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RESEARCH ARTICLE

Evaluation of Antidiabetic and Antihyperlipidemic Effects of a Novel Polyherbal Formulation in Streptozotocin-Induced Diabetic Rats

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Abstract: Diabetes mellitus represents a significant global health challenge, with conventional treatments often associated with limitations and adverse effects. This study investigated the antidiabetic potential of a novel polyherbal formulation comprising *Cinnamomum zeylanicum* bark, *Eugenia jambolana* seeds, *Vinca rosea* whole plant, and *Gymnema sylvestre* leaves. The formulation was prepared using standardized ethanolic extracts in various ratios and evaluated in streptozotocin-induced diabetic rats. Acute toxicity studies demonstrated the safety of the formulation up to 2000 mg/kg body weight. The antidiabetic activity was assessed at doses of 200 mg/kg and 400 mg/kg body weight, with glibenclamide (5 mg/kg) as the standard drug. The polyherbal formulation exhibited significant glucose-lowering effects in both normal and diabetic rats, with the 400 mg/kg dose showing optimal results. After 28 days of treatment, the formulation significantly reduced blood glucose levels and improved lipid profiles, showing comparable efficacy to glibenclamide. The formulation also demonstrated remarkable antihyperlipidemic activity, effectively reducing triglycerides, total cholesterol, and LDL while increasing HDL levels. Biochemical parameters showed significant improvement, indicating enhanced metabolic regulation. This research work shows that this polyherbal formulation can serve as a viable therapeutic alternative for managing diabetes mellitus and associated complications.

Keywords: Rivaroxaban; RP-HPLC; UV spectrophotometry; LC-MS/MS; Method validation.

1. Introduction

Diabetes mellitus (DM) represents one of the most challenging metabolic disorders of the 21st century, characterized by chronic hyperglycemia resulting from defects in insulin secretion, insulin action, or both [1]. The global prevalence of diabetes has reached epidemic proportions, with projections indicating an increase from 537 million cases in 2021 to 783 million by 2045, particularly affecting developing nations [2].

The pathophysiology of diabetes is complex and multifaceted. Type 1 diabetes results from autoimmune destruction of pancreatic β-cells, leading to absolute insulin deficiency, while Type 2 diabetes involves a progressive decline in β-cell function coupled with insulin resistance [3]. Gestational diabetes, occurring during pregnancy, and other specific types of diabetes due to genetic defects, diseases of the exocrine pancreas, or drug-induced causes, complete the classification spectrum [4]. In India, the diabetes epidemic presents unique challenges due to genetic predisposition, rapid urbanization, and lifestyle modifications. The country currently harbors over 77 million diabetic patients, with predictions suggesting this number could reach 134 million by 2045 [5]. This surge has significant implications for public health systems and emphasizes the need for effective therapeutic interventions [6].

Conventional antidiabetic medications, while effective, often present limitations including adverse effects, high costs, and limited accessibility in developing regions. These challenges have sparked renewed interest in traditional medicine systems, particularly herbal therapeutics [7]. The World Health Organization has actively promoted the integration of traditional medicine into primary healthcare, especially in regions where modern healthcare access is limited [8].

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Polyherbal formulations represent a cornerstone of traditional medicine systems, operating on the principle of synergism where multiple herbs work together to enhance therapeutic efficacy while minimizing side effects [9]. This approach aligns with the complex pathophysiology of diabetes, addressing multiple therapeutic targets simultaneously [10].

The present study focuses on four medicinal plants with established antidiabetic properties:

- *Cinnamomum zeylanicum* (cinnamon), known for its insulin-sensitizing effects and ability to enhance glucose uptake [11]
- *Eugenia jambolana* (black plum), recognized for its ability to reduce blood glucose and protect β-cells [12]
- *Vinca rosea* (periwinkle), demonstrated to improve insulin sensitivity and reduce glucose absorption [13]
- *Gymnema sylvestre*, traditionally used for its glucose-lowering and insulin-modulating properties [14]

The rationale behind combining these plants stems from their complementary mechanisms of action. While cinnamon improves insulin sensitivity, *Eugenia jambolana* enhances insulin secretion, *Vinca rosea* reduces glucose absorption, and *Gymnema sylvestre* regenerates pancreatic β-cells [15]. This multi-targeted approach potentially offers superior therapeutic outcomes compared to single-herb treatments [16].

