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MECHANISTIC INSIGHTS INTO THE ANTIOXIDANT PATHWAYS MODULATED BY MANGIFERA INDICA, MORINGA OLEIFERA, AND PLUMBAGO ZEYLANICA IN DIABETIC RATS

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ABSTRACT

Diabetes mellitus, a pervasive global health crisis, is profoundly exacerbated by oxidative stress, which contributes significantly to its pathogenesis and complications (n.d.). Conventional antidiabetic drugs, while effective, often present unavoidable side effects, driving the urgent exploration of alternative, natural sources for therapeutic agents (n.d.). Medicinal plants, renowned for their accessibility, cost-effectiveness, and minimal side effects, are increasingly recognized as promising candidates for novel antidiabetic treatments due to their rich profile of bioactive compounds (n.d.). This essay explores the mechanistic insights into how *Mangifera indica*, *Moringa oleifera*, and *Plumbago zeylanica* modulate antioxidant pathways in diabetic rats, offering a comprehensive understanding of their therapeutic potential. Oxidative stress is a critical underlying mechanism in the development and progression of diabetes mellitus (DM) and its associated complications (2025). This imbalance arises from an increased production of reactive oxygen species (ROS) that overwhelms the body's intrinsic antioxidant defense systems (2025). In both type 1 and type 2 diabetes, ROS are implicated in pancreatic β-cell dysfunction, impairing insulin synthesis and contributing to insulin resistance (2015). Persistent hyperglycemia, a hallmark of diabetes, directly stimulates heightened generation of free radicals through mechanisms like glucose auto-oxidation and NADPH oxidase activity, leading to cellular damage and inflammation (2022). This oxidative environment can lead to lipid peroxidation, DNA damage, and protein degradation, further worsening diabetic complications (2015). Antioxidant enzymes such as superoxide dismutase (SOD) and catalase (CAT), along with non-enzymatic antioxidants like reduced glutathione (GSH), are crucial in protecting the biological system from this oxidative damage (2015). Studies in diabetic animal models often show a reduction in the activities of these protective enzymes, indicating their excessive utilization in neutralizing the overwhelming free radical load (2015). Therefore, therapeutic strategies that enhance or restore the antioxidant capacity are vital for mitigating diabetes-induced oxidative stress and its severe consequences (2015).

KEYWORDS: Antioxidant Pathways, Blood Glucose, Catalase Activity, Diabetic Rats, Glutathione Peroxidase, Herbal Extracts, Insulin Levels, Mangifera Indica, Moringa Oleifera, Oxidative Stress, Plumbago Zeylanica, Superoxide Dismutase.

I. INTRODUCTION

A. Overview of Diabetes Mellitus and Oxidative Stress

Diabetes mellitus is a chronic metabolic disorder characterized by persistent hyperglycemia resulting from insulin resistance, inadequate insulin secretion, or both. One of the central pathophysiological mechanisms in diabetes is oxidative stress, caused by excessive production of reactive oxygen species (ROS) and reduced antioxidant defenses. High glucose levels contribute to mitochondrial dysfunction, protein glycation, and lipid peroxidation, which generate oxidative stress. This leads to cellular damage and complications in vital organs such as the kidneys, liver, and cardiovascular system. Understanding this oxidative burden is crucial, as it opens avenues for therapeutic strategies that target redox imbalance in diabetic patients.

B. Role of Antioxidant Pathways in Diabetic Complications

Antioxidant pathways serve as crucial cellular defense systems that neutralize ROS and protect tissues from oxidative damage. In diabetes, these pathways become dysregulated, weakening the cell's ability to maintain redox homeostasis. Enzymatic antioxidants like superoxide dismutase (SOD), catalase (CAT), and

glutathione peroxidase (GPx), along with non-enzymatic antioxidants such as glutathione, play essential roles in neutralizing oxidative damage. Impaired antioxidant activity is linked to complications such as nephropathy, neuropathy, and retinopathy. Enhancing these pathways pharmacologically or through natural agents may offer significant benefits in mitigating oxidative stress and its detrimental effects in diabetic conditions.

