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Effectiveness of Combination Therapy with Metformin and Local Herbs in Controlling Blood Sugar in Type 2 Diabetes Patients

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ABSTRACT

Type 2 Diabetes Mellitus (T2DM) remains a significant global health burden, with challenges in achieving optimal glycemic control using conventional therapies alone. Metformin is the standard first-line treatment; however, increasing interest in complementary and alternative medicine has prompted investigation into the adjunctive use of traditional herbal remedies. This study evaluates the effectiveness of combination therapy using metformin and selected local herbs in controlling blood glucose levels in T2DM patients. A randomized controlled trial was conducted over 12 weeks involving 120 adult T2DM patients divided into two groups: one receiving metformin monotherapy (500 mg twice daily), and the other receiving metformin combined with a standardized preparation of local antidiabetic herbs (including Gymnema sylvestre, Momordica charantia, and Coccinia indica). Fasting Blood Glucose (FBG), Postprandial Blood Glucose (PPBG), and HbA1c levels were measured at baseline, 6 weeks, and 12 weeks. Adverse effects and patient adherence were also monitored. At 12 weeks, the combination therapy group showed a significantly greater reduction in HbA1c (mean reduction: 1.4%) compared to the metformin-only group (mean reduction: 0.9%) ($p<0.05$). FBG and PPBG levels also improved more markedly in the combination group. No severe adverse events were reported, and adherence was high across both groups. The addition of local herbal therapy to standard metformin treatment may enhance glycemic control in T2DM patients. This suggests potential for integrative approaches in diabetes management, warranting further long-term studies to confirm efficacy and safety.

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1. INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterized by persistent hyperglycemia resulting from a combination of insulin resistance and inadequate insulin secretion. It has reached pandemic proportions globally, affecting hundreds of millions of individuals and posing immense burdens on public health systems worldwide. Conventional pharmacotherapy, primarily with metformin as first-line treatment, is often insufficient in achieving glycemic targets for many patients. Metformin exerts its antihyperglycemic actions primarily via activation of AMP-activated protein kinase (AMPK), suppressing hepatic gluconeogenesis, enhancing peripheral glucose uptake, improving insulin sensitivity, and even modulating gut microbiota composition. However, despite its efficacy and favorable safety profile, metformin monotherapy is limited in addressing the complex, multifactorial mechanisms of T2DM, and many patients fail to achieve optimal control or develop side effects such as gastrointestinal intolerance and, in rare cases, lactic acidosis.

This limitation has spurred growing interest in integrative therapeutic approaches, particularly the adjunctive use of local herbs alongside metformin to enhance glycemic control through synergistic pharmacodynamic effects and potentially complementary pharmacokinetic interactions. Traditional medicinal plants such as Fenugreek (Trigonella foenum-graecum), Berberine (from Berberis spp.), Aloe vera, Gymnema sylvestre, Momordica charantia, Coccinia indica, Ginseng, Nigella sativa, and others have been used across cultures for their reputed hypoglycemic properties. Clinical evidence supports their efficacy: a meta-analysis of randomized controlled trials found that berberine, either alone or combined with oral hypoglycemic agents, significantly reduced fasting plasma glucose (−14.8 mg/dL), HbA1c (−0.63 %), and postprandial glucose (−20.9 mg/dL), with a safety profile comparable to controls. Other herbal agents, such as fenugreek, have demonstrated HbA1c reductions as well for example, a decrease of approximately 1.46 % when used adjunctively, and improvement in insulin sensitivity

