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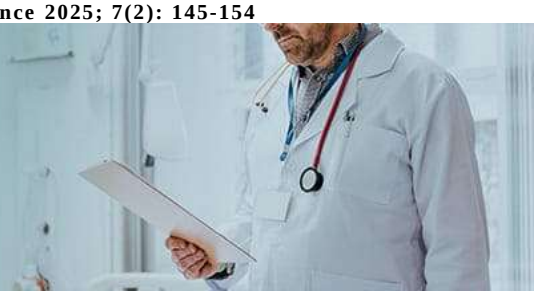

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Antidiabetic and antioxidant effects of raxi polyherbal formulation in fructose/streptozotocin-induced type 2 diabetic rats

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Abstract
Background: Type 2 diabetes mellitus (T2DM) is a growing global health concern characterized by hyperglycemia and oxidative stress. Despite the efficacy of current pharmacotherapies, they are often associated with adverse effects and limited accessibility in low-resource settings. RAXI, a traditional polyherbal formulation containing *Xylopia aethiopica* and *Irvingia gabonensis*, is used in West Africa for diabetes management but lacks scientific validation.
Objective: To evaluate the antihyperglycemic, antioxidant, and lipid-lowering effects of RAXI in a rat model of T2DM.
Methods: Male Wistar rats were rendered diabetic using a high-fructose diet followed by streptozotocin (STZ) injection (35 mg/kg). Diabetic rats were treated orally with RAXI at doses of 100, 200, and 400 mg/kg for 14 days. Glibenclamide (5 mg/kg) served as the reference drug. Fasting blood glucose (FBG), oral glucose tolerance (OGTT), body weight, blood pressure, biochemical markers (ALT, AST, urea, creatinine, lipid profile), and antioxidant enzymes (CAT, SOD, MDA, GSH, GST, nitrite) were measured. Histological analysis of pancreatic tissues was also conducted.
Results: RAXI at 200 mg/kg significantly reduced FBG levels ($p<0.05$), comparable to glibenclamide. While it did not significantly affect body weight or pulse pressure, it decreased diastolic blood pressure to 400 mg/kg. RAXI also significantly improved lipid profiles and reduced serum ALT, AST, urea, and creatinine levels. Antioxidant analysis revealed a significant increase in catalase activity at 100 mg/kg, though other markers remained unchanged. Histological examination showed mild regeneration of pancreatic β-cells.
Conclusion: RAXI exhibited significant antihyperglycemic, nephroprotective, and hepatoprotective effects in diabetic rats, supporting its ethnomedicinal use. The modest antioxidant effect suggests longer treatment duration may be necessary for full efficacy. These findings provide a scientific basis for the development of RAXI as a complementary therapy for T2DM.

Keywords: Type 2 diabetes, RAXI, *Xylopia aethiopica*, *Irvingia gabonensis*, polyherbal formulation, antioxidant activity, glucose tolerance, lipid profile, β-cell regeneration.

Introduction
Diabetes mellitus is a chronic metabolic disorder primarily characterized by persistent hyperglycemia resulting from defects in insulin secretion, insulin action, or both (American Diabetes Association [ADA], 2014) [2]. Globally, the disease is recognized as a significant public health threat and has reached epidemic proportions, affecting over 537 million individuals as of 2021, with projections reaching 783 million by 2045 (Sun *et al*., 2022). Type 2 diabetes mellitus (T2DM) accounts for more than 90% of all diabetes cases and is associated with endocrine dysfunctions that disrupt the metabolism of carbohydrates, lipids, and proteins (Zheng *et al*., 2018) [33].
The burden of T2DM is most pronounced among the ageing population, though younger demographics are increasingly affected due to poor diet and sedentary lifestyles (Zheng *et al*., 2018; [33] International Diabetes Federation [IDF], 2021) [26]. In Africa, an estimated 24 million adults aged 20–79 years were living with T2DM as of 2021, with a projected 143% increase by 2045 (Malek, 2020) [16]. In Sierra Leone, prevalence rose from 2.4% in 1997 to 7.0% in 2017 and is expected to reach 15% by 2030 (Sundufu *et al*., 2017) [28]. Alarmingly,

approximately 1.5 million deaths are directly attributed to diabetes annually (World Health Organization [WHO], 2023) [31].

Risk factors for T2DM include hyperglycemia, obesity, hypertriglyceridemia, poor dietary habits, physical inactivity, ageing, genetics, alcohol consumption, and psychological stress (Zheng *et al*., 2018; Wong *et al*., 2016) [33, 32]. Conventional management strategies involve lifestyle modifications and pharmacotherapy. Common pharmacologic agents include insulin secretagogues (e.g., glibenclamide), insulin sensitizers (e.g., metformin, thiazolidinediones), α-glucosidase inhibitors, and incretin-based therapies such as GLP-1 agonists and DPP-IV inhibitors (Chehade & Mooradian, 2000; Feingold, 2022) [6, 12]. While effective, these agents often cause adverse effects such as weight gain, gastrointestinal discomfort, and hypoglycemia, and are frequently unaffordable in low-income settings (Bastaki, 2005; Chentli *et al*., 2015) [4, 7].

In response, attention has shifted toward herbal medicines, particularly in developing regions where they serve as accessible, affordable, and culturally accepted alternatives to conventional drugs (Arumugam *et al*., 2013) [3]. Medicinal plants are rich in phytochemicals like flavonoids, saponins, alkaloids, and terpenoids, which have demonstrated antidiabetic activities via mechanisms such as enhancing insulin secretion, reducing insulin resistance, and preserving pancreatic β-cell function (Jeeva & Sheebha, 2014; Akhlaghipour *et al*., 2023) [15, 1]. Over 800 plant species, including *Xylopia aethiopica* and *Irvingia gabonensis*, have been identified for their potential in managing diabetes and its complications (Hadjzadeh *et al*., 2018; Tripathi *et al*., 2017) [13, 29].

