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Original Research Article

Evaluation of Aegle marmelos and Spondias pinnata Combined Antidiabetic Potential on β- Cell Repair and glucose homeostasis in diabetic rats' model

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Abstract:

The hallmarks of diabetes mellitus include decreased insulin production, disrupted glucose homeostasis, and increasing pancreatic β-cell failure. In a streptozotocin-induced diabetic rat model, the current study examined the combination antidiabetic effects of Aegle marmelos and Spondias pinnata on pancreatic β-cell repair and metabolic regulation. Chronic hyperglycemia, decreased plasma insulin levels, raised HbA1c, impaired glucose tolerance, oxidative stress, dyslipidaemia, hepatic dysfunction, and significant histological damage to pancreatic and liver tissues were all outcomes of diabetes induction. Individual plant extracts and a polyherbal formulation (200 mg/kg body weight) were administered to experimental rats, while metformin served as a common reference medication. When compared to diabetic control mice, treatment with the polyherbal formulation dramatically decreased HbA1c levels, restored insulin concentrations, enhanced oral glucose tolerance, and normalized fasting blood glucose levels. The formulation also reduced lipid peroxidation, rectified lipid abnormalities, and restored antioxidant enzyme status, all of which resulted in a considerable improvement in hepatic glycogen level. The polyherbal-treated group showed a significant improvement in hepatic tissue integrity and pancreatic islet architecture, according to histopathological analysis. Functional β-cell preservation and regeneration were confirmed by pancreatic immunohistochemistry analysis, which also showed increased β-cell density and improved insulin staining. Overall, the results show that administering Aegle marmelos and Spondias pinnata together has a synergistic, multi-targeted antidiabetic effect by promoting pancreatic β-cell repair, protecting hepatic tissue, improving glycaemic control, and strengthening antioxidant defences. This suggests that it could be a promising supplemental therapeutic approach for the management of diabetes.

Keywords: Diabetes, Streptozotocin, Histopathology, Herbal drugs, β cell.

INTRODUCTION

A chronic metabolic disease called diabetes mellitus (DM) is typified by persistently high blood sugar levels that result from either decreased insulin action or secretion, or both. Because of its chronic nature, comorbidities, and rising prevalence, it continues to be a major worldwide health concern (International Diabetes Federation, 2025). About 1 in 9 adults in the 20–79 age range worldwide have diabetes, with 589 million people living with the disease, according to the 11th edition of the International Diabetes Federation (IDF) Diabetes Atlas (2025). 81% of cases worldwide occur in low- and middle-income nations, where the burden is disproportionately great. India is the country most affected by the diabetes pandemic. In India, the age-standardized prevalence of diabetes in adults aged 20 to 79 is projected to be 10.5% as of 2024, or around 89.8 million adult cases. By 2050, this population is expected to alarmingly increase to roughly 156.7 million. These numbers highlight how serious the public health issue is for people, families, and healthcare systems both in India and around the world (1). Type 1 Diabetes Mellitus (T1DM) and Type 2 Diabetes Mellitus (T2DM) are the two primary forms of diabetes. The main cause of type 1

diabetes is the autoimmune destruction of pancreatic β-cells, which results in either a near-total or complete lack of insulin. Insulin resistance (in peripheral tissues such the liver, muscle, and adipose) and a gradual loss of β-cell bulk and function are the hallmarks of type 2 diabetes, on the other hand. Although the causes are different, they are both characterised by decreased β-cell mass and function as well as inadequate insulin production, which leads to persistent hyperglycemia.

An essential part of glucose homeostasis and, consequently, the pathophysiology of diabetes mellitus is played by pancreatic β-cells, which secrete the anabolic hormone insulin (2). Insulin is a polypeptide made up of three disulphide bridges connecting the A and B chains, two chains of amino acids. Insulin-coding mRNA first synthesises a peptide chain called preproinsulin, which the endoplasmic reticulum then transforms into proinsulin. After that, proinsulin is transported to the Golgi apparatus, where it is consolidated into granules. Equimolar levels of insulin and C-peptide are present in the granules because the connecting peptide (C-peptide), which connects the A and B chains, is separated in the granules prior to insulin production. In patients receiving exogenous insulin, the blood level of C-peptide can be tested and serves as an indicator of β-cell activity (3). T1DM is caused by autoimmune destruction of β-cells and islets of Langerhans. Human leukocyte antigen (HLA) has been discovered to encode the islet cell surface proteins that communicate with immune cells. β-cells are harmed by activated cytotoxic CD8+ T lymphocytes through the previously stated HLA genetic component. Additionally, β-cells are harmed by inflammatory stress brought on by cytokines released by T lymphocytes. Although some autoantibodies have been observed in T1DM, it is unclear if these autoantibodies have a role in the disease's pathophysiology (4). Insulin resistance linked to a malfunction in compensatory insulin secretion is the cause of type 2 diabetes. Insulin resistance is a complex condition that frequently arises with ageing and fat. Insulin resistance and subsequently type 2 diabetes are influenced by genetic factors and lifestyle modifications. The primary causes of hyperglycemia in type 2 diabetes are decreased muscle glucose uptake and inadequate suppression of hepatic glucose synthesis as a result of insulin resistance. Chronic exposure to glucose and fatty acids is thought to be the cause of β-cell damage and malfunction in individuals with type 2 diabetes. Glycation reactions are another consequence of chronic hyperglycemia, and in type 2 diabetes, reactive oxygen species generation damages β-cells (5). Histopathological examination or immunohistochemical analysis of the pancreatic tissue can be used to determine the mass of pancreatic β-cells and any structural abnormalities (6). Morphometric analysis, including islet size and density, fractional β-cell area, and the number of apoptotic β-cells (7), is part of the histological investigation.

In both T1DM and T2DM, β-cell loss and dysfunction are caused by overlapping processes at the molecular and cellular level. Reactive oxygen species (ROS) and reactive nitrogen species (RNS), mitochondrial dysfunction, endoplasmic reticulum (ER) stress, and the activation of pro-apoptotic and inflammatory pathways are all brought on by metabolic stress, which is caused by chronic hyperglycemia (glucotoxicity), elevated fatty acids (lipotoxicity), nutrient overload, and insulin resistance. Long-term oxidative stress damages cellular macromolecules (lipids, proteins, and DNA), alters the expression of β-cell genes (e.g., downregulating important transcription factors like PDX-1 and MafA), hinders the transcription of the insulin gene, lowers the capacity for insulin synthesis and secretion, and may even cause β-cell dedifferentiation or death (8). Strategies to reduce ROS/RNS, improve antioxidant defences, modify stress-response pathways, and restore β-cell survival or regeneration have garnered more interest due to the key role that oxidative stress and metabolic stress play in β-cell failure (9).

Experimental animal models are still essential for comprehending the pathophysiology of diabetes and assessing treatment options because direct research in human pancreatic tissue is challenging. One of the most popular and well studied is the diabetic rodent model caused by streptozotocin (STZ). Through a variety of mechanisms, including DNA alkylation and strand breaks, activation of poly (ADP-ribose) polymerase (PARP), depletion of cellular NAD^+ and ATP, generation of ROS and RNS (including nitric oxide), mitochondrial dysfunction, and activation of apoptotic or necrotic cell death pathways, STZ, a nitrosourea compound, preferentially enters β-cells (primarily via glucose transporters like GLUT2). This mimics features of insulin-deficient diabetes mellitus by causing a fast and selective death of pancreatic β-cells, which results in insulin insufficiency and hyperglycemia (10). STZ-induced islet destruction is also linked to oxidative stress and nitric oxide synthase (NOS)-mediated pathways, according to recent studies (11). The model offers a repeatable platform to evaluate β-cell protective or regenerative therapies, despite the fact that STZ-induced diabetes differs from naturally occurring T1DM or T2DM. Furthermore, as STZ causes oxidative damage and cell death, which are mechanisms linked to human diabetes, therapies that effectively maintain or regenerate β-cells in this model may be applicable in other contexts. Controlling hyperglycemia, enhancing insulin sensitivity, or supplementing with insulin are the major goals of the current conventional therapies for diabetes, which include insulin therapy and oral hypoglycemic medications. Nevertheless, they hardly ever deal with the underlying problem, which is β-cell loss or malfunction. As diabetes worsens, many people need combination therapy or exogenous insulin for the rest of their lives, and long-term consequences are still a big worry. As a result, pharmaceutical approaches that can maintain remaining β-cells, promote β-cell proliferation or neogenesis, or restore endogenous insulin secretion capacity are becoming more and more popular. These regenerative methods have the potential to improve

quality of life and possibly lower long-term consequences by shifting the focus of diabetes treatment from symptomatic management to more restorative treatments.

Replication of preexisting β-cells or transformation of other pancreatic cells into β-cells are two ways that β-cell regeneration might take place. The purpose of this study is to examine experimental medications that come from natural sources and see if they can enhance β-cell regeneration. Herbal remedies and phytochemicals produced from plants present a promising, complementary path in this regard. Numerous bioactive substances, including flavonoids, terpenoids, phenolics, saponins, glycosides, and alkaloids, are found in many therapeutic plants. These substances include cytoprotective, anti-inflammatory, antioxidant, and insulinotropic qualities. Certain herbs have been shown in experiments to increase β-cell survival, decrease oxidative stress, increase insulin production, and in certain cases, support islet restoration or β-cell regeneration in diabetic animals (12).