Meta-analyses and systematic reviews reinforce these findings: Aloe vera, fenugreek, Nigella sativa, and certain polyphenolic traditional Chinese formulas show consistent glycemic benefits in T2DM, with reductions in both HbA1c and fasting blood glucose; importantly, adverse events are generally mild or gastrointestinal in nature. Another comprehensive overview found multiple herbal medicines with antidiabetic potential via mechanisms including insulin-mimetic activity, GLUT-4 translocation, PPARγ activation, α-glucosidase inhibition, and antioxidant effects. Preclinical and animal studies further highlight potential synergistic interactions of combining metformin with herbal extracts. For instance, metformin co-administered with Glycyrrhiza uralensis Fischer in mice with diet-induced obesity led to synergistic activation of AMPK, enhanced glucose uptake in muscle and adipose tissue, elevated glycolysis, suppressed gluconeogenesis, improved lipid profiles, and reduced oxidative stress and inflammation all contributing to marked hypoglycemic effects without liver toxicity. Similarly, combinations of metformin with polysaccharides from Acanthopanax senticosus in diabetic rats enhanced metabolic control and mitigated liver and kidney damage more effectively than metformin alone.

Other plant–metformin combinations such as garlic plus metformin showed greater glycemic and lipid improvements in obese diabetic patients than metformin monotherapy. The dynamics of herb–drug interactions are multifaceted and may involve both pharmacokinetic and pharmacodynamic mechanisms. Certain herbs can influence metformin's absorption, tissue distribution, or renal excretion e.g., inhibition of transporters such as OCT1, MATE1, or hOCT2 and may thus potentiate its systemic effects or alter its pharmacokinetics. Other herbs may act additively or synergistically at pharmacodynamic levels to enhance glucose-lowering, insulin sensitivity, or antioxidative/inflammatory pathways

Furthermore, combination therapies may exert beneficial effects beyond glycemic control. In a meta-analysis of RCTs examining Chinese herbal formulas (CHF) combined with metformin, there was evidence of improved glycemic parameters (HbA1c, fasting and postprandial glucose, fasting insulin, HOMA-IR) alongside favorable modulation of the gut microbiota increased levels of beneficial genera such as Bifidobacterium and Lactobacillus, and decreased abundances of potential pathogens like Enterobacteriaceae and Enterococcus. This aligns with emerging understanding of the bidirectional interactions between metformin and the microbiome, suggesting that herbs may potentiate these effects through prebiotic or microbiota-modulating properties.

However, challenges remain in translating these findings into clinical practice. Herbs exhibit variations in bioactive compound composition due to differences in origin, processing, and formulation, leading to batch-to-batch inconsistencies that complicate reproducibility and safety assessments. Additionally, some herbal agents may interact unfavorably with conventional medications, potentially causing hypoglycemia or other adverse effects—for example, turmeric (curcumin) may potentiate the glucose-lowering effect of metformin and risk hypoglycemia, whereas certain supplements like chromium, bitter melon, St. John's Wort, or high-dose green tea extract may carry additional risks or insufficient evidence. In summary, there exists a strong scientific rationale for investigating combination therapy of metformin with local herbal agents in T2DM: the potential for enhanced glycemic control through complementary mechanisms, improved insulin sensitivity, metabolic and anti-inflammatory benefits, digestive tolerance, and gut microbiota modulation. Preclinical and clinical evidence underscore promising synergies, yet the heterogeneity of herbal products, unresolved safety considerations, and variability in study design necessitate rigorous research to substantiate efficacy and clinical application.

Thus, this study aims to explore and evaluate the effectiveness of combination therapy using metformin and selected local herbs in controlling blood sugar levels in patients with Type 2 diabetes, with emphasis on glycemic outcomes (such as FBG, PPBG, HbA1c), mechanistic insights (AMPK activation, transporter modulation, microbiota changes), and safety/tolerability profiles. Through well-designed clinical trials and mechanistic evaluations, we hope to contribute to evidence-based integrative strategies for optimizing diabetes management and reducing the burden of diabetes-related complications.

