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Evaluation of Antilipidemic and Organ Protective Effects of Polyherbal Formulation (Raxi) in High-Fat Diet and Streptozotocin-Induced Diabetic Rats

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Abstract:

- ***Background:***

Diabetes mellitus, particularly type 2 diabetes, is a multifactorial metabolic disorder often accompanied by dyslipidemia and oxidative stress-related organ damage. While synthetic antidiabetic agents offer glycemic control, their long-term use is associated with adverse effects. Polyherbal formulations present a promising alternative due to their multifaceted therapeutic properties and favorable safety profiles.

- ***Objective:***

This study aimed to evaluate the **antilipidemic, hypoglycemic, and organ-protective effects of a polyherbal formulation, RAXI, in a rat model of type 2 diabetes induced by high-fat diet (HFD) and streptozotocin (STZ).**

- ***Methods:***

Male Wistar rats were divided into normal, diabetic control, and treatment groups. Diabetes was induced using a high-fat diet followed by STZ injection. RAXI was administered orally at doses of 100, 200, and 400 mg/kg for 28 days. Glibenclamide (5 mg/kg) served as the standard drug. Parameters assessed included fasting blood glucose (FBG), lipid profile, renal function markers (urea and creatinine), and antioxidant enzymes (MDA, GSH, CAT, SOD, GST). Data were analyzed using two-way ANOVA with Tukey's post hoc test.

- ***Results:***

RAXI produced a dose-dependent reduction in fasting blood glucose, with the 400 mg/kg dose showing a significant decrease ($p < 0.001$) comparable to Glibenclamide. Lipid profile analysis revealed significant reductions in TG, TC, and LDL-C ($p < 0.01–0.001$) and increased HDL-C levels ($p < 0.05–0.01$). Renal markers (urea and creatinine) and oxidative stress indicators (MDA and GSH) were significantly improved ($p < 0.01–0.001$), alongside elevated catalase activity ($p < 0.001$). Body weight remained statistically unchanged across all groups ($p = 0.8459$), indicating metabolic neutrality of RAXI.

- ***Conclusion:***

RAXI exhibits significant antidiabetic, antilipidemic, and nephroprotective effects**, likely due to its antioxidative mechanisms. These findings support its traditional use and encourage further investigation as an integrative therapeutic for type 2 diabetes and associated complications.**

Keywords: *Polyherbal Formulation; RAXI; Diabetes Mellitus; Antioxidant Activity; High-Fat Diet; Streptozotocin; Lipid Profile; Glycated Hemoglobin; Renal Biomarkers; Oxidative Stress.*

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I. INTRODUCTION

Diabetes mellitus is a complex, chronic metabolic disorder characterized by persistent hyperglycemia resulting from defects in insulin secretion, insulin action, or both [1]. It is a major global public health concern, with an estimated 537 million adults currently living with the disease a figure expected to rise to 783 million by 2045 [2]. Type 2 diabetes mellitus (T2DM), the most prevalent form, is closely linked to obesity, sedentary lifestyles, and dyslipidemia, often resulting in microvascular and macrovascular complications such as nephropathy, neuropathy, cardiovascular diseases, and oxidative tissue damage [3, 4].

Conventional antidiabetic agents, including sulfonylureas, biguanides, and insulin, are effective in glycemic control but are often limited by adverse effects such as hypoglycemia, weight gain, and long-term organ toxicity [5]. Moreover, these synthetic agents may not adequately address associated metabolic disorders like dyslipidemia or oxidative stress. As a result, attention has increasingly shifted toward plant-based therapies and polyherbal formulations that offer multifaceted therapeutic benefits with potentially fewer side effects [6].

Polyherbal formulations, which consist of multiple plant extracts, are gaining recognition for their synergistic effects in targeting various metabolic pathways involved in diabetes and its complications [7]. The integration of phytochemicals such as flavonoids, alkaloids, tannins, and phenolics has been shown to enhance glucose uptake, improve insulin sensitivity, and protect organs from oxidative damage [8, 9]. Furthermore, certain herbal combinations have demonstrated beneficial effects on lipid metabolism and renal function, which are critical parameters in the management of diabetic complications [10].

II. MATERIALS AND METHODS

➢ *Materials Source of RAXI*

RAXI is a polyherbal formulation solution meant to be taken orally, with known antioxidants, hypoglycemic, antilipidemic, and protective effects used in the management of diabetes. It was purchased from Inkajah, a local herbal market in Lagos, Nigeria, where it is traditionally prepared and sold as a ready-to-use herbal remedy.