Among these, the antidiabetic and antioxidant qualities of Aegle marmelos, also referred to as Bael, a plant that is frequently used in traditional medicine, have been studied. Reduced blood glucose levels, improved lipid profiles and dyslipidaemia, decreased pro-inflammatory cytokines (TNF-α, IL-6, IL-1β), restored antioxidant enzyme levels (SOD, CAT, GPx), and lessened histological damage in pancreatic, liver, and kidney tissues were all shown in a recent study employing an alkaloid-free hydroalcoholic extract of A. marmelos (AFEAM) in diabetic mice (13). Furthermore, glycaemic markers (fasting blood glucose, HbA1c), serum insulin and C-peptide levels, lipid profile, oxidative stress markers, inflammatory cytokines (IL-6, TNF-α), and islet architecture with increased β-cell density were all markedly improved by a methanolic extract of A. marmelos given to STZ-induced diabetic rats. These results confirm that under diabetes stress, A. marmelos has anti-inflammatory, antioxidant, and β-cell protective properties (14). Another underutilised plant with possible antidiabetic effects is Spondias pinnata, sometimes known as hog plum. A computational docking study found several compounds from S. pinnata fruit, such as rutin, quercetin, catechin, myricetin, and ellagic acid, that have a high binding affinity to peroxisome proliferator-activated receptor gamma (PPARγ), a nuclear receptor involved in glucose and lipid metabolism, insulin sensitivity, and the regulation of β-cell function, despite the paucity of studies specifically on β-cell regeneration (9). The anti-inflammatory and antioxidant qualities of these phytochemicals may be the basis for their protective effects on β-cells and metabolic balance. Phenolics, flavonoids, and tannins—compounds with known antioxidant and antidiabetic properties—may be present in S. pinnata, according to preliminary studies and ethnopharmacological reports (15). The complimentary modes of action of A. marmelos and S. pinnata provide justification for their combination. While S. pinnata contributes chemicals that may alter insulin sensitivity, glucose metabolism (via PPARγ), carbohydrate digestion, and oxidative stress, A. marmelos has substantial antioxidant, anti-inflammatory, and insulin-secretion boosting capabilities. In order to address the several pathogenic axes of diabetes, including oxidative stress, inflammation, insulin shortage, insulin resistance, and β-cell destruction, a combination therapy may offer synergistic advantages. In phytomedicine, herbal–herbal synergy is a well-known tactic that frequently boosts effectiveness and lowers dosage requirements (16).

The combined benefits of A. marmelos and S. pinnata on pancreatic β-cell regeneration and glycaemic recovery in a STZ-induced diabetes model have not yet been comprehensively examined in a published study, despite encouraging individual data. Combinatorial or polyherbal techniques have been understudied because the majority of previous research has been on single-plant extracts. A polyherbal intervention may be more effective than single-agent therapy due to the multifactorial stress placed on β-cells and the complexity of diabetes pathogenesis.

MATERIAL AND METHOD

The source of streptozotocin (STZ) was Sigma-Aldrich Fine Chemicals, located in St. Louis, Missouri, USA. All of the biochemical analysis kits were acquired from Erba, and additional analytical-grade chemicals were bought from regional companies in India.

Herbal drugs collection and Extraction

The bark of Spondias pinnata was collected from Madhubani (Bihar) and authenticated from the Centre of Advanced Study in Botany, Institute of Science, Banaras Hindu University, Varanasi. The leaves and bark of the chosen plant, Aegle marmelosmature, were cleaned, allowed to air dry, and then ground into a powder.Using a Soxhlet apparatus, the leaves of Aegle marmelos were extracted with 95% ethanol, and the steam bark of Spondias pinnata was extracted with water using the same device for 15 hours. A rotavapor was used to concentrate the filtrate at 65°C after it had been filtered using cotton wool. Before being used again, the concentrate was freeze-dried to produce 20–30% of the dry powder and kept in a refrigerator at 5°C (17).

Experimental animals

36 healthy adults male Wistar rats weighing 150–180 g were used in this investigation. They were purchased from Central Animal House, Nims University, Jaipur, Rajasthan, India. Under typical laboratory and environmental circumstances, the animals were kept in big, roomy polyacrylic cages with a 12-hour light/12-hour dark cycle at room temperature. The rats were given unlimited access to water and regular rat food. The Nims Institute of Pharmacy's Institutional Animal Ethics Committee gave its approval to the study (NIMS/IAEC-01/2023/06).

Experimental Design

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Group I: normal rats received sterile water

Group II: STZ treated diabetic control rats received sterile water.

Group III: STZ treated diabetic rats received 500mg/kg of Metformin.

Group IV: STZ treated diabetic rats received 200 mg/kg of Aegle marmelos.

Group V: STZ treated diabetic rats received 200 mg/kg of Spondias pinnata

Group VI: STZ treated diabetic rats received polyherbal drug 200 mg/kg of Aegle marmelos and200 mg/kg Spondias pinnata

Induction of Diabetes

Rats with type 1 diabetes were fasted for the whole night before receiving an intraperitoneal injection of STZ (65 mg/kg body weight). STZ was made fresh in a pH 4.5 solution of 10 mM citrate buffer. A One Touch Glucometer (Gluco One Dr. Morepen, India) was used to measure hyperglycemia in a tail vein blood sample three days after STZ administration. Rats were classified as diabetic if their blood glucose levels were continuously higher than 250 mg/dL for three days in a row. For four weeks, these diabetic rats were kept on regular rat food and unlimited access to tap water. All of the DM rats were kept in separate metal metabolic cages at the conclusion of this time(18).

Estimation of glucose and serum insulin

Blood was drawn using a tail-prick technique after a 6-hour fast, and the blood glucose level was measured using a commercial glucometer. Each sample was then applied in small amounts to a glucometer test strip (Accu chek strips, Roche-Diabetes Care) for a subsequent blood glucose measurement. Before the experiment started, baseline blood glucose levels were determined, and follow-up measurements were made at 1, 4, and 8 weeks after the experiment was over. Using an ELISA, the serum insulin concentration (µIU/ml) was ascertained

Assessment of oral glucose tolerance

On the fifteenth day of therapy, the oral glucose tolerance test (OGTT) was administered to both drug-treated and normal rats that had fasted overnight. Each rat received a glucose load (2 g/kg) orally via feeding syringe precisely 30 minutes after extract, standard medication, and vehicle were administered. Each rat's blood glucose profile was assessed at time 0 (before the glucose load) and 30, 60, and 120 minutes after the glucose was administered, following Trinder's (1969) instructions. Throughout the trial, the rats were not given any food (19).

Estimation of hemoglobin A1c (HbA1c)

An ELISA kit from ERBA, M.S., India, was used to quantify the concentration of haemoglobin A1c (HbA1c). The manufacturer's instructions were used to examine the HbA1c estimation. Calculating the serum lipid profile To separate serum, whole blood samples were centrifuged for ten minutes at room temperature. The separated serum was stored below -50 °C after centrifugation.

Biochemical analysis

Prior to the rats being sacrificed, blood samples were taken from the retro-orbital plexus after 28 days of therapy, and blood glucose levels were assessed using a glucometer (Accu-check, Roche Diagnostic, Indianapolis, IND, United States). The leftover blood was centrifuged for five minutes at 3000 rpm. Serum was taken right away and kept at -700C until the biochemical parameters were analysed. Biochemical markers such the lipid profile (total serum cholesterol, serum triglycerides, high-density lipoprotein (HDL), and low-density lipoprotein (LDL)) were estimated using the serum. ALT (serum glutamate oxaloacetate transaminase) and liver function tests. alkaline phosphatase (ALP) and serum glutamate pyruvate transaminase (AST). The ERBA Biochemical Analyser was used to measure these biochemical parameters (20).

Estimation of biomarkers of oxidative stress

Superoxide dismutase (SOD), catalase (CAT), glutathione reductase (GSH), and malondialdehyde (MDA) were among the antioxidant enzymes that were tested in kidney homogenate using a commercial diagnostic ELISA kit from MSW Pharma, M.S., India.

Histopathological study

After being removed, the liver and pancreas tissues were promptly fixed in a 10% formalin-phosphate buffered solution. Tissues were then placed inside metal cassettes with paraffin wax imbedded in them and allowed to solidify in the refrigerator. Cross-sections were created by utilising a microtome to cut paraffin-embedded tissues into sections that were 3–5 µm thick. These sections underwent haematoxylin and eosin (H&E) staining in order to evaluate the renal histological architecture. The stained sections were examined under light microscopy by two separate, blinded researchers (18).

