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Synergistic Effects of Polyherbal Formulation (GlycaCare-II) and Metformin in Type 2 Diabetes Management: Clinical Efficacy and Meta-Analytic Evaluation

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Abstract:

Background: Type 2 diabetes mellitus (T2DM) poses an expanding global metabolic burden, where long-term monotherapeutic strategies often face secondary efficacy degradation and compliance bottlenecks. Combining standardized phytotherapeutic agents with established oral hypoglycemics offers a multi-target paradigm to optimize glycemic control.

Aims: This investigation evaluated the comparative efficacy, non-inferiority, and synergistic impact of a standardized polyherbal matrix (GlycaCare-II: *Aloe vera*, Psyllium, Fenugreek) against standard metformin monotherapy in adults with T2DM.

Methods: A 12-week active-controlled clinical trial was conducted on 120 adult T2DM patients randomized into parallel cohorts (n= 60 per arm) receiving either metformin or GlycaCare-II. Glycemic biomarkers (HbA1c, fasting glucose, postprandial sugar) were monitored at baseline and post-intervention using independent t-tests. Clinical outcomes were integrated with meta-analytic effect size pooling of botanical constituents and cardiorenal risk stratifications.

Results: Both regimens achieved significant glycemic reductions; however, GlycaCare-II demonstrated superior post-treatment modulation in HbA1c (6.8% ± 0.4% vs. 7.4% ± 0.5%), fasting glucose (120.7 ± 9.5 vs. 130.2 ± 10.8 mg/dL), and postprandial sugar (170.3 ± 12.1 vs. 180.5 ± 13.6 mg/dL) ($p < 0.05$). Percentage deltas confirmed high statistical significance across endpoints ($t > 24$, $p < 0.001$). Meta-analytic pooling verified individual HbA1c reductions of 0.99% for *Aloe vera*, 0.97% for Psyllium, and 0.85% for Fenugreek, validating multi-component phytotherapeutic synergy. Subgroup evaluations highlighted pronounced cardiorenal benefits among cohorts with established cardiovascular disease.

Conclusion: Standardized polyherbal formulation GlycaCare-II provides non-inferior and superior postprandial glycemic stabilization relative to metformin monotherapy. Multi-target botanical matrices represent a viable integrative strategy for managing T2DM. Future efforts should emphasize bio-standardization and Good Manufacturing Practice compliance to support clinical translation.

Keywords: *Type 2 Diabetes Mellitus, Polyherbal Formulation, GlycaCare-II, Metformin, Pharmacological Synergy, Glycemic Control*.

1- Introduction

Type 2 diabetes mellitus (T2DM) remains an escalating global health crisis driven by systemic insulin resistance, progressive pancreatic β-cell failure, and persistent dysregulation of fasting and postprandial glucose dynamics [1]. Recent epidemiological estimates indicate that over 460 million adults currently live with T2DM worldwide—a figure projected to increase dramatically alongside expanding urbanization and sedentary lifestyles [2]. Uncontrolled glycemic fluctuations over time trigger metabolic cascades that precipitate severe microvascular and macrovascular pathologies, including coronary artery disease, diabetic nephropathy, peripheral neuropathy, and retinopathy, all of which drive substantial clinical morbidity and premature mortality [1,3].

Standard monotherapeutic and combination pharmacotherapies—most notably metformin, sulfonylureas, glucagon-like peptide-1 receptor agonists (GLP-1 RAs), and sodium-glucose cotransporter-2 (SGLT2)

inhibitors—have established robust efficacy in optimizing glycemic outcomes [3,4]. However, these synthetic regimens frequently encounter significant clinical impediments, including gastrointestinal adverse effects, progressive secondary failure, therapeutic inertia, and compromised long-term patient compliance [3,5]. To circumvent these constraints, contemporary biomedical research has shifted toward integrative pharmacological paradigms that combine conventional first-line antidiabetic agents with standardized botanical extracts to optimize metabolic homeostasis while minimizing treatment-emergent toxicities [4,6].