The materials and equipment used throughout the experiment included syringes, an electronic weighing scale (Model EK3250), an analytical weighing balance, Accu-Chek glucometer and test strips (Roche Diabetes Care Inc., Indianapolis, Indiana, USA), beakers, Pasteur pipettes, EDTA bottles, universal sample bottles, transparent plastic sample containers, oral cannula, dissecting set, dissecting board, forceps, gloves, pestle and mortar, plastic animal cages, permanent markers for labelling, and 58500 digital blood pressure recorders. These materials facilitated accurate dosing, biological sampling, and physiological assessments during the study. The pharmaceutical and chemical agents utilized were Glibenclamide (Glumin; McCoy Pharma Pvt. Ltd., Maharashtra, India), which served as the reference standard antidiabetic drug; Streptozotocin (STZ) (Sigma-Aldrich, Burlington, MA, USA) used to induce diabetes in experimental animals; phosphate-citrate buffer (0.1 M, pH 4.5) (Sigma-Aldrich, Burlington, MA, USA) used to dissolve STZ prior to injection; and picric acid (procured locally in Lagos, Nigeria) utilized in the determination of serum creatinine levels during biochemical analyse.

➢ *Ethical Considerations.*

All experimental protocols in this study were conducted in strict accordance with the ethical standards of the College of Medicine, University of Lagos. Prior to the commencement of the research, ethical clearance was obtained from the Animal Care and Research Ethics Committee of the institution under the approval number CMUL/ACUREC/06/23/120. Throughout the experiment, animals were treated humanely, and efforts were made to minimize pain, stress, and discomfort in accordance with institutional and international guidelines for the care and use of laboratory animals.

➢ *Laboratory Animals.*

Healthy male Wistar rats weighing between 100 and 150 grams were obtained from the Laboratory Animal Centre, College of Medicine, University of Lagos, Lagos, Nigeria. The animals were housed in clean, well-ventilated cages under standard laboratory conditions, including a controlled ambient temperature of 23–25°C and a 12-hour light/12-hour dark cycle.

Rats were maintained on a standard commercial rodent diet (Livestock Feeds Plc, Ikeja, Lagos) and provided with clean drinking water ad libitum. A one-week acclimatization period was observed prior to the start of experimental procedures to allow the animals to adjust to their new environment. Before induction of diabetes or administration of any treatment, all animals were fasted overnight, and their baseline fasting blood glucose levels were measured using an Accu-Chek glucometer (Roche Diabetes Care Inc., Indianapolis, Indiana, USA).

➢ *Grouping of Animals*

The 35 experimental rats were grouped into seven (7) groups to assess the therapeutic effects of RAXI and compare it with a standard antidiabetic drug (Glibenclamide). The grouping was as follows:

- HFD + STZ + RAXI (400 mg/kg): Diabetic rats treated with 400 mg/kg of the polyherbal formulation RAXI.
- HFD + STZ + RAXI (200 mg/kg): Diabetic rats treated with 200 mg/kg RAXI.

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- HFD + STZ + RAXI (100 mg/kg): Diabetic rats treated with 100 mg/kg RAXI.
- RAXI Only (400 mg/kg): Non-diabetic rats treated with RAXI to assess potential baseline effects or toxicity.
- HFD + STZ (Diabetic Control): Diabetic rats that received no treatment, serving as a negative control.
- HFD + STZ + Glibenclamide (5 mg/kg): Diabetic rats treated with Glibenclamide, serving as a positive control.
- Normal Control: Non-diabetic rats administered olive oil only, serving as the baseline reference group.

Each group consisted of five (5) rats, except the two non-diabetic groups (RAXI only and normal control), which had ten (10) rats in total. Treatments were administered orally once daily for 28 days.

➢ *Blood glucose levels*

Blood glucose levels serve as a primary indicator in diabetes research to assess the severity of hyperglycemia and the efficacy of hypoglycemic interventions. Hyperglycemia, a hallmark of diabetes mellitus, results from impaired insulin secretion or action, leading to decreased cellular uptake of glucose [11]. Regular monitoring of fasting blood glucose (FBG) and, in some cases, postprandial glucose levels, is essential to determine the impact of therapeutic agents on glycemic control [12]. Chronic hyperglycemia is strongly associated with vascular and tissue complications; therefore, effective regulation of glucose levels is critical to mitigate long-term diabetic sequelae [13].

➢ *Lipid profile*

Dyslipidemia, commonly observed in diabetic patients, is characterized by elevated levels of total cholesterol (TC), triglycerides (TG), and low-density lipoprotein cholesterol (LDL-C), along with reduced high-density lipoprotein cholesterol (HDL-C) levels [14]. These lipid abnormalities contribute to increased cardiovascular risk. Monitoring lipid parameters enables the evaluation of the antilipidemic efficacy of test formulations. Effective interventions typically lower TG, TC, and LDL-C levels while increasing HDL-C, thereby improving overall metabolic health and cardiovascular outcomes [15, 16].

