

# Evaluation of Hypoglycemic Activity of the Aqueous Extract of the Leaf and Root Bark of *Ficus exasperata* Vahl. (Moraceae) in Wistar Rats: Absence of Synergistic Effects

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## Abstract

**Background:** The ethnomedicinal use of *Ficus exasperata* Vahl (Moraceae) in the management of various diseases is popular in most Sub-Saharan African regions. Different parts of the plant have been exploited and used for various local remedies. In this study, the hypoglycemic effect of the aqueous leaf and root bark of *Ficus exasperata* Vahl (Moraceae) was evaluated using an experimental rat model. **Aim:** The aim of this study is to evaluate the hypoglycemic effect of the aqueous extract of the leaf and root bark of *Ficus exasperata* Vahl (Moraceae). **Objectives:** The chief objective was to determine the hypoglycemic activity of the aqueous extract of the root bark of *Ficus exasperata* in Wistar albino rats and to determine if there exists a synergy in the hypoglycemic effect between the aqueous extract of the leaf and root bark of the plant, thus justifying its local use. **Method:** Wistar rats, 100–180g, used for the experiment, were diabetically induced with Alloxan monohydrate. The 40 Wistar rats used for the experiment were divided into six groups (A, B, C, D, E, and F) with 7 animals in each group, except group F, which had only 5. Diabetes was experimentally induced in groups A, B, C, D, and E with a single intraperitoneal administration of Alloxan (150 mg/kg), while group F was administered an equivalent 1ml of distilled water. Group A was treated with aqueous leaf extract (FL) (400 mg/kg/day), group B was treated with aqueous root bark extract (FR) (400 mg/kg/day), group C was treated with a combination of leaf and root bark aqueous extract at a ratio of 1:1 (200 mg: 200 mg/kg/day), and group D was treated with Metformin (150 mg/kg/day), while groups E and F were treated as controls (given only regular food and water). The extracts were administered orally by intragastric intubation, and treatment lasted for three weeks, with the fasting blood sugar measured weekly. **Result:** At the end of the experimental period, the consecutive treatment of the animals with the leaf and root bark extracts of *Ficus exasperata* resulted in a significant reduction ( $p < 0.05$ ) in the blood sugar of the test animal groups A ( $73.4 \pm 2.64$  mg/dL), B ( $66 \pm 3.29$  mg/dL), and C ( $80 \pm 4.29$  mg/dL) compared to the control group E ( $610 \pm 15.5$  mg/dL) (diabetically induced but not treated). These results also compare favourably with those of animals treated with the standard drug Metformin (150mg/kg/day), group D ( $57 \pm 7.02$  mg/dL), and the control group F ( $74.4 \pm 2.54$  mg/dL) (not diabetically induced and not treated). **Conclusion:** The results suggest that the aqueous root extract of *Ficus exasperata* may have a slightly higher hypoglycemic effect than the aqueous leaf extract of the plant ( $p < 0.05$ ). More importantly, the result indicates that the combination of the leaf and root extract of *Ficus exasperata*, as demonstrated in group C ( $80 \pm 4.29$  mg/dL) and as commonly used locally, may not hold any advantage over the use of either the leaf, as in group A ( $73.4 \pm 2.64$  mg/dL), or root bark extract, as in group B ( $66 \pm 3.29$  mg/dL), of the plant.

**Keywords:** *ethnomedicinal; Ficus exasperata; diabetes; Wistar rats; Alloxan*

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## 1. Introduction

Diabetes mellitus (DM) is a chronic carbohydrate metabolism disease that is characterized by the impaired ability of the body to produce or respond to insulin and thereby maintain proper levels of sugar (glucose) in the blood (Frederick et al.,

2024) [1]. Diabetes is one of the four non-communicable diseases that are the leading causes of disability-adjusted life years (DALYs) (Jianran et al., 2023) [2].