Polyherbal formulations are gaining popularity due to their synergistic efficacy and reduced toxicity profiles. RAXI, a polyherbal preparation comprising *Xylopia aethiopica* and *Irvingia gabonensis*, is traditionally used in West Africa for diabetes management but lacks scientific validation. Previous studies have shown that these plants possess hypoglycemic, antioxidant, and lipid-lowering properties in experimental models.

Therefore, the aim of this study is to evaluate the antidiabetic and antioxidant effects of RAXI (polyherbal) formulation in fructose/streptozotocin-induced type 2 diabetic rats. The study will assess its impact on fasting blood glucose, lipid profile, antioxidant status, and pancreatic histology to validate its ethnomedicinal use and support its potential as a natural antidiabetic agent.

Chapter three

Materials and Methods

Study Design, Location, and Period

This study was a controlled laboratory-based experimental animal study conducted between September 2023 and October 2024 at the Laboratory Animal Centre, College of Medicine, University of Lagos (CMUL), Lagos, Nigeria. The aim was to evaluate the antidiabetic and antioxidant effects of the polyherbal formulation RAXI in a fructose-induced type 2 diabetic rat model.

Selection Criteria of Experimental Animals

Healthy Wistar rats (weighing 100–200g) were procured from the CMUL Laboratory Animal Centre. Only rats with normal fasting blood glucose (<120 mg/dL) and no signs of illness were selected. The animals were acclimatized for two weeks under standard conditions (12 h light/dark cycle, temperature 22–25 °C) and provided with standard rat chow (Livestock Feeds Plc., Ikeja, Lagos) and clean drinking water ad libitum. Overnight fasting (12 h) was ensured before experimental procedures commenced.

Experimental Procedure

Induction of Type 2 Diabetes Mellitus

Type 2 diabetes was induced using a two-step protocol, combining dietary fructose with a low-dose, as described by Elamine *et al*. (2018) [9]. First, rats were given 40% D-fructose (MOLYCHEM Ltd., Mumbai, India) in their drinking water for 14 days to induce insulin resistance. On day 15, rats were fasted for 16 hours, and fasting blood glucose levels were measured as baseline. A fresh solution of STZ (40 mg/kg; Sigma-Aldrich, USA) was prepared in 0.1 M citrate buffer (pH 4.5) and injected intraperitoneally within 20 minutes of preparation to avoid degradation. Seventy-two hours post-injection, blood glucose was measured using an Accu-Chek® glucometer (Roche DiabetesCare Inc., Indianapolis, USA), and rats with FBG levels ≥250 mg/dL were considered diabetic and included for treatment.

Grouping and Treatment

Rats were randomized into eight groups of six rats each, as shown in Table 1:

Table 1: Experimental animal groups and treatments

Group	Condition	Treatment
F1	Diabetic	Fructose only
F400 mg	Diabetic	RAXI 400 mg/kg
F200 mg	Diabetic	RAXI 200 mg/kg
F100 mg	Diabetic	RAXI 100 mg/kg
G	Diabetic	Glibenclamide 5 mg/kg
E400 mg	Non-diabetic	RAXI 400 mg/kg
OO	Non-diabetic	Olive oil only
NC	Non-diabetic	Normal control (no treatment)

Drug Preparation

- **RAXI Polyherbal Formulation:** Ten grams of RAXI extract (in sticky liquid form) was dissolved in 10 mL of olive oil to prepare a 400 mg/mL stock. Serial dilutions were done to prepare 200 mg/mL and 100 mg/mL concentrations for oral administration based on animal weight.
- **Glibenclamide:** A 5 mg Glibenclamide tablet (GLANIL®, Sygen Pharmaceuticals Ltd., Nigeria) was pulverized using a mortar and pestle, then dissolved in 1 mL of distilled water to create a homogenous solution for oral dosing (5 mg/kg body weight).

Oral Glucose Tolerance Test (OGTT)

Following overnight fasting, rats were given a glucose solution (3 g of glucose in 15 mL distilled water) orally, based on body weight. Fasting blood glucose (FBG) levels were recorded, and the respective treatment regimens (RAXI or glibenclamide) were administered accordingly.

Measurement of Blood Glucose

Blood glucose levels were assessed by collecting two drops of tail vein blood and applying them to Accu-Chek® test

strips. The glucometer provided digital readouts of the fasting blood glucose levels at baseline and at subsequent intervals post-treatment.

Drugs, Chemicals, and Apparatus

- **Drugs and Chemicals:** Glibenclamide 5 mg tablets (GLANIL®; Sygen Pharmaceuticals Ltd., Nigeria), D-fructose (MOLYCHEM Ltd., India), Streptozotocin (STZ; Sigma-Aldrich, USA), sodium chloride (Pharma Impex Laboratories, India).
- **Apparatus:** Measuring cylinder, digital weighing scale, syringes, Pasteur pipette, Accu-Chek® glucometer and strips, spectrophotometer, micro-pipette, stopwatch, mortar and pestle, forceps, beakers, EDTA bottles, and other routine lab materials.

Acute Toxicity Study

On day one of treatment, all rats were administered their respective interventions according to group assignment. Following administration of RAXI extract at varying doses (100, 200, and 400 mg/kg), animals were observed for 6 hours for signs of toxicity and behavioral changes. Blood glucose levels were measured at 0, 30, 60, 120, 240, and 360 minutes post-administration using an Accu-Chek® glucometer (Roche Diagnostics, USA). Observed clinical signs included restlessness, weakness, climbing, leaning on hind limbs, gripping, and agitation, especially after two hours of treatment administration (Dada *et al*., 2013) [8].

Blood Pressure Determination

Arterial blood pressure was measured using a non-invasive tail-cuff infrared photoplethysmography (PPG) sensor (Masato *et al*., 2021) [17]. Rats were placed in a 32 °C heating chamber for 3 minutes to facilitate vasodilation. The appropriate tail-cuff size was selected and attached to the midpoint of the tail. Once the animal was relaxed in the restrainer, systolic and diastolic blood pressure and heart rate were recorded.