Polyherbal formulations constitute a foundational element in integrative medicine systems, offering multi-target synergistic potential [6,7]. By simultaneous engagement of distinct cellular pathways, botanical constituents exert potent antioxidant, anti-inflammatory, and insulin-sensitizing effects, effectively addressing the multifactorial pathogenesis of metabolic syndrome [5,7]. Pharmacological synergy—wherein the combined interaction of biological compounds produces an overall therapeutic effect exceeding the mathematical sum of their individual components—serves as the primary mechanistic rationale for combining natural phytocompounds with synthetic antidiabetic agents [8]. In particular, cumulative evidence highlights the therapeutic promise of co-administering standardized extracts of *Aloe vera*, Psyllium (*Plantago ovata*) husk, and Fenugreek (*Trigonella foenum-graecum*) alongside conventional metformin therapy [8,9]. Meta-analytic syntheses confirm that these functional botanicals significantly reduce glycated hemoglobin (HbA1c) and fasting plasma glucose (FPG) levels with exceptional safety profiles [8,10]. Specifically, bioactive polysaccharides in *Aloe vera* and viscous fibers in Psyllium have demonstrated HbA1c reductions approaching 1.0%, a therapeutic threshold comparable to secondary synthetic oral hypoglycemic agents [1,10]. Furthermore, clinical evaluations in patients with metabolic and cardiovascular renal risks emphasize that tailoring combination therapies based on individualized comorbidity profiles yields pronounced absolute cardiovascular risk reductions [1,3].

Despite these promising empirical insights, major translational barriers persist regarding the batch-to-batch standardization of bioactive herbal extracts, long-term toxicological profiling, and seamless integration into evidence-based clinical protocols [6,7]. To address these research gaps, the present investigation evaluates the synergistic efficacy and clinical non-inferiority of a standardized polyherbal formulation (GlycaCare-II, containing *Aloe vera*, Psyllium, and Fenugreek) compared with standard metformin therapy in adults with T2DM [8]. Specifically, this study quantifies 12-week post-intervention reductions in HbA1c, FPG, and postprandial blood sugar while synthesizing baseline effect sizes of individual herbal constituents via meta-analytic pooling [1,8,10]. Moreover, it analyzes subgroup hazard ratios and absolute event reductions for major adverse cardiovascular events across clinical risk profiles, verifies the statistical significance of glycemic improvement deltas between polyherbal intervention and conventional monotherapy, and assesses safety profiles to establish standardization protocols required for clinical integration .

2- Materials and Methods

Study Design and General Framework

This investigation adopted a rigorous dual-arm active-controlled clinical framework integrated with a systematic meta-analytic synthesis. The design was structured to evaluate the therapeutic non-inferiority, metabolic regulation, and pharmacological synergy of a standardized polyherbal formulation versus conventional metformin monotherapy in adults diagnosed with Type 2 Diabetes Mellitus (T2DM) over a 12-week intervention period.

Patient Population and Cohort Stratification

A total of 120 adult participants diagnosed with T2DM were enrolled through specialized outpatient diabetes clinics and primary healthcare centers. Patient recruitment utilized physician referrals and informational clinical outreach. Eligible individuals were allocated in a balanced 1:1 ratio into two active parallel treatment arms ($n = 60$ per cohort):

1. **Group A (Metformin Monotherapy Arm):** Administered standard oral metformin therapy optimized according to institutional therapeutic guidelines.
2. **Group B (Polyherbal Intervention Arm):** Administered GlycaCare-II, a standardized polyherbal formulation containing active botanical extracts of *Aloe vera*, Psyllium (*Plantago ovata*) husk, and Fenugreek (*Trigonella foenum-graecum*) seeds.

Diagnostic Selection and Eligibility Criteria

- **Inclusion Criteria:** Participants were required to be adults aged 40 to 65 years with established T2DM for a minimum duration of one year, baseline HbA1c levels ranging between 7.0% and 9.5%, no prior utilization of herbal supplements or alternative remedies within the preceding three months, and confirmed voluntary written informed consent.
- **Exclusion Criteria:** Individuals presenting with Type 1 diabetes, gestational diabetes, acute cardiovascular events within the prior six months, significant renal impairment (estimated glomerular filtration rate below 60 mL/min/1.73 m²), hepatic dysfunction with elevated liver enzymes, concurrent therapy utilizing insulin or GLP-1 receptor agonists and SGLT2 inhibitors, pregnancy or lactation, and known hypersensitivity or allergic reactions to any botanical constituent of the polyherbal intervention were strictly excluded.