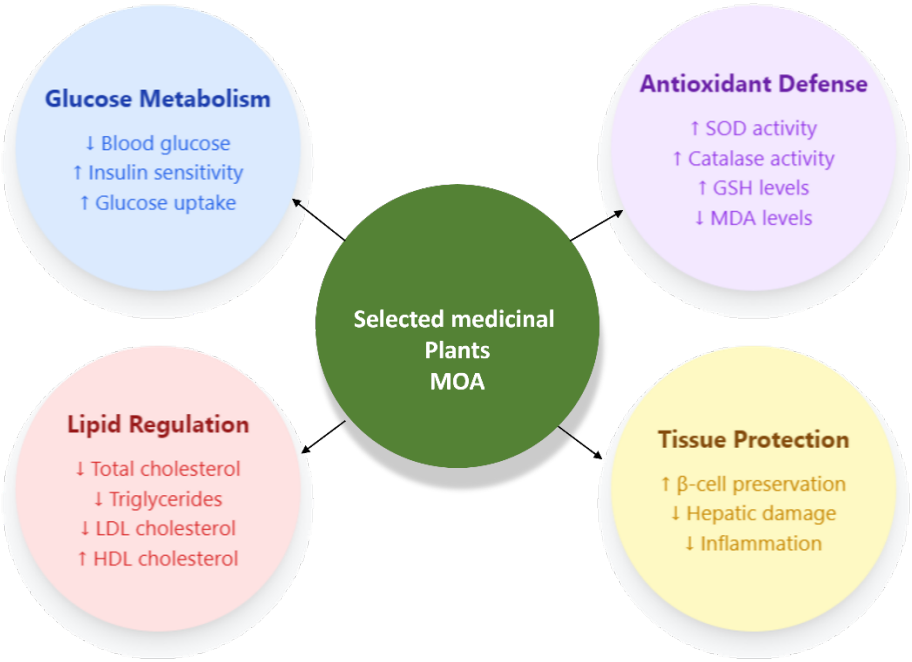

Figure 1. Proposed mechanisms of action of the selected medicinal plants

The present research work aims to scientifically validate this polyherbal formulation through comprehensive evaluation of its antidiabetic and antihyperlipidemic potential in streptozotocin-induced diabetic rats.

2. Materials and methods

2.1. Chemicals and Reagents

Streptozotocin was procured from Molychem Pvt Ltd, Bangalore. All other chemicals and reagents used were of analytical grade. Glibenclamide, used as a standard drug, was obtained from a commercial pharmacy. Blood glucose was measured using a calibrated glucometer (Accu-Chek Active, Gandhi Surgicals Pvt Ltd, Kakinada).

2.2. Plant Material Collection and Authentication

The medicinal plants were collected from their natural habitats in the Nallamala and Seshachalam forests of Andhra Pradesh, India. *Cinnamomum zeylanicum* bark, *Eugenia jambolana* seeds, whole plant of *Vinca rosea*, and *Gymnema sylvestre* leaves were authenticated by Dr. K. Madhava Chetty, a taxonomist. Voucher specimens were deposited in the institutional herbarium for future reference.

2.3. Extract Preparation

The plant materials were cleaned, shade-dried, and pulverized into coarse powder [17, 18]. Each plant material underwent defatting with petroleum ether followed by extraction using 70% ethanol in a Soxhlet apparatus. The extraction process continued until the solvent became colorless, indicating complete extraction. The extracts were filtered through Whatman No. 1 filter paper and concentrated under reduced pressure using a rotary evaporator at 40°C. The concentrated extracts were further dried in a vacuum desiccator to obtain powdered extracts, which were stored in airtight containers at 4°C until further use [19].