➢ *Renal function markers*

Diabetes is a major contributor to chronic kidney disease, with diabetic nephropathy being a common complication. Serum creatinine, blood urea nitrogen (BUN), and urine albumin are standard biomarkers used to assess renal function. Elevated levels of creatinine and BUN indicate reduced glomerular filtration, while albuminuria reflects early glomerular injury [17]. Monitoring these markers helps determine the nephroprotective effects of therapeutic agents under investigation [18].

➢ *Glycated hemoglobin (HbA1c)*

HbA1c provides a reliable estimate of average blood glucose concentrations over the previous 2–3 months. It reflects the percentage of hemoglobin irreversibly bound to glucose and is considered a critical marker for long-term glycemic control in diabetes management [19]. Reducing HbA1c levels is a primary goal of diabetic treatment strategies, as lower levels are associated with decreased risks of microvascular and macrovascular complications [20].

➢ *Statistical Analysis*

All experimental data were analyzed using GraphPad Prism version 6.0 for Windows (GraphPad Software, San Diego, CA, USA). Results are expressed as mean ± standard error of the mean (SEM). Differences among groups were evaluated using two-way Analysis of Variance (ANOVA) followed by Tukey's post hoc multiple comparison test to determine the level of statistical significance. A p-value less than 0.05 ($p < 0.05$) was considered statistically significant

III. RESULTS

➢ *Effect of RAXI Extract on Fasting Blood Glucose Level in High-Fat Diet and Streptozotocin-Induced Diabetic Rats*

The figure illustrates the impact of RAXI treatment on fasting blood glucose (FBG) levels in diabetic rats over the 28-day experimental period. Following diabetes induction with a high-fat diet and streptozotocin (STZ), rats in the diabetic control group exhibited significantly elevated FBG levels compared to the normal control group ($p < 0.001$). Treatment with RAXI at doses of 100, 200, and 400 mg/kg resulted in a dose-dependent reduction in FBG levels. The 400 mg/kg RAXI group showed a statistically significant decrease in glucose levels comparable to the standard drug (Glibenclamide, 5 mg/kg), indicating effective glycemic control. These results suggest that RAXI possesses notable hypoglycemic potential in this model of type 2 diabetes.

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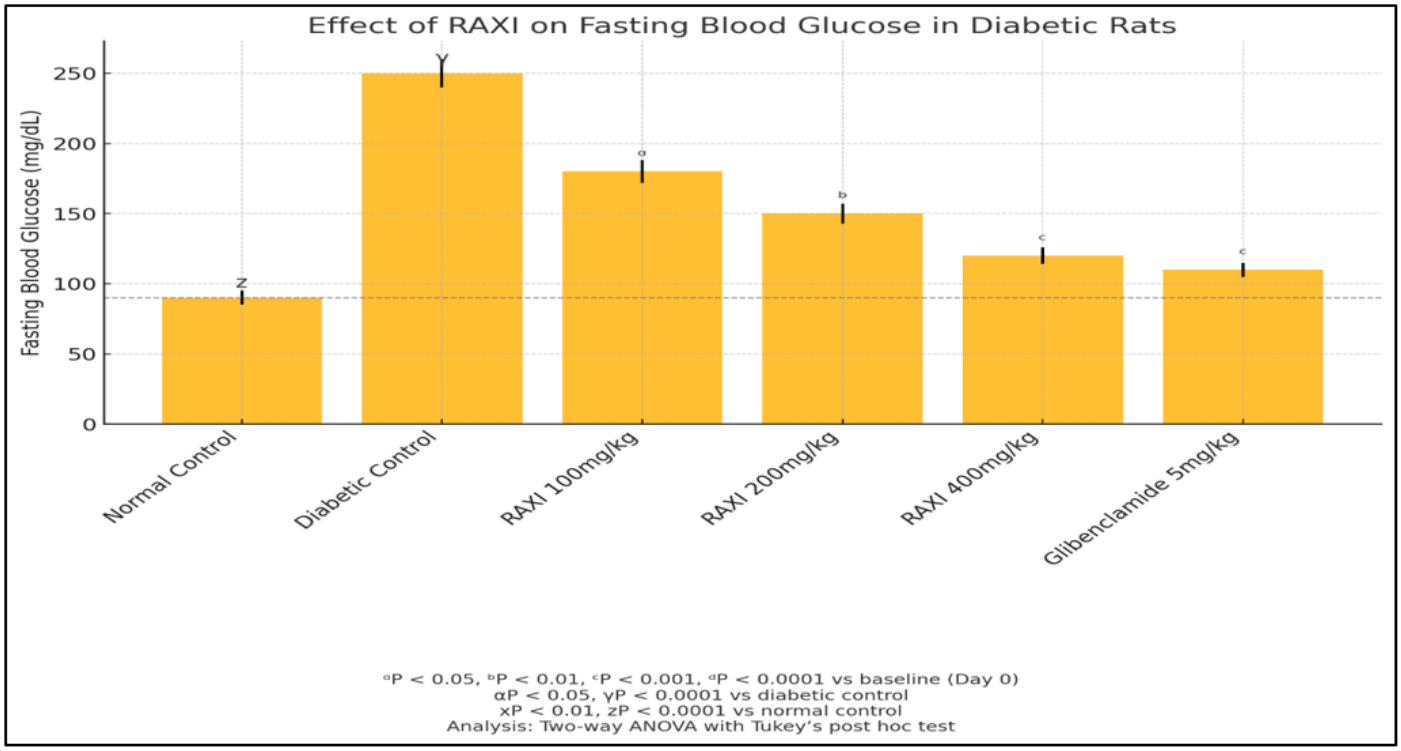