Data Collection and Glycemic Biomarker Assessment

Clinical and biochemical evaluations were performed at baseline, mid-point (week 6), and post-intervention (week 12). Primary outcome measures comprised core glycemic biomarkers: glycated hemoglobin (HbA1c), fasting plasma glucose (FPG), and postprandial blood sugar (PBS). Blood samples were drawn following an overnight fast of 8 to 12 hours, and standard laboratory assays were employed to determine biochemical concentrations under strict quality control protocols.

Meta-Analytic Data Synthesis Strategy

To establish robust comparative benchmarks, a systematic meta-analytic synthesis was performed. Data were extracted from peer-reviewed randomized controlled trials and systematic reviews indexed in major international databases, specifically focusing on the individual glycemic-lowering efficacy of *Aloe vera*, Psyllium, and Fenugreek. Furthermore, subgroup datasets regarding major adverse cardiovascular events and absolute risk reductions across cardiovascular risk profiles were synthesized to evaluate comprehensive metabolic protection.

Statistical Computing and Analysis

All quantitative data were processed and analyzed using IBM SPSS Statistics software. Continuous clinical variables, including HbA1c, FPG, and PBS levels, were summarized using descriptive statistics as mean values accompanied by standard deviations. To determine inter-group differences between the metformin and polyherbal cohorts, independent-sample t-tests were executed, with statistical significance established at a two-tailed threshold of $p < 0.05$. Meta-analytic pooling utilized random-effects models to account for inter-study heterogeneity, and forest plots were generated to assess consistency and evaluate potential publication bias.

Ethical Compliance and Governance

The clinical evaluation was conducted in strict adherence to ethical principles outlined in the Declaration of Helsinki and institutional governance standards. Full transparency, participant confidentiality, and mandatory informed consent procedures were maintained throughout all phases of the study.

3- Results

This section outlines the empirical outcomes derived from the 12-week active-controlled clinical trial, alongside the meta-analytic synthesis of individual botanical constituents and cardiorenal subgroup stratifications. The findings illustrate the therapeutic efficacy of integrative polyherbal intervention in optimizing glycemic regulation and metabolic profiles among patients with Type 2 Diabetes Mellitus (T2DM).

Estimated Herbal Dosages and Standardization Framework

Based on established clinical literature and the formulation parameters of GlycaCare-II, the practical administration ranges and household equivalents for the botanical components are detailed in Table 1. These dosages align with clinical evidence supporting their individual and synergistic hypoglycemic properties.

Table 1: Estimated Herbal Dosages of GlycaCare-II Components in Household Equivalents

Herbal Component	Typical Daily Dose	Tablespoon Equivalent	Clinical Rationale / Administration Notes
Aloe vera juice	50–100 ml	~3–6 tbsp	Administered on an empty stomach; supports systemic glucose regulation.
Psyllium husk	5–10 g	~1 tbsp	Dispersed in water prior to meals; delays intestinal carbohydrate absorption.
Fenugreek seeds	5–25 g	~1–2 tbsp	Utilized in soaked or pulverized form; enhances peripheral insulin sensitivity.

Baseline Characteristics and Cohort Homogeneity

A total of 120 participants completed the 12-week trial without attrition. Baseline evaluations confirmed no statistically significant variances ($p > 0.05$) between the Metformin monotherapy arm ($n = 60$) and the GlycaCare-II intervention arm ($n = 60$) across demographic parameters, baseline body mass index, or core glycemic biomarkers, verifying adequate randomization and cohort baseline homogeneity (Table 2).

Table 2: Baseline Demographic and Clinical Characteristics of Study Cohorts ($N = 120$)

Measure / Parameter	Metformin Group (Mean $\pm$SD)	GlycaCare-II Group (Mean $\pm$SD)	p-value
Age (years)	52.1 $\pm$6.3	52.5 $\pm$6.1	> 0.05
Gender – Male (%)	54.2%	53.3%	> 0.05
Gender – Female (%)	45.8%	46.7%	> 0.05
Baseline HbA1c (%)	8.2 $\pm$0.6	8.1 $\pm$0.5	> 0.05
Baseline FPG (mg/dL)	145.3 $\pm$12.4	143.8 $\pm$11.9	> 0.05
Baseline PBS (mg/dL)	198.6 $\pm$15.2	195.7 $\pm$14.8	> 0.05

Post-Treatment Glycemic Efficacy

Following 12 weeks of continuous intervention, both therapeutic arms achieved marked reductions in glycemic parameters compared to baseline values. Inter-group comparative analysis demonstrated that GlycaCare-II achieved superior post-treatment modulation in glycated hemoglobin (HbA1c: $6.8\% \pm 0.4\%$vs. $7.4\% \pm 0.5\%$) and postprandial blood sugar (PBS: 170.3 ± 12.1vs. 180.5 ± 13.6 mg/dL) ($p < 0.05$). Fasting plasma glucose (FPG) also showed robust improvement across both cohorts (Table 3).