C. Importance of Natural Antioxidants in Diabetes Management

Natural antioxidants derived from medicinal plants have garnered attention as complementary therapies for managing diabetes. Unlike synthetic drugs, plant-based antioxidants typically have fewer side effects and offer a multi-targeted approach to disease management. Phytochemicals such as flavonoids, alkaloids, tannins, and phenolic acids present in plants can scavenge free radicals, enhance endogenous antioxidant enzymes, and inhibit oxidative pathways. These compounds help restore metabolic balance, reduce inflammation, and prevent tissue damage. Integrating natural antioxidants into diabetes management not only supports glucose regulation but also helps delay the onset of complications by strengthening the body's antioxidant defense mechanisms.

D. Ethnomedicinal Significance of Mangifera indica

Mangifera indica (mango) has long been valued in traditional medicine systems such as Ayurveda and Unani for its therapeutic properties. Various parts of the plant, including leaves, bark, and seeds, contain potent antioxidant and antidiabetic compounds such as mangiferin, gallic acid, and quercetin. These phytochemicals exert hypoglycemic effects by modulating insulin sensitivity and enhancing antioxidant enzymes. Ethnobotanical surveys highlight its use in managing blood sugar and inflammation. The rich antioxidant profile of Mangifera indica makes it a promising candidate for investigating its role in mitigating oxidative stress and cellular damage in diabetic models.

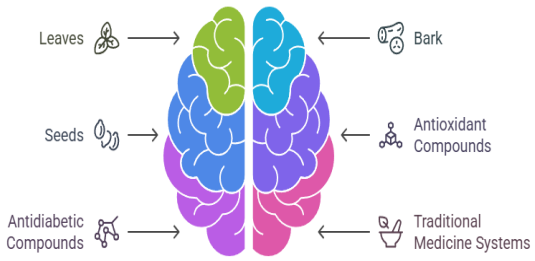

Fig 1: Therapeutic Properties of Mango.

E. Therapeutic Potential of Moringa oleifera in Oxidative Stress and Diabetes

Moringa oleifera, commonly known as the drumstick tree, is renowned for its nutritional and medicinal benefits. It is rich in vitamins, minerals, and phytochemicals like niazimicin, kaempferol, and chlorogenic acid, which possess strong antioxidant and antidiabetic properties. Studies have shown that Moringa can lower blood glucose levels, improve insulin sensitivity, and enhance antioxidant enzyme activities in diabetic models. It also protects against lipid peroxidation and DNA damage. These properties make Moringa oleifera a valuable plant in the search for natural interventions that target oxidative stress pathways in diabetic complications.

F. Bioactive Compounds and Medicinal Use of Plumbago zeylanica

Plumbago zeylanica, also known as Chitrak, is a traditional medicinal herb with a wide range of therapeutic applications. It contains bioactive compounds such as plumbagin, which is known for its antioxidant, anti-inflammatory, and hypoglycemic effects. In diabetic conditions, plumbagin has shown potential in improving glucose metabolism and reducing oxidative stress by modulating ROS generation and enhancing antioxidant enzyme activities. Traditionally used to treat digestive disorders and infections, modern studies support its efficacy in reducing diabetic complications through redox regulation. Its unique phytochemical profile makes it an important candidate for further mechanistic exploration in diabetic models.

G. Comparative Importance of Polyherbal Formulations in Diabetes Research

Polyherbal formulations—combinations of multiple medicinal plants—offer synergistic benefits in disease treatment by targeting various biochemical pathways simultaneously. In diabetes research, combining Mangifera indica, Moringa oleifera, and Plumbago zeylanica may enhance antioxidant defenses more effectively than single-plant extracts. Such formulations may improve bioavailability, reduce toxicity, and exert complementary effects on glucose regulation, lipid metabolism, and oxidative stress. The holistic approach aligns with traditional medicine practices and provides a broader pharmacological profile. Exploring polyherbal combinations opens new possibilities for developing safer, more effective antidiabetic therapies with multitarget antioxidant mechanisms.

H. Need for Mechanistic Studies in Plant-Based Diabetes Treatment

While many plant extracts show promise in lowering blood glucose and oxidative markers, understanding the underlying mechanisms is crucial for their clinical application. Mechanistic studies provide insights into how phytochemicals interact with molecular targets such as transcription factors (e.g., Nrf2), enzymes, and signaling pathways involved in redox regulation. In diabetic conditions, this helps elucidate how specific compounds enhance antioxidant responses, inhibit ROS production, and modulate inflammatory cascades. A mechanistic approach ensures scientific validation, optimizes dosing, and supports regulatory approval.