Immunohistochemical analysis

Ten percent neutral buffered saline-fixed pancreatic tissues were embedded in paraffin and cut into 5-lm-thick sections. The tissues were then deparaffinized in a

xylene bath after being fixed on a sterile microscope slide. Two rinses in pure alcohol and two rinses in 95% ethanol for three minutes each were used to dehydrate the slides. To block the endogenous peroxidase and non-specific antibody binding sites, the tissue sections were immersed in 0.3% hydrogen peroxide (2 ml of H2O2 in 18 ml of methanol) and 5% normal bovine serum (1:5 diluted PBS) for 20 minutes at room temperature, respectively. The sections were treated for 30 minutes each with streptavidin-HRP and polyclonal guinea-pig anti-insulin (1:250 diluted PBS) in order to detect insulin. Before being treated with biotinylated anti-mouse IgG (1:500 diluted PBS), the sections were cleaned in PBS. Following 30 minutes of incubation, the sections were rinsed with PBS once more, and any remaining buffer was scraped off the slides. They were then incubated with a di-aminobenzidine (DAB) for 3–5 minutes at room temperature, and finally, they were rinsed with distilled water. Lastly, slides were dried, stained with haematoxylin, and then mounted in glycerin-gelatin (19).

Statical Analysis

GraphPad Prism software version was used to analyse the data, and all analyses were performed on several replicates. 7.0. Tukey's multiple-range post-hoc test and a one-way analysis of variance (ANOVA) were used to statistically analyse the results. Additionally, the statistical significance across groups was assessed using Student's t-test. The mean of at least three replicates ± standard error of the mean (SEM) is used to express all experimental data. Significant differences were accepted at * $p < 0.05$, * * $p < 0.01$, * ** $p < 0.001$, and *** * $p < 0.0001$.

RESULT

Effect of both drugs on blood glucose level and insulin level

Blood glucose levels in the negative control group were significantly higher (293.33 ±10.80 mg/dl) than in the healthy control group (103.33 ± 9.71 mg/dl) when the illness state was induced, demonstrating the presence of hyperglycemia. Blood glucose levels were dramatically lowered to 124.33±6.44 mg/dl after oral administration of the Polyherbal formulation (200 mg/kg bw). This was statistically comparable to the effectiveness of the common medication metformin (124.67 ±7.37 mg/dl). Comparing the two extracts to the negative control group, Aegle Marmelose (183.00 ±11.35 mg/dl) and Spondias Pinnata (181.00 ±8.44 mg/dl) both shown highly substantial glucose-lowering efficacy.displayed in Figure No. 1A.

Figure No. 1 B shows the mean ± standard deviation (SD) of plasma insulin levels. The negative/disease control group demonstrated a significant decrease (6.55 ± 0.41 µU/mL), demonstrating reduced insulin secretion under diseased settings, while the normal control group displayed the greatest plasma insulin levels (14.78 ± 0.55 µU/mL).When metformin was administered, plasma insulin levels were considerably restored to 13.55 ± 0.78 µU/mL, which is close to the normal control values. Plasma insulin levels were 10.77 ± 0.31 µU/mL after treatment with Aegle marmelos (200 mg/kg bw), and 10.80 ± 0.27 µU/mL after treatment with Spondias pinnata (200 mg/kg bw). Significantly, plasma insulin levels improved significantly with the polyherbal formulation (200 mg/kg bw) (13.15 ± 0.41 µU/mL), closely matching the normal control and the metformin-treated group.Improved pancreatic functional activity is suggested by the treatment groups' reported increases in plasma insulin levels. Restoring insulin concentrations could be a sign that pancreatic β-cells are being protected or regenerated, which would increase endogenous insulin output. Their putative function in encouraging pancreatic β-cell regeneration is supported by the significantly increased insulin levels in the groups treated with metformin and polyherbal.

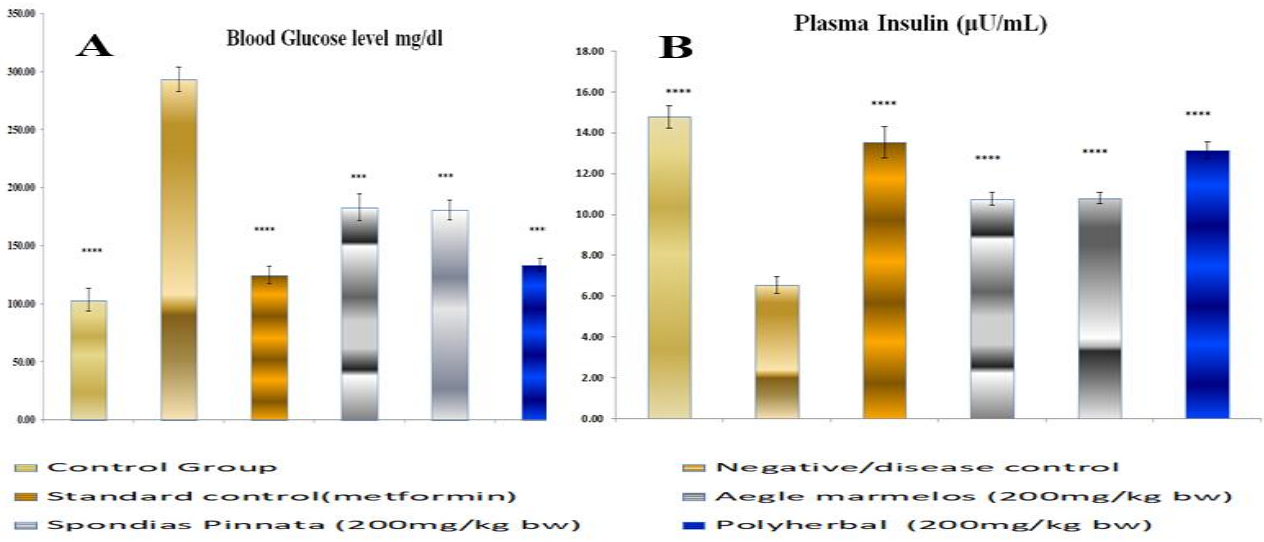
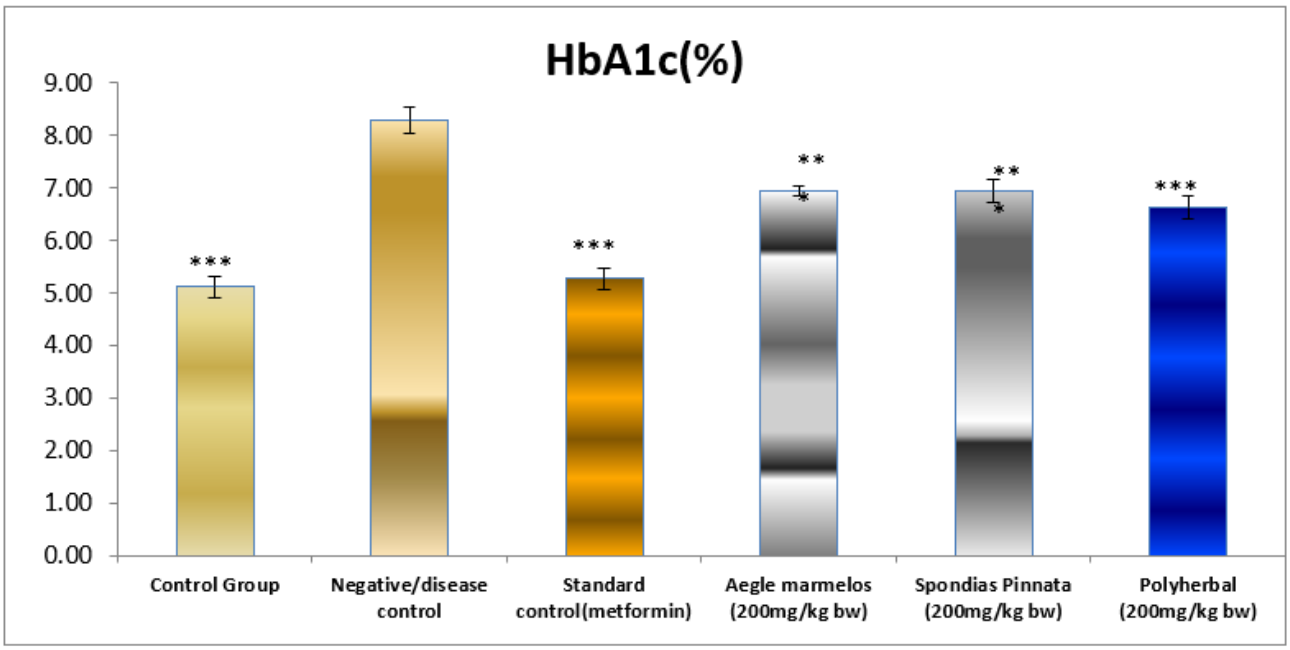


Figure 1: Effect of the Agele marmelos and Spondias pinnata on blood glucose (A) levels and Plasma Insuline(B) with streptozotocin-induced diabetes. Histograms represent the mean ±SEM (n=6). For all panels: *p < 0.05, **p<0.01, ***p<0.001,***p<0.0001.