Blood Sample Collection

Blood samples were collected via ocular puncture under light anesthesia. For hematological assays, samples were collected into EDTA-treated tubes. For serum biochemical and lipid profile analyses, blood was collected into plain tubes, allowed to clot on ice, and centrifuged at 10,000 rpm for 10 minutes. The serum was separated and stored at −20 °C for further analysis (Shafik, 2012) [24].

Sub-Acute Toxicity Study

All treatment regimens continued for 14 consecutive days. Fasting blood glucose (FBG) was assessed on days 0, 7, and 14. Blood samples for hematological, biochemical, and lipid profile analyses were collected on days 0 and 14, as described above. At the end of the experiment, animals were euthanized under ketamine anesthesia (0.1 mL/100 g, intraperitoneally), and organs (liver, pancreas, kidney, and heart) were harvested for histopathological and oxidative stress analysis (Shafik, 2012) [24].

Oxidative Stress Biomarker Assessment

Superoxide Dismutase (SOD) Activity

SOD activity was determined by its ability to inhibit the auto-oxidation of epinephrine. The change in absorbance at 480 nm was measured for 5 minutes (Sun & Zigman, 1978) [27].

Catalase Activity

Catalase activity was measured at 620 nm and expressed as µmol of H_2O_2 consumed per minute per mg protein at 25 °C. The reaction was terminated using dichromate-acetic acid reagent (Sinha, 1972) [25].

Reduced Glutathione (GSH) Level

GSH levels were determined using Ellman's reagent. Absorbance was measured at 412 nm (Sedlak & Lindsay, 1968) [23].

Malondialdehyde (MDA) Level

MDA, an index of lipid peroxidation, was measured using thiobarbituric acid reactive substances (TBARS) at 532 nm (Buege & Aust, 1978) [5].

Clinical Biochemistry Assessment

Serum biochemical parameters, including AST, ALT, ALP, albumin, total cholesterol (TC), triglycerides (TGs), HDL, LDL, creatinine, bilirubin, and urea, were analyzed using Chema Diagnostic kits (Monsano, Italy) on a Mindray analyzer.

Serum Electrolyte Analysis

Serum levels of Na^+, K^+, and Cl^- were analyzed using a flame photometer (Sherwood, Model 410, UK).

Determination of Glycosylated Hemoglobin (HbA1c)

HbA1c levels were measured using Fortress Diagnostics HbA1c Kit, according to the manufacturer's protocol.

Histopathological Examination

Histopathology of kidney and pancreas tissues was conducted at the Department of Anatomic and Molecular Pathology, College of Medicine, University of Lagos. Tissues were fixed in 10% formal saline, dehydrated in graded alcohol, cleared in xylene, embedded in paraffin wax, and sectioned at 5 µm using a rotary microtome. Sections were stained with hematoxylin and eosin, mounted with DPX, and examined under a Leica DM750 microscope for pathological changes (Shafik, 2012) [24].

Observation of Clinical Signs

Animals were monitored continuously for 24 hours post-administration for signs of morbidity or mortality. Clinical observations including onset, duration, and severity were recorded. Gross pathological changes in liver and kidney were assessed on day 14 post-sacrifice.

Ethical Approval

This study received ethical clearance from the Animal Care and Research Ethics Committee of the College of Medicine, University of Lagos (Approval No: CMUL/ACREC/2023/0042). All experimental procedures were conducted in compliance with institutional and international guidelines on the ethical use of laboratory animals.

Statistical Analysis

Data were presented as mean±standard deviation (SD). Statistical analysis was conducted using GraphPad Prism version 9.0. One-way analysis of variance (ANOVA) followed by Tukey's multiple comparison post hoc test was used to determine statistical significance among groups. A

p-value of less than 0.05 was considered statistically significant.

Results

Effect of RAXI (Polyherbal) Formulation on Fasting Blood Glucose (FBG) Levels in Fructose/Streptozotocin-Induced Diabetic Rats

Fasting blood glucose (FBG) levels were significantly elevated in the diabetic control group (F1), which received fructose and streptozotocin without treatment, compared to the normal control group administered olive oil only ($p < 0.0001$) (Table 3). This confirms successful induction of type 2 diabetes mellitus.

Administration of RAXI (polyherbal formulation) and glibenclamide led to a progressive reduction in FBG levels over the 14-day treatment period. Notably, by day 14, the group treated with RAXI at 200 mg/kg (FR200) showed a statistically significant reduction in FBG levels ($p < 0.0001$) when compared to the diabetic control group (F1), indicating a potent antihyperglycemic effect comparable to glibenclamide.

However, a mild transient increase in FBG was observed within the first 72 hours of treatment in all RAXI-treated groups (100, 200, and 400 mg/kg) as well as the glibenclamide group, relative to the normal olive oil control and non-diabetic RAXI control group (E400). Despite this early increase, glucose levels declined steadily thereafter.

Conversely, treatment with the lowest dose of RAXI (100 mg/kg) resulted in a statistically significant elevation in FBG at day 14 compared to baseline values ($p < 0.05$), suggesting suboptimal glycemic control at this dose.

These findings suggest that the antidiabetic activity of RAXI is dose-dependent, with optimal efficacy observed at 200 mg/kg. The results also affirm the model's sensitivity in differentiating between effective and ineffective therapeutic doses.

Table 2: The effect of RAXI (polyherbal) formulation on fasting blood glucose level of Fructose/ Streptozotocin-Induced Diabetic Rats.

