icrrd
Quality Index Research Journal
INTERNATIONAL CENTER FOR RESEARCH AND RESOURCES DEVELOPMENT article
ISSN Number: 2773-5958, https://doi.org/10.53272/icrrd, www.icrrd.com

Comparative Analysis of the Effects of Selected Medicinal Plants on Gut Microbiota and Glycemic Control in Streptozotocin-Induced Diabetic Rats

Daniel Oyinloye[1 2], Adeleke Osho[1*]

[1] *Biological Sciences Department, College of Natural Sciences, Redeemer's University, Ede., Nigeria*
[2] *Nutrition and Dietetics Department, Applied Sciences, Federal Polytechnic, Ede. Nigeria*

**Corresponding author; Email: oyinloyed7118@run.edu.ng*

Received: 25 May 2024 **Accepted:** 22 August, 2024
Revision: 12 July 2024 **Published:** 01 September 2024. **Vol**-5, **Issue**-3

Cite as: Oyinloye, D.; Osho, A. (2024). Comparative Analysis of the Effects of Selected Medicinal Plants on Gut Microbiota and Glycemic Control in Streptozotocin-Induced Diabetic Rats. *ICRRD Journal, 5*(3), 185-199.

Abstract*:* The study focused on conducting a comparative analysis of the impact of selected medicinal plants on intestinal flora during diabetes management in rats induced with streptozotocin. Thirty male albino rats were utilised for the experiment, with 36 rats subjected to the induction of diabetes using streptozotocin. By injecting streptozotocin intraperitoneally at a dose of 75 mg/kg body weight dissolved in normal saline, diabetes type 2 was induced. Following the induction, the rats were administered a 5% glucose solution to prevent hypoglycemic shock. Blood glucose levels were monitored regularly, and rats above 200 mg/dl were deemed diabetic and added to the study. Glibenclamide 45 mg/kg b.w., Bitter melon, Okra, and akuamma leaves. 200 mg/kg b.w., and leaves were administered daily for 28 days in diabetic rats. Some intestinal taxa changed as a result of streptozotocin-induced diabetes. The percentage of Enterobacteriaceae increased versus Control. Pseudomonas aeruginosa, influenced the quantitative proportion of some intestinal species (Bacillus subtilis, proteus mirabilis, E. coli, shigella flauor). Glibenclamide stimulates the growth of Lactobacilli and Eubacterium spp. But suppresses the G+/G- ratio in small intestinal samples. The results indicated that administering plant extracts significantly reduced blood glucose and a notable presence of microbes suitable for insulin secretion and sugar fermentation. Additionally, the study highlighted the potential of plant extracts to positively impact intestinal flora, suggesting a promising avenue for managing diabetes in streptozotocin-induced rats.

Keywords: Medicinal plants; Diabetes; microflora. Guts

INTRODUCTION

Diabetes Mellitus (DM) disrupts protein, fat, and carbohydrate metabolism, increasing blood sugar levels because of either impaired insulin action (type-2) or insufficient insulin production (type-1). (Mohammed & Tajuddeen, 2022) Although type 2 diabetes and dysfunctional beta cells are related, type 1 diabetes is characterised by immune-mediated death of pancreatic beta cells and is often linked

to obesity and sedentary lifestyles. Globally, diabetes prevalence is rising, especially in developing nations. (Mohammed & Tajuddeen, 2022)Seeking new treatments, medicinal plants are being explored due to their historical use in traditional medicine and demonstrated anti-diabetic properties, although their exact mechanisms are still being researched.(Muralidharan & Linnemann, 2021) The gut microbiota, comprising various microorganisms, influences diabetes development by regulating glucose levels. Changes in gut microbiota can affect insulin sensitivity and glucose metabolism. Medicinal plant extracts have shown potential in modulating gut microbiota composition, but their specific impact on the intestinal flora of diabetic rats remains unclear, necessitating further investigation through comparative studies.(Gonzalez-Rellan et al., 2023; Erez-Burillo et al., 2017; Wan et al., 2022a)

Medicinal plants are increasingly sought after for managing diabetes globally, especially in regions where traditional medicine prevails.(Alam et al., 2022; Milutinović et al., 2021; Wan et al., 2022a, 2022b) While insulin-dependent diabetes relies on medical intervention, non-insulin-dependent cases can be partially managed with herbal products, reflecting a widespread practice.(Awuchi & Kate Echeta, 2020; Lyngbaek et al., 2021) Plants offer potential as dietary supplements and sources for new therapeutic agents. Despite many plants claiming anti-glycemic properties, only a fraction has been thoroughly studied, with even fewer having their active components identified. In Nigeria. (Ezeako et al., 2023) Limited information exists on traditional medicinal plants for diabetes management, highlighting the need for further research.

Around 500–1000 gut microorganisms inhabit the human body, outnumbering human cells tenfold(Ghiamati et al., 2022; Wei et al., 2024). These bacteria possess genes crucial for metabolising carbohydrates, including those indigestible by the host. This metabolic activity is implicated in diabetes development. (Cunningham et al., 2021)Moreover, gut microbes help sustain the function of the barrier in the intestines by supporting the structural integrity of the stomach's lining.(Stolfi et al., 2022) Changes in intestinal permeability, molecular mimicry, and modulation of immune systems are connected to T2DM (Type 2 Diabetes Mellitus). Metabolites produced by gut microbes that affect immunological and metabolic functions include bile acids after amino acid short-chain fatty acids and derivatives—potentially influencing diabetes development.(Salinas et al., 2021) Reduced levels of specific metabolites like fatty acids with a short chain The balance of metabolism can be upset by SCFAs.(Blaak et al., 2020; Portincasa et al., 2022) Furthermore, dysregulated bile acid metabolism affects glucose metabolism pathways. Additionally, innate immunity contributes to how the gut microbiota interacts with diabetes, highlighting the intimate connection between gut flora and diabetes mellitus.