Diabetes mellitus is basically classified into two categories: type 1 and 2. Type 2 diabetes is the most common type of DM, and usually occurs in adults; it occurs when the body becomes resistant to insulin or does not make enough insulin. Over the past three decades, the prevalence of type 2 diabetes has risen dramatically in countries of all income levels. Type 1 diabetes, once known as juvenile diabetes or insulin-dependent diabetes, is a chronic condition in which the pancreas produces little or no insulin by itself. Type 1 diabetes is usually diagnosed in children and young adults, but it can develop at any age. The other variant of type 2 diabetes includes gestational diabetes, which usually occurs in women during pregnancy.

According to the World Health Organization Report, about 422 million people worldwide are living with diabetes, the majority living in low- and middle-income countries. The dramatic increase in diabetes has occurred in all countries, and in rural as well as urban areas. Accurate global, regional, and country-level estimates and projections of diabetes prevalence are necessary for prevention and treatment strategies to be planned and monitored and to assess progress toward reaching the targets set by the Global Action Plan for Non-Communicable Diseases and the Sustainable Development Goals (Ogurtsova et al., 2017) [3].

The WHO global report from 2014 further revealed that 8.5% of adults aged 18 years and older had diabetes. In 2019, diabetes was the direct cause of 1.5 million deaths and 48% of all deaths due to diabetes occurring before the age of 70 years (WHO Report 2019). The International Diabetes Federation estimated that globally, about 463 million people aged 20 years and older are living with diabetes, and this number is expected to increase to 700.2 million by 2045 (Saedi et al., 2019) [4].

Additionally, there has been a reported significant increase in the mortality rate of diabetes over the past few years; between 2000 and 2019, there was a 3% increase in age-standardized mortality rates from diabetes. In lower-middle-income countries, the mortality rate due to diabetes has increased by 13% (Global Burden Report 2020) [5].

In its usual update report entitled “Diabetes the silent killer in Africa,” the WHO reported that the regional prevalence of DM in Africa is 4.5%, and fifty-four percent of people living with diabetes in the region are undiagnosed, the highest proportion of all IDF regions.

Type 2 diabetes occurrence has recently been growing in Sub-Saharan Africa (SSA), along with the epidemiological transition. Fast-paced urbanization, urban poverty, and globalization are the key factors in this transition. The prevalence is still low in some rural populations, but high prevalence has been observed in people living in urban areas. Infectious and chronic non-communicable diseases are major contributing causes of morbidity and mortality, giving rise to a double burden, with all social classes affected.

Wealthy people have a higher risk of chronic diseases while poor individuals experience higher risks of infectious diseases (Yach et al., 2004) [6].

Diabetes is one of the most common diseases in Nigeria. It is so popular that almost all the major tribes have local names for this disorder. Among the Yoruba-speaking dwellers in the southwest, it is usually referred to as “Ito Sugar” (sugar in urine); it is also called “Atogbe” in the Igbo language, it is called “Orja mamiri” and “Ciwon Sukari” in the Hausa language, all indicating the symptoms or effects of the disease.

A previous study revealed that the overall pooled prevalence of DM was 5.77% (95% CI 4.3–7.1). The pooled prevalences of DM in the six geopolitical zones of Nigeria were 3.0% (95% CI 1.7–4.3) in the northwest, 5.9% (95% CI 2.4–9.4) in the northeast, 3.8% (95% CI 2.9–4.7) in the north-central zone, 5.5% (95% CI 4.0–7.1) in the southwest, 4.6% (95% CI 3.4–5.9) in the southeast, and 9.8% (95% CI 7.2–12.4) in the south-south zone. Risk factors for the pooled prevalence of DM were a family history of DM (4.6%; 95% CI 3.5–5.6); urban dwelling (6.0%; 95% CI 4.3–7.8); unhealthy dietary habits (8.0%; 95% CI 5.4–10.5); cigarette smoking (4.4%; 95% CI 1.3–10.2); older age (6.6%; 95% CI 4.5–8.7); physical inactivity (4.8%; 95% CI 3.2–6.4); and obesity (5.3%; 95% CI 3.8–6.9), (Andrew et al., 2018) [7].

