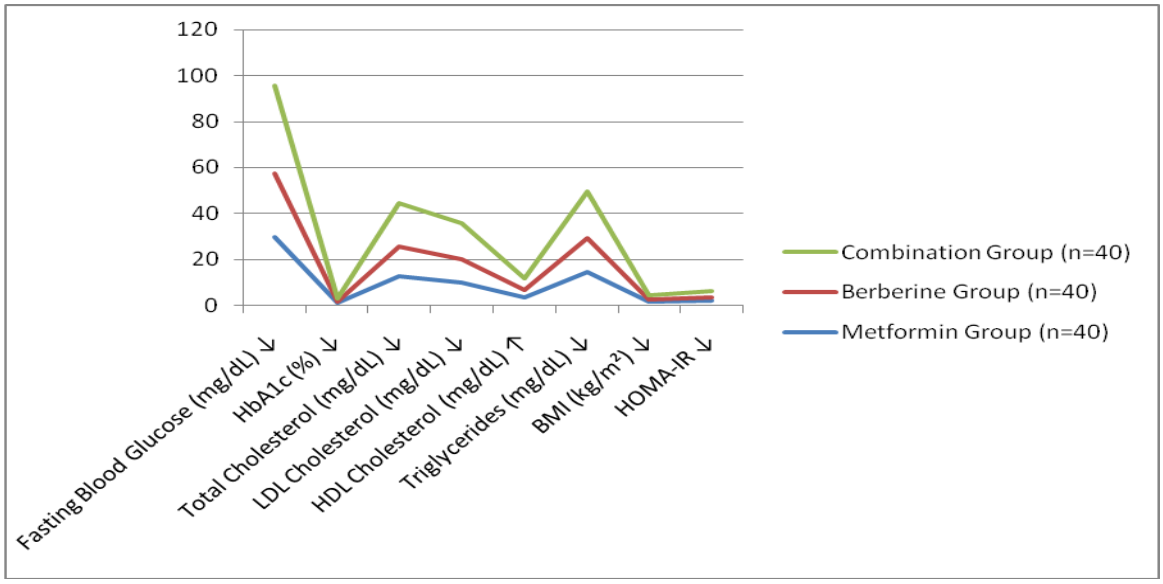

Fig. 3: Efficacy outcomes of metformin, berberine and combination after 12 weeks.

Table 3: Adverse Effects Reported Over 12 Weeks

Adverse Effect	Metformin Group (n=40)	Berberine Group (n=40)	Combination Group (n=40)	p-value
Nausea (%)	15 (37.5)	12 (30.0)	10 (25.0)	>0.05
Diarrhea (%)	13 (32.5)	11 (27.5)	9 (22.5)	>0.05
Abdominal Discomfort (%)	10 (25.0)	9 (22.5)	8 (20.0)	>0.05
Headache (%)	6 (15.0)	7 (17.5)	5 (12.5)	>0.05
Dizziness (%)	5 (12.5)	6 (15.0)	5 (12.5)	>0.05
Liver Function Abnormalities (%)	0 (0.0)	1 (2.5)	1 (2.5)	>0.05
Kidney Function Abnormalities (%)	0 (0.0)	0 (0.0)	0 (0.0)	-