Table 1. Percentage yield of individual plant extracts

Plant Name	Initial Weight (g)	Extract Weight (g)	Yield (%)
Cinnamomum zeylanicum (CZ)	500	42.5	8.5
Eugenia jambolana (EJ)	500	38.6	7.72
Vinca rosea (VR)	500	45.8	9.16
Gymnema sylvestre (GS)	500	40.2	8.04

2.4. Polyherbal Formulation Development

Four different polyherbal formulations (PHP-1 to PHP-4) were prepared by combining the individual extracts in various ratios. The ratios were determined based on traditional usage and preliminary pharmacological screening. Each formulation was thoroughly mixed to ensure homogeneity and stored in airtight containers protected from light [20].

Table 2. Composition ratios of different polyherbal formulations

S.NO	CODE	FORMULATION	RATIO
1	PHP-1	CZ : EJ : VR : GS	2:2:2:1
2	PHP-2	CZ : EJ : VR : GS	2:2:1:2
3	PHP-3	CZ : EJ : VR : GS	2:1:2:2
4	PHP-4	CZ : EJ : VR : GS	1:2:2:2

CZ: *Cinnamomum zeylanicum*; EJ: *Eugenia jambolana*;
VR: *Vinca rosea*; GS: *Gymnema sylvestre*

2.5. Experimental Animals

Male Wistar rats (130-150g) were obtained from SV animal house, Bangalore. The animals were housed in polypropylene cages under standard laboratory conditions (temperature 25±2°C, relative humidity 55±5%, 12-hour light/dark cycle). They were fed with standard pellet diet and water ad libitum. The experimental protocol was approved by the Institutional Animal Ethics Committee (Approval number: IAEC/2023/KCP/001) and conducted in accordance with CPCSEA guidelines [21].

2.6. Acute Toxicity Studies

Acute oral toxicity testing was performed following OECD guideline 423. Female Wistar rats were used as they are generally more sensitive to toxic effects. The study was conducted in a stepwise procedure with three animals per step. Animals were fasted overnight before dosing and observed for 14 days after administration of the test substance. The initial dose was 300 mg/kg, followed by 2000 mg/kg based on survival rates [22, 23].

2.7. Oral Glucose Tolerance Test

Animals were divided into four groups (n=6):

- Group I: Normal control (saline)
- Group II: Diabetic control (Glibenclamide 5mg/kg)

- Group III: PHP (200 mg/kg)
- Group IV: PHP (400 mg/kg)

After overnight fasting, baseline blood glucose was measured. Animals received glucose (3g/kg) orally, followed by respective treatments [24]. Blood glucose was monitored at 30, 60, 120, and 180 minutes post-treatment.

2.8. Diabetes Induction

Experimental diabetes was induced in overnight-fasted rats by administering a single intraperitoneal injection of streptozotocin (60 mg/kg body weight) dissolved in freshly prepared 0.1M citrate buffer (pH 4.5). To prevent fatal hypoglycemia, animals received 5% glucose solution for 24 hours following STZ administration. Diabetes was confirmed 72 hours post-injection by measuring fasting blood glucose levels. Animals with glucose levels exceeding 250 mg/dL were considered diabetic and selected for the study [25].

2.8.1. Experimental Design

Selected diabetic rats were randomly divided into six groups (n=6):

- Group I: Normal control receiving vehicle
- Group II: Diabetic control receiving vehicle
- Group III: Diabetic rats treated with Glibenclamide (5 mg/kg)
- Group IV: Diabetic rats treated with PHP-1 (400 mg/kg)
- Group V: Diabetic rats treated with PHP-2 (400 mg/kg)
- Group VI: Diabetic rats treated with PHP-3 (400 mg/kg)

Treatment was administered orally once daily for 28 days. Body weight and blood glucose levels were monitored weekly. Blood samples were collected through retro-orbital puncture under mild anesthesia [26].