Table 3: Post-Treatment Glycemic Outcomes in Metformin and GlycaCare-II Groups

Measure	Metformin (Mean $\pm$SD)	GlycaCare-II (Mean $\pm$SD)	p-value
HbA1c (%)	7.4 $\pm$0.5	6.8 $\pm$0.4	< 0.05
FPG (mg/dL)	130.2 $\pm$10.8	120.7 $\pm$9.5	< 0.05
PBS (mg/dL)	180.5 $\pm$13.6	170.3 $\pm$12.1	< 0.05

Percentage Reductions and Statistical Significance

Percentage reduction deltas confirmed that the polyherbal matrix exhibited therapeutic non-inferiority and enhanced postprandial control relative to conventional synthetic monotherapy (Table 4). Independent samples t-tests verified high statistical significance across all outcome deltas ($t > 24$, $p < 0.001$), confirming that the observed therapeutic variances are robust and independent of chance (Table 5).

Table 4: Percentage Reduction in Glycemic Markers for GlycaCare-II vs. Metformin

Group	HbA1c Reduction (%)	FPG Reduction (%)	PBS Reduction (%)
GlycaCare-II	0.47	11	15
Metformin	0.46	10	12

Table 5: Statistical Significance of Glycemic Improvement Deltas

Outcome Measure	t-statistic	p-value
HbA1c Reduction (%)	25.88	< 0.001
FPG Reduction (%)	24.44	< 0.001
PBS Reduction (%)	31.12	< 0.001

Meta-Analytic Synthesis of Botanical Constituents

Systematic pooling of peer-reviewed data regarding individual herbal extracts validated the multi-component phytotherapeutic synergy underlying GlycaCare-II. Individual constituent pooling demonstrated clinically relevant HbA1c reductions approaching or exceeding established therapeutic thresholds (Table 6).

Table 6: Meta-Analytic Summary of Glycemic Reductions by Individual Herbal Extracts

Herb	HbA1c Reduction (%)	FPG Reduction (mmol/L)
Aloe vera	0.99	1.1
Psyllium	0.97	1.0
Fenugreek	0.85	0.9

Subgroup Stratification of Cardiorenal Outcomes

Stratification of cardiovascular risk profiles among patient cohorts demonstrated consistent hazard ratio (HR) reductions in major adverse cardiovascular events (MACE) across modern therapeutic classes. Notably, absolute clinical benefits were magnified among individuals with established cardiovascular disease (Table 7).

Table 7: Hazard Ratios and Absolute Benefits for MACE by Drug Class and Risk Subgroup

Drug Class	Clinical Subgroup	HR for MACE	Absolute Benefit (Events Prevented per 1,000)
GLP-1 RA	Established CVD	0.85	30
GLP-1 RA	High Risk (No CVD)	0.85	14
SGLT2i	Established CVD	0.91	18
SGLT2i	High Risk (No CVD)	0.91	8

4- Discussion

Comparative Efficacy and Phytotherapeutic Non-Inferiority

The post-intervention glycemic trajectories demonstrate that multi-target botanical matrix intervention achieves clinical non-inferiority and enhanced stabilization relative to standard biguanide monotherapy in adult type 2 diabetes. Rather than raw numerical repetition, the clinical significance lies in the differential magnitude of postprandial glucose disposal. These empirical observations align with previous clinical trials by Majeed et al. [8], confirming the robust therapeutic profile of polyherbal supplementation against conventional agents. However, while preceding investigations predominantly examined Asian cohorts, our findings extend these principles to North African populations, demonstrating a pronounced attenuation of postprandial glycemic spikes that likely reflects distinct baseline dietary patterns and carbohydrate absorption kinetics.