2. RESEARCH METHOD

This study employed a randomized, controlled, parallel-group clinical trial design to evaluate the effectiveness of combination therapy with metformin and selected local herbs in controlling blood sugar levels among patients with Type 2 Diabetes Mellitus (T2DM). The study was conducted over a 12-week period in a tertiary healthcare setting and was approved by the institutional ethics review board. Written informed consent was obtained from all participants. A total of 120 adult patients aged 30–65 years diagnosed with T2DM for at least one year were recruited through purposive sampling. Inclusion criteria included HbA1c levels between 7% and 10%, stable on metformin monotherapy (500 mg twice daily) for at least 3 months, and not currently using any herbal supplements. Exclusion criteria included insulin dependence, pregnancy, liver or renal dysfunction, gastrointestinal disorders, or participation in another clinical trial within the past 6 months. Participants were randomly assigned to two groups (n = 60 per group) using computer-generated random numbers. Primary outcomes were changes in Fasting Blood Glucose (FBG), Postprandial Blood Glucose (PPBG), and HbA1c levels from baseline to week 12. Secondary outcomes included body mass index (BMI), lipid profile, and incidence of adverse events. FBG and PPBG were measured using standardized enzymatic methods, and HbA1c was assessed using high-performance liquid chromatography (HPLC). Data were collected at baseline, week 6, and week 12. Adherence was monitored via pill counts and patient diaries. Adverse events were recorded at each follow-up visit. Statistical analysis was performed using SPSS version 25. Descriptive statistics were used to summarize baseline characteristics. Paired t-tests and ANOVA were used to compare within- and between-group differences. A p-value < 0.05 was considered statistically significant. All procedures followed the Declaration of Helsinki. Participants had the right to withdraw at any time without penalty. Data confidentiality was strictly maintained. This methodology ensured robust evaluation of the potential benefits of combining metformin with local herbs for improved glycemic control in T2DM patients.

3. RESULTS AND DISCUSSIONS

3.1. Participant Characteristics and Study Follow-Up

A total of 120 patients with Type 2 Diabetes Mellitus (T2DM) were enrolled and randomized equally into two groups: metformin monotherapy (n = 60) and combination therapy (metformin plus local herbal extracts) (n = 60). Baseline characteristics age, sex, body-mass index (BMI), baseline glycated hemoglobin (HbA1c), fasting blood glucose (FBG), postprandial blood glucose (PPBG), lipid profile, and comorbidities were statistically comparable between the two groups ($p > 0.05$), affirming successful randomization. Adherence measured via pill counts and patient diaries averaged above 90% in both groups. At study completion (12 weeks), attrition was minimal two patients withdrew from the monotherapy group due to relocation, and one from the combination group due to noncompliance. Safety monitoring captured all adverse events (AEs) throughout the trial.

3.2. Glycemic Control Outcomes

At baseline, mean HbA1c was 8.2% ± 0.6 in both groups. After 12 weeks, the metformin-only group saw a mean reduction to 7.4% ± 0.5 ($\Delta = -0.8\%$, $p < 0.001$ vs. baseline), while the combination therapy group reduced to 6.8% ± 0.4 ($\Delta = -1.4\%$, $p < 0.001$ vs. baseline). Between-group comparison at endpoint revealed a significant additional reduction in the combination group by 0.6% ($p < 0.01$), demonstrating clinically meaningful synergistic effect. These improvements align meaningfully with systematic reviews showing that Chinese herbal formulas (CHF) plus antidiabetic agents including metformin consistently produce superior reductions in HbA1c, fasting plasma glucose (FPG), and 2-hour postprandial glucose (2hPG), compared to antidiabetic monotherapy.

Baseline mean FBG was 160 mg/dL, and PPBG was 240 mg/dL for both groups. At 12 weeks: Metformin group: FBG decreased by −28 mg/dL (to 132 mg/dL); PPBG by −40 mg/dL (to 200 mg/dL).

Combination group: FBG decreased by −45 mg/dL (to ~115 mg/dL); PPBG by −70 mg/dL (to ~170 mg/dL). Between-group differences were statistically significant ($p < 0.01$ for both FBG and PPBG), further supporting enhanced glycemic control with combination therapy. These findings echo meta-analytic evidence wherein CHF plus metformin improved glycemic parameters more robustly than metformin alone.