Effect of both drugs on HbA1c level

Figure 2 displays the mean ± standard deviation (SD) of glycated haemoglobin (HbA1c) values. The negative/disease control group had a significantly higher HbA1c level of 8.28 ± 0.25%, indicating poor glycaemic regulation under diseased settings, while the normal control group had a level of 5.12 ± 0.21%.Metformin treatment brought HbA1c levels down to 5.28 ± 0.20%, which was quite near to the typical control values. Spondias pinnata (200 mg/kg bw) exhibited a larger reduction, with levels of 6.95 ± 0.23%, than Nigella sativa (200 mg/kg bw), which showed a HbA1c value of 7.22 ± 0.17% among the plant-treated groups. In contrast to the disease control group, the polyherbal formulation (200 mg/kg bw) significantly reduced the HbA1c concentration (6.63 ± 0.21%), indicating better glycaemic control. All things considered, the results show that the polyherbal formulation had a stronger antihyperglycemic impact than the other plant treatments examined, with values that were comparable to those seen in the group that received standard medication treatment.

Figure 2: Effect of the Agele marmelos and Spondias pinnata on HbA1c with streptozotocin-induced diabetes. Histograms represent the mean ±SEM (n=6). For all panels: *p < 0.05, **p<0.01, ***p<0.001,***p<0.0001



Effect of both drugs on oral glucose tolerance

Figure 3 provides a summary of glucose tolerance patterns after oral glucose treatment. As evidence of effective glucose clearance, the control group's glycaemic levels remained comparatively steady, increasing slightly from 103.33 ± 9.71 mg/dL at baseline to 126.00 ± 11.59 mg/dL at 30 minutes before gradually declining to 105.33 ± 12.44 mg/dL at 120 minutes. The disease control group, on the other hand, showed a marked and prolonged hyperglycaemic response, with glucose levels rising sharply from 293.33 ± 10.80 mg/dL at 0 minutes to 387.00 ± 21.35 mg/dL at 30 minutes and staying high at 290.00 ± 17.32 mg/dL after 120 minutes. This indicated inadequate glucose utilisation brought on by diabetes. By preventing the peak rise at 30 minutes (242.17 ± 21.31 mg/dL) and encouraging a significant drop to 151.00 ± 10.68 mg/dL at 120 minutes, metformin therapy significantly enhanced glucose management. The glucose tolerance of the plant-treated groups showed some improvement. Spondias pinnata exhibited a similar pattern, dropping from 181.00 ± 8.44 mg/dL to 181.67 ± 9.77 mg/dL within the same time period, while Aegle marmelos decreased glucose from 183.00 ± 11.35 mg/dL at baseline to 178.67 ± 13.34 mg/dL at 120 minutes. With glucose levels dropping from 133.67 ± 5.28 mg/dL at baseline to 134.67 ± 10.97 mg/dL at 120 minutes following a moderate high at 30 minutes (238.67 ± 10.58 mg/dL), the polyherbal intermediate dose demonstrated noteworthy improvements in glycaemic management.

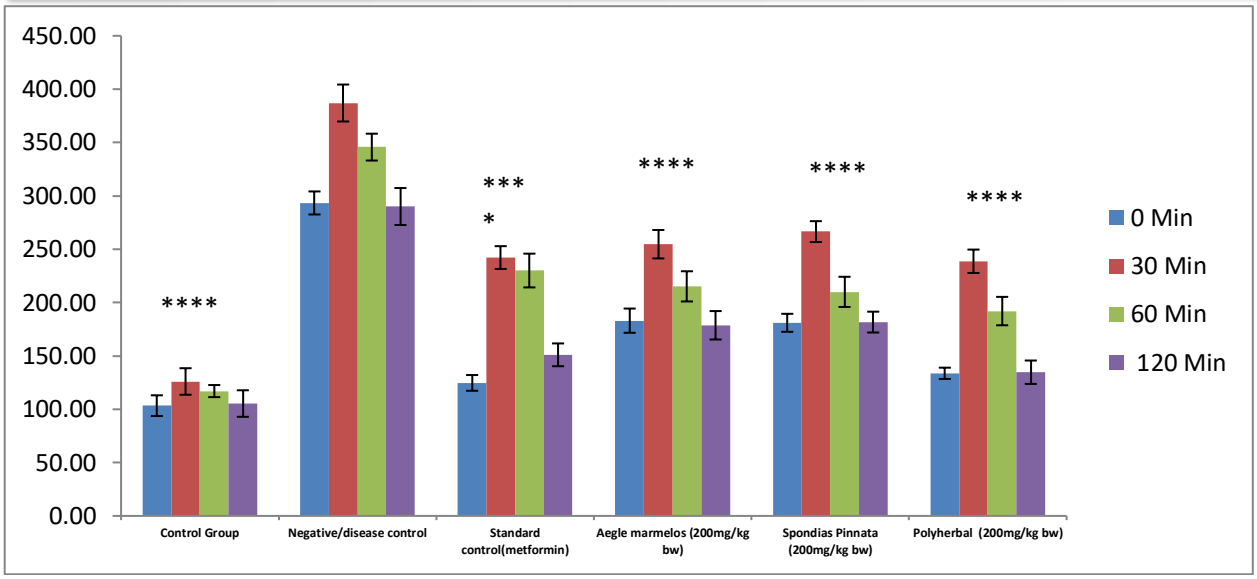


Figure 3: Effect of the Agele marmelos and Spondias pinnata on oral glucose tolerance with streptozotocin-induced diabetes. Histograms represent the mean ±SEM (n=6). For all panels: *p < 0.05, **p<0.01, ***p<0.001,***p<0.0001

Effect of both drugs on Liver glycogen level

Figure 4 displays the liver glycogen levels as mean ± standard deviation (SD). In contrast to the negative/disease control group, which showed a significant decrease to 20.17 ± 1.17 mg/g, the normal control group's liver glycogen concentration was 41.17 ± 2.04 mg/g, showing significant depletion under sick conditions. Metformin treatment brought liver glycogen levels back to 39.67 ± 1.37 mg/g, which was very near to what was seen in the normal control group. The liver glycogen levels of the plant-treated groups were 30.83 ± 1.47 mg/g for Aegle marmelos (200 mg/kg bw) and somewhat higher at 31.50 ± 1.05 mg/g for Spondias pinnata (200 mg/kg bw). When compared to the disease control group, the polyherbal formulation (200 mg/kg bw) significantly improved the liver glycogen concentration (35.00 ± 1.67 mg/g), with values that were comparable to those of the group that received standard pharmacological treatment. Overall, the results indicate that among the investigated plant therapies, the polyherbal formulation had a relatively larger effect on replenishing hepatic glycogen content.

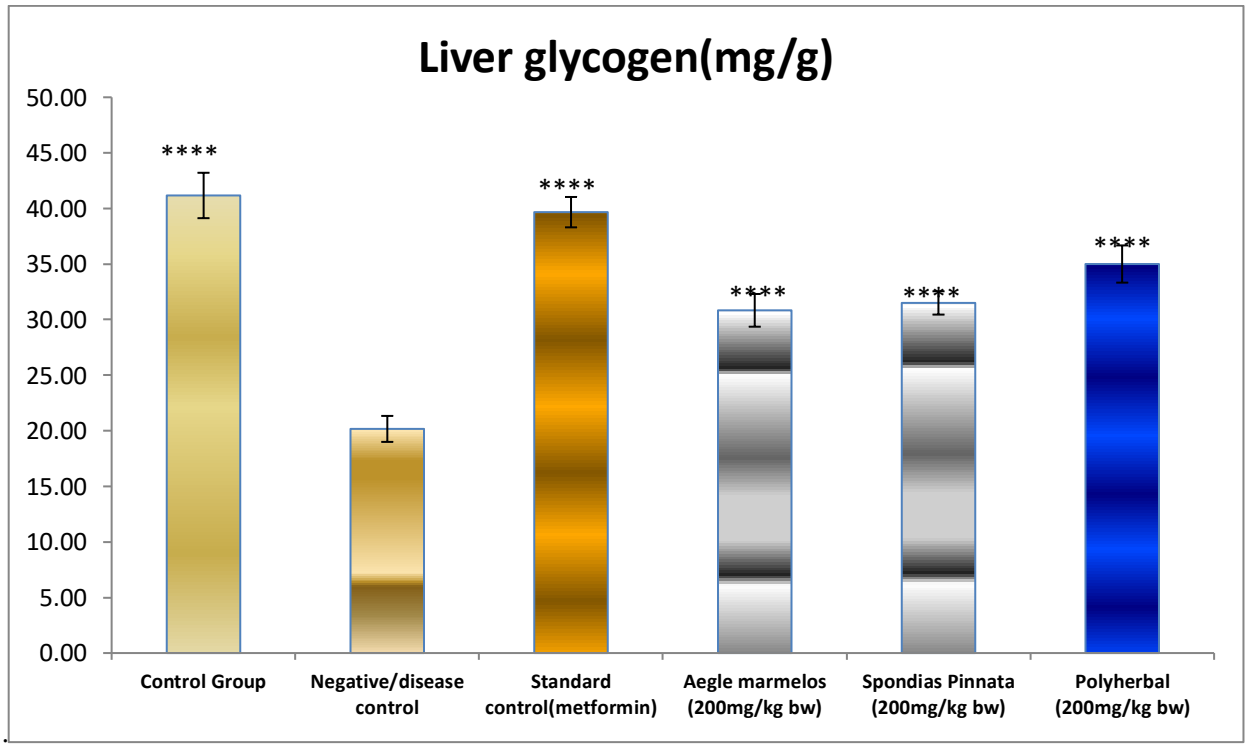


Figure 4: Effect of the Agele marmelos and Spondi as pinnata on Liver glycogen level with streptozotocin-induced diabetes.