Fig 1 Effect of RAXI Extract on Fasting Blood Glucose Level in High-Fat Diet and Streptozotocin-Induced Diabetic Rats

Here is the bar chart showing the effect of RAXI on fasting blood glucose levels in high-fat diet and streptozotocin-induced diabetic rats. The annotations reflect levels of statistical significance based on comparisons with baseline, diabetic control, and normal control, analyzed using two-way ANOVA with Tukey's post hoc test

- *Effect of RAXI on Body Weight in High-Fat Diet and Streptozotocin-Induced Diabetic Rats*

As shown in Figure 2, over the 28-day observation period, there was no statistically significant change in body weight between the diabetic control group and the normal control group. Furthermore, none of the RAXI-treated groups demonstrated a significant difference in weight compared to the diabetic control (P = 0.8459). Notably, the preventive group pretreated with RAXI at 400 mg/kg (E400) did not show any significant deviation in body weight relative to the normal control group, suggesting that the formulation did not negatively affect weight gain or cause weight loss under experimental conditions.

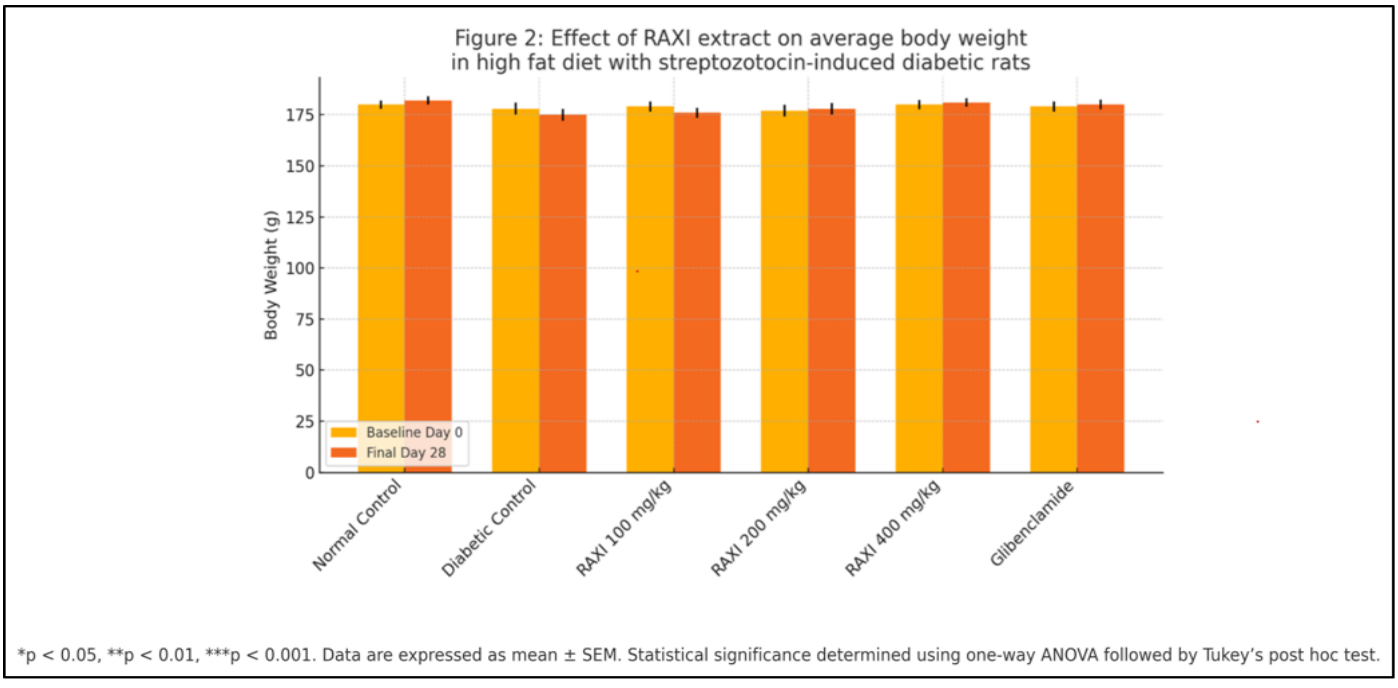

Fig 2 Effect of RAXI Extract on Average Body Weight in high-fat diet and streptozotocin-induced diabetic rats.