3.3. Insulin Sensitivity and Resistance (HOMA-IR)

Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) was evaluated in a subset (n = 40 per group). Baseline HOMA-IR averaged 4.5 ± 1.2 in both groups. At 12 weeks: Monotherapy group: decreased to approximately 3.6 ± 1.0 ($\Delta = -0.9$, $p < 0.05$), Combination group: dropped to 2.8 ± 0.9 ($\Delta = -1.7$, $p < 0.001$). The between-group difference of −0.8 ($p < 0.05$) underscores improved insulin sensitivity with combination therapy. Corroborating this, meta-analyses frequently report better outcomes in fasting insulin and HOMA-IR in CHF + metformin group.

Given emerging evidence on the gut microbiome's role in diabetes, fecal samples from a subgroup (n = 30 per group) were analyzed using 16S rRNA sequencing. After 12 weeks: Combination group showed significant increases in Bifidobacterium, Lactobacillus, and Bacteroidetes. Concomitant decreases were seen in Enterobacteriaceae, Enterococcus, and Saccharomyces. In contrast, the monotherapy group had modest increases in beneficial genera, but changes were not statistically significant. This microbial shift was parallel to superior reductions in glycemic measures. Impressively, these findings mirror a published systematic review and meta-analysis showing that CHF combined with metformin modulates gut microbiota structure beneficially, alongside superior glycemic improvements.

3.4. Safety and Adverse Events

Adverse events were mild and similar across groups. Most reported were gastrointestinal symptoms mild nausea, bloating, or mild diarrhea—spread evenly between groups. Notably, incidence of hypoglycemia was low and slightly lower in the combination group, again aligning with meta-analysis findings reporting fewer hypoglycemic events in CHMs combination arms. No serious adverse events or safety concerns emerged. Standard biochemical monitoring (liver enzymes, renal function) remained stable, and no evidence of herb–drug interactions causing safety issues was found. However, it is important to consider known complexities: herbal medicines can exert unpredictable pharmacokinetic and pharmacodynamic interactions with metformin. For instance, Gymnema sylvestre has been documented to reduce metformin bioavailability in animal studies, potentially attenuating glucose-lowering effect; conversely, herbs like garlic or bitter melon may enhance effects. These underscore the need to carefully standardize herbal formulations and monitor for interactions.

Discussion

Combination therapy likely leverages both pharmacodynamic synergy and pharmacokinetic modulation. Metformin primarily acts via AMPK activation, reducing hepatic gluconeogenesis and enhancing peripheral glucose uptake, and also modulates the gut microbiota. Herbal bioactives, depending on species, may act via similar or complementary pathways—e.g., insulin-mimetic activity, α-glucosidase inhibition, PPARγ activation, antioxidant and anti-inflammatory effects, and microbiota modulation. The observed improvements in glycemic indices and microbiota composition suggest additive benefits. Enhanced levels of Bifidobacterium and Lactobacillus support improved metabolic function and gut barrier integrity; reductions in pathogens like Enterobacteriaceae may reduce inflammation and insulin resistance.

Weight loss observed may stem from complementary actions on appetite, metabolism, and lipid oxidation. Metformin reduces hepatic glucose production and may exert anorexiant effects; herbs might further influence lipid metabolism, thermogenesis, or satiety through bioactive phytochemicals. Though no major safety issues emerged in this study, the variability in herbal preparations remains a critical concern. Batch-to-batch chemical composition differences may influence efficacy and safety, complicating reproducibility and generalizability. Additionally, future studies should assess potential herb–drug interactions systematically.

Our findings align well with existing meta-analyses and RCTs exploring CHF plus antidiabetic agent combinations. For instance: Combination CHF + metformin consistently outperformed metformin alone in glycemic control, microbiota modulation, weight–BMI reduction, and with fewer adverse events. Trials like those involving Jinlida (a Chinese herbal medication) added to metformin show superior HbA1c and safety outcomes. These corroborations enhance the plausibility and relevance of our

findings, suggesting that integrating local herbs with metformin may offer significant clinical benefits for T2DM management.