The aim of this study is to evaluate the hypoglycemic effect of the aqueous extract of the leaf and root bark of *Ficus exasperata* Vahl (Moraceae). The chief objective is to determine the hypoglycemic activity of the aqueous extract of the root bark of *Ficus exasperata* in Wistar albino rats and to determine if there exists a synergy in the hypoglycemic effect between the aqueous extract of the leaf and root bark of the plant, thus justifying its local use.

## 2. Materials and Methods

### 2.1. Plant Material

Fresh leaves and roots of *Ficus exasperata* were collected in an overgrown bush area at Magboro, a suburban town in Obafemi-Owode Local Government Area, Ogun State, Nigeria. The leaves were identified by a taxonomist, Dr Nodza G. I., of the Department of Botany, University of Lagos, with the identification number 100745.

### 2.1.1. Preparation of the Aqueous Extract of the Leaf and Root Bark of *Ficus exasperata*

The fresh leaves were shade-dried, while the root bark was sequestered from the root and sun-dried until constant weight was achieved. About 1 kg each of the dried leaves and root bark was ground into fine powder using separate commercial blenders. A mass of 690 g of the powdered leaves and 830 g of the powdered root bark were macerated (separately) in distilled water and extracted twice, on each occasion with 2.5 L of distilled water at room temperature for 48 h (Adewole et al., 2011) [8]. The combined aqueous extract solubles of each extract were concentrated to dryness in a boiling water bath at 100 °C. The resulting sticky, brown, crude extract was refrigerated in a glass container at 2–8 °C. Aliquot portions of the crude extract were weighed and dissolved in distilled water for use on each day of the experiment.

### 2.1.2. Experimental Animals

The research was carried out at the College of Medicine, University of Lagos, in compliance with the Animal Care and Use Research Ethics Committee of the Institution, with the approval number CMUL/ACUREC/03/24/1389.

This study was carried out using male and female Wistar rats (100–180 g). The animals were acquired and housed in the Animal House of the Anatomy Department, College of Medicine, University of Lagos, under standard laboratory conditions of light, temperature, and humidity. Animal grooming and collection and testing of blood samples were conducted as described by Akhtar et al. (1981) [9]. The animals were given standard rat chow and tap water for drinking ad libitum.

### 2.1.3. Chemical and Devices

Alloxan monohydrate (1,3-Diazinane-2,4,5,6-tetrone) employed in the course of the experiment was produced by May and Baker Ltd., Dagenham, England. Metformin (Diabetmin 500 mg) made by HOVID Bhd., Ipoh, Malaysia, was purchased at a pharmacy store in Idi-Araba, Lagos State, Nigeria. The blood glucose measurements were taken using an Accu-chek glucometer, which was made by Roche Diagnostics, Mannheim, Germany.

### 2.1.4. Oral Glucose Tolerance Testing

The oral glucose tolerance test was carried out according to the method described by Taiwo et al. (2009) [10]. A total of 20 male and female Wistar rats weighing between 100 and 150 g were used for this experiment. In summary, the animals were divided into 4 groups of five in each group and kept in standard rat cages where they were adequately fed with free access to water. All the animals in each group were fasted for 12 h, after which groups I–III were administered various plant extracts through oral intragastric intubation: group I was given leaf extract of *Ficus exasperata* at 400 mg/kg, group II was given root extract at 400 mg/kg, and group III was administered the combination of leaf and root extract at 200:200 mg/kg. The control group IV was given distilled water at 10 mL/kg. The blood glucose of the animals was measured immediately after this.

A period of 30 min later, the animals were administered a loading dose of oral glucose at 3 g/kg. The blood glucose was measured using an Accu-chek glucometer through repetitive puncture of the tips of the animals' tails at 30 min, 60 min, 90 min, and 120 min.

### 2.1.5. Hypoglycemic Testing of the Extracts

#### Grouping of Animals

A method similar to Toyin et al., 2014 [11] was used in this study. A total of 40 male and female Wistar rats (100–180 g) were used for this experiment. The animals were divided into 6 groups (A, B, C, D, E, and F) with seven per group. The rats were fasted for 12 h (overnight) ad libitum and the blood glucose was measured by venipuncture of the tips of the tails of the animals. This blood glucose was taken as the baseline.