TIME	CONTROL	F+STZ	FR100	FR200	FR400	G	E400
BGL	53.60±1.69	85.67±4.15	93.75±3.90	98.67±1.65	82.33±4.15	90.25±1.65	75.80±9.26
72hrs	53.60±1.69	204.00±25.06	314.00± 95.22^{d}	309.67±22.66^{d}	230.00±13.36^{b}	300.75±6.79^{c}	75.80±9.26α
day 7	84.40± 4.44	219.00±22.77	162.00±82.38	133.33±26.23	97.67±1.47α	157.50±29.68	90.80±3.58α
day 14	78.20± 3.84	217.33 23.93	171.75±66.27	92.67±6.63α	92.33±1.52α	75.25±8.89α	78.67±0.84β

Statistical Notations

- Values are expressed as Mean±SEM (n = 7 per group).
- $^{a}P < 0.05$, $^{b}P < 0.01$, $^{c}P < 0.001$, $^{d}P < 0.0001$ vs. baseline (Day 0) within the same group.
- $\alpha P < 0.05$, $\beta P < 0.01$ vs. diabetic control (F + STZ).
- Statistical significance assessed using two-way ANOVA, followed by Tukey's post hoc multiple comparisons test.

Effect of RAXI (Polyherbal) Formulation on Systolic Blood Pressure, Diastolic Blood Pressure, and Pulse Rate in Fructose/Streptozotocin-Induced Type 2 Diabetic Rats

Administration of RAXI (polyherbal formulation) at different doses exhibited no statistically significant effect on systolic blood pressure (SBP), diastolic blood pressure (DBP), or pulse rate (PR) when compared with the non-diabetic control group (E400), as shown in Tables 3. Specifically, systolic pressure ($P = 0.1650$), diastolic pressure ($P = 0.3788$), and pulse rate ($P = 0.9239$) did not significantly differ across treatment groups on day 14.

Interestingly, RAXI at 400 mg/kg (FR400) induced a reduction in diastolic blood pressure when compared to the normal olive oil control group over the 14-day treatment period. This decrease was statistically significant and may suggest a mild vasorelaxant effect of RAXI at higher doses.

However, no statistically significant changes in SBP, DBP, or PR were observed in the diabetic control (F+STZ) group relative to the normal control group, indicating that type 2 diabetes induction with fructose and streptozotocin did not notably alter cardiovascular parameters within the observation window.

Furthermore, the group pretreated with RAXI at 400 mg/kg (E400) before induction of diabetes did not exhibit any significant deviation in SBP, DBP, or PR compared to the normal control, suggesting a possible preventive effect against cardiovascular disturbances in early-stage diabetes.

These results indicate that RAXI, particularly at 400 mg/kg, may have a stabilizing effect on blood pressure without causing adverse cardiovascular outcomes in diabetic or non-diabetic rats.

Table 3: The effect of RAXI (polyherbal) formulation on Systolic Blood pressure in fructose/streptozotocin-induced type 2 diabetic mellitus rats

TIME	CONTROL	F+STZ	FR100	FR200	FR400	G	E400
B. I	140.80±10.26	150.66± 8.164	161.83±5.77	159.67±2.96	159.67 ±7.89	146.14±8.70	140.80±10.26
day1	140.80±10.26	135.5±9.25	145±19.36	134.5 ±18.59	157.67 ±2.974	158.25 ±1.54	140.80±10.26
day7	113.40±16.17	139.33 ±2.65	161.75 ±5.45	115.67±8.01	147.33±10.23	149.5±7.94	137.40±9.03
day14	140.80±10.26	131.67 ±12.55	148.75±5.52	154.33±3.51	136.67±11.80	164.75±6.35	140.80±10.26

Values are expressed as Mean±SEM (n=7); $^{a}P < 0.05$, versus baseline day 0, Statistical level of significance analysis by two-way ANOVA followed by Tukey's post hoc multiple comparisons test.

Table 4: The effect of RAXI (polyherbal) formulation on Diastolic blood pressure in fructose streptozotocin-induced diabetic rats

TIME	CONTROL	F+STZ	FR100	FR200	FR400	G	E400
B. I	77.6±1.25	79.00±0.45	72.34±5.47	78.66±0.49	94.17±16.58	85±4.83	77.6±1.25
day1	77.6±1.29	79.166±0.54	79.25±0.25	73.25±5.75	78.67±0.21	74.25±4.77	77.6±1.25
day7	73.8±8.58	80.00±0.00	78.00±1.08	79.00±0.00	78.67±0.21	78.75±0.48	72.6±7.15
day14	77.6±1.25	78.34±0.558	74.25±4.25	78.34±0.42	68.33±1.73	79±0.71	77.6±1.25

Values are expressed as Mean±SEM (n=7); $^{a}P < 0.05$, versus baseline day 0, Statistical level of significance analysis by two-way ANOVA followed by Tukey's post hoc multiple comparisons test.

Table 5: The effect of RAXI (polyherbal) formulation on pulse pressure in Fructose/Streptozotocin-Induced Diabetic Rats

TIME	CONTROL	F	FR100	FR200	FR400	G	E400
B. I	296.60±38.28	292.33±49.39	303.00±22.15	330.33±32.53	274.00 ±18.48	315.28±20.81	298.60±36.25
day1	296.60±38.28	332.83±14.72	334.00±36.95	304.00±17.05	317.00±11.40	261.50± 30.00	298.60±36.25
day7	308.00±7.73	337.33±17.39	317.50 ±31.66	341.67 ±31.58	367.67±23.48	331.75±20.28	308.20±54.75
day14	296.60±38.28	328.33 ±11.06	309.25±40.67	371.67 ±40.67	295.00 ±21.85	282.25±13.32	298.60±36.25

Values are expressed as Mean±SEM (n=7); $^{a}P < 0.05$, versus baseline day 0, Statistical level of significance analysis by two-way ANOVA followed by Tukey's post hoc multiple comparisons test.

The Effect of RAXI (Polyherbal) Formulation on Average Body Weight in Fructose/Streptozotocin-Induced Diabetic Rats

As shown in Table 6, over the 14-day treatment period, there was no statistically significant change in average body weight in the diabetic control group (F1) compared to the normal olive oil control group (P = 0.8459). Similarly, no significant differences in body weight were observed between any of the RAXI-treated groups (FR100, FR200, FR400) or the glibenclamide group (G) when compared to the diabetic control (F1). Furthermore, the group that received RAXI 400 mg/kg as a preventive treatment (E400) did not demonstrate any significant variation in average body weight relative to the normal control group.