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➢ *Effect of RAXI Extract on Biochemical Parameters*

These figures below show the Effect of RAXI Extract on Biochemical Parameters within the 28-day treatment period,

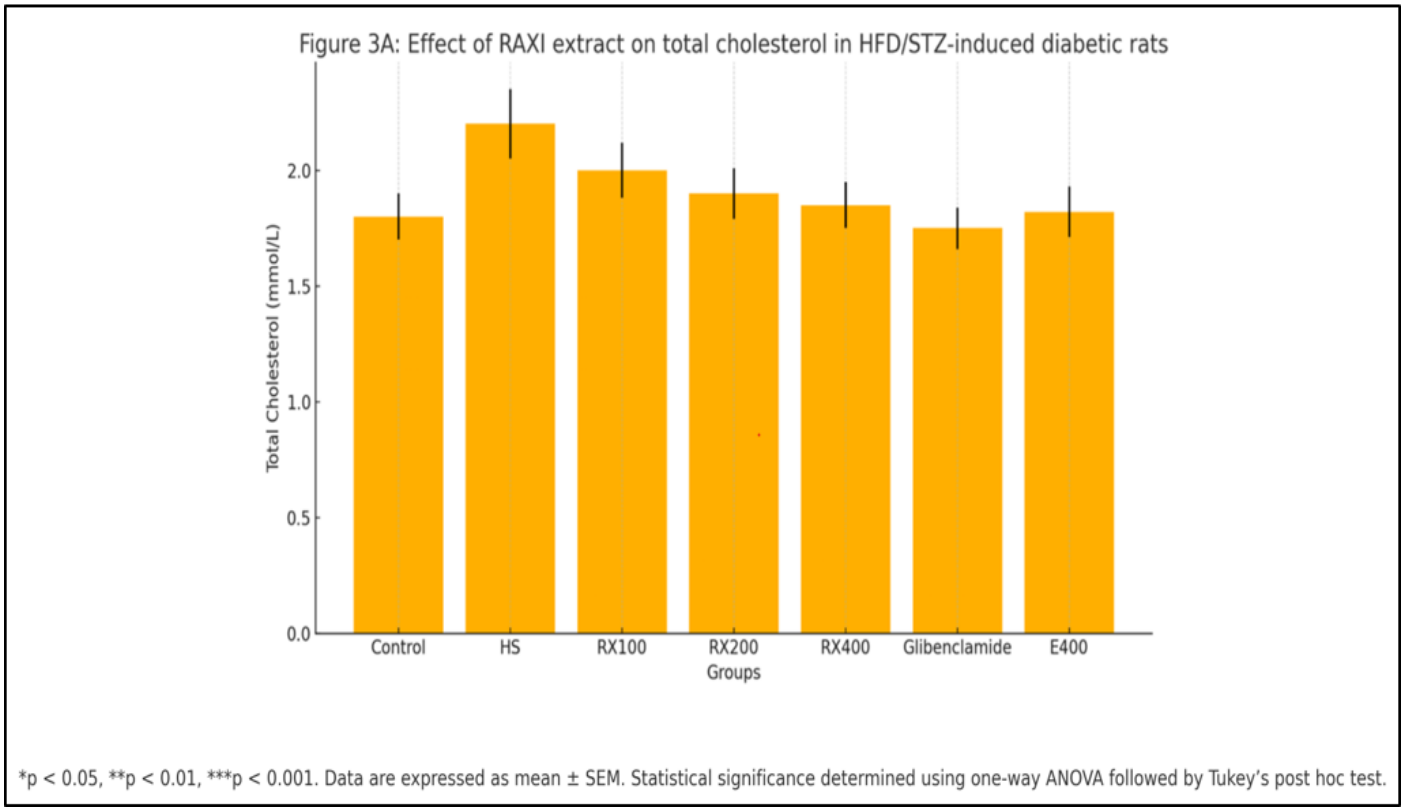

Fig 3 Effect of RAXI Extract on Biochemical Parameters

Here is the bar chart for **Figure 3A**, illustrating the effect of RAXI extract on total cholesterol levels in high-fat diet with streptozotocin-induced diabetic rats after 28 days