### 2.1.6. Induction of Experimental Diabetes and Treatment

Groups A–E were induced with diabetes through the peritoneal administration of Alloxan at 150 mg/kg. After four hours, the blood glucose was measured again, and this blood glucose was taken as the zero-hour value. Only the animals with blood glucose levels of 200 mg/dL and above were classed as diabetic and selected for this experiment. The animals were stabilized and fed adequately with regular diets ad libitum, and treatment was commenced after 12 h.

Group A was treated with leaf extract at 400 mg/kg/day.

Group B was treated with root extract at 400 mg/kg/day.

Group C was treated with a combination of leaf and root extract at a ratio of 1:1 (200 mg: 200 mg/kg/day).

Group D was treated with Metformin at 150 mg/kg/day.

Group E was treated with an equal volume of distilled water.

Group F was not induced and not treated. The blood glucose of the animals was measured once weekly on days 7, 14, and 21. The weight, behaviour, and reactions of the animals were also observed throughout the course of the experiment.

#### 2.1.7. Statistical Analysis

Data obtained from 'control' and 'test' (treated) rats were pooled and expressed as means ( $\pm$ SEM), and analyzed using repeated measures of variance. The differences between the means were analyzed statistically with a one-way analysis of variance (ANOVA; 95% confidence interval), SPSS 26 supplemented by a post hoc test (Tukey's Test) was used for the analysis. Values of  $p \leq 0.05$  were taken to imply statistical significance (Adewole et al., 2011) [8].

### 3. Results

Group A: treated with leaf extract at 400 mg/kg/day.

Group B: treated with root extract at 400 mg/kg/day.

Group C: treated with a combination of leaf and root extract at a ratio of 1:1 (200 mg: 200 mg/kg/day).

Group D: treated with Metformin at 150 mg/kg/day.

Group E: treated with an equal volume of distilled water.

Group F: not induced and not treated (given regular meals and distilled water).

Keys:

BWT: Body weight

NINT: Not Induced Not Treated

INT: Induced Not Treated

FL: Aqueous extract of the leaf of *Ficus exasperata*

FR: Aqueous extract of the root bark of *Ficus exasperata*

FST: Standard Treatment with Metformin

F 1:1: Treated with equal ratio of the aqueous extracts of the leaf and root bark of *F. exasperata*

### 4. Discussion

The acceptance and use of herbal medicines around the world continue to surpass expectations. The pervasive health technology evolution and cutting-edge developments have further improved interest in phytomedicines rather than diminishing it. Most of the current research on medicinal plants has ended up appraising or justifying their use locally for various diseases.

The results of this research (**Table 1** and **Table 2**) indicate that the aqueous extract of the leaf and root bark of *Ficus exasperata* demonstrated a hypoglycemic effect on the experimental animals (Wistar rats). When used separately, (**Table 2, Figure 1**) the leaf and root extract demonstrated a significant hypoglycemic effect ( $p < 0.05$ ), with the root extracts showing a slightly more significant effect than the leaf extract ( $p < 0.05$ ), the combination of the leaf and root extracts at a ratio of 1:1 did not, however, translate to a commensurate improvement (increase) in hypoglycemic activity, although this was administered at a considerably reduced dose of 200 mg of each extract.