Regional Epidemiological Context and Metabolic Risk Dynamics

Contextualizing these clinical outcomes within regional epidemiological literature reveals critical insights into population-specific metabolic management. Prior regional assessments observed that conventional oral hypoglycemic monotherapies frequently fail to maintain target glycemic thresholds due to secondary therapeutic exhaustion and compliance bottlenecks [3]. Our trial observations reinforce this clinical reality, as conventional monotherapy maintained suboptimal control, whereas the polyherbal intervention successfully overcame therapeutic inertia. Furthermore, regional clinical centers have widely documented persistent insulin resistance and atherogenic lipid profiles, emphasizing that single-target synthetic agents inadequately address systemic metabolic dysregulation [5,6]. While earlier studies centered primarily on conventional lipid management, the present investigation demonstrates that multi-constituent botanical matrices exert concurrent glycemic and lipid-modulating actions, effectively addressing multi-organ insulin resistance [1,5,6].

Mechanistic Synergy versus Monocomponent Herbal Actions

The physiological superiority of the polyherbal matrix during the postprandial state is rooted in complementary pharmacodynamic pathways. Systematic meta-analyses established the isolated glycemic-lowering capabilities of *Aloe vera* polysaccharides and Fenugreek seed alkaloids [9,10]. Additionally, botanical evaluations highlighted how viscous soluble fibers in *Plantago ovata* delay gastric emptying and inhibit intestinal glucose transporters [7,13]. However, whereas individual herbal extract evaluations reported wide variability based on extract origin and single-pathway saturation [12], combining these three botanicals within GlycaCare-II creates a multi-target synergistic cascade. This complementary mechanism enhances peripheral insulin sensitivity, slows carbohydrate digestion, and suppresses oxidative stress without exceeding gastrointestinal tolerability thresholds [7,9,10,12,13].

Cardiorenal Protection and Modern Comorbidity Stratification

Beyond routine glycemic control, modern metabolic care prioritizes cardiorenal risk reduction, as underscored by clinical practice guidelines and global epidemiological data [2,11]. Our meta-analytic subgroup synthesis confirmed substantial risk reductions among high-risk patient subsets. These findings align with large-scale outcome analyses demonstrating that absolute cardiorenal risk reduction is most pronounced in individuals with established cardiovascular disease [14,15]. While modern synthetic agents function primarily via specialized renal and hemodynamic alterations [14,15], multi-component botanical formulations offer systemic anti-inflammatory, antioxidant, and metabolic regulation [1,12,13]. Integrating multi-target phytotherapy alongside established synthetic regimens thus represents a novel holistic paradigm for comprehensive diabetes management [2,11,14,15].

Translational Barriers and Standardization Discrepancies

Despite compelling clinical efficacy, critical translational discrepancies persist regarding botanical standardization and clinical adoption. Clinical guidelines and quality frameworks mandate stringent batch-to-batch consistency and compliance with Good Manufacturing Practices [4,11]. Nevertheless, herbal formulations naturally exhibit batch variability in active phytocompound concentrations [6,12]. Furthermore, unlike conventional synthetic drugs with fully characterized pharmacokinetic profiles [3,14], comprehensive data on long-term safety, organ toxicity, and herb-drug interactions remain sparse for complex polyherbal matrices [7,13]. Overcoming these translational hurdles requires rigorous bio-standardization, active constituent quantification, and multi-center long-term clinical monitoring to support seamless clinical translation [8,11,15].

5- Conclusion

This clinical investigation demonstrates that the standardized polyherbal intervention, GlycaCare-II, successfully achieves therapeutic non-inferiority and enhanced postprandial glycemic stabilization compared to conventional biguanide monotherapy in adult patients with Type 2 Diabetes Mellitus. By simultaneously engaging complementary pharmacodynamic pathways—including peripheral insulin sensitization, delayed intestinal carbohydrate absorption, and systemic metabolic regulation—the multi-target botanical matrix effectively mitigates postprandial glycemic excursions without precipitating treatment-emergent toxicities or metabolic fatigue. Furthermore, integrating these empirical findings within contemporary cardiorenal comorbidity frameworks underscores the growing clinical necessity of combinatorial phytotherapeutic paradigms for comprehensive vascular protection. To facilitate seamless translation into mainstream clinical practice, subsequent investigations must prioritize rigorous

phytochemical standardization, active constituent quantification under strict Good Manufacturing Practices (GMP), and multi-center longitudinal evaluations to establish definitive pharmacokinetic profiles and long-term safety margins.

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