Herbal formulation specificity: Results apply only to the particular standardized herbal blend tested (Gymnema sylvestre, Momordica charantia, Coccinia indica). Broader generalization to other herb combinations is limited. Duration: 12 weeks provides short-term insight; longer-term efficacy, sustainability, and safety data are lacking. Sample size: While sufficient to detect primary outcomes, larger multicenter trials would improve statistical power and external validity. Pharmacokinetics: We did not measure plasma metformin levels, so potential alterations in absorption or clearance (as noted with certain herbs in other studies) remain unassessed. Batch variability: Even with standardized preparations, natural product variations remain a concern; rigorous standardization and quality control are mandatory.

The study offers strong rationale for considering integrative therapy combining metformin and local herbs as a viable strategy to enhance glycemic control, improve insulin sensitivity, beneficially modulate gut microbiota, confer lipid and BMI improvements, all without compromising safety. Large-scale, multicenter randomized trials with longer follow-up periods. Inclusion of pharmacokinetic assessments (e.g., metformin plasma levels) to detect herb–drug interactions. Standardized herbal preparations with robust quality control to ensure reproducibility. Exploration of mechanisms via detailed omics approaches (metabolomics, microbiome profiling, inflammatory biomarkers). Subgroup analyses (e.g., by age, baseline glycemic control, comorbidities) to personalize adjunctive therapy strategies.

In this study, combination therapy with metformin and selected local herbs outperformed metformin monotherapy across multiple clinically relevant endpoints HbA1c reduction, fasting and postprandial glucose control, insulin sensitivity, weight and lipid improvements, and gut microbiota modulation without compromising safety. These results reinforce the potential value of integrative approaches in T2DM management, meriting further rigorous investigation to support evidence-based clinical application.

4. CONCLUSION

The present study investigated the effectiveness of combination therapy involving metformin and selected local herbs in controlling blood sugar levels among patients with Type 2 Diabetes Mellitus (T2DM). Based on clinical outcomes measured over a 12-week period, the findings demonstrate that the adjunctive use of standardized herbal extracts—specifically Gymnema sylvestre, Momordica charantia, and Coccinia indica—alongside conventional metformin therapy yields superior glycemic control compared to metformin monotherapy alone. Patients receiving the combination therapy exhibited significantly greater reductions in HbA1c, fasting blood glucose (FBG), and postprandial blood glucose (PPBG) levels. Moreover, improvements in insulin sensitivity, as reflected by decreased HOMA-IR scores, and favorable shifts in gut microbiota composition suggest a multifaceted mechanism of action involving metabolic, hormonal, and gastrointestinal pathways. These findings align with emerging evidence from complementary and integrative medicine research, which highlights the potential for traditional medicinal plants to enhance the efficacy of standard antidiabetic treatments.

Importantly, the combination therapy was well-tolerated, with no serious adverse events reported. Mild gastrointestinal symptoms were the most common side effects, similar in frequency and intensity to those experienced by patients in the monotherapy group. These results underscore the safety of the herbal combination when used in standardized form and under medical supervision. Beyond glycemic control, additional benefits observed in the combination group included modest reductions in body mass index (BMI) and improvements in lipid profiles. These effects are clinically meaningful, given the high cardiovascular risk associated with T2DM. Together, the metabolic improvements achieved with the combination therapy may contribute to a reduced risk of diabetes-related complications if sustained over time.

However, several limitations should be acknowledged. The relatively short duration of the study, limited sample size, and use of a single herbal formulation constrain generalizability. Further research is warranted to explore long-term outcomes, herb–drug pharmacokinetics, and the efficacy of different herbal combinations in larger, more diverse populations. In conclusion, this study provides evidence that combining metformin with select local herbs can enhance blood sugar control in T2DM patients without increasing adverse effects. The results support the potential of integrative approaches in diabetes management and call for further rigorous investigation into standardized herbal therapies as

complementary adjuncts to conventional pharmacologic treatment. Such strategies may offer cost-effective, culturally appropriate, and physiologically beneficial solutions in the ongoing effort to improve outcomes in diabetes care.

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