**Table 1.** Results of oral glucose tolerance test using aqueous extracts of *Ficus exasperata* on Wistar rats.

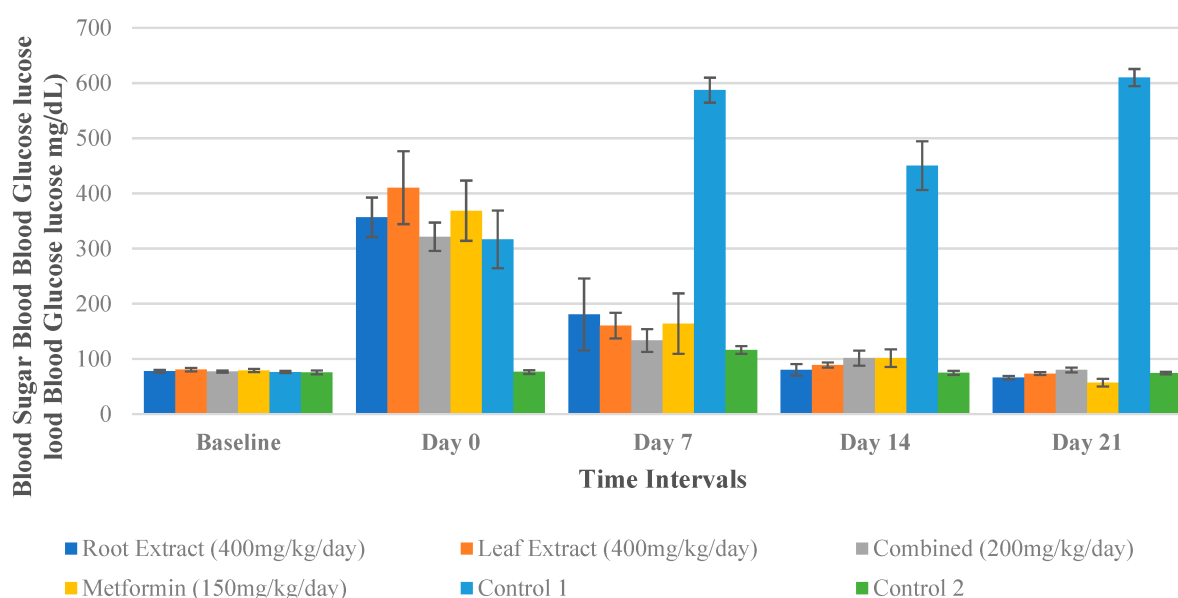
Parameters/Days	Blood Glucose (mg/dL)				
	0 min	30 min	60 min	90 min	120 min
Root Extract at 400 mg/kg (B)	66.6 $\pm$ 2.38	156 $\pm$ 3.62 <sup>a</sup>	108 $\pm$ 3.03 <sup>ab</sup>	90 $\pm$ 2.88 <sup>ab</sup>	72 $\pm$ 1.30 <sup>bcd</sup>
Leave Extract at 400 mg/kg (A)	67.4 $\pm$ 3.37	158 $\pm$ 1.41 <sup>a</sup>	111 $\pm$ 8.89 <sup>ab</sup>	109 $\pm$ 3.36 <sup>ab</sup>	74 $\pm$ 1.70 <sup>bcd</sup>
Combined Leaf and Root at 200 mg/kg (C)	68 $\pm$ 4.15	170 $\pm$ 1.76 <sup>a</sup>	115 $\pm$ 5.59 <sup>ab</sup>	115 $\pm$ 5.45 <sup>ab</sup>	83 $\pm$ 2.51 <sup>bcd</sup>
Distilled Water at 10 mL/kg (D)	70.2 $\pm$ 3.47	193 $\pm$ 3.67 <sup>a</sup>	152 $\pm$ 3.07 <sup>ab</sup>	139 $\pm$ 3.92 <sup>ab</sup>	124 $\pm$ 2.92 <sup>abcd</sup>

<sup>a</sup> =  $p \leq 0.05$  when compared to 0 min, <sup>b</sup> =  $p \leq 0.05$  when compared to 30 min, <sup>c</sup> =  $p \leq 0.05$  when compared to 60 min, <sup>d</sup> =  $p \leq 0.05$  when compared to 90 min.