The high prevalence of diabetes poses challenges in healthcare, mainly due to the limitations and side effects of conventional medications.(Choudhury & Devi Rajeswari, 2021) Medicinal plant extracts offer a promising alternative with fewer side effects, affordability, and availability.(Jan et al., 2020) Research indicates that these extracts may modulate microorganisms, potentially impacting insulin secretion. This study compares the effects of medicinal plant extracts and commercial medications on diabetes treatment using animal models. The adoption of these new medicinal plants in diabetes treatment will help to reduce morbidity and mortality and coexisting diseases caused by diabetes. The identified associated microflora will be determined and introduced into the diabetic’s environment to modulate the organisms responsible for sugar breakdown. Wistar rats will be induced with streptozotocin, and

the diabetic rats will be treated with selected remedial plant extracts. The effect of these extracts on the microbiota will be examined.

METHODOLOGY

Materials and Procedures Obtaining Plant Resources

The newly cut leaves of Bitter melon *(Momordica charantia),* Akuamma *(Picralima nitida),* and Okra *(Abelmoschus esculentu)s* were collected randomly from Federal Polytechnic Ede South Campus forests and open fields in the Ede South Osun State of Nigeria. The plants were identified at Moore Plantation Research Institute Ibadan. Oyo State Nigeria. Streptozotocin chemical was imported. The Redeemer's University Animal House is where the wistar rats were bought. Other equipment was obtained from the Microbiology laboratory at Redeemer's University Ede.

Animals used in experiments and the study protocol.

Male Wistar albino rats in a lab setting (245 -255) grams, 6 weeks of age, were obtained from Redeemer's University the Animal House. The Department of Biological Sciences approved all procedures involving experimental animals, and all adhere to the requirements specified under the committee's rules for using and maintaining animals used in experiments and managing the oversight of animal experiments. Ethical Approval was obtained from the Ministry of Health and Public Health Department of Osogbo, Osun state. Nigeria No. OSHRC/PRS/569T/240. The rats were kept in a regulated environment in a wire cage measuring 30 by 13 by 15 centimetres, with a weekly replacement of sawdust substrate and a 12/12 cycle of light and dark with a temperature of $(25\pm2)^0$C. As the experiment continued, the rats were given water at will and a typical commercial pellet diet at a dose of (100–150) gm/kg, per the Animal House manager's recommendation.

Preparation of Aqueous Plant Extract.

Preparation of extract:

Bitter melon, Okra and Akuama fruits are dried powdered according to the method described by (Abebe et al., 2022; Afolabi et al., 2021). Each of the three plants' 200 grammes of leaves was air-dried in the lab before being blended with an electric blender until a powder. The plants' powdered leaves were taken separately and soaked in water for 72 hours at a ratio of 1:10g/v of distilled water in a bowl, which was sieved with muslin cloth. A rotary evaporator filtered and concentrated the extracts under low pressure at 100°C until solid crude extracts were produced. The extracts were then oven-dried to eliminate all traces of solvent. Some extracts were suspended in a 0.5% water solution for the trials.

Figure 1 The pictorial representation of the fresh medicinal plant, Source: Samsung A22 snapshot

Diabetes Induction with Streptozotocin

The (Azad & Sulaiman, 2020a). The technique was to dissolve streptozotocin in a 4.5 pH citrate buffer at 0.1 M concentration. Next, each Group B, C, D, E, and F rat received a 120 mg/kg intraperitoneal dose (body weight) of streptozotocin to develop diabetes as described. by (Azad & Sulaiman, 2020a). Following a 72-hour infusion of streptozotocin, blood glucose levels were assessed (Hernandez et al., 2021), (Min et al., 2021). From day one to day 28, The rats had unrestricted access to drinking water and were fed a regular diet. An Accucheck glucose meter was utilised to confirm if the patient was hyperglycemic or diabetic.

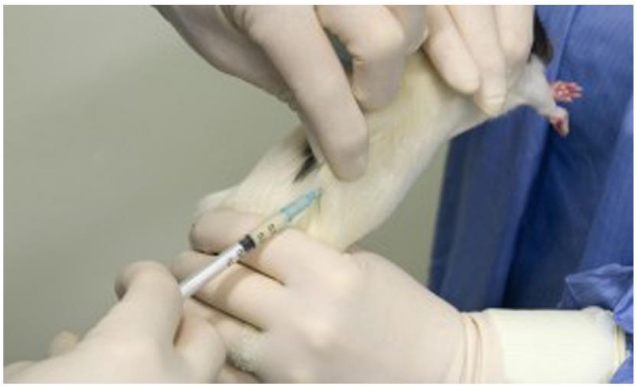

Figure 2. Intraperitoneal injection of STZ, Source: Samsung A22 snapshot

Experimental Design

Design of Experiment 42 male Wistar albino rats was used to carry out this evaluation. Six equal groups of six rats each were created from these rats: A group was the conventional control group, while Group B was given glibenclamide treatment. 100% bitter melon, okra, and akuamma extracts found in Groups C, D, and E. were retained for research.

Administration of Plant Extracts to Albino Rats

The administration of Bitter melon, Okra, and Akuamma extract was re-constituted. Using a micropipette, the extract was given orally (75mg/kg b/w) to the various treatment groups of experimental rats. The administration of the required amount, determined by each rat's body weight, was guaranteed when using a micropipette.(Munyati, 2020)

Figure 3. Administration of plant extract through oral gavage, Source: Samsung A22 snapshot

Testing Blood Glucose Levels

After a 72-hour fast, animals whose blood glucose levels were higher than 200 mg/dl were categorised. as rats with diabetes and enrolled in the study. At intervals of three days, blood samples were obtained from the tip of the tail. A glucometer was used to check blood glucose levels, and the tail vein was cut off without sacrificing the animals (Mechchate et al., 2021), (Azeez et al., 2021).