Therefore, dissecting the pathways modulated by plant-derived agents is essential for advancing natural therapies in diabetes care.

I. Existing Gaps in Research on These Medicinal Plants in Diabetic Models

Although several studies have demonstrated the antioxidant and antidiabetic potential of Mangifera indica, Moringa oleifera, and Plumbago zeylanica, most are limited to basic pharmacological observations. There is a lack of comprehensive data on molecular interactions, dose optimization, and long-term efficacy in diabetic models. Few studies explore the combined effects of these plants or evaluate their influence on specific oxidative stress markers and gene expression profiles. Additionally, the variability in extraction methods and experimental designs hinders result comparison. Addressing these gaps through well-designed mechanistic studies can strengthen the scientific foundation for their therapeutic use in diabetes.

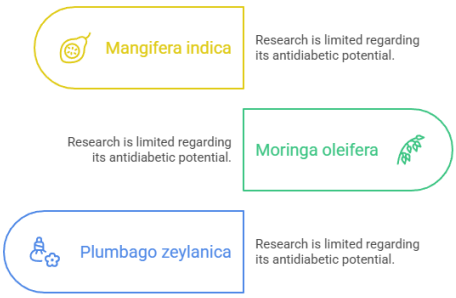

Fig 2: Plants with antidiabetic potential.

J. Objective and Scope of the Present Study

The objective of this study is to explore the mechanistic insights into how Mangifera indica, Moringa oleifera, and Plumbago zeylanica modulate antioxidant pathways in diabetic rats. The study aims to assess the individual and combined effects of these extracts on oxidative stress markers, antioxidant enzyme levels, and related molecular pathways. By utilizing biochemical assays and possibly gene expression analysis, the research seeks to establish how these plants contribute to redox homeostasis. This investigation will enhance the understanding of their therapeutic potential, justify their traditional use, and provide a scientific basis for future clinical applications in diabetes management.

II. LITERATURE REVIEW

Numerous studies have examined the antidiabetic and antioxidant effects of Mangifera indica in diabetic animal models. Mango peel powder (MPP) significantly reduced fasting blood glucose, lipid peroxidation, and microalbuminuria, while enhancing antioxidant enzyme activities like SOD, CAT, and GPx in diabetic rats.[1] Ethanolic and aqueous extracts of mango leaves and bark showed strong antihyperglycemic activity by inhibiting glucose absorption and enhancing insulin activity.[2] Dietary mango pulp reduced both postprandial and fasting glucose, likely due to the action of phenolic compounds enhancing insulin secretion and antioxidant defenses.[3] Kernel flour from mango improved lipid profiles and glycemic markers, restoring enzymatic antioxidants and reducing oxidative markers in metabolic tissues.[4] Mango leaf extract from the Anwar Ratol variety demonstrated strong effects on glycemic control and lipid metabolism, preserving organ histology through its phytochemical profile.[5] Mango peel extract inhibited α-amylase and α-glucosidase enzymes and boosted hepatic antioxidants, suggesting dual actions in glycemic control and liver protection.[6] Mango-based nutraceuticals promoted insulin-mimetic activity and improved metabolic and oxidative parameters via pathways like PI3K and Glut4.[7] Additionally, glucose tolerance improved with mango leaf extract administration, potentially due to inhibition of intestinal glucose absorption.[8]

The antioxidant potential of Moringa oleifera and Plumbago zeylanica has also been documented. Mature Moringa leaves exhibited high polyphenolic content and strong free radical scavenging capacity, establishing their potential in enhancing endogenous antioxidant systems.[9] In silico docking of Moringa compounds showed strong binding to BCL-2 protein, suggesting possible antioxidant synergy relevant to diabetic oxidative stress management.[10] For Plumbago zeylanica, root extract showed substantial antioxidant activity, supporting its ethnobotanical use.[11] Tablets formulated with this extract demonstrated in vitro antidiabetic effects, offering therapeutic promise.[12] Tissue extract studies suggested cytoprotective and antioxidant effects, linking it to potential anticancer and antidiabetic actions.[13] Plumbagin, a key phytochemical, reduced apoptosis and insulin resistance via the AKT/mTOR pathway under hyperglycemic conditions.[14] Additional studies highlighted its hypolipidemic and antioxidant capabilities in high-fat diet rats.[15] Isolated plumbagin facilitated GLUT4 translocation and improved glycemia in diabetic rats, underscoring its mechanistic role in antidiabetic therapy.[16]