**Table 2.** Results of hypoglycemic testing of the aqueous extracts of *Ficus exasperata* in Wistar rats.

Parameters/Days	Blood Sugar (mg/dL)				
	Baseline	Day 0	Day 7	Day 14	Day 21
Root Extract at 400 mg/kg/day (b)	77.57 ± 2.72	356.8 ± 35.8 <sup>a</sup>	180.8 ± 64.96 <sup>b</sup>	80.33 ± 10.64 <sup>b</sup>	66 ± 3.29 <sup>b</sup>
Leaf Extract at 400 mg/kg/day (a)	80.57 ± 3.21	410.5 ± 66.14 <sup>a</sup>	160.4 ± 23.19 <sup>b</sup>	88.8 ± 4.68 <sup>b</sup>	73.4 ± 2.64 <sup>b</sup>
Combined Leaf and Root Extract at 200 mg/kg/day (c)	77.14 ± 2.15	321.4 ± 25.78 <sup>a</sup>	133.4 ± 20.65 <sup>b</sup>	101.4 ± 13.68 <sup>b</sup>	80 ± 4.29 <sup>b</sup>
Standard Treatment with Metformin at 150 mg/kg/day (d)	79.14 ± 2.83	368.6 ± 54.63 <sup>a</sup>	164 ± 54.83 <sup>b</sup>	101.4 ± 16 <sup>b</sup>	57 ± 7.02 <sup>b</sup>
Control 1—Induced and Not Treated (e)	76.29 ± 2.09	316.7 ± 52.4 <sup>a</sup>	587.3 ± 22.75 <sup>ab</sup>	450.3 ± 44.13 <sup>a</sup>	610 ± 15.5 <sup>ab</sup>
Control 2—Not Induced and Not Treated (f)	75.4 ± 3.54	76.4 ± 3.56	116.2 ± 6.9 <sup>ab</sup>	74.8 ± 3.89 <sup>c</sup>	74.4 ± 2.54 <sup>c</sup>

<sup>a</sup> =  $p \leq 0.05$  when compared to baseline, <sup>b</sup> =  $p \leq 0.05$  when compared to Day 0, <sup>c</sup> =  $p \leq 0.05$  when compared to Day 7.

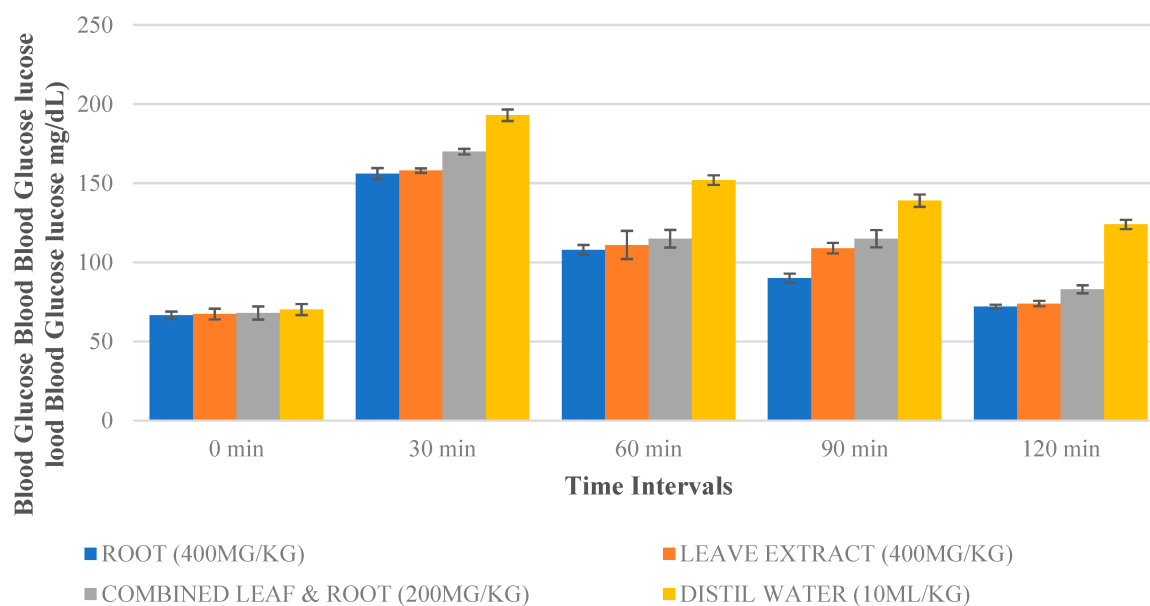


**Figure 1.** A bar chart showing the result of hypoglycemic testing of different extracts of *F. exasperata* on the blood sugar of Wistar rats.