Blood Glucose Concentration Measurement

Using the strip method, the Accu-Chek glucose counter was used to measure the amounts of glucose in the blood of albino rats (Q. Wei et al., 2019), (Hernandez et al., 2021). The glucometer code and strip were placed inside with an indicator showing it was ready for use. A droplet of blood was extracted after taking a pair of scissors to the tip of the rats' tails. Next, the blood was poured onto one end of the glucometer strip. The reading was taken ten seconds later.

Determination of gut microbes

Rat sacrifice and dissection: The intestines are harvested from the rat using a humane dissection and sacrifice. The intestinal contents, particularly the big and small intestines, were sliced, preserved in a sterile container of saline water, and then brought to the laboratory. After slicing the intestines into smaller pieces, the contents were homogenised. They were then serially diluted for culturing onto agar medium and incubated at 37 °C for a whole day.

Isolation of gut microbes

For isolation determination, various methods were used; the bacteria were sub-cultured to obtain pure colonies, and the listed steps were observed: Gram staining, Biochemical tests (mobility test,

tests for catalase, oxidase, indole, citrate utilisation, and sugar fermentation all these tests were employed to determine the specific microbes present the gut.

Colony count method

Colonial Morphological Examination: Following a 24-hour incubation period at 37°C, the isolated microorganism colonies on agar are examined and described based on their colonial morphological features, which include size, shape, colour, opacity, margin, elevation, and texture, among other things. This procedure is significant and offers insightful information on microbe identification. The colonies were counted using a "Labochema colony counter" machine to count all of the colonies on the agar. The number of viable cells in the sample was determined using the computation of colony-forming units, or CFU.

Statistical Analysis

The One-way analysis of variance was used to evaluate the data (ANOVA) statistically. For tests deemed significant, the least significant difference (LSD) was used next. The means for the five animals in each group were used to express all results.

RESULTS AND DISCUSSION

Blood glucose result

Table 1 Comparative test on blood glucose level of diabetes treatments.

Treatment	week 1	week2	week3	week4
Neg Cntrl	99.1±0.01^{a}	96.2±0.01^{a}	97.0±0.00^{a}	97.0±0.00^{a}
Pos Cntrl	90.2±0.02^{a}	78.1±0.02^{b}	54.1±0.04^{c}	37.0±0.00^{d}
TMEo	74.0±0.01^{a}	51.0±0.01^{b}	34.0±0.03^{c}	21.0±0.00^{d}
TMEa	66.0±0.00^{a}	47.0±0.01^{b}	26.0±0.02^{c}	24.0±0.01^{d}
TMEb	92.1±0.00^{a}	68.0±0.01^{b}	46.0±0.00^{c}	23.0±0.02^{d}

-ve cntrl = Negative control, +ve cntrl = Positive control, TMEo = Treated medicinal extract of Okro, TMEa = Treated medicinal extract Akuamma, TMEb = Treated medicinal extract Bitter melon. According to Duncan's multiple range test, mean and std (n = 6) with the same letter in a column within the same treatment regime are statistically similar at $p< 0.05$.

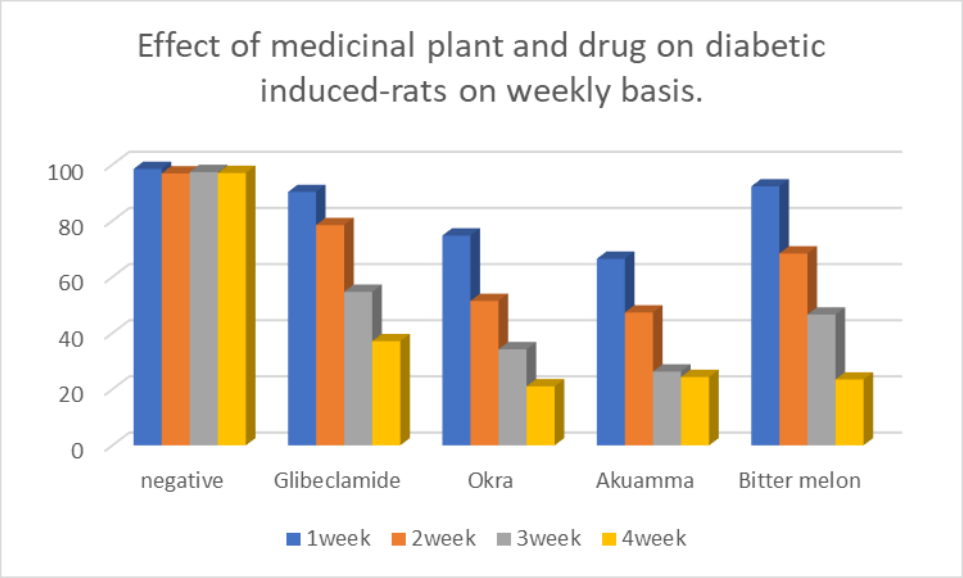

Figure 4. Graphical representation of medicinal plant and drug on diabetic-induced rats

Colony count

Table 2 Comparative test of gut microflora colony counts of diabetes treatments.

Treatment	week 1	week2	week3	week4
Neg Cntrl	79.1±0.20^{a}	80.2±0.43^{a}	78.0±0.43^{a}	70.0±0.21^{a}
Pos Cntrl	83.2±0.23^{d}	72.1±0.85^{c}	58.1±0.85^{b}	41.0±0.11^{a}
TMEo	86.0±0.43^{d}	70.0±0.43^{c}	61.0±0.34^{b}	32.0±0.14^{a}
TMEa	91.0±0.78^{d}	82.0±0.32^{c}	75.0±0.21^{b}	43.0±0.01^{a}
TMEb	67.1±0.32^{d}	50.0±0.21^{c}	42.0±0.32^{b}	38.0±0.03^{a}

-ve cntrl = Negative control, +ve cntrl = Positive control, TMEo = Treated medicinal extract of Okro, TMEa = Treated medicinal extract Akuamma, TMEb = Treated medicinal extract Bitter melon. According to Duncan's multiple range test, mean and std (n = 6) with the same letter in a column within the same treatment regime are statistically similar at $p< 0.05$.

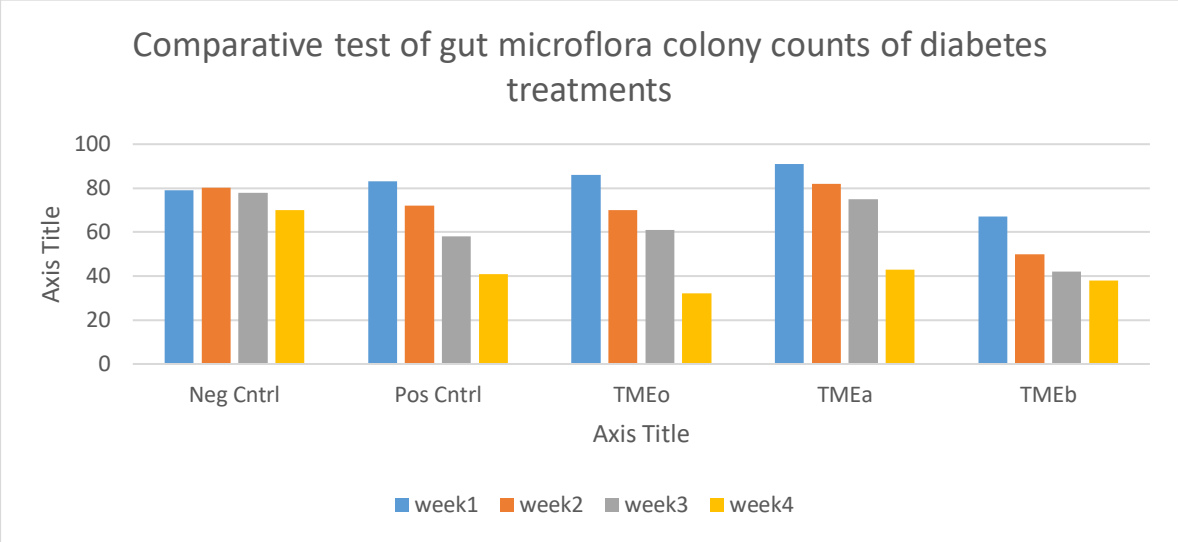

Figure 5 Graphical representation of colony count in the gut microflora of treated diabetes

Table 3 Percentage reduction of intestinal microflora in diabetes-induced rat treatment day1- 28

Intestinal microbes	Day1	Day28	% reduction
-ve cntrl	79	70	13
+ve cntrl	83	41	42
TMEo	86	32	62
TMEa	91	42	53
TMEb	63	38	40

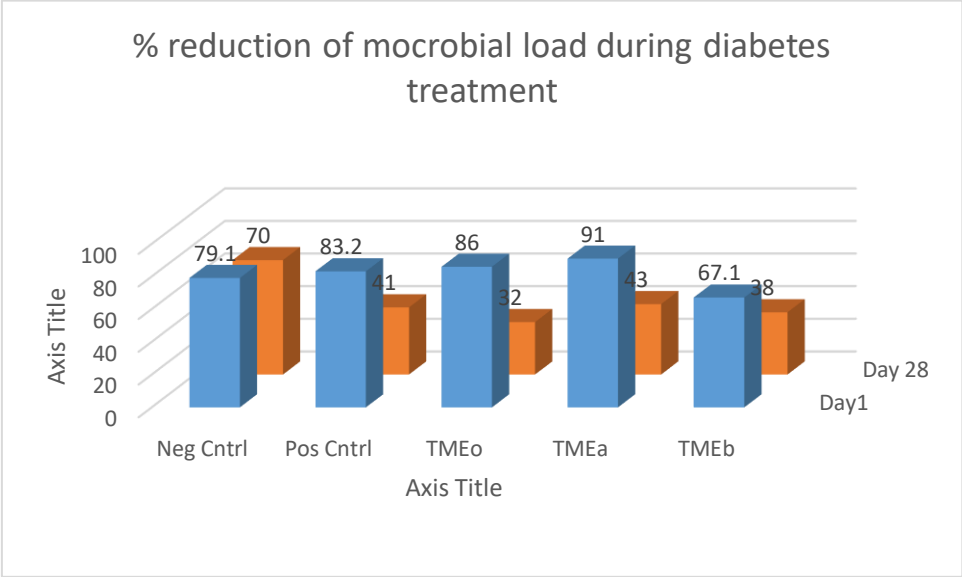

Figure 6 Percentage reduction in the microflora of diabetes-treated rats using plant extracts.

Table 4 Different isolation of gut microorganisms identified from diabetes treatments.

Treatments	primary organisms identified.
-ve Cntrl	*Pseudomonas aeruginosa, Bacillus subtilis, Proteus mirabilis, Proteus mirabilis, Escherichia coli, Staphylococcus aureus,*
+ve Cntrl	*Proteus mirabilis, Pseudomonas aeruginosa, Escherichia coli*
TMEo	*Pseudomonas aeruginosa, Escherichia coli, Enterococcus faecalis,*
TMEa	*Pseudomonas aeruginosa, Staphylococcus aureus, Proteus mirabilis*
TMEb	*Shigella flexneri, Staphylococcus aureus, Pseudomonas aeruginosa, Bacillus subtilis, Streptpcoccus spp*

Note: -ve cntrl = Negative control, +ve cntrl = Positive control, TMEo = Treated medicinal extract of Okro, TMEa = Treated medicinal extract Akuamma, TMEb = Treated medicinal extract Bitter melon.

DISCUSSIONS

Rats in the trials did not show any overt indicators of poisoning, and no fatalities occurred Due to medicinal plant extracts and glibenclamide administration. The blood level of blood sugar reduction: The week that the experiment begins shows insignificant blood sugar reduction compared to other weeks that show a high level of reduction. There is no significant difference in the negative control across the experimental weeks; this aligns with the findings of (Azeez et al., 2021) and (Mechchate et al., 2021). Also, the other treatment indicates a higher level of sugar reduction across the experimental period, which is also in line with the research of (Hernandez et al., 2021; Min et al., 2021). This was in consonant with a study by (Alema et al., 2020; Bari et al., 2020). After the groups' microflora was counted, all five treated groups in this study showed greater mean and standard deviation analyses (compared to Day 1); the week 1 final mean colony counts were higher than the weeks 2, 3, and 4. This result is following (Azad & Sulaiman, 2020b; Buddhakala & Talubmook, 2020)

The findings indicate that when the medicinal plant extract was given to the experimental rats, there was a greater degree of intestinal microbiota reduction. This is consistent with research by (Nikolic et al., 2022) as well. Also, there was a significant decrease in the antibiotic medication used to treat diabetes. This ranges from week 1 to week 4 of the experimental period. (83.20±0.23 – 41.0±0.11) table1. The percentage reduction is higher by 42% in Table 2 than the work done by (Tu et al., 2020)

Following the study's 28-day medicinal plant extracts administration, total intestinal microflora was reduced in all three colon sample analyses (86.00 and 61.00 reductions) (Table 1) in Okro extract treatment, and Akuamma treatments also showed a significant level of reduction from 91.01 – 43.00) similar result was obtained in the treatment of Bitter melon treatment with the range of 67.10 – 38.00) The high microflora counts observed on week 1 of the experiment from the colon samples might have been contaminated with coliform by the animals or the cage floor. Cecal contents showed the most significant reduction in intestinal microbiota (63%) following okro therapy.

Table 3 reveals the results of the microorganisms identified in the guts of the experimental rats. The group without streptozotocin has the same group of organisms from week 1 to the last week 4. *Bacillus subtilis, Proteus mirabilis, Staphylococcus aureus, Escherichia coli, and Pseudomonas aeruginosa.* While the group with glibenclamide, Okro extract, Akuamma extracts, and bitter melon extract has a fluctuation in the species of microorganisms in the guts, *Escherichia coli, Proteus mirabilis, Pseudomonas aeruginosa* were found at the last week of the experiment in the glibenclamide treatment. *Pseudomonas aeruginosa, Enterococcus faecalis, and Escherichia coli* were found in the treatment of okro. *Pseudomonas aeruginosa, Proteus mirabilis, Staphylococcus aureus.* It was found in the intestines of rats treated with Akuamma, and Staphylococcus aureus, Bacillus subtilis, Pseudomonas aeruginosa, Shigella flexneri, and Streptococcus spp. was found in the treatment of bitter melon. These results support the research work of (A et al., 2021).(Aabed et al., 2021)

Okro, Spondias mombin, and bitter melon are traditionally used plant extracts with anti-diabetic properties. Recent studies have also investigated their effects on the gut microbiota and the potential for this to play a role in diabetes treatment. (Malongane et al., 2024) examined how bitter melon and okro affected the gut microbiome in streptozotocin-induced diabetic rats. The study found that both plant extracts improved glucose tolerance and reduced blood glucose levels. Additionally, both Okro and bitter melon increased the quantity of good bacteria, such as Bifidobacterium and Lactobacillus, while reducing the amount of harmful bacteria, including Clostridium and Escherichia coli. However, compared to bitter melon, okro was more successful in modifying the bacteria in the gut, leading to a more significant rise in advantageous bacteria and a more considerable drop in harmful bacteria. (Agboola et al., 2021)

Another study compared the effects of Spondias mombin and bitter melon on the gut microbiota in rats given alloxan to develop diabetes. According to the survey, both plant extracts decreased blood glucose levels and enhanced glucose tolerance. Furthermore, Spondias mombin and bitter melon reduced the amounts of harmful bacteria like Enterococcus and Staphylococcus while boosting the population of beneficial bacteria such as Lactobacillus and Bifidobacterium. However, Spondias mombin was more effective in modulating the gut microbiota, with a tremendous increase in beneficial bacteria and a more significant decrease in harmful bacteria than bitter melon (Jacob et al., 2021.; JvS, 2020)

The remedial plant extract shows the microbes that can promote insulin secretion and stabilise blood glucose, as suggested by (Nikolic et al., 2022; Q. Wei et al., 2019) Also, all three plant extracts have been demonstrated to have anti-diabetic qualities. The available information points to Okro and Spondias mombin as more beneficial than bitter melon. However, more research is needed to fully understand how these plant extracts modulate the gut microbiota and their potential for use in diabetes management.

CONCLUSION

The study's findings indicate that local plant extracts can be used as an alternative treatment for diabetes instead of expensive drugs. The study found that the gut microflora In all of them, there was no apparent difference between any of the therapy groups. They indicated that the natural plant extracts did not negatively impact the gut microbiome.

These findings are significant as they suggest that natural plant extracts help stabilize the gram-positive microbes in the guts. These helps ferment and increase insulin production and can be used to

manage diabetes without causing any harm to the microbiome of the gut, which is essential for preserving general health.

Based on the research, it can be concluded that okra extracts, akuamma extracts, and bitter melon extracts can potentially be medicinal plants for treating diabetes. These extracts have been found to exhibit anti-diabetic properties, which may make them effective in managing blood glucose levels in individuals with diabetes.

Furthermore, the study has revealed that these plant extracts have potential, such as Glipalamide, a commonly used antibiotic in diabetes treatment. The microbes in the gut of diabetes rats using glipalamide are also present in the remedial plant extracts. This indicates that these organic plant extracts can serve as a substitute for synthetic drugs to treat diabetes.

These medicinal plants are available locally and can be afforded by low-income people for diabetes treatments.

Acknowledgements: Tertiary Education Trust Fund Scholarship grant FASTS/POLY/OSUN/TSAS/2022/ VOL.1 Nigeria Government

Funding: The research did not receive financial assistance from any funding entity.

Conflicts of Interest: The author has no conflicts of interest to disclose concerning this study.

Declarations: This manuscript has not been published to any other journal or online sources.

Data Availability: The author has all the data employed in this research and is open to sharing it upon reasonable request.

References

Aabed, K., Moubayed, N., & Alzahrani, S. (2021). Antimicrobial resistance patterns among different Escherichia coli isolates in the Kingdom of Saudi Arabia. *Saudi Journal of Biological Sciences*, *28*(7), 3776–3782. https://doi.org/10.1016/j.sjbs.2021.03.047

Abebe, A., Hilawea, K. T., Mekonnen, A., Tigineh, G. T., Sitotaw, B., Liyew, M., & Wubieneh, T. A. (2022). Assessment on antioxidant activity of the aqueous leaf extracts of Combretum microphyllum and the effect of Co(II)-leaf extract complex on antibacterial activity of leaf extracts of the plant material. *Scientific African*, *18*. https://doi.org/10.1016/j.sciaf.2022.e01432

Afolabi Olajide, J., Simon-Oke Iyabo, A., & Oladokun Oluwatobiloba, I. (2021). Antiplasmodial Activity of Ethanolic Extract of Neem Leaf (Azadirachta indica) in Albino Mice Infected with Plasmodium berghei. *International Archives of Clinical Pharmacology*, *7*(1). https://doi.org/10.23937/2572-3987.1510024

Agboola, J. O., Øverland, M., Skrede, A., & Hansen, J. Ø. (2021). Yeast as major protein-rich ingredient in aquafeeds: a review of the implications for aquaculture production. In *Reviews in Aquaculture* (Vol. 13, Issue 2, pp. 949–970). John Wiley and Sons Inc. https://doi.org/10.1111/raq.12507

Alam, S., Sarker, M. M. R., Sultana, T. N., Chowdhury, M. N. R., Rashid, M. A., Chaity, N. I., Zhao, C., Xiao, J., Hafez, E. E., Khan, S. A., & Mohamed, I. N. (2022). Antidiabetic Phytochemicals From Medicinal

Plants: Prospective Candidates for New Drug Discovery and Development. In *Frontiers in Endocrinology* (Vol. 13). Frontiers Media S.A. https://doi.org/10.3389/fendo.2022.800714

Alema, N. M., Periasamy, G., Sibhat, G. G., Tekulu, G. H., & Hiben, M. G. (2020). Antidiabetic activity of extracts of terminalia brownii fresen. Stem bark in mice. *Journal of Experimental Pharmacology*, *12*, 61–71. https://doi.org/10.2147/JEP.S240266

Awuchi, C. G., & Kate Echeta, C. (2020). Diabetes and the Nutrition and Diets for Its Prevention and Treatment: A Systematic Review and Dietetic Perspective Citation Chinaza Godswill Awuchi, Chinelo Kate Echeta, Victory Somtochukwu Igwe. Diabetes and the Nutrition and Diets for Its Prevention and Treatment: A Systematic Review and Dietetic Perspective. In *Health Sciences Research* (Vol. 6, Issue 1). http://www.aascit.org/journal/hsr

Azad, A. K., & Sulaiman, W. M. A. W. (2020a). Antidiabetic effects of P. macrocarpa ethanolic fruit extract in streptozotocin-induced diabetic rats. *Future Journal of Pharmaceutical Sciences*, *6*(1). https://doi.org/10.1186/s43094-020-00073-7

Azad, A. K., & Sulaiman, W. M. A. W. (2020b). Antidiabetic effects of P. macrocarpa ethanolic fruit extract in streptozotocin-induced diabetic rats. *Future Journal of Pharmaceutical Sciences*, *6*(1). https://doi.org/10.1186/s43094-020-00073-7

Azeez, S., Jafar, S., Aziziaram, Z., Fang, L., Mawlood, A., & Ercisli, M. (2021). Insulin-producing cells from bone marrow stem cells versus injectable insulin for the treatment of rats with type I diabetes. *Cellular, Molecular and Biomedical Reports*, *1*(1), 42–51. https://doi.org/10.55705/cmbr.2021.138888.1006

Bari, Md. W., Islam, Md. M., Khatun, M., Sultana, M. J., Ahmed, R., Islam, A., Hossain, Md. I., Rahman, Md. M., & Islam, M. A. (2020). Antidiabetic effect of Wedelia chinensis leaf extract in alloxan induced Swiss albino diabetic mice. *Clinical Phytoscience*, *6*(1). https://doi.org/10.1186/s40816-020-00197-6

Blaak, E. E., Canfora, E. E., Theis, S., Frost, G., Groen, A. K., Mithieux, G., Nauta, A., Scott, K., Stahl, B., van Harsselaar, J., van Tol, R., Vaughan, E. E., & Verbeke, K. (2020). Short chain fatty acids in human gut and metabolic health. In *Beneficial Microbes* (Vol. 11, Issue 5, pp. 411–455). Wageningen Academic Publishers. https://doi.org/10.3920/BM2020.0057

Buddhakala, N., & Talubmook, C. (2020). Toxicity and antidiabetic activity of ethanolic extract of Sphagneticola trilobata (L.) Pruski flower in rats. *Journal of Ethnopharmacology*, *262*. https://doi.org/10.1016/j.jep.2020.113128

Choudhury, A. A., & Devi Rajeswari, V. (2021). Gestational diabetes mellitus - A metabolic and reproductive disorder. In *Biomedicine and Pharmacotherapy* (Vol. 143). Elsevier Masson s.r.l. https://doi.org/10.1016/j.biopha.2021.112183

Cunningham, A. L., Stephens, J. W., & Harris, D. A. (2021). Gut microbiota influence in type 2 diabetes mellitus (T2DM). In *Gut Pathogens* (Vol. 13, Issue 1). BioMed Central Ltd. https://doi.org/10.1186/s13099-021-00446-0

Ezeako, E. C., Nworah, F. N., & Osuji, D. O. (2023). Phytocompounds, antioxidant potential, and inhibitory actions of ethanolic leaf fraction of Sida linifolia Linn. (Malvaceae) on enzymes linked to inflammation, diabetes, and neurological disorders. *Future Journal of Pharmaceutical Sciences*, *9*(1). https://doi.org/10.1186/s43094-023-00527-8

Ghiamati Yazdi, F., Barner Dalgaard, L., Li, Q., Ruscheweyh, H. J., Thøgersen, R., Christine Bertram, H., Hansen, M., & Schwab, C. (2022). Long-term daily high-protein, drained yoghurt consumption alters abundance of selected functional groups of the human gut microbiota and fecal short-chain fatty acid profiles in a cohort of overweight and obese women. *Journal of Functional Foods*, *93*. https://doi.org/10.1016/j.jff.2022.105089

Gonzalez-Rellan, M. J., Fernández, U., Parracho, T., Novoa, E., Fondevila, M. F., da Silva Lima, N., Ramos, L., Rodríguez, A., Serrano-Maciá, M., Perez-Mejias, G., Chantada-Vazquez, P., Riobello, C., Veyrat-Durebex, C., Tovar, S., Coppari, R., Woodhoo, A., Schwaninger, M., Prevot, V., Delgado, T. C., … Nogueiras, R. (2023). Neddylation of phosphoenolpyruvate carboxykinase 1 controls glucose metabolism. *Cell Metabolism*, *35*(9), 1630-1645.e5. https://doi.org/10.1016/j.cmet.2023.07.003

Hernandez, J. O., An, J. Y., Combalicer, M. S., Chun, J. P., Oh, S. K., & Park, B. B. (2021). Morpho-Anatomical Traits and Soluble Sugar Concentration Largely Explain the Responses of Three Deciduous Tree Species to Progressive Water Stress. *Frontiers in Plant Science*, *12*. https://doi.org/10.3389/fpls.2021.738301

Jacob, F., Promise, ;, Ugben, O., Great, E. &, & Akujuru, C. A. (n.d.). *Poverty Alleviation Programme And Community Development In Nigeria: A Study Of Implementation Of SEEFOR Project In Rivers State, 2013-2020*. www.seahipublications.org

Jan, H. A., Jan, S., Bussmann, R. W., Wali, S., Sisto, F., & Ahmad, L. (2020). Complementary and alternative medicine research, prospects and limitations in Pakistan: A literature review. In *Acta Ecologica Sinica* (Vol. 40, Issue 6, pp. 451–463). Science Press. https://doi.org/10.1016/J.CHNAES.2019.12.005

JvS. (2020). *Phase 1 Cultural Heritage Impact Assessment: THE NEWLY CONSTRUCTED DAM ON THE FARM BERGVIEW 15150, SOUTHWEST OF WINTERTON IN THE OKHAHLAMBA LOCAL MUNICIPALITY, KWAZULU-NATAL PROVINCE*.

Lyngbaek, M. P. P., Legaard, G. E., Bennetsen, S. L., Feineis, C. S., Rasmussen, V., Moegelberg, N., Brinkløv, C. F., Nielsen, A. B., Kofoed, K. S., Lauridsen, C. A., Ewertsen, C., Poulsen, H. E., Christensen, R., Van Hall, G., Karstoft, K., Solomon, T. P. J., Ellingsgaard, H., Almdal, T. P., Pedersen, B. K., & Ried-Larsen, M. (2021). The effects of different doses of exercise on pancreatic β-cell function in patients with newly diagnosed type 2 diabetes: study protocol for and rationale behind the “DOSE-EX” multi-arm parallel-group randomised clinical trial. *Trials*, *22*(1). https://doi.org/10.1186/s13063-021-05207-7

Malongane, F., Phoswa, W. N., & Berejena, T. (2024). The effect of indigenous African Diet on inflammatory markers linked to Type 2 Diabetic Mellitus. In *Human Nutrition and Metabolism* (Vol. 35). Elsevier B.V. https://doi.org/10.1016/j.hnm.2023.200236

Mechchate, H., Es-Safi, I., Amaghnouje, A., Boukhira, S., Alotaibi, A. A., Al-Zharani, M., Nasr, F. A., Noman, O. M., Conte, R., Amal, E. H. E. Y., Bekkari, H., & Bousta, D. (2021). Antioxidant, anti-inflammatory and antidiabetic proprieties of LC-MS/MS identified polyphenols from coriander seeds. *Molecules*, *26*(2). https://doi.org/10.3390/molecules26020487

Milutinović, M., Dimitrijević-Branković, S., & Rajilić-Stojanović, M. (2021). Plant Extracts Rich in Polyphenols as Potent Modulators in the Growth of Probiotic and Pathogenic Intestinal Microorganisms. *Frontiers in Nutrition*, *8*. https://doi.org/10.3389/fnut.2021.688843