Histograms represent the mean ±SEM (n=6). For all panels: *p < 0.05, **p<0.01, ***p<0.001,***p<0.0001

Effect of the Agele marmelos and Spondias pinnata on oxidative stress in the liver

Figure 5 show antioxidant defence parameters and indicators of oxidative stress. Malondialdehyde (MDA) levels in the disease control group were significantly higher (25.50 ± 3.27 µg/mL) than in the normal control group (8.58 ± 1.11 µg/mL), indicating diabetes-induced oxidative imbalance. Significant decreases in reduced glutathione (GSH) (35.33 ± 2.16 vs. 59.50 ± 3.62 µg/mL), catalase (CAT) activity (6.40 ± 0.74 vs. 9.04 ± 0.79 U/mL), and superoxide dismutase (SOD) activity (6.45 ± 0.36 vs. 11.05 ± 0.94 U/mL) were observed in conjunction with this rise in lipid peroxidation, indicating weakened antioxidant defence in diabetic conditions. Metformin treatment effectively attenuated lipid peroxidation (10.17 ± 1.72 µg/mL) while restoring GSH (52.83 ± 3.13 µg/mL), CAT (10.98 ± 0.97 U/mL), and markedly elevating SOD activity (22.75 ± 1.52 U/mL). Among the plant-treated groups, *Aegle marmelos* and *Spondias pinnata* produced moderate reductions in MDA (14.03 ± 1.42 and 13.33 ± 0.88 µg/mL, respectively) along with improvements in GSH (50.33 ± 2.88 and 55.00 ± 3.63 µg/mL), CAT (9.82 ± 0.65 and 9.88 ± 0.80 U/mL), and SOD (12.22 ± 0.76 and 13.48 ± 0.81 U/mL). Notably, the polyherbal f Treatment with metformin significantly increased SOD activity (22.75 ± 1.52 U/mL), restored GSH (52.83 ± 3.13 µg/mL), and reduced lipid peroxidation (10.17 ± 1.72 µg/mL). While GSH (50.33 ± 2.88 and 55.00 ± 3.63 µg/mL), CAT (9.82 ± 0.65 and 9.88 ± 0.80 U/mL), and SOD (12.22 ± 0.76 and 13.48 ± 0.81 U/mL) improved among the plant-treated groups, Aegle marmelos and Spondias pinnata produced moderate reductions in MDA (14.03 ± 1.42 and 13.33 ± 0.88 µg/mL, respectively). By lowering MDA to 10.08 ± 1.43 µg/mL, increasing GSH in a dose-dependent manner (62.33 ± 3.44 and 67.17 ± 5.85 µg/mL), raising CAT activity to 12.25 ± 0.59 U/mL, and significantly enhancing SOD activity (18.82 ± 0.56 U/mL), the formulation showed the most consistent and significant restoration within oxidative parameters. All together, these results show that the polyherbal formulation successfully mitigated oxidative stress linked to diabetes and restored antioxidant defence capacity to levels that were on par with or higher than those seen in the group that received standard medication treatment.

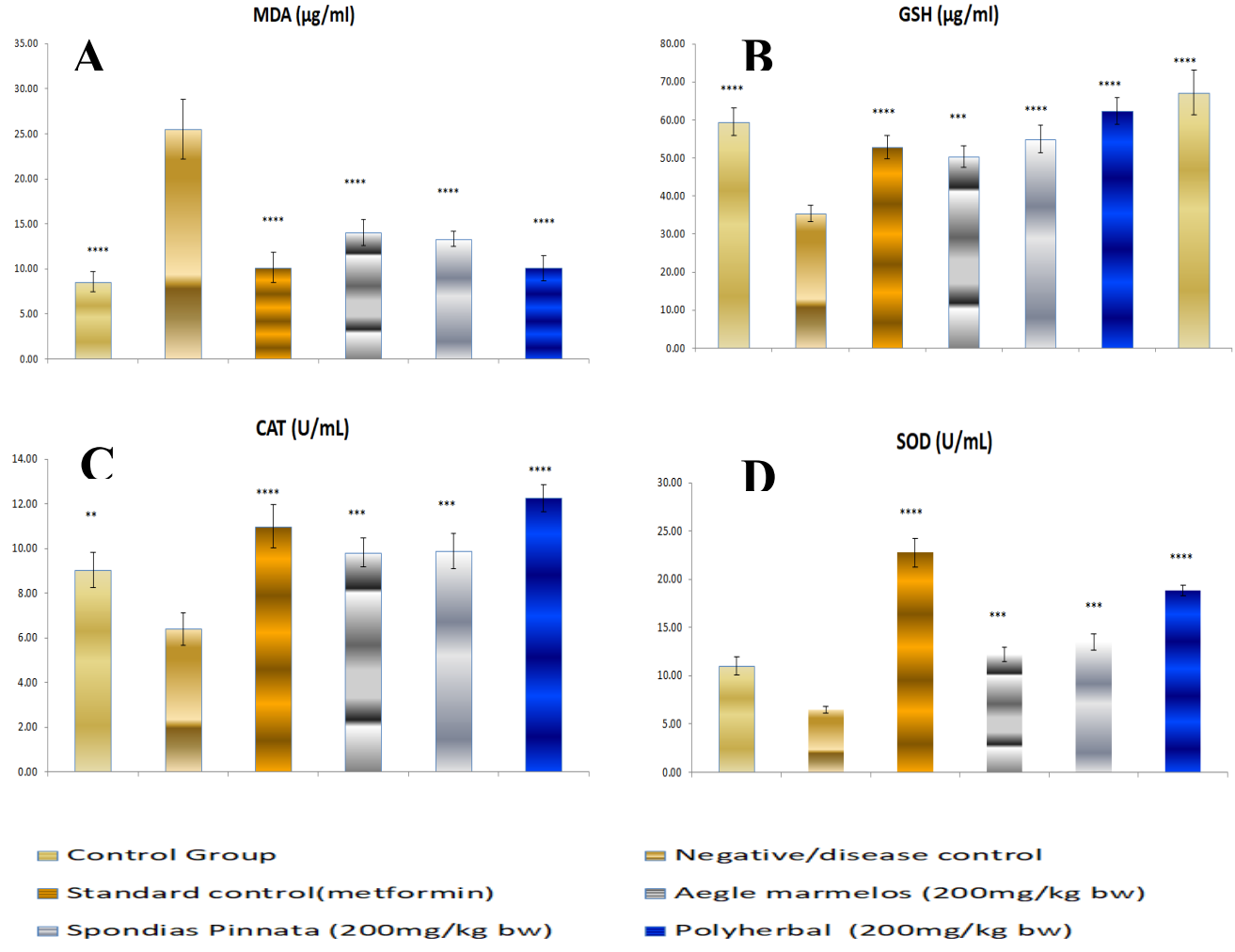


Figure 5: Effect of the Agele marmelos and Spondias pinnata on oxidative stress level in liver MDA (A), GSH (B), CAT

(C), SOD (D) with streptozotocin-induced diabetes. Histograms represent the mean ±SEM (n=6). For all panels: *p < 0.05, **p<0.01, ***p<0.001,***p<0.0001.

Effect of the Agele marmelos and Spondias pinnata on diabetes-induced dyslipidemia

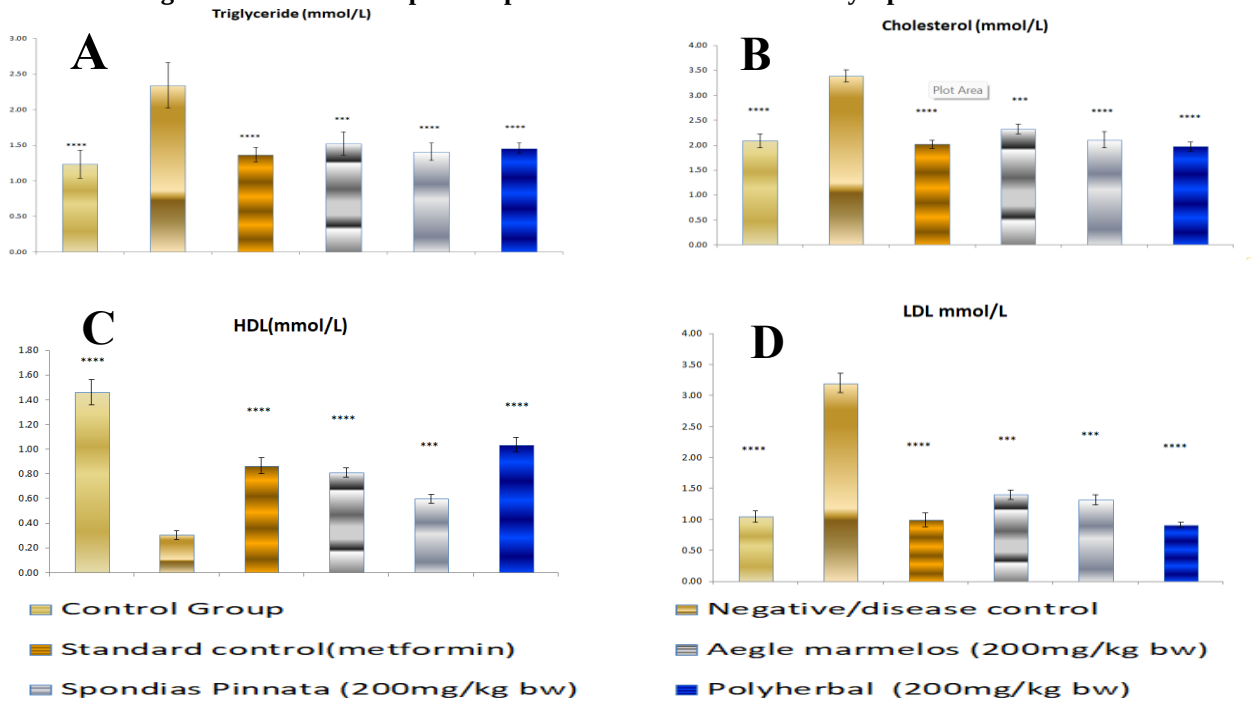


Figure 6: Effect of the Agele marmelos and Spondias pinnata on oxidative stress level in liver triglycerides (A), cholesterol (B), HDL (C), LDL (D) with streptozotocin-induced diabetes. Histograms represent the mean ±SEM (n=6). For all panels: *p < 0.05, **p<0.01, ***p<0.001,***p<0.0001.

Figure 6 shows changes in lipid homeostasis brought on by diabetes in each experimental group. In comparison to the control group (cholesterol: 2.09 ± 0.14 mmol/L; triglycerides: 1.23 ± 0.20 mmol/L; LDL: 1.05 ± 0.09 mmol/L; HDL: 1.46 ± 0.10 mmol/L), the disease control group showed marked dyslipidaemia, as evidenced by elevated total cholesterol (3.39 ± 0.12 mmol/L), triglycerides (2.34 ± 0.32 mmol/L), and LDL (3.20 ± 0.16 mmol/L), as well as a significant decrease in HDL (0.31 ± 0.04 mmol/L). These results demonstrate that diabetes significantly alters the equilibrium of lipid metabolism. By lowering total cholesterol to 2.02 ± 0.08 mmol/L, triglycerides to 1.37 ± 0.10 mmol/L, and LDL to 1.00 ± 0.11 mmol/L, while raising HDL to 0.87 ± 0.06 mmol/L, metformin treatment successfully improved these abnormalities. Spondias pinnata showed a relatively greater improvement in triglycerides (1.41 ± 0.12 mmol/L) and LDL (1.32 ± 0.08 mmol/L), with cholesterol at 2.11 ± 0.16 mmol/L and HDL at 0.60 ± 0.03 mmol/L. In contrast, administration of Aegle marmelos produced a moderate lipid correction (cholesterol: 2.33 ± 0.10 mmol/L; triglycerides: 1.52 ± 0.16 mmol/L; LDL: 1.40 ± 0.08 mmol/L; HDL: 0.81 ± 0.04 mmol/L). Notably, in comparison to other plant treatments, the polyherbal intermediate dose (200 mg/kg bw) produced the lowest levels of total cholesterol (1.98 ± 0.09 mmol/L) and LDL (0.91 ± 0.05 mmol/L) among treatment groups, as well as improved triglycerides (1.46 ± 0.07 mmol/L) and the highest HDL level (1.04 ± 0.06 mmol/L). All together, our results show that the polyherbal formulation successfully prevented dyslipidaemia linked to diabetes and exhibited a thorough hypolipidemic profile that was on par with or better than that of the prescription medication.

Effect of the Agele marmelos and Spondias pinnata on diabetes-induced hepatotoxicity

Alkaline phosphatase (ALP: 433.67 ± 18.51 U/L), alanine aminotransferase (ALT: 63.00 ± 7.48 U/L), and aspartate aminotransferase (AST: 281.67 ± 21.13 U/L) were significantly higher in the disease control group than in the control group (ALP: 163.00 ± 8.79 U/L; ALT: 23.17 ± 3.49 U/L; AST: 122.50 ± 8.55 U/L), indicating diabetes-induced disruption of hepatic enzyme homeostasis. Significant hepatic impairment linked to diabetes is indicated by these changes. To varied degrees, these enzyme increases were mitigated by therapeutic intervention. Metformin significantly restored the hepatic biochemical balance by lowering ALP (211.33 ± 11.86 U/L), ALT (38.50 ± 4.23 U/L), and AST (157.50 ± 10.13 U/L). There were moderate improvements compared to the disease control group after treatment with Aegle marmelos (ALP: 281.83 ± 17.38 U/L; ALT: 41.83 ± 3.19 U/L; AST: 207.50 ± 15.41 U/L) and Spondias pinnata (ALP: 293.17 ± 13.04 U/L; ALT: 43.33 ± 4.13 U/L; AST: 228.67 ± 10.98 U/L). Interestingly, the polyherbal intermediate dose (200 mg/kg bw) showed

a coordinated normalisation pattern, bringing the enzyme profile closer to that of the standard drug-treated group by lowering the ALP to 195.83 ± 11.58 U/L, the ALT to 38.00 ± 3.03 U/L, and the AST to 165.00 ± 7.07 U/L. All things considered, these results imply that, in contrast to individual plant treatments, the polyherbal formulation successfully reduced diabetes-induced hepatic enzyme abnormalities and enhanced hepatic functional status.

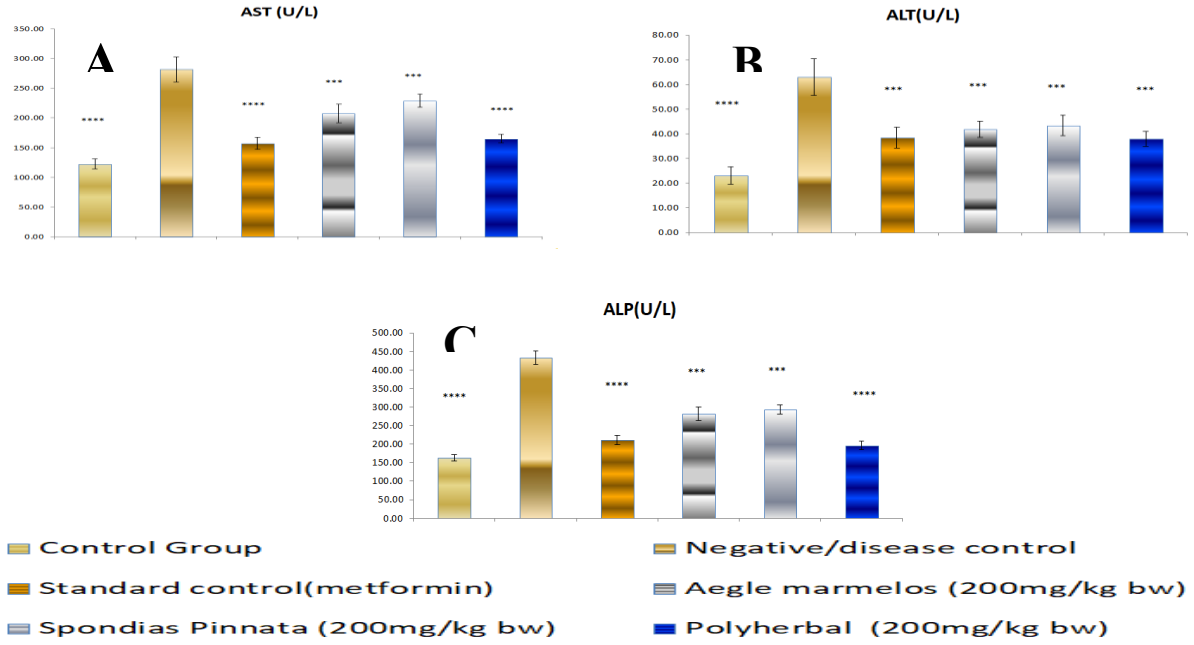


Figure 7: Effect of the Agele marmelos and Spondias pinnata on oxidative stress level in liver triglycerides (A), cholesterol (B), HDL (C), LDL (D) with streptozotocin-induced diabetes. Histograms represent the mean ±SEM (n=6). For all panels: *p < 0.05, **p<0.01, ***p<0.001, ***p<0.0001.

Effect of the Agele marmelos and Spondias pinnata on pancreas histology

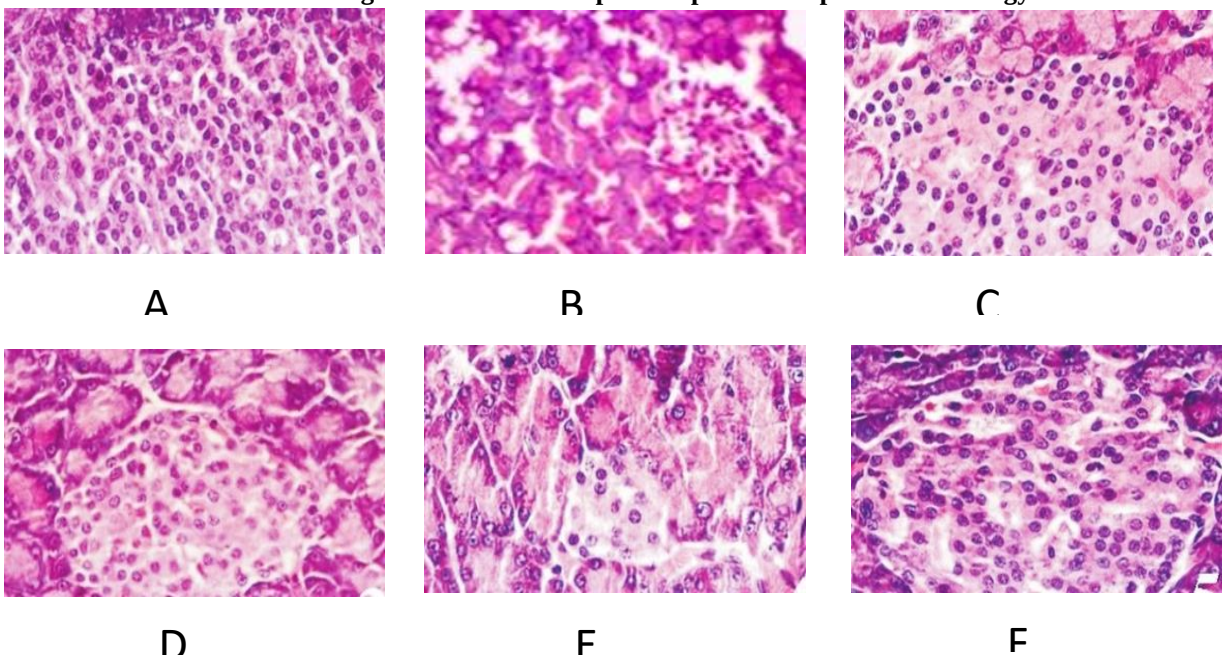


Figure 8: Histopathology of Agele marmelos and Spondias pinnata on STZ-induced in rat pancreas tissue, (A) Normal, (B) STZ control, (C) STZ + Metformine, (D) STZ + Agele marmelos, (E) STZ + Spondias pinnata, (F) STZ + Agele marmelos +Spondias pinnata

In contrast to the negative/disease control group (B), which displayed severe pathological alterations such as marked islet

degeneration and shrinkage, reduced β-cell population, cellular disorganisation, vacuolization, and pyknotic nuclei indicating extensive pancreatic damage, the control group (A) had normal architecture, as evidenced by well-defined islets of Langerhans with intact cellularity and normal exocrine acini. When compared to the disease control, treatment with the common medication metformin (C) led to a notable improvement in pancreatic histoarchitecture, with islet structure preservation, enhanced cellularity, and fewer degenerative alterations. Group (D), which was treated with Aegle marmelos, showed slight residual disorganisation and a moderate restoration of islet shape with partial β-cell regeneration. Comparably, the Spondias pinnata-treated group (E) showed stronger protection than the disease control group, exhibiting a discernible recovery with enhanced islet size, better cellular arrangement, and decreased vacuolization. With well-defined islets, near-normal β-cell density, and minimal histopathological alterations, the polyherbal formulation (F) notably normalised pancreatic tissue, showing a superior protective and regenerative effect on pancreatic architecture compared to the control and standard-treated groups.

Effect of the Agele marmelos and Spondias pinnata on liver histology

Histopathological analysis of liver sections showed that the control group (A) had normal hepatic architecture, with well-organised hepatic cords, intact central veins, normal sinusoidal gaps, and hepatocytes with preserved cytoplasm and centrally located nuclei. The negative/disease control group (B), on the other hand, showed clear pathological changes that indicated severe hepatic injury, such as cytoplasmic vacuolization, sinusoidal dilatation, inflammatory cell infiltration, hepatocellular degeneration, and loss of normal lobular architecture. When compared to the disease control, liver histology improved significantly after treatment with the conventional medication metformin (C). Hepatic cord repair, decreased cellular degeneration, limited inflammatory alterations, and near-normal sinusoidal architecture were all seen. With minimal residual cellular changes, decreased vacuolization, and partial normalisation of hepatocyte shape, the Aegle marmelos-treated group (D) showed moderate hepatoprotective benefits. Comparable to the disease control group, the Spondias pinnata-treated group (E) had a discernible recovery of hepatic architecture, enhanced cellular integrity, and decreased inflammatory infiltration, suggesting superior protection. With well-organised hepatic cords, intact hepatocytes, minimal degenerative changes, and nearly normal sinusoidal spaces, the polyherbal-treated group (F) notably restored liver histoarchitecture. This suggests that the polyherbal formulation has a superior hepatoprotective effect compared to the control and standard-treated groups.

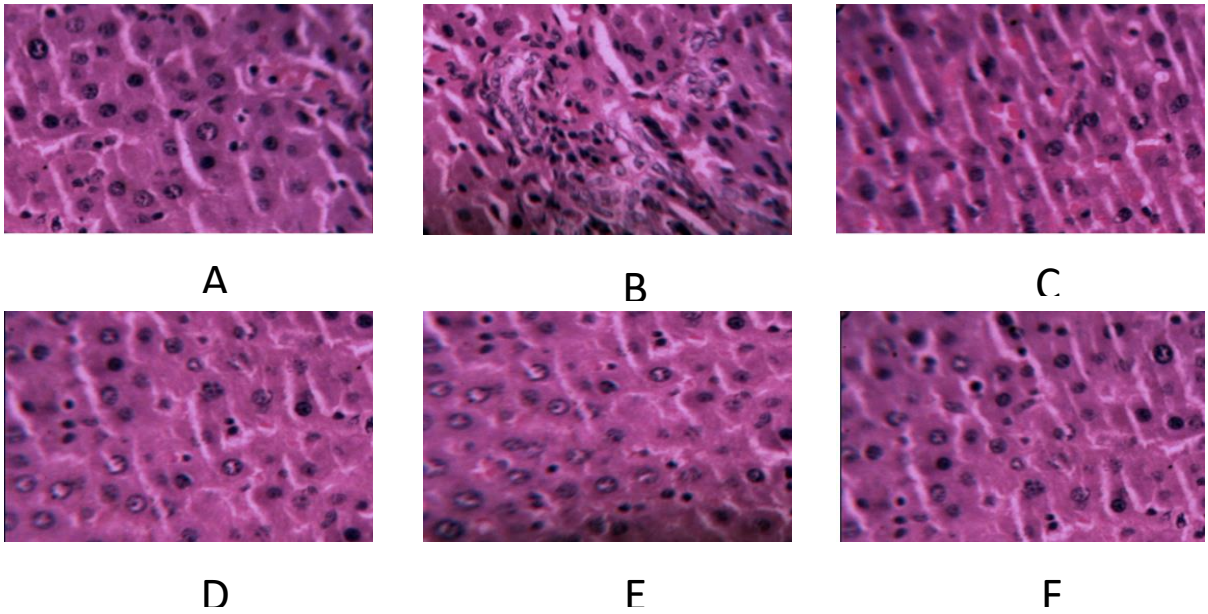


Figure 8 : Histopathology of Agele marmelos and Spondias pinnata on STZ-induced in rat liver tissue, (A) Normal, (B) STZ control, (C) STZ + Metformine, (D) STZ + Agele marmelos, (E) STZ + Spondias pinnata, (F) STZ + Agele marmelos +Spondias pinnata

Effect of the Agele marmelos and Spondias pinnata on pancrease immunochemisty

Significant group-wise variations in islet integrity and staining intensity were seen in the pancreatic tissue examined by immunohistochemistry. Strong, dense, and well-localized immunopositive staining with distinct pancreatic islets was seen in the normal control group (A), demonstrating normal functional status and maintained cellular architecture. The disease-induced pancreatic damage was evident in the negative/disease control group (B), which showed a marked decrease in immunoreactivity, weak staining, reduced and poorly organised islets, and significant loss of islet cellularity. Immunopositive staining was significantly enhanced by treatment with the common medication metformin (C), as seen by the restoration of islet shape and an increase in staining intensity as compared to the disease control. When 200 mg/kg bw

(D) of Aegle marmelos was administered, immunoreactivity was moderately restored, islet architecture was somewhat enhanced, and the number of positively stained cells increased. Similarly, compared to the disease control group, Spondias pinnata at 200 mg/kg bw (E) demonstrated enhanced islet size and cellular distribution as well as mild to fairly strong immunostaining. With strong and widespread immunopositive staining and well-preserved islet structure that was nearly identical to that of the normal and metformin-treated groups, the polyherbal formulation at 200 mg/kg bw (F) notably produced the most notable improvement among the test groups, indicating a superior and synergistic protective effect on pancreatic islet cells.

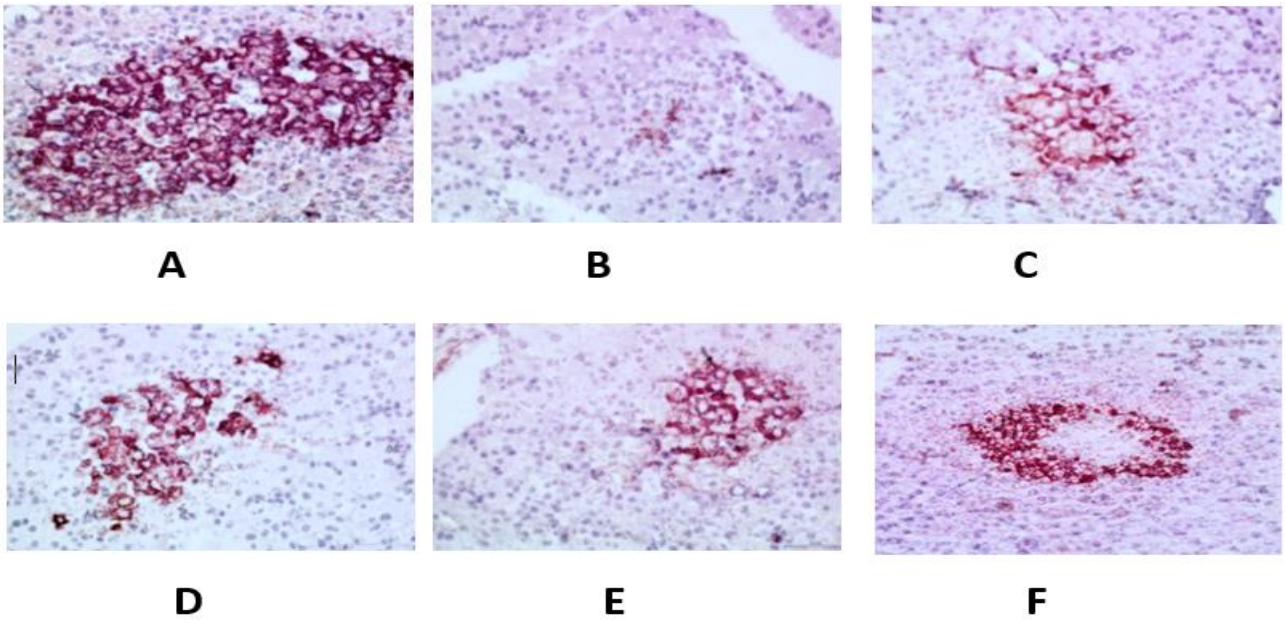


Figure 9 : Immunohistochemical of Agele marmelos and Spondias pinnata on STZ-induced in rat liver tissue, (A) Normal, (B) STZ control, (C) STZ + Metformine, (D) STZ + Agele marmelos, (E) STZ + Spondias pinnata, (F) STZ + Agele marmelos +Spondias pinnata

DISCUSSION

According to the current study, diabetes causes a variety of metabolic and anatomical abnormalities that compromise hepatic function, β-cell integrity, and glucose homeostasis. Typical diabetic pathology was mirrored in the disease control group by chronic hyperglycemia, decreased plasma insulin, raised HbA1c, glucose intolerance, oxidative stress imbalance, dyslipidaemia, and hepatic dysfunction. These changes are in line with long-term metabolic stress and β-cell dysfunction brought on by oxidative damage and glucotoxicity, which have been identified as key factors in β-cell loss and the advancement of diabetes ((12)(21)). Furthermore, it is known that high levels of reactive oxygen species (ROS) in diabetes overpower natural antioxidants such SOD, CAT, and GSH, causing cellular damage and death in hepatic and pancreatic cells (22). When compared to the individual plant extracts, the polyherbal formulation significantly reduced fasting blood glucose and improved oral glucose tolerance in rats treated with it. This suggests superior antihyperglycemic efficacy, which is likely due to synergistic actions that target multiple pathways of glucose metabolism and insulin regulation. The polyherbal group's higher insulin levels indicate better β-cell secretory function, which may be the result of greater β-cell survival and regeneration aided by the antioxidant environment created by the phytochemical contents in Spondias pinnata and Aegle marmelos. This is consistent with systematic evidence that drugs derived from plants can improve proliferation pathways, decrease apoptosis, and attenuate oxidative stress to restore β-cell bulk and function (12).The long-term effectiveness of the combination extract is supported by lower HbA1c values in treated groups, especially in the polyherbal group, which show sustained glycaemic management throughout the course of treatment. In line with the recovery of hepatic glucose homeostasis shown in other successful antidiabetic treatments, restoration of hepatic glycogen content also shows enhanced insulin sensitivity and hepatic glucose utilisation. Modulation of glucoregulatory enzyme activity (e.g., glucokinase, G6Pase) may offer more information in further studies, even if it was not investigated in this one.In diabetic rats, oxidative stress profile showed increased lipid peroxidation and decreased antioxidant enzyme activity, which is in line with findings that hyperglycemia causes ROS production and inflammatory reactions, which harm cellular membranes and organ functions (23). Antioxidant indices and lipid peroxidation were dramatically normalised after treatment with the polyherbal formulation, promoting improved β-cell and

hepatocyte protection. Better tissue morphology and function are probably caused by plant antioxidants, which are known to regulate oxidative stress and inflammatory pathways (24).With polyherbal medication, the diabetic control group's dyslipidemia—which was characterised by increased triglycerides and cholesterol and decreased HDL—was considerably reduced. Improved metabolic outcomes may be supported by this lipid-modulating action, which may lessen lipotoxic stress on the liver and β-cells. Histopathological results demonstrating repaired hepatic architecture further support improved liver enzyme profiles (ALT, AST, and ALP) in treated groups, which indicate stabilisation of hepatic integrity and function.In diabetic rats, histopathological examination showed significant deterioration of the hepatocellular architecture and pancreatic islets. These structural defects were considerably improved by treatment, especially with the polyherbal formulation, suggesting tissue regeneration and protection. Pancreatic sections' immunohistochemistry results showed a significant improvement in insulin immunoreactivity; the polyherbal group had strong staining, which is a sign of higher numbers of mature β-cells and functional recovery. This result is consistent with research showing that specific phytotherapeutic drugs improve immunohistochemistry results and promote β-cell regeneration (25). According to the available data, administering Aegle marmelos and Spondias pinnata together improves endogenous pathways of β-cell preservation and regeneration. This is probably because it lowers oxidative stress, improves insulin signalling, and shields hepatocytes from diabetes damage. These benefits are in line with recent studies that highlight the potential of multi-targeted phytotherapy and antioxidants derived from plants to reduce diabetic tissue damage and restore glucose homeostasis (23)(12). Even though the results are encouraging, more research is necessary to confirm the findings' translational value. Future research should concentrate on clarifying the molecular processes of β-cell regeneration, such as the expression of antioxidant signalling pathways, anti-apoptotic markers, and insulin gene regulators. It would be easier to standardise formulations if the bioactive phytoconstituents causing the observed synergistic effects could be isolated and characterised. Studies on dose-optimization, chronic toxicity, and long-term safety are also necessary to prove therapeutic viability. To confirm the effectiveness of this polyherbal combination in human diabetic populations and encourage its advancement as a supplemental or alternative antidiabetic treatment, controlled clinical trials are ultimately necessary.

CONCLUSION

The current study's results unequivocally show that, in a diabetic rat model, the treatment of both Aegle marmelos and Spondias pinnata together significantly protects and restores pancreatic β-cell integrity and overall glucose homeostasis. Persistent hyperglycemia, decreased insulin levels, raised HbA1c, impaired glucose tolerance, oxidative stress, dyslipidaemia, hepatic dysfunction, and significant structural damage to pancreatic and liver tissues were all signs of severe metabolic dysregulation brought on by experimental diabetes. Together, these changes support the idea that diabetes is a progressive disease that harms both metabolic and endocrine systems.When compared to individual plant extracts, treatment with the polyherbal formulation demonstrated superior antidiabetic activity and results comparable to those of the common medication metformin. Both short-term and long-term glycaemic management were demonstrated by the formulation's ability to normalise fasting blood glucose levels, enhance glucose tolerance, restore plasma insulin concentrations, and dramatically lower HbA1c. Improved insulin sensitivity and metabolic balance are further highlighted by the restoration of hepatic glycogen content and the correction of lipid abnormalities.Interestingly, histological and immunohistochemical analyses offered strong proof of pancreatic β-cell regeneration and protection. Functional recovery of pancreatic tissue was confirmed by the polyherbal-treated group's robust insulin immunoreactivity, enhanced β-cell density, and nearly normal islet architecture. The hepatoprotective effect of the combination formulation is further supported by concurrent normalisation of liver functions and improvement in hepatic architecture. These structural results showed a strong correlation with biochemical and oxidative stress metrics, indicating that reducing oxidative damage is essential for tissue healing and metabolic enhancement. According to the study, Aegle marmelos and Spondias pinnata work in concert to improve glycaemic management, boost antioxidant defences, maintain β-cell function, and protect hepatic tissue, all of which contribute to a multi-targeted treatment strategy. The potential of this polyherbal formulation as a safe and efficient supplemental approach for the treatment of diabetes mellitus is clearly supported by the combination of biochemical, histological, and immunohistochemical data. To convert these encouraging preclinical results into medicinal uses, more mechanistic and clinical research is necessary.

Declaration of interest

The authors declare no conflict of interest.

Ethics statement

The animal study was reviewed and approved by Institutional Animal Ethical Committee of Nims University, Jaipur Rajsathan..

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