The observations of this study corroborate previous findings (Adewole et al., 2011) [8], which indicated the hypoglycemic effect of the aqueous extract of the leaf of *Ficus exasperata* in Wistar rats. Famobuwa et al., 2019 [12] also reported that Bergapten, a coumarin compound isolated from the root bark of *Ficus exasperata*, demonstrated hypoglycemic activity in Wistar rats. This justifies the use of this plant for the management of diabetes mellitus among local people.

This research investigated for the first time the result of the combination of the leaf and root bark of *F. exasperata*, which is typical of the exact manner it is used for locally in the management of diabetes mellitus. The choice of the aqueous solvent as used in this study also follows the same pattern as is used locally.

However, this study observes that the combination of the leaf and root bark extracts of the plant may not offer any additional benefits, and the results even suggest the opposite; for example, on Day 21 of the experiment (Table 2), the average blood glucose for the leaf, root bark, and combination of leaf and root bark extracts were  $73.4 \pm 2.64$ ,  $66 \pm 3.29$  and  $80 \pm 4.29$  respectively. This implies that the blood sugar after twenty-one days of treatment was lowest in the root extract-treated animals, and highest in the combination of leaf and root extract-treated animals. This observation is in harmony with the preliminary oral glucose tolerance test carried out during this study (Table 1, Figure 2).



**Figure 2.** A bar chart showing the result of the oral glucose tolerance test on Wistar rats (blood glucose in mg/dL treated with different extracts of *F. exasperata*).

The administration of Alloxan at 150mg/kg caused a spike in the blood sugar of the test animals (groups A, B, C, D, and E); all the animals became diabetic within 48 h, with blood sugar levels between 300 and 600 mg/dL (**Table 2**). Sudden loss of weight, polyuria, excessive thirst, lethargy, and even the death of some test animals were observed in this period. This observation was pronounced and continued in the positive control group E (induced and not treated, INT) throughout the course of the experiment. The treatment of the test animals (groups A, B, C, and D) with the aqueous extracts of *F. exasperata* and the standard drug Metformin for 3 weeks reversed this observation, as indicated by the reversal of blood sugar to a normal level (pre-induction) and the return to almost normal life. The animals in the second control group F, which were not induced nor treated, displayed no signs of illness or lethargy throughout the course of the experiment.

Although the specific mechanism of the hypoglycemic action of *Ficus exasperata* remains speculative at present, previous phytochemical studies on some Moraceae families of plants have indicated the presence of several chemical compounds, including alkaloids, flavonoids, saponins, tannins, glycosides, and so forth (Obatomi et al.; 1996) [13].

#### 4.1. Conclusion

Based on the findings of this study, it can be concluded that the aqueous extract of the root bark of *Ficus exasperata* had a significant hypoglycemic effect on the experimental animals (Wistar rats).

Having observed the outcome of the combination of the extract of the leaf and root bark of *Ficus exasperata* in this study, it can be concluded that the combination of both parts of the plant (leaf and root bark), as is used locally for the treatment/management of type 2 diabetes mellitus, may not have any substantive benefits. The use of aqueous extract of either the root bark or leaf of the plant may be more beneficial.

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#### Author contributions

O.O.C. conceptualized and carried out this research under the direct supervision of O.O. All authors have read and agreed to the published version of the manuscript.

## Conflicts of interest

The authors declare no conflicts of interest.

## Data availability statement

The data that support the findings of this study are available from the corresponding author [oluwaseyi4jesus@gmail.com] upon reasonable request. Data sharing is subject to ethical approval and a data sharing agreement due to participant confidentiality.

## Institutional review board statement

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Animal Care and Use Research Ethics Committee of the University of Lagos, College of Medicine, with the approval number CMUL/ACUREC/03/24/1389.

## Informed consent statement

Not applicable.

## Additional information

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## Abbreviations

FR: Aqueous extract of the root bark of *Ficus exasperata*

FL: Aqueous extract of the leaf of *Ficus exasperata*

INT: Induced and not treated

NINT: Not induced and not treated

FST: Standard Treatment with Metformin

F 1:1: A combination of the aqueous extracts of the leaf and root bark of *F. exasperata* at 1:1

DM: Diabetes mellitus

IDF: International Diabetes Federation

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