Table 6: Effect of RAXI (polyherbal) formulation on average body weight in fructose/ streptozotocin-induced diabetic rats

TIME	CONTROL	F+STZ	FR100	FR200	FR400	G	E400
B. I	126.60± 5.31	175.33±5.66	183.25±8.18	169.33±3.66	161.67±11.53	164.75±9.49	136.00±6.72
day1	135.20± 6.73	171.33±5.85	171.25±10.87	167.00 ±4.94	159.00±9.85	159.75 ±11.63	126.80±5.67
day7	146.40± 8.96	167.33 ±6.29	170.75±14.49	169.67±9.11	163.00 ±11.11	155.25±18.64	148.80 ±10.88
day14	157.60±11.04	168.00±5.79	165.75 ±18.08	170.67 ±9.01	159.33 ±11.39	153.50±7.59	150.80± 10.77

Values are expressed as Mean±SEM (n=7). Statistical level of significance analysis by two-way ANOVA followed by Tukey's post hoc multiple comparisons test.

The Effect of Raxi (Polyherbal) Formulation on Oral Glucose Tolerance Test (OGTT)

Figure 4 illustrates the effect of RAXI at varying doses on glucose tolerance over a 4-hour period. Compared to the baseline fasting blood glucose level measured at 1 hour, treatment with all doses of RAXI (100, 200, and 400 mg/kg) did not result in any statistically significant reduction in glucose levels throughout the 4-hour monitoring period. In contrast, glibenclamide administration significantly reduced fasting blood glucose levels at each time point from 2 to 4 hours post-glucose administration (P = 0.0002), indicating a superior antihyperglycemic response compared to the polyherbal treatment.

Table 7: The effect of RAXI (polyherbal) formulation on oral glucose tolerance test (OGTT)

TIME	CONTROL	FR100	FR200	FR400	G
1hr	130.67±3.90	106.33±0.21	92.66±1.18	100.00±7.19	92.33±2.74
2hr	119.00±3.48	109.33±2.49	99.67± 2.43	105.67±6.45	59.00 ±11.85
3hr	124.33±4.77	114.00 ±5.27	89.33±1.80	104.00±8.88	52.00±10.01
4hr	109.67±2.14	104.00±1.93	101.67±2.23	87.66±4.90	44.67±8.45

Values are expressed as Mean±SEM (n=5); $^{b}P < 0.01$, $^{c}P < 0.001$, $^{d}P < 0.0001$ versus baseline (1 hour). Statistical level of significance analysis by two-way ANOVA followed by Tukey's post hoc multiple comparisons test.

The Effect of Raxi (Polyherbal) Formulation on Biochemical Parameters

Post hoc analysis after 14 days of fructose administration revealed significant elevations in the levels of several biochemical markers in the diabetic control group when compared to the normal olive oil control group. These included aspartate aminotransferase (135.2±10.37, p=0.0164), alanine aminotransferase (38.45±4.76, p=0.0174), triglycerides (1.70±0.07, p=0.0002), urea (14.15±4.99, p=0.0279), and creatinine (146.3±20.96, p=0.0005).

Treatment with RAXI formulation significantly reversed these elevations at specific doses:

- Aspartate aminotransferase (AST): reduced to 200 mg/kg
- Alanine aminotransferase (ALT): reduced at 200 and 400 mg/kg
- Triglycerides (TG): reduced to 100 and 200 mg/kg
- Urea: reduced to 100 and 200 mg/kg
- Creatinine: reduced to 100, 200, and 400 mg/kg

In contrast, no significant changes were observed in glycated haemoglobin (HbA1c), direct bilirubin, alkaline phosphatase, total protein, albumin, total cholesterol, potassium, chloride, sodium bicarbonate, total bilirubin, high-density lipoprotein (HDL), low-density lipoprotein (LDL), or alkaline phosphatase levels across treatment groups (p>0.05) (Table 8).

Table 8: Effect of RAXI (polyherbal) formulation on biochemical parameters in fructose/streptozotocin-induced diabetics rats

PARAMETER	Control	F+STZ	FR100	FR200	FR400	G	E400
TP g/l	63.73±2.497	61.95±2.79	67.90±5.25	67.80±2.79	71.20±2.24	61.48±4.22	62.30±5.02
ALBUMIN g/l	34.77±1.562	34.78±1.55	37.98±3.03	37.57±1.70	39.87±1.73	34.40±2.16	35.23±2.38
AST u/l	68.63±17.8	135.20±10.37 a	89.70±7.64	80.20±22.89α	83.07±8.04	101.30±4.15	93.73±3.37
ALT u/l	24.93±2.106	38.45±4.76	25.48±2.03	23.87±2.15α	22.80±2.19α	29.40±1.51	23.63±4.19α
ALP u/l	795.30±31.29	710.70±28.81	741.70±29.78	671.50±77.27	665.70±49.40	774.80±50.32	756.90±60.31
T. CHOL mmol/l	2.43±0.2667	2.725±0.225	2.70±0.21	2.17±0.40	2.20±0.06	2.15±0.19	1.70±0.15
TRIG mmol/l	0.80±0.05774	1.71±0.071^{b}	0.72±0.12δ	0.83±0.12β	1.13±0.13	0.92±0.13β	0.76 0.18δ
HDL CHOL mmol/l	1.10± 0.1	1.05±0.05	1.00±0.091	0.83±0.09	0.93±0.03	0.85±0.18	0.80± 0.1155
LDL CHOL mmol/l	0.97±0.2404	0.90±0.14	1.35±0.12	0.93±0.26	0.73±0.03	0.87±0.08	0.53±0.120
UREA mmol/l	5.13±0.8511	14.15±4.99	3.15±0.53α	5.23±0.78	4.10±0.40	4.00±0.46α	3.07±0.28α
CREATINumpl/l	50.80±16.35	146.30±20.96^{c}	65.55 ±2.65β	68.10±4.41β	58.93±8.30β	75.45±10.05β	67.07±4.67β
K mmol/l	4.37±0.2926	4.51± 0.09	4.98±0.44	4.83±0.16	4.59±0.26	4.41±0.19	4.46±0.29
SODIUM mmol/l	137.30±6.313	141.91±0.99	141.50±0.39	140.10±1.32	142.60±1.04	140.70±2.13	141.70 ±1.65
CHLORIDE mmol/l	95.00±4.163	99.00±0.91	99.00±0.58	97.33±97.33	99.33±1.86	98.75±2.87	98.33±0.88
HCO3 mmol/l	18.67±1.333	18.00±1.22	19.00±2.16	18.33±1.33	20.00±1.53	18.75±2.59	19.67 ±0.33
T BIL umol/l	5.97±0.6489	6.05±0.19	6.17±0.40	6.13±0.37	5.30±0.25	6.05±0.41	5.73±0.40
B BIL umol/l	0.70±0.05774	0.57±0.05	0.75±0.06	0.57±0.03	0.77±0.08	0.67±0.12	0.63±0.18
HBA1C %	1.60±0.4115	1.60±0.26	1.45±0.49	1.00±0.40	1.20±0.29	1.50±0.23	0.70±0.06