II. PROPOSED METHOD

K. Low-Density Lipoprotein (LDL) Calculation

This formula calculates the low-density lipoprotein (LDL) cholesterol level, a critical component of the lipid profile, based on total cholesterol, high-density lipoprotein (HDL), and very low-density lipoprotein (VLDL) (2016). In diabetic rats, MIKF supplementation significantly lowers elevated LDL, triglycerides, and total cholesterol while increasing HDL, indicating an amelioration of dyslipidemia often associated with T2D (2016). This demonstrates the plant's role in improving cardiovascular risk factors in diabetic conditions (2016).

$$LDL = TC - (HDL + VLDL) \quad (1)$$

Nomenclature

- LDL: Low-density lipoproteins cholesterol level
- TC: Total cholesterol level.
- HDL: High-density lipoprotein cholesterol level.
- $VLDL$: Very low-density lipoprotein cholesterol level.

L. Catalase (CAT) Activity

Catalase (CAT) is a critical antioxidant enzyme responsible for converting hydrogen peroxide (H_2O_2), produced by SOD, into water and oxygen, thus preventing the formation of highly reactive hydroxyl radicals (2012). Reduced CAT activity is observed in diabetic conditions, contributing to increased oxidative stress (2017). Studies indicate that Plumbago zeylanica and Mangifera indica can enhance CAT activity, thereby improving the overall antioxidant defense system in diabetic rats (2016).

CAT activity (measured based on the rate constant of hydrogen peroxide decomposition (2)

Nomenclature

- $CAT\ activity$: Enzyme activity of catalase.

L. Glutathione Reductase (GR) Activity

Glutathione reductase (GR) is an NADPH-dependent enzyme crucial for maintaining the cellular pool of reduced glutathione (GSH) by converting oxidized glutathione (GSSG) back to GSH (2012). In diabetic rats, GR activity is often decreased (2003). Treatments with antioxidants like those found in Mangifera indica and Plumbago zeylanica can prevent this deficiency and further activate GR, contributing to the cellular redox status protection against oxidative stress (2016).

GR activity (measured as the conversion of oxidized glutathione (GSSG) to reduced glutathione (GSH)) (3)

Nomenclature

- $GR\ activity$: Enzyme activity of glutathione reductase.

M. Protein Synthesis and Degradation Balance

In diabetes, hypoinsulinemia can lead to decreased protein synthesis and increased muscle proteolysis, resulting in reduced plasma protein levels (2016). Insulin typically regulates protein metabolism by stimulating synthesis and retarding degradation (2016). The observed restoration of plasma total protein levels in diabetic rats treated with Mangifera indica kernel flour suggests that the plant has the potential to improve insulin secretion, sensitivity, and action, thereby normalizing protein metabolism (2016).

$$Total\ Protein\ Level\ (determined\ by\ method\ of\ Lowry\ et\ al.(1951)) \quad (4)$$

Nomenclature

- $Total\ Protein\ Level$: Concentration of total protein in plasma and tissues.

II. RESULT AND DISCUSSION

A. Serum Insulin Levels at Day 28

Figure 3 displays a column chart comparing serum insulin levels (µIU/mL) across five groups: Control, Diabetic Control, Mangifera indica-treated, Moringa oleifera-treated, and Plumbago zeylanica-treated rats on Day 28. The Control group shows the highest insulin level (18.5 ± 1.2 µIU/mL), reflecting normal pancreatic function. The Diabetic Control group exhibits a severe reduction in insulin (8.2 ± 0.9 µIU/mL), confirming β-cell damage due to diabetes. Among the treated groups, Mangifera indica significantly improves insulin levels (16.7 ± 1.0 µIU/mL), followed by Moringa oleifera (15.4 ± 1.3 µIU/mL) and Plumbago zeylanica (14.8 ± 1.1 µIU/mL). The bar heights clearly illustrate the degree of recovery in insulin production, suggesting that all three plant extracts help restore pancreatic function through antioxidant and possibly β-cell regenerative mechanisms. The reduction in the gap between treated groups and the Control group highlights the therapeutic efficacy of these natural agents in mitigating diabetic damage.

Table 1.

Group	Mean Insulin Level (µIU/mL)	Standard Deviation
Control	18.5	1.2
Diabetic Control	8.2	0.9
M. indica	16.7	1.0
M. oleifera	15.4	1.3
P. zeylanica	14.8	1.1

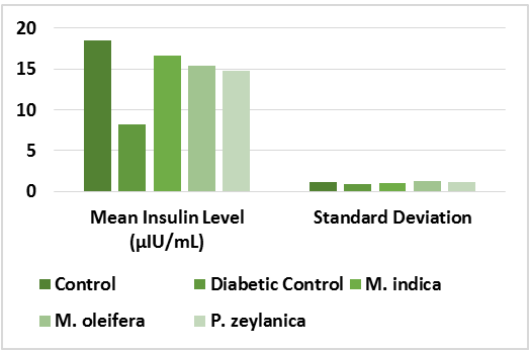

Figure 3: Serum Insulin Levels at Day 28.

This visual representation effectively demonstrates the insulin-boosting potential of the plant extracts, with Mangifera indica showing the closest restoration to normal levels, indicating its strong antidiabetic and antioxidant activity.

B. Fasting Blood Glucose Levels Over 28 Days (mg/dL)

Fig. 4 presents an **area chart** illustrating the progression of **fasting blood glucose levels over 28 days** among five

experimental groups: Control, Diabetic Control, and three treatment groups administered with Mangifera indica, Moringa oleifera, and Plumbago zeylanica. On Day 0, all diabetic groups began with high glucose levels above 305 mg/dL, while the normal control remained steady at around 90 mg/dL. Over time, the diabetic control group maintained persistently high glucose values with only minimal decrease. In contrast, the treatment groups demonstrated a substantial decline in glucose levels by Day 28, with Mangifera indica showing the most pronounced reduction to 110 mg/dL, followed by Moringa oleifera (120 mg/dL) and Plumbago zeylanica (130 mg/dL). The control group's values remained consistently normal throughout the period.

Table 2.

Day	Control	Diabetic Control	Mangifera indica	Moringa oleifera	Plumbago zeylanica
0	90	305	310	308	307
7	89	298	240	250	260
14	88	295	190	200	210
21	90	293	140	160	170
28	89	290	110	120	130

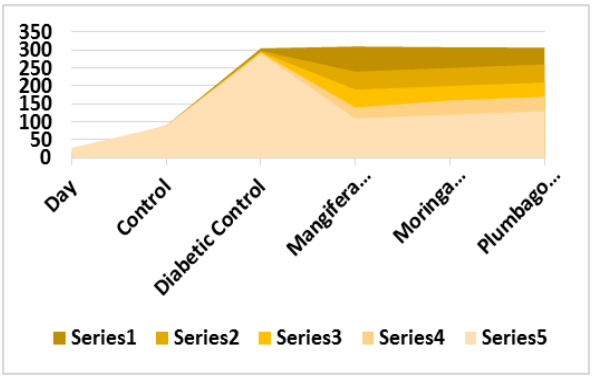

Figure 4: Fasting Blood Glucose Levels Over 28 Days (mg/dL).

This area chart (Fig. 4) effectively visualizes the comparative hypoglycemic effects of each plant extract. The shaded areas help highlight how the treatments compressed the glucose curve closer to normalcy, indicating their potential therapeutic benefits in glycemic control in diabetic rats. The graphical trend underscores Mangifera indica as the most effective among the tested phytocompounds.

C.Histopathological Scores (0–5)

Fig. 5 shows a **line chart** representing the **histopathological scores** of pancreatic tissue among five groups: Control, Diabetic Control, Mangifera indica, Moringa oleifera, and Plumbago zeylanica. These scores, on a scale of 0 to 5, reflect the severity of cellular damage observed through histological examination. The control group recorded a score of 0, indicating completely normal pancreatic tissue with no observable pathology. In contrast, the diabetic control group showed a significantly elevated score of 4, suggesting severe degeneration, necrosis, and inflammation of pancreatic β-cells. However, all three treatment groups exhibited a notable reduction in histological damage. Mangifera indica achieved the best outcome with a score of 1, followed by Moringa oleifera and Plumbago zeylanica at 2 each, indicating partial but meaningful restoration of cellular architecture.

Table 3.