Min, Q., Marcelis, L. F. M., Nicole, C. C. S., & Woltering, E. J. (2021). High Light Intensity Applied Shortly Before Harvest Improves Lettuce Nutritional Quality and Extends the Shelf Life. *Frontiers in Plant Science*, *12*. https://doi.org/10.3389/fpls.2021.615355

Mohammed, A. E., Abdul-Hameed, Z. H., Alotaibi, M. O., Bawakid, N. O., Sobahi, T. R., Abdel-Lateff, A., & Alarif, W. M. (2021). Chemical diversity and bioactivities of monoterpene indole alkaloids (Mias) from six apocynaceae genera. *Molecules*, *26*(2). https://doi.org/10.3390/molecules26020488

Mohammed, A., & Tajuddeen, N. (2022). Antidiabetic compounds from medicinal plants traditionally used for the treatment of diabetes in Africa: A review update (2015–2020). *South African Journal of Botany*, *146*, 585–602. https://doi.org/10.1016/J.SAJB.2021.11.018

Munyati, A. (2020). *AN INVESTIGATION INTO THE DEMOGRAPHIC AND SOCIO-ECONOMIC FACTORS ASSOCIATED WITH FEMALE INFERTILITY; ITS RISK FACTORS AND TREATMENT SEEKING BEHAVIOR AMONG INFERTILE WOMEN IN LUSAKA URBAN DISTRICT: A CASE STUDY OF RESIDENTS OF MISISI, LIBALA AND WOODLANDS TOWNSHIPS OF LUSAKA*.

Muralidharan, C., & Linnemann, A. K. (2021). *b-Cell autophagy in the pathogenesis of type 1 diabetes*. https://doi.org/10.1152/ajpendo.00151.2021

Nikolic, D. M., Dimitrijevic-Sreckovic, V., Ranin, L. T., Stojanovic, M. M., Ilic, I. D., Gostiljac, D. M., & Soldatovic, I. A. (2022). Homeostatic microbiome disruption as a cause of insulin secretion disorders. Candida albicans, a new factor in pathogenesis of diabetes: A STROBE compliant cross-sectional study. *Medicine (United States)*, *101*(45), E31291. https://doi.org/10.1097/MD.0000000000031291

P Erez-Burillo, S., Hinojosa-Nogueira, D., Pastoriza, S., & Rufi An-Henares, J. A. (2017). *Plant extracts as natural modulators of gut microbiota community structure and functionality*. https://doi.org/10.1016/j.heliyon.2020.e05474

Portincasa, P., Bonfrate, L., Vacca, M., De Angelis, M., Farella, I., Lanza, E., Khalil, M., Wang, D. Q. H., Sperandio, M., & Di Ciaula, A. (2022). Gut Microbiota and Short Chain Fatty Acids: Implications in Glucose Homeostasis. In *International Journal of Molecular Sciences* (Vol. 23, Issue 3). MDPI. https://doi.org/10.3390/ijms23031105

Salinas, E., Reyes-Pavón, D., Cortes-Perez, N. G., Torres-Maravilla, E., Bitzer-Quintero, O. K., Langella, P., & Bermúdez-Humarán, L. G. (2021). Bioactive compounds in food as a current therapeutic approach to maintain a healthy intestinal epithelium. In *Microorganisms* (Vol. 9, Issue 8). MDPI AG. https://doi.org/10.3390/microorganisms9081634

Stolfi, C., Maresca, C., Monteleone, G., & Laudisi, F. (2022). Implication of Intestinal Barrier Dysfunction in Gut Dysbiosis and Diseases. In *Biomedicines* (Vol. 10, Issue 2). MDPI. https://doi.org/10.3390/biomedicines10020289

Tu, C., Wei, J., Guan, F., Liu, Y., Sun, Y., & Luo, Y. (2020). Biochar and bacteria inoculated biochar enhanced Cd and Cu immobilization and enzymatic activity in a polluted soil. *Environment International*, *137*. https://doi.org/10.1016/j.envint.2020.105576

Wan, F., Wang, M., Zhong, R., Chen, L., Han, H., Liu, L., Zhao, Y., Lv, H., Hou, F., Yi, B., & Zhang, H. (2022a). Supplementation With Chinese Medicinal Plant Extracts From Lonicera hypoglauca and Scutellaria baicalensis Mitigates Colonic Inflammation by Regulating Oxidative Stress and Gut Microbiota in a Colitis Mouse Model. *Frontiers in Cellular and Infection Microbiology*, *11*. https://doi.org/10.3389/fcimb.2021.798052

Wan, F., Wang, M., Zhong, R., Chen, L., Han, H., Liu, L., Zhao, Y., Lv, H., Hou, F., Yi, B., & Zhang, H. (2022b). Supplementation With Chinese Medicinal Plant Extracts From Lonicera hypoglauca and Scutellaria baicalensis Mitigates Colonic Inflammation by Regulating Oxidative Stress and Gut Microbiota in a

Colitis Mouse Model. *Frontiers in Cellular and Infection Microbiology*, *11*. https://doi.org/10.3389/fcimb.2021.798052

Wei, M., Liu, H., Wang, Y., Sun, M., & Shang, P. (2024). *Mechanisms of Male Reproductive Sterility Triggered by Dysbiosis of Intestinal Microorganisms*. https://doi.org/10.20944/preprints202404.1553.v1

Wei, Q., Zhang, Z., Luo, J., Kong, J., Ding, Y., Chen, Y., & Wang, K. (2019). Insulin treatment enhances pseudomonas aeruginosa biofilm formation by increasing intracellular cyclic di-GMP levels, leading to chronic wound infection and delayed wound healing. In *Am J Transl Res* (Vol. 11, Issue 6). www.ajtr.org