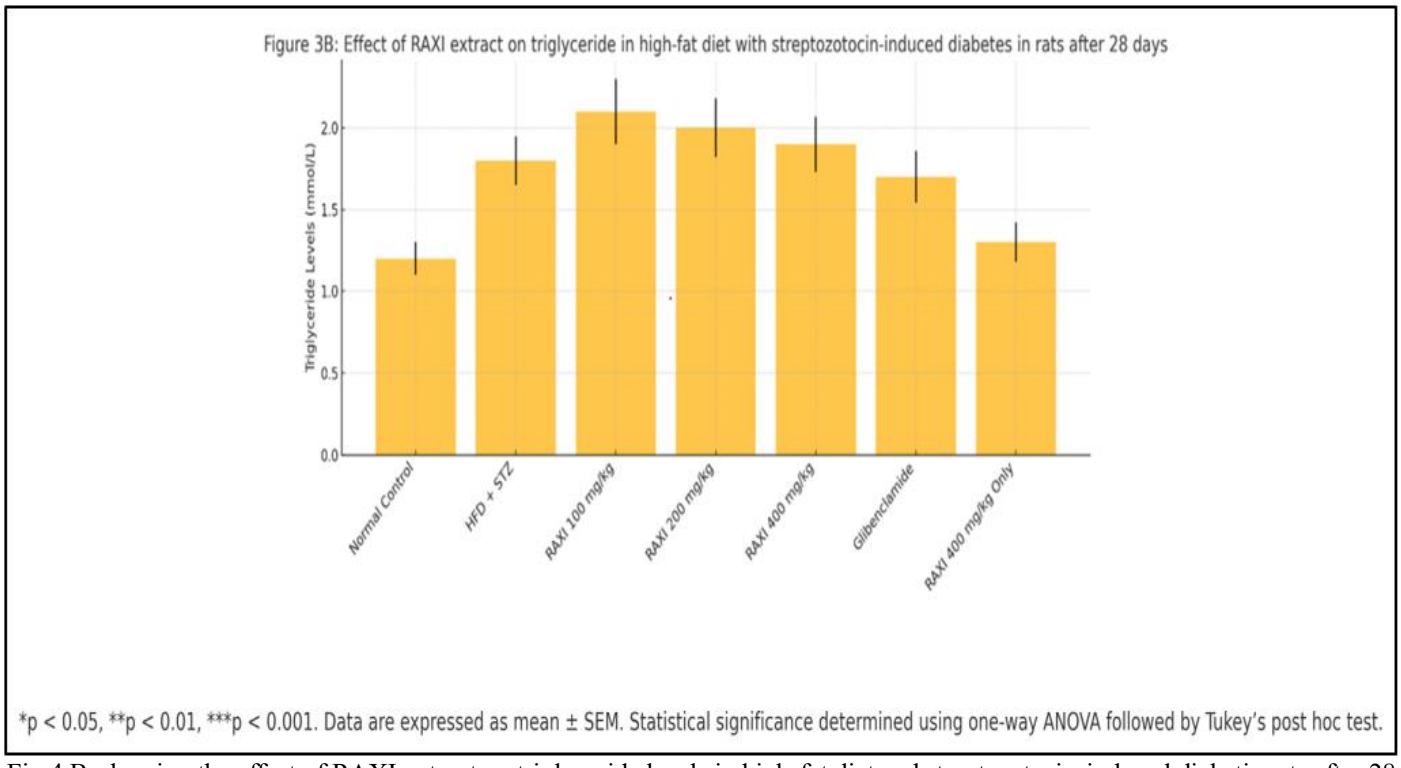

Fig 4 B, showing the effect of RAXI extract on triglyceride levels in high-fat diet and streptozotocin-induced diabetic rats after 28 days.