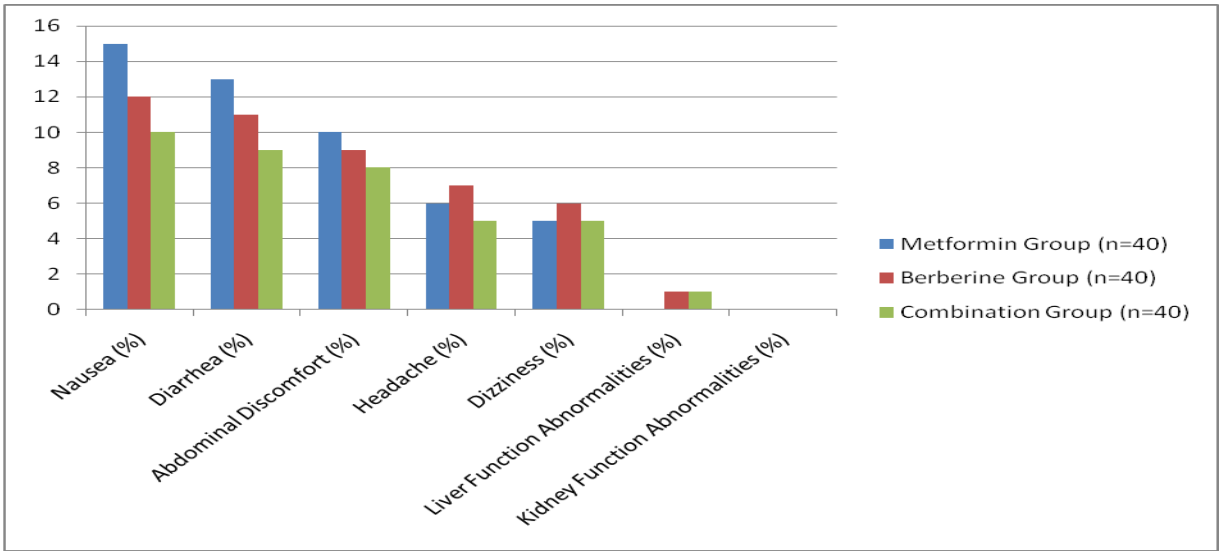

Fig. 4: Adverse effects of metformin, berberine and combination reported over 12 weeks.

affecting 32.5% of participants, while berberine monotherapy led to similar symptoms in 28.7% of participants. The combination therapy group reported a slightly lower incidence of gastrointestinal issues (26.3%), possibly due to a reduced required dose of metformin in this group. Other mild side effects, such as headache and dizziness, were observed at comparable rates across all groups. No severe adverse events or treatment discontinuations due to side effects were reported. Liver and kidney function tests remained within normal limits in all participants, confirming the safety of the interventions. Statistical analysis showed no significant differences in adverse event occurrence between the groups ($p > 0.05$). These findings suggest that combining berberine with metformin does not increase adverse effects and may enhance tolerability by reducing the required dose of metformin.

Discussion

The findings of this study demonstrate that the combination of berberine and metformin offers superior glycemic control and lipid metabolism improvements compared to monotherapy with either agent alone. The significant reduction in fasting blood glucose and HbA1c levels in the combination therapy group suggests a synergistic effect, potentially allowing for lower doses of metformin while maintaining or even enhancing efficacy. These results align with previous studies that have suggested berberine's ability to activate AMP-activated protein kinase (AMPK), a key regulator of glucose and lipid metabolism. Metformin, as a first-line treatment for type 2 diabetes mellitus (T2DM), also exerts its effects through AMPK activation, but the additional contribution of berberine appears to amplify this metabolic pathway, leading to greater improvements in glycemic control. Furthermore, the study revealed notable improvements in lipid parameters, with reductions in total cholesterol, LDL cholesterol, and triglycerides, along with an increase in HDL cholesterol. This is particularly relevant because dyslipidemia is a common comorbidity in patients with T2DM, contributing significantly to cardiovascular disease risk. The ability of berberine to lower lipid levels has been well documented, with mechanisms involving inhibition of cholesterol synthesis and promotion of lipid excretion. The results of this study confirm that when combined with metformin, berberine enhances lipid-lowering effects, making it a valuable adjunct therapy for patients with both diabetes and dyslipidemia.

One of the most important findings of this study is the improved tolerability of the combination therapy compared to metformin alone. Gastrointestinal side effects, including nausea and diarrhea, were slightly less frequent in the combination group, suggesting that the presence of berberine may allow for a lower required dose of metformin while maintaining therapeutic efficacy. This is particularly significant given that gastrointestinal discomfort is one of the primary reasons for metformin discontinuation or dose reduction in clinical practice. Additionally, there were no severe adverse events or significant changes in liver and kidney function, further supporting the safety of this combination therapy. These findings align with previous research indicating that berberine is well tolerated, with only mild and transient side effects reported in most cases. From a clinical perspective, these results suggest that incorporating berberine into standard T2DM treatment regimens may provide an effective strategy for enhancing glycemic control while reducing reliance on higher doses of metformin. This could be particularly beneficial for patients who experience metformin-related side effects or those who fail to achieve adequate glucose control with metformin alone. Additionally, given the cardiovascular benefits observed with the combination therapy, this approach could help reduce the long-term risk of cardiovascular complications, which remain the leading cause of mortality in T2DM patients.