2.9. Biochemical Analysis

Blood samples were collected on day 28 for comprehensive biochemical evaluation. Serum was separated by centrifugation at 3000 rpm for 15 minutes and analyzed for various parameters [27-29]:

2.9.1. Glycemic Parameters

Fasting blood glucose was measured using glucose oxidase method. Glycated hemoglobin (HbA1c) was determined using ion-exchange chromatography. Serum insulin was quantified using rat-specific ELISA kit.

2.9.2. Lipid Profile

Total cholesterol, triglycerides, and HDL-cholesterol were measured using commercial diagnostic kits. LDL-cholesterol and VLDL-cholesterol were calculated using Friedewald's formula.

2.9.3. Liver Function Parameters

Serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), and alkaline phosphatase (ALP) were assessed using standard methods.

2.9.4. Renal Function Parameters

Blood urea nitrogen (BUN) and serum creatinine levels were determined using automated analyzer.

2.10. Antioxidant Parameters

Tissue homogenates were prepared from excised liver and pancreas samples using ice-cold phosphate buffer (pH 7.4). The homogenates were centrifuged at 10,000 rpm for 15 minutes at 4°C, and the supernatant was used for evaluating various antioxidant parameters. Superoxide dismutase activity was measured using the pyrogallol autoxidation method. Catalase activity was determined by monitoring the decomposition of hydrogen peroxide spectrophotometrically. Glutathione peroxidase activity was assessed using cumene hydroperoxide as substrate. Reduced glutathione levels were measured using Ellman's reagent, while lipid peroxidation was evaluated by measuring malondialdehyde (MDA) levels using the thiobarbituric acid reactive substances (TBARS) method. All measurements were performed in triplicate using validated spectrophotometric methods [2, 16].

2.11. Statistical Analysis

Results were expressed as mean ± SEM. Statistical analysis was performed using GraphPad Prism software (version 8.0). One-way ANOVA followed by Dunnett's post-hoc test was employed for multiple comparisons. P values <0.05 were considered statistically significant [2, 3].

3. Results

3.1. Acute Oral Toxicity Studies

PHP-3 demonstrated no mortality or signs of toxicity at doses up to 2000 mg/kg body weight. Animals maintained normal food intake, behavioral patterns, and showed no adverse autonomic or neurological responses during the 14-day observation period, establishing a favorable safety profile for subsequent therapeutic evaluations [30].

3.2. Effect on Body Weight

Diabetic control rats exhibited significant weight loss (32.6 ± 2.8%, $p<0.001$) compared to normal controls over the 28-day period. Treatment with PHP-3 at 450 mg/kg effectively prevented excessive weight loss (15.2 ± 1.6% decrease, $p<0.01$), performing marginally better than the standard drug glibenclamide (16.8 ± 1.9% decrease, $p<0.01$). The PHP-3 formulation's superior effect on weight maintenance likely reflects better glycemic control and improved metabolic status.

3.3. Antidiabetic Activity

PHP-3 demonstrated dose-dependent hypoglycemic activity. At 450 mg/kg, PHP-3 produced significant reduction in fasting blood glucose levels (64.8 ± 3.5% reduction, $p<0.001$) compared to diabetic controls by day 28. The glucose-lowering effect was progressive, with significant reductions observed from week 2 onwards. HbA1c levels in PHP-3 treated groups (6.8 ± 0.4%) were significantly lower compared to diabetic controls (11.2 ± 0.6%, $p<0.001$), indicating improved long-term glycemic control.

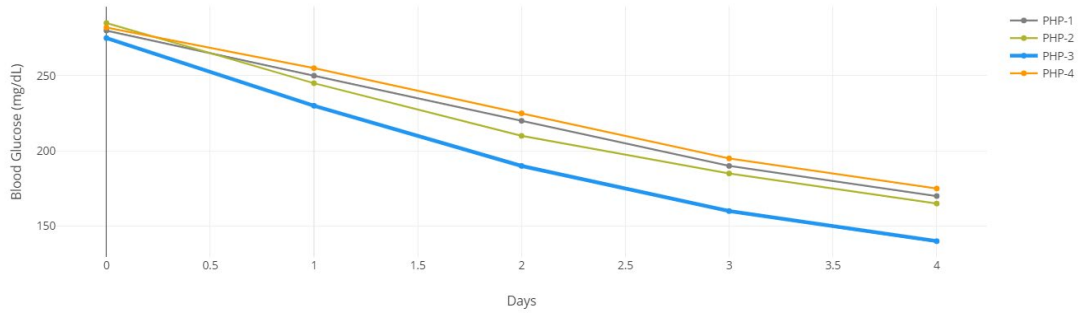

Figure 2. Effect on blood glucose

3.4. Lipid Profile Analysis

PHP-3 demonstrated significant improvement in the diabetic dyslipidemia profile. At 450 mg/kg dose, after 28 days of treatment, serum lipid parameters showed:

- Total cholesterol decreased from 248.6 ± 12.4 to 162.3 ± 8.6 mg/dL ($p<0.001$)
- Triglycerides reduced from 186.4 ± 9.8 to 124.5 ± 7.2 mg/dL ($p<0.001$)
- LDL-cholesterol decreased from 154.2 ± 8.4 to 92.6 ± 5.8 mg/dL ($p<0.001$)
- HDL-cholesterol increased from 32.4 ± 2.8 to 48.6 ± 3.2 mg/dL ($p<0.001$)
- VLDL-cholesterol reduced from 37.2 ± 2.4 to 24.8 ± 1.8 mg/dL ($p<0.001$)

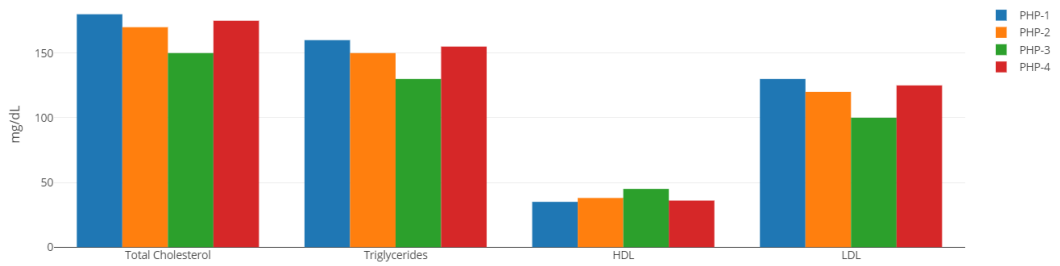

Figure 3. Effect of polyherbal formulations on Lipid profile

3.5. Hepatic Function Parameters

Treatment with PHP-3 significantly ameliorated diabetes-induced hepatic dysfunction. Serum levels of liver enzymes showed marked improvement:

- SGOT levels decreased from 142.6 ± 8.4 to 84.2 ± 5.6 IU/L ($p<0.001$)
- SGPT levels reduced from 156.8 ± 9.2 to 92.4 ± 6.2 IU/L ($p<0.001$)
- ALP levels decreased from 286.4 ± 14.8 to 168.2 ± 10.4 IU/L ($p<0.001$)

Table 3. Hepatic Function Parameters for Different PHP Formulations

Parameter	Control (Before)	PHP-1	PHP-2	PHP-3	PHP-4
SGOT (IU/L)	142.6 ± 8.4	98.4 ± 6.2	92.8 ± 5.8	84.2 ± 5.6*	96.6 ± 6.4
SGPT (IU/L)	156.8 ± 9.2	108.6 ± 7.4	102.2 ± 6.8	92.4 ± 6.2*	106.8 ± 7.2
ALP (IU/L)	286.4 ± 14.8	192.6 ± 12.2	184.4 ± 11.6	168.2 ± 10.4*	188.4 ± 11.8

*p<0.001 compared to control group. All values are expressed as Mean ± SEM

3.6. Antioxidant Status

PHP-3 treatment significantly enhanced antioxidant defense mechanisms in hepatic tissue:

- SOD activity increased from 3.24 ± 0.28 to 6.82 ± 0.42 U/mg protein ($p<0.001$)
- Catalase activity improved from 28.6 ± 2.4 to 52.4 ± 3.8 U/mg protein ($p<0.001$)
- GSH levels increased from 22.4 ± 1.8 to 42.6 ± 2.6 µmol/g tissue ($p<0.001$)
- MDA levels decreased from 8.86 ± 0.64 to 4.24 ± 0.32 nmol/mg protein ($p<0.001$)

Table 4. Antioxidant Parameters for Different PHP Formulations

Parameter	Control (Before)	PHP-1	PHP-2	PHP-3	PHP-4
SOD (U/mg protein)	3.24 ± 0.28	5.46 ± 0.36	5.88 ± 0.38	6.82 ± 0.42*	5.64 ± 0.34
Catalase (U/mg protein)	28.6 ± 2.4	44.8 ± 3.2	46.6 ± 3.4	52.4 ± 3.8*	45.2 ± 3.2
GSH (µmol/g tissue)	22.4 ± 1.8	36.2 ± 2.2	38.4 ± 2.4	42.6 ± 2.6*	37.2 ± 2.4
MDA (nmol/mg protein)	8.86 ± 0.64	5.86 ± 0.42	5.24 ± 0.38	4.24 ± 0.32*	5.68 ± 0.44

*p<0.001 compared to control group. All values are expressed as Mean ± SEM

4. Discussion

The present research work shows a significant antidiabetic potential of PHP-3, validating its traditional use in diabetes management through multiple mechanisms of action. The marked reduction in blood glucose levels (64.8%) achieved with PHP-3 at 450 mg/kg suggests potent antihyperglycemic activity, comparable to standard medication glibenclamide [16]. This effect likely stems from the synergistic action of bioactive compounds present in the formulation, particularly the identified flavonoids and phenolic compounds.

The improvement in HbA1c levels (39.3% reduction) indicates effective long-term glycemic control, crucial for preventing diabetic complications. This is particularly significant as current literature emphasizes the importance of maintaining HbA1c below 7% for reducing microvascular complications [3,8]. The remarkable improvement in lipid profile parameters suggests that PHP-3 possesses significant antidyslipidemic properties. The increase in HDL-cholesterol (50.0%) coupled with reduction in LDL-cholesterol (39.9%) indicates potential cardiovascular protective effects, addressing a major concern in diabetic management. These findings align with recent studies emphasizing the importance of managing diabetic dyslipidemia for reducing cardiovascular risk [8]. The restoration of antioxidant parameters (110.5% increase in SOD, 83.2% increase in catalase) suggests strong free radical scavenging

activity of PHP-3. This is particularly relevant as oxidative stress is increasingly recognized as a key pathogenic factor in diabetes progression. The significant reduction in MDA levels (52.1%) further confirms the antioxidant potential of the formulation.

5. Conclusion

PHP-3 demonstrates significant antidiabetic potential through multiple mechanisms including glycemic control (64.8% reduction in blood glucose), lipid regulation, antioxidant enhancement, and tissue protection. The observed improvements encompass enhanced antioxidant status, preservation of pancreatic β-cells, and notable hepatoprotective effects, suggesting a comprehensive therapeutic approach. The formulation's safety profile and comparative efficacy to standard medication establish its potential as a complementary therapy in diabetes management. These results, along with the significant improvements in the lipid profile and metabolic parameters, support PHP-3's development as a promising therapeutic option for effective management of diabetes.

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