Values are expressed as Mean±SEM (n=7); a P < 0.05, ^{b}P < 0.01, ^{c}P < 0.001 versus normal control, αP < 0.05, βP < 0.01, δP < 0.001 versus diabetic control. Statistical level of significance analysis by one-way ANOVA followed by Tukey's post hoc multiple comparisons test.

AST = Aspertate aminotransferase, ALT = alanine aminotransferase, ALP = alkalin phosphatase, TRIG = triglyceride, T. CHOL = total cholesterol, HDL CHOL = high density lipoprotein cholesterol, LDL CHOL = low density lipoprotein cholesterol, HCO3 = bicarbonate, T. BIL = total bilirubin, D. BIL = direct bilirubin and HBA1C = Glycated Hemoglobin

Effect of Extract Raxi On Antioxidant Parameters in The Rat Kidney

One-way ANOVA revealed that the induction of diabetes using fructose/streptozotocin significantly increased catalase (CAT) activity in the kidney compared to the normal control group. Interestingly, treatment with RAXI at 100 mg/kg further elevated renal CAT levels significantly ($F(6, 35)$ = 3.377; p=0.0099) in comparison to the normal control (Figure 3D). However, no significant changes in CAT activity were observed at the 200 mg/kg and 400 mg/kg doses of RAXI when compared to both the normal and diabetic control groups.

Additionally, there were no statistically significant differences in the levels of renal malondialdehyde (MDA) (Figure 3A), reduced glutathione (GSH) (Figure 3B), nitrite (Figure 3C), superoxide dismutase (SOD) (Figure 3E), or glutathione S-transferase (GST) (Figure 3F) among all RAXI-treated groups (100, 200, and 400 mg/kg) when compared to both the normal and diabetic controls (p>0.05

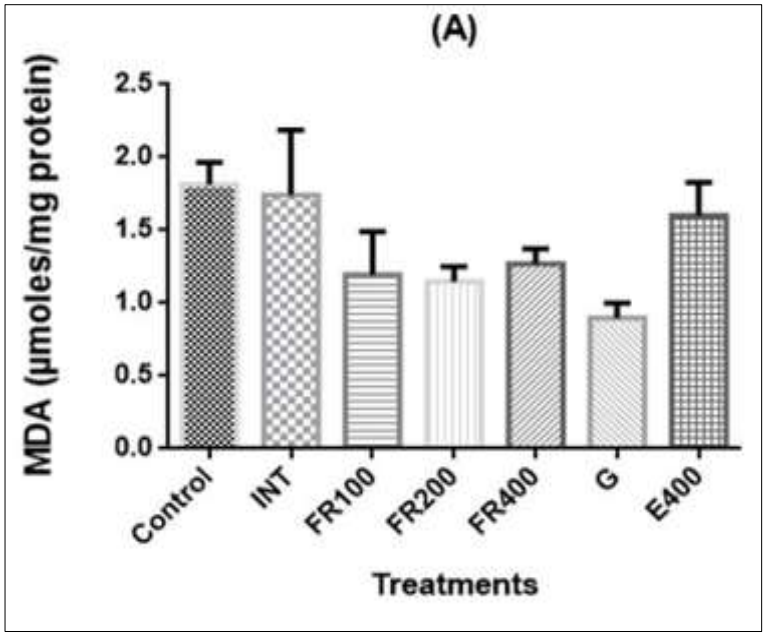

Fig 1: Effect of extract RAXI on antioxidant parameter (MDA) in the kidney. Bar Chart represent the Mean±SEM (n=7). Statistical level of significance analysis by one-way ANOVA followed by Tukey's post hoc multiple comparisons test.

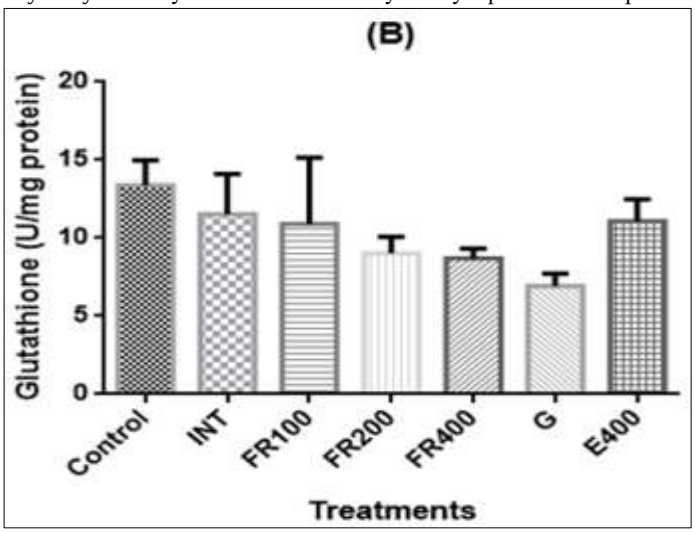

Fig 2: Effect of extract RAXI on antioxidant parameter (Glutathione) in the kidney. Bar Chart represent the Mean±SEM (n=7). Statistical level of significance analysis by one-way ANOVA followed by Tukey's post hoc multiple comparisons test.

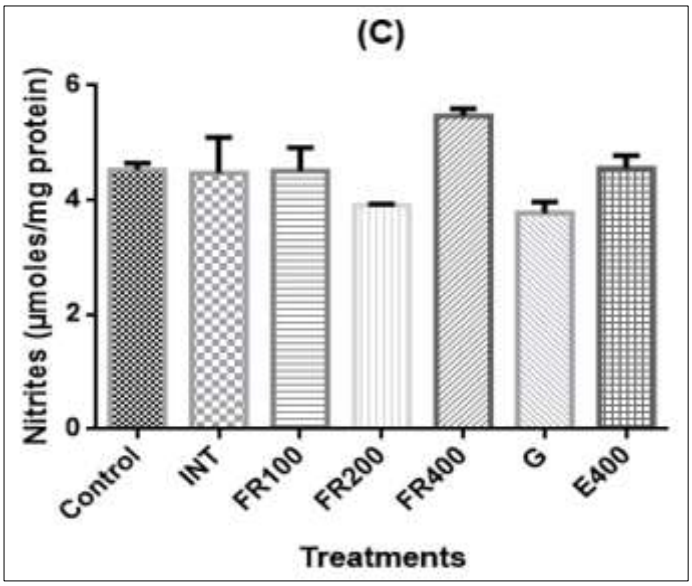

Fig 3: Effect of extract RAXI on antioxidant parameter (Nitrites) in the kidney. Bar Chart represent the Mean±SEM (n=7). Statistical level of significance analysis by one-way ANOVA followed by Tukey's post hoc multiple comparisons test.

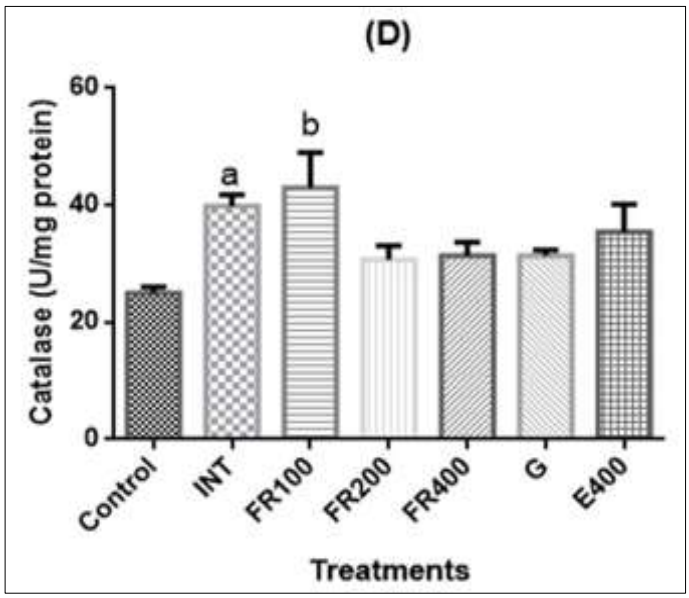

Fig 4: Effect of extract RAXI on antioxidant parameter (catalase) in the kidney. Bar Chart represent the Mean±SEM (n=7). Statistical level of significance analysis by one-way ANOVA followed by Tukey's post hoc multiple comparisons test.

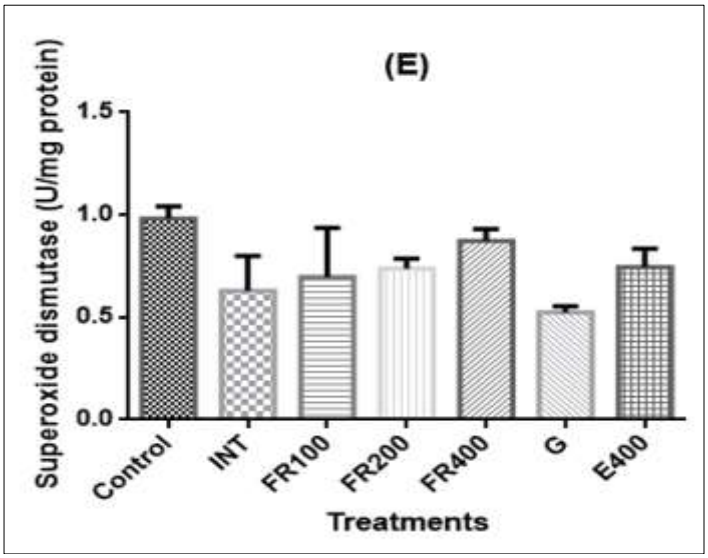

Fig 5: Effect of extract RAXI on antioxidant parameter (Superoxide S-dismutase) on the kidney. Bar Chart represent the Mean±SEM (n=7). Statistical level of significance analysis by one-way ANOVA followed by Tukey's post hoc multiple comparisons test