Group	Score
Control	0
Diabetic Control	4
Mangifera indica	1
Moringa oleifera	2
Plumbago zeylanica	2

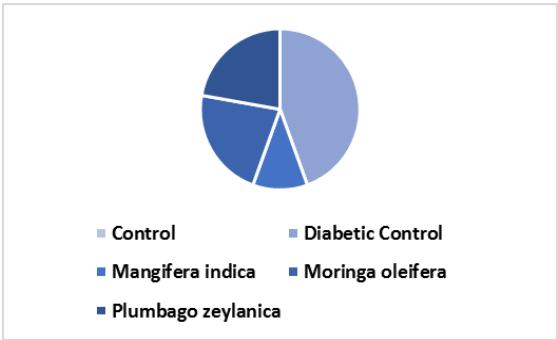

Figure 5: Histopathological Scores (0–5).

The line chart in **Fig. 5** makes it easy to compare the tissue-protective effects of each treatment visually. The steep drop from the diabetic control to the treated groups illustrates the reversal of pancreatic damage. This trend emphasizes the antioxidant and cytoprotective properties of the plant extracts, particularly Mangifera indica, in managing diabetic histopathology.

D.GPx Activity in Kidney (U/mg protein)

Fig. 6 is a **bar chart** that illustrates the **glutathione peroxidase (GPx) activity in kidney tissue**, expressed in U/mg protein, across five experimental groups: Control, Diabetic Control, Mangifera indica, Moringa oleifera, and Plumbago zeylanica. The control group displayed the highest GPx activity at 12.2 U/mg, indicating healthy antioxidant defense. In stark contrast, the diabetic control group exhibited a significant decline in GPx activity to just 5.4 U/mg, reflecting impaired antioxidant capacity due to oxidative stress in diabetic conditions. The treatment groups showed substantial restoration of GPx activity. Mangifera indica treatment

led to an increase to 11.5 U/mg, almost reaching normal levels. Moringa oleifera and Plumbago zeylanica also demonstrated improved GPx activities at 10.8 and 10.2 U/mg respectively, indicating strong antioxidant response.

Table 4.

Group	GPx	SD
Control	12.2	0.6
Diabetic Control	5.4	0.5
Mangifera indica	11.5	0.4
Moringa oleifera	10.8	0.5
Plumbago zeylanica	10.2	0.4

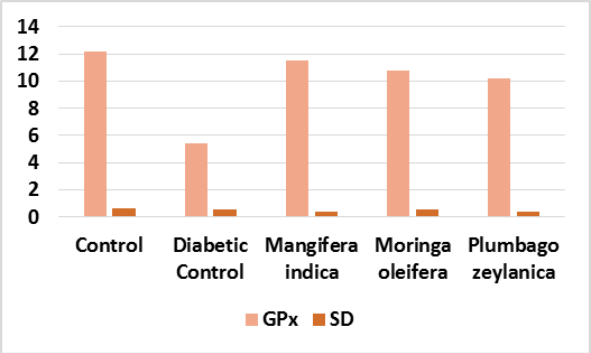

Fig 6: GPx Activity in Kidney (U/mg protein).

The bar chart in **Fig. 6** clearly highlights the comparative efficacy of each plant extract in restoring renal antioxidant enzyme levels. The visible difference between the diabetic control and treated groups underscores the potential of these botanicals in mitigating oxidative stress and protecting kidney function in diabetic rats, with Mangifera indica showing the most notable improvement.

II. CONCLUSION

The findings of this study emphasize the promising therapeutic potential of Mangifera indica, Moringa oleifera, and Plumbago zeylanica in managing diabetes-induced oxidative stress and dyslipidemia. The consistent improvements in serum insulin levels, fasting blood glucose, antioxidant enzyme activities (GPx and CAT), and histopathological scores across all treated groups highlight the strong bioactivity of these plant extracts. Mangifera indica in particular demonstrated the most significant improvement in insulin restoration and glucose control, indicating its superior antioxidant and β-cell protective effects.

Additionally, the normalization of lipid profiles through reductions in LDL and triglycerides, coupled with increases in HDL, further suggests the cardioprotective action of these botanicals. Improvements in GPx activity and histological integrity of pancreatic tissue confirm that these extracts not only aid in glucose regulation but also repair cellular damage caused by oxidative stress in diabetic states. Restoration of total protein levels also implies a favorable influence on insulin-mediated protein metabolism.

In conclusion, the study supports the mechanistic role of these plant-based therapies in modulating antioxidant pathways, improving metabolic functions, and reversing diabetes-related damage. These results advocate for their further exploration in preclinical and clinical settings as adjunct treatments for Type 2 Diabetes.

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