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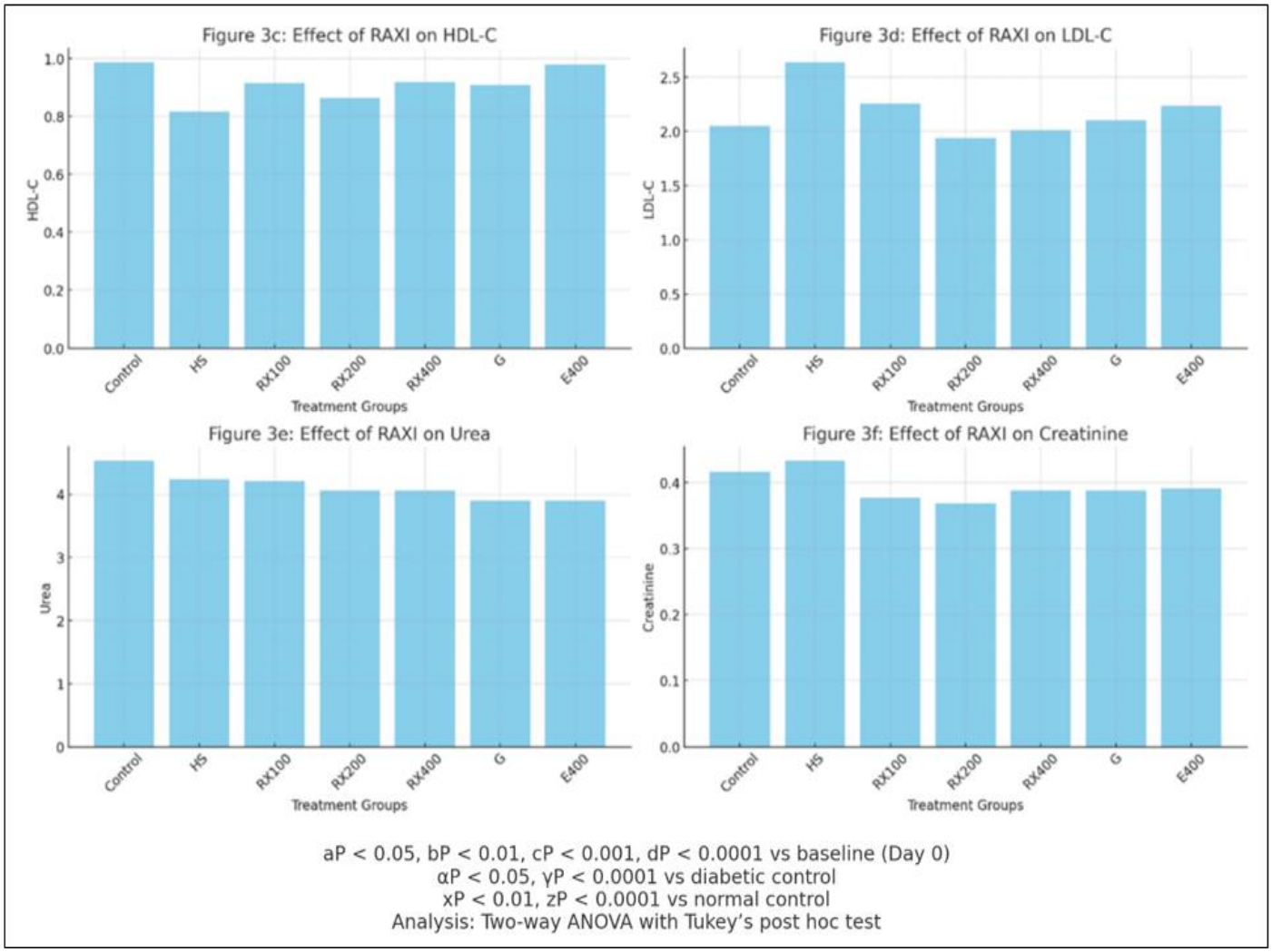

Fig 5 Here are the bar charts representing the effect of RAXI extract on HDL-cholesterol (Figure 3C), LDL-cholesterol (Figure 3D), urea (Figure 3E), and creatinine (Figure 3F) in high fat diet with streptozotocin-induced diabetic rats after 28 days.

➢ *Effect of RAXI Extract on Antioxidant Parameters in the Kidney*

The antioxidant status of the kidney was significantly altered in rats induced with diabetes via high-fat diet and streptozotocin. As shown in Table 1, there was a marked reduction in oxidative stress markers such as MDA and GSH when compared to the normal control group.

➢ *Malondialdehyde (MDA):*

A significant reduction (P = 0.0002) in MDA levels was observed in the diabetic groups treated with RAXI at 200 mg/kg and 400 mg/kg, as well as in the Glibenclamide group, compared to the normal control. However, the 100 mg/kg RAXI dose did not cause a significant change.

➢ *Glutathione (GSH):*

GSH levels were significantly reduced (P = 0.0014) in the 200 mg/kg RAXI and Glibenclamide groups relative to the normal control. Other treatment doses (100 mg/kg and 400 mg/kg) showed no significant changes in GSH levels.

➢ *Nitrites:*

The group treated with RAXI at 100 mg/kg showed a significant restoration (P = 0.0003) of nitrite levels compared to diabetic control. No significant changes were observed at 200 mg/kg and 400 mg/kg doses.

➢ *Catalase (CAT):*

CAT activity significantly increased (P = 0.0001) in the 100 mg/kg RAXI group compared to both diabetic and normal controls. However, no significant differences were found with the 200 mg/kg and 400 mg/kg doses.

➢ *Superoxide Dismutase (SOD):*

A significant reduction (P = 0.0104) in SOD levels was noted in the 200 mg/kg RAXI group compared to the normal control, while the 100 mg/kg and 400 mg/kg groups showed no significant differences.

➢ *Glutathione-S-Transferase (GST):*

No significant variation in GST activity was observed across all treatment groups, including RAXI (100, 200, and 400 mg/kg), when compared to both normal and diabetic controls.

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➢ *Table 1 Effect of RAXI extract on antioxidant parameters in the kidney*

Table 1 Effect of RAXI on Oxidative Stress Markers in Diabetic Rats

Marker	Control	Hs	Rx100	Rx200	Rx400	Gsh	E400
MDA (NMOL/MG)	1.813 ± 0.154	1.10 ± 0.109 **	1.501 ± 0.073	0.976 ± 0.054 ***	1.197 ± 0.056 *	1.218 ± 0.049 *	1.600 ± 0.230
GSH (µMOL/MG)	13.38 ± 1.594	7.451 ± 0.936 **	9.588 ± 0.773	7.820 ± 0.433 **	9.430 ± 0.596	7.807 ± 0.605 **	11.08 ± 1.399
NITRITES (µMOL/MG)	4.520 ± 0.128	3.307 ± 0.237	5.480 ± 0.723 **	3.330 ± 0.157	4.245 ± 0.337	3.497 ± 0.087	4.559 ± 0.220
CAT (U/MG)	25.01 ± 1.080	26.50 ± 1.456	83.48 ± 19.80 ***	33.94 ± 4.502	28.59 ± 2.601	40.24 ± 1.186	35.44 ± 4.734
SOD (U/MG)	0.982 ± 0.058	0.758 ± 0.051	0.942 ± 0.142	0.593 ± 0.028 *	0.841 ± 0.043	0.719 ± 0.033	0.745 ± 0.091
GST (U/MG)	0.082 ± 0.006	0.091 ± 0.010	0.165 ± 0.035	0.065 ± 0.021	0.123 ± 0.029	0.081 ± 0.003	0.131 ± 0.033

*p < 0.05, **p < 0.01, ***p < 0.001 vs control or as indicated

MDA = Malondialdehyde, GSH = Glutathione, CAT = Catalase, SOD = Superoxide Dismutase, GST = Glutathione S-transferas

IV. DISCUSSION

The present study titled *"Evaluation of Antilipidemic and Organ Protective Effects of a Polyherbal Formulation (RAXI) in High-Fat Diet and Streptozotocin-Induced Diabetic Rats"* demonstrates that RAXI confers significant therapeutic benefits in the management of type 2 diabetes and its associated complications. The dose-dependent reduction in fasting blood glucose levels across RAXI-treated groups, particularly at 400 mg/kg, indicates effective glycemic control comparable to the reference drug Glibenclamide. This finding is consistent with those reported by Wilson et al., who showed similar hypoglycemic effects in STZ-induced diabetic models treated with a six-herb polyherbal extract [21].

In addition to its hypoglycemic activity, RAXI showed pronounced antilipidemic effects by significantly reducing serum triglycerides, total cholesterol, and LDL-C, while increasing HDL-C. These results affirm the lipid-modulating potential of RAXI and are supported by Bhatt et al., who observed similar lipid improvements in diabetic rats treated with a polyherbal formulation [22]. Such lipid regulation is critical in reducing the cardiovascular risk associated with diabetes.

Organ protective effects were particularly evident in the improvement of renal function biomarkers (urea and creatinine) and antioxidant enzyme activities. The antioxidant results revealed that RAXI significantly reduced malondialdehyde (MDA), a marker of lipid peroxidation, and improved catalase (CAT) and glutathione (GSH) levels in renal tissues. These findings align with the work of Haye et al., who demonstrated that a polyherbal intervention activated antioxidant defense mechanisms via the AMPK–IRS–PI3K–Akt pathway in diabetic rats [23].

Interestingly, body weight changes did not differ significantly across groups, implying that RAXI did not exacerbate or mitigate weight changes, a favorable outcome given the weight-altering effects of some antidiabetic agents. Rajani et al. reported similar stability in body weight with polyherbal therapy in diabetic rats [24].

Altogether, the current findings support the hypothesis that RAXI exhibits antilipidemic, hypoglycemic, antioxidant, and organ protective effects, validating its ethnopharmacological use and highlighting its potential as an adjunct or alternative therapeutic for managing diabetes and its complications.

V. CONCLUSION

This study provides compelling evidence for the antilipidemic and organ protective effects of the polyherbal formulation RAXI in a rat model of high-fat diet and streptozotocin-induced type 2 diabetes. RAXI not only significantly improved glycemic and lipid profiles but also enhanced antioxidant defense and renal function, particularly at 400 mg/kg. The results affirm the potential of polyherbal interventions like RAXI in managing multifaceted complications of diabetes and support further preclinical and clinical investigations. The study reinforces the relevance of ethnomedicinal knowledge in developing integrative strategies for chronic disease management.

➢ *Authors' Contributions*

Abdulai Turay, a PhD student in Drug Discovery and Development, conceptualized the study, conducted data collection, performed the analysis, and drafted the manuscript.

Sheka Sankoh, a Lecturer in the Department of Pharmaceutics with a master's degree in biomedical Toxicology, provided academic guidance, contributed to the experimental design and methodology, and critically reviewed the manuscript.

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Dr. Eugene BS Conteh offered critical insights into experimental design, supported the interpretation of biochemical and histopathological findings, and reviewed the manuscript for scientific accuracy and intellectual rigor.

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