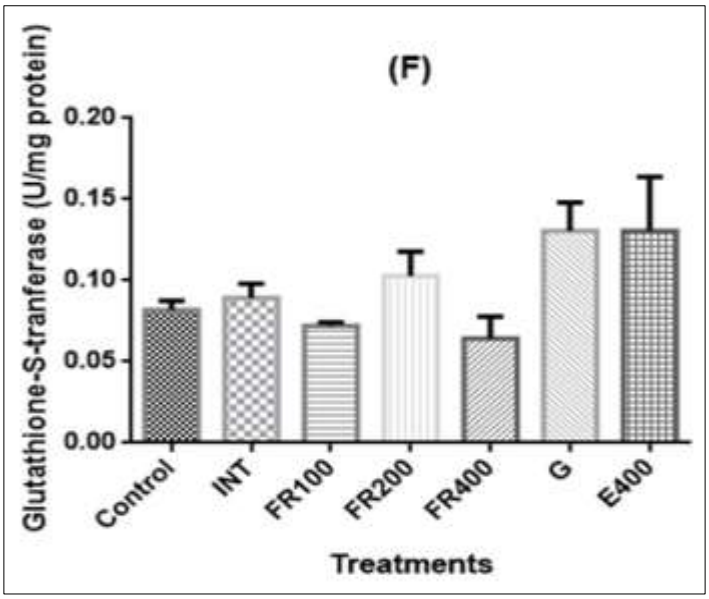

Fig 6: Effect of extract RAXI on antioxidant parameter (Gutathione S-tranferase) in the kidney. Bar Chart represent the Mean±SEM (n=7). Statistical level of significance analysis by one-way ANOVA followed by Tukey's post hoc multiple comparisons test.

Discussion

Antihyperglycemic Effect

The present study revealed a significant reduction in fasting blood glucose (FBG) levels in diabetic rats treated with RAXI at 200 mg/kg, comparable to glibenclamide. This dose-dependent antihyperglycemic effect is consistent with the findings of Mohammed *et al*. (2019) [18], who reported that the acetone fraction of *Xylopia aethiopica* significantly lowered serum glucose levels in fructose/STZ-induced diabetic rats. Similarly, Enechi *et al*. (2015) [10] demonstrated that aqueous X. aethiopica extract facilitated pancreatic β-cell regeneration, supporting its insulinotropic activity. The early transient rise in FBG observed in RAXI-treated rats could reflect an initial metabolic adaptation or delayed pharmacodynamic response typical of polyherbal formulations (Okokon *et al*., 2017) [22].

Body Weight and Cardiovascular Parameters

RAXI treatment did not significantly alter body weight across the 14-day period, corroborating findings by Oben *et al*. (2008) [21] where *Irvingia gabonensis* seed extract had no significant effect on weight gain in diabetic rats. Additionally, the observed non-significant changes in systolic and pulse pressure, alongside a significant reduction in diastolic pressure at 400 mg/kg, suggest a mild vasorelaxant effect of RAXI. This is consistent with the lipid-lowering and endothelium-protective properties previously attributed to I. gabonensis (Ngondi *et al*., 2009) [9].

Lipid and Biochemical Modulation

Biochemical analysis revealed that RAXI significantly reversed elevations in ALT, AST, triglycerides, urea, and creatinine in a dose-dependent manner. These findings align with Uhegbu *et al*. (2014) [30], who showed that methanolic extracts of I. gabonensis significantly decreased serum transaminases and lipid profiles in diabetic rats. Moreover, reductions in renal markers such as urea and creatinine suggest nephroprotective effects, a feature also reported by Eteng *et al*. (2006) [11] with similar polyherbal formulations.

Antioxidant Activity

While catalase (CAT) levels increased significantly to 100 mg/kg, no significant changes were observed in MDA, SOD, GSH, nitrite, or GST levels. This finding contrasts with the work of Nwozo *et al*. (2011) [20], where long-term administration of I. gabonensis enhanced multiple antioxidant enzyme activities. The lack of significant antioxidant modulation in the current study may be due to the short duration of treatment or insufficient tissue accumulation of active compounds.

Glucose Tolerance

The oral glucose tolerance test (OGTT) revealed that RAXI did not significantly lower glucose levels over the 4-hour period, unlike glibenclamide. This agrees with Iwu *et al*. (2013) [14], who observed that polyherbal extracts often exhibit slower onset of action and require prolonged administration to achieve peak efficacy in glucose modulation.

Conclusion

This study demonstrates that RAXI, a polyherbal formulation comprising *Xylopia aethiopica* and *Irvingia gabonensis*, exhibits promising antihyperglycemic activity in a dose-dependent manner, with the 200 mg/kg dose producing a significant reduction in fasting blood glucose comparable to glibenclamide. While no significant changes were observed in glucose tolerance over a 4-hour period, the long-term administration of RAXI improved biochemical indices such as AST, ALT, triglycerides, urea, and creatinine, suggesting hepatoprotective, lipid-lowering, and renoprotective potentials. Although antioxidant markers in the kidney remained largely unchanged, the increase in catalase activity at 100 mg/kg indicates potential oxidative stress modulation.

RAXI did not significantly affect body weight or pulse pressure, and its impact on systolic and diastolic blood pressure was minimal, with a notable reduction in diastolic pressure observed at the highest dose. These findings suggest that RAXI may offer metabolic and end-organ protection in type 2 diabetes without inducing adverse cardiovascular effects.

Recommendations

- **Further Pharmacodynamic Studies:** Future research should extend the treatment duration beyond 14 days to evaluate long-term glycemic control, pancreatic regeneration, and insulin secretion mechanisms.
- **Mechanistic Investigations:** Biochemical and molecular studies should be conducted to elucidate the precise pathways through which RAXI exerts its antihyperglycemic, antioxidant, and lipid-modulatory effects.
- **Standardization and Phytochemical Profiling:** Comprehensive phytochemical analyses and standardization of the formulation are necessary to identify and quantify the bioactive compounds responsible for the observed effects.
- Toxicological Evaluation: Chronic toxicity and safety studies should be performed to determine the therapeutic index and safety margins of RAXI.
- **Clinical Trials:** Given their promising results in animal models, clinical trials should be considered to evaluate the efficacy, safety, and tolerability of RAXI in human subjects with type 2 diabetes mellitus.
- **Formulation Optimization:** Development of improved dosage forms (e.g., capsules or sustained-release tablets) could enhance patient compliance and therapeutic outcomes in future applications

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