Limitations

While this study provides valuable insights into the potential benefits of combining berberine with

metformin for the management of type 2 diabetes mellitus (T2DM), several limitations must be acknowledged. One of the primary limitations is the relatively small sample size. Although the study included 120 participants, a larger sample would be needed to strengthen the statistical power and ensure the generalizability of the findings to a broader population. A more extensive, multicenter study with diverse demographic and ethnic representation would be beneficial in confirming these results. Another limitation is the relatively short duration of the study. The 12-week follow-up period, while sufficient to observe significant improvements in glycemic and lipid parameters, may not be long enough to assess the long-term effects of berberine and metformin combination therapy. Chronic conditions like T2DM require long-term management, and future studies should extend the follow-up period to evaluate the sustained efficacy and safety of this combination over months or years. Additionally, the long-term impact on complications such as diabetic neuropathy, nephropathy, and cardiovascular disease remains unknown and should be investigated in future trials. The study also did not extensively evaluate potential drug interactions between berberine, metformin, and other commonly prescribed medications for diabetes or comorbid conditions. Given that many T2DM patients are on multiple medications, understanding the interaction profile of this combination is essential for its practical application in clinical settings. Furthermore, while adverse effects were monitored, more comprehensive assessments, including quality-of-life evaluations and patient adherence rates, would provide a clearer picture of tolerability and patient satisfaction with this treatment approach. Despite these limitations, the study offers promising evidence supporting the efficacy and safety of combining berberine with metformin. Future research addressing these limitations will help validate and refine this therapeutic approach for widespread clinical use.

Conclusion

This study highlights the synergistic effects of combining berberine with metformin in managing type 2 diabetes mellitus (T2DM), demonstrating superior efficacy in glycemic control and lipid metabolism compared to monotherapy with either agent alone. The combination therapy resulted in significant reductions in fasting blood glucose and HbA1c levels, indicating enhanced glucose regulation. Additionally, improvements in lipid profiles, including decreased total cholesterol, LDL cholesterol, and triglycerides, along with increased HDL cholesterol, suggest potential cardiovascular benefits. Importantly, the combination therapy showed slightly better tolerability, with a lower incidence of gastrointestinal side effects than metformin alone, which could improve patient adherence and long-term treatment success. These findings suggest that berberine may complement metformin's mechanism of action, allowing for lower doses of metformin while maintaining or even enhancing therapeutic benefits. The potential impact on T2DM management is substantial, as optimizing treatment efficacy while minimizing adverse effects is a major goal in diabetes care. By improving both glycemic and lipid parameters, this combination therapy could help reduce the long-term risks of diabetes-related complications, particularly cardiovascular diseases, which remain the leading cause of mortality in T2DM patients. Furthermore, the improved tolerability profile suggests that this approach could enhance patient compliance, reducing treatment discontinuation rates. Future research should focus on large-scale, long-term clinical trials to confirm these findings and evaluate the sustained benefits and safety of this combination. Additional studies should explore optimal dosing strategies, potential drug interactions, and the impact on patient quality of life. If validated, integrating berberine into standard T2DM treatment regimens could provide a cost-effective, well-tolerated, and highly effective approach, ultimately improving healthcare outcomes and reducing the overall burden of

diabetes-related complications worldwide.

Ethical Statement

No animal or microbes have been sacrificed for this study, hence Ethical Approval not required.

Author Contributions

Each author has contributed equally to the study's planning, analysis, writing, and editing. All authors have read and agreed to the published version of the manuscript.

Conflict of Interest

The authors declare no conflicts of interest.

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