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The Synergistic Effect of Two Remedial Plant Extracts on Hyperglycemia and Selected Associated Complications in Streptozotocin-induced Rats

Daniel Oyinloye[a*], Adeleke Osho[b], Pranabendu Mitra[c]

[a]*Biological Sciences Department, College of Natural Sciences, Redeemer's University, postcode 232101 Ede., Nigeria*

[b]*Department of Biological Sciences, College of Natural Sciences, Redeemer's University, Ede., Nigeria*

[c]*Department of Kinesiology, Health, Food and Nutritional Sciences, University of Wisconsin-Stout, Menomonie, WI, 54751, USA*

[a]*Email:oyinloyed7118@run.edu.ng,*[b]*Email: oshoa@run.edu.ng*

[c]*Email: mitrap@uwstout.edu*

Abstract

The study investigated the synergistic effects of remedial plant extracts from Musa accuminata (banana) and Momordica charantia (bitter melon) on hyperglycemia and associated complications in streptozotocin-induced diabetic rats—a widely accepted model for studying diabetes mellitus and its complications. Diabetes mellitus, characterised by elevated blood glucose levels and potential organ system complications, prompted the exploration of herbal remedies with minimal adverse effects. Rats induced with diabetes were treated with Musa accuminata extract, Momordica charantia extract, and a combination of both extracts. Blood glucose levels were monitored, and markers of complications, including blood pressure and weight management, were assessed.Results revealed that the combined treatment demonstrated a synergistic effect, effectively lowering blood glucose levels (350.43±0.14 to 291.59±23.26) compared to individual extract treatments: Banana extract, Bitter melon extract and Glibenclamide (350.43±0.10 to 300.39±21.02, 347.34±0.06 to 292.23±24.53 and 348.30±0.12 to 287.64±24.06) respectively. Furthermore, the combined treatment exhibited significant improvements in blood pressure (127.92/91.25mmHg, 129.19/98.06, 127.20/99.58mmHg and 130.75/99.83mmHg, combined extract, banana bitter melon and Glibenclamide respectively) and weight management in the animal model, surpassing the outcomes of glibenclamide and untreated diabetic rats. The average weight gain across all the groups ranges from 250g to 321g per rat.These findings highlight the potent anti-hyperglycemic and anti-complication properties of the Musa accuminata and Momordica charantia extracts and their combination in streptozotocin-induced diabetic rats.

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* Corresponding author.

It is suggested that additional research be done on the underlying mechanisms and clinical trials to confirm the plant extracts' medicinal potential in treating diabetes mellitus and its related problems.

Keywords: Plants extract; Diabetes; weight gain; blood pressure; animal model.

1. Introduction

Diabetes is a severe and long-term condition that has an impact on people's lives and general health worldwide, impacting individuals, families, and society as a whole. Diabetes is one of the top 10 causes of death in the world, Which was projected to have claimed four million lives worldwide in 2017 [1] .According to recent data, 9.3% of people worldwide were estimated to have diabetes in 2019. Over the next 10 and 25 years, a steady increase in this number is anticipated. In Nigeria, DM is quickly becoming a serious public health issue [2] .The World Health Organization and the International Diabetes Foundation estimated that over ten years, 3.4% of 24 million Nigerians between the ages of 20 and 79 would have Type II diabetes [3,4] .Throughout history, numerous cultures have employed medicinal plants in their traditional medical systems to treat and manage diabetes mellitus (DM). The World Health Organization (WHO) has proposed employing therapeutic plants and expanded the boundaries of scientific research on the hypoglycemic qualities of many plant species. To manage diabetes mellitus (DM). As a result, in human and animal models, the hypoglycemic action of a wide range of plant items has been assessed and verified. The bioactive components of medicinal plants have occasionally been separated and identified.

Maintaining blood glucose homeostasis—avoiding ketosis and its associated complications—is the goal of treating diabetes. Focusing on a critical aspect of diabetes, the main methods of controlling the disease are nutrition and exercise, insulin replacement therapy, and insulin or oral hypoglycemic medications.The best source of naturally occurring molecules thought to be responsible for medication development has been considered herbal medicine; nevertheless, the method is costly, time-consuming, and complicated [5,6,77] .There have been reports of using polyherbal formulations to treat type 2 diabetes, a chronic metabolic disease brought on by either insulin malfunction or insufficiency [8] .According to recent reports, diabetes affects about one-third of stroke patients. Diabetes mellitus is also linked to an elevated risk of breast cancer mortality[6,9].

1.1. Common Anti-Diabetic Medicinal Plants

It is important to remember that there is currently no treatment for diabetes mellitus despite the availability of medications [10,11]. Moreover, insulin treatment, which is used to manage the condition, has several unfavourable side effects [11] .The search for medicinal plants with hypoglycemic properties to treat diabetes mellitus was prompted by anti-diabetic medications' unfavourable side effects and expensive nature [12]. Numerous plant species utilised medicinally to treat diabetes mellitus globally have been assessed. Aloe vera, Cinnamomum Cassie, Allium cepa (onion), and Allium sativum (garlic) are a few examples of plants [10,13]. An overview of various therapeutic herbs. Most bioactive substances that showed glycemic control in test animals included amino acids, polysaccharides, sterols, terpenoids, alkaloids, saponins, flavonoids, and their

derivatives.

1.2. Bitter Melon

Momordica charantia is a dietary supplement that is found naturally. For millennia, it has been utilised as traditional medicine to treat various illnesses, including diabetes, cancer, inflammation, and other conditions [14]. Worldwide research is being done on M. charantia because of its natural medical qualities, which include antioxidant and antibacterial, anticancer, antidiabetic, and antimalarial effects. A plant with many uses, the bitter guard can treat almost any illness. [14]. The plant has several therapeutic components that can function jointly or individually to produce therapeutic effects. Like the plant itself or its crude extracts, the phytochemicals, such as alkaloid-like extracts, insulin-like peptides, and charantin, have hypoglycemic benefits for diabetes. Different plant extracts contain chemicals that help regulate multiple systems in managing and treating diabetes mellitus. M. charantia is a workable and naturally occurring choice for people who are more likely to develop diabetes.

The banana, or Musa acuminate, is a widely consumed fruit valued for its flavour, texture, and nutritional content. It is also a convenient fruit to peel and eat [15]. It is packed full of health-promoting elements and minerals. It has 15% of vitamin C, recognised as a well-known antioxidant. Typically, bananas are plucked before reaching full maturity for household use [16]. They are usually stored at room temperature.

One of the fruits consumed the most worldwide is the banana (Musa acuminata) [17]. With an annual production capacity of 29.1 million tonnes, India is a significant producer of bananas. This fruit is a staple cuisine in impoverished nations like Nigeria. Because it contains a lot of potassium, magnesium, and sugar,

Most commonly, the diabetic rat model caused by streptozotocin (STZ) is utilised to investigate the mechanisms underlying painful diabetic neuropathy and assess possible treatments [18]. The University of Michigan's Michigan Diabetes Research and Training Centre recommends the STZ procedure used in many labs. By giving adult rats a single, modest dose of the cytotoxic drug STZ, diabetes is experimentally generated in this manner. Like type I insulin-dependent diabetic mellitus (IDDM) in people, the ensuing diabetes affects animals injected with STZ. Within 72 hours of the injection, the animals become hyperglycemic, and four weeks later, they start exhibiting behavioural symptoms that indicate the development of a painful neuropathy.

Combining the therapeutic benefits of bitter melon (Momordica charantia) and banana (Musa acuminata) may help with type 2 diabetes. Bitter melon improves insulin sensitivity, whereas bananas stabilise blood sugar by providing fibre and minerals. Their combined effects may successfully control blood sugar levels, which may help manage type 2 diabetes.

3. Material and Method

3.1. Experimental Design

This experimental work was conducted at an animal laboratory under the Department of Biological Sciences, Redeemer's University, Ede, Nigeria, for 28 days to evaluate the comparative study on blood pressure, weight

loss, and blood glucose levels among two medicinal plant extracts and their mixture against streptozotocin-induced diabetes (STZ) in rats.

3.1.1. Animals Used in Experiments and the Study Protocol

Six-week-old male Wistar albino rats weighing 245 and 255 grammes were purchased from Redeemer's University Animal House. The Department of Biological Sciences approved all experimental animal methods, which followed the committee's criteria for the care and use of experimental animals to supervise 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 (25±2)0C temperature and a 12/12 light/dark cycle. Throughout the trial, the rats were given water at will and a regular commercial pellet meal at a dose of (100–150) gm/kg as instructed [19] and given by the Animal House management.

The layout of experiment 36 This assessment was performed on male Wistar albino rats. Six equal groups of six rats each were created from these rats: The three control groups were Group A (standard), Group B (diabetes), and Group C. received glibenclamide treatment, and Groups D, E, and F were maintained for experimental purposes. After starving the ray for eighteen hours, measurements were made of its body weight, blood pressure, and blood glucose levels. The streptozotocin was dissolved in a 0.1 M citrate buffer with a pH of 4.5. Next, each rat in Groups B, C, D, E, and F received a 120 mg/kg body weight intraperitoneal injection of streptozotocin to cause diabetes. Following an injection of streptozotocin, blood pressure, body weight, and blood glucose were evaluated 72 hours later. From day one to day 28, the rats were given a regular meal and unlimited access to water. To check for hyperglycemia or diabetes, a glucometer (Accu-Chek) was utilised, along with the body weight (Electronic digital scale ID B0B222) and blood pressure (CODA mouse and rat tail-cuff system). During treatment with extracts, body weight, blood pressure, and blood glucose levels were recorded on days 1 and 28.

3.2. Preparation and Preservation of Extract: Bitter Melon Extract

Reference[20] Sample preparation was adhered to but with some modifications. We picked up fresh bitter melon leaves from the campus of Redeemer's University Ede. Using an electric grinder, “Cuisinart CBT-2000 3.5 Peak Hurricane Pro Blender, Gunmetal, Gun Metal”, the gathered leaves were cleaned under running water, shade-dried, and then sealed in an airtight container. For 72 hours, 500 mL of distilled water was soaked with 50 g of dried leaf powder. After the aqueous extract was concentrated under decreased pressure using filter paper and vacuum and his colleagues. (SB-XZZFY-5299), it was refrigerated at four °C until needed [21].The procedure described, albeit with a few minor adjustments, was followed to process the banana flour. After washing the banana fingers to remove any remaining soil particles, they were peeled, sliced into thin slices about 2 cm thick, blanched for 5 minutes at 800C in 1.25% NaHS03 solution, and drained. The slices of blanched banana were oven-dried for 20 hours at 600C. Hot-air oven (Plus11 and his colleagues, UK), laboratory blender (Model KM 901D; Kenwood and his colleagues, UK), and 60 mm mesh sieve (British Standard) were used in the milling process. Next, for 72 hours, 500 grams of ground-powder banana was steeped in 1000 millilitres of ethanol,

stirring and filtering intermittently. A rotatory vacuum evaporator condensed the filtrate, which was then kept refrigerated.

3.3. Composition of the Extract Mixture

Procedure for Administration of Bitter Melon and Banana Extract: Using a micropipette, the bitter melon and banana fruits were produced and given orally to the various treatment groups of the experimental rats. The administration of the required amount, determined by each rat's body weight, was guaranteed using a micropipette.

3.4. Documentation of Various Parameters

3.4.1. Calculating One's Body Weight

Before treatment, each group's body weight was noted. On 0 days and twice per week, I used an electronic digital scale (ID B0B222) throughout the experiment.

3.4.2. Blood Glucose Levels

Blood glucose levels were estimated by drawing blood samples on day 0 (pre-treatment) from the tail vein and at 3-day intervals, concluding with the study period. The blood glucose levels were estimated using Accu-check, a monitoring device.

3.4.3. Determination of Blood Pressure

Before treatment, the blood pressure of each group was measured on 0 days and twice per week using Mouse and rat blood pressure (MRBP) throughout the experiment.

3.5. Statistical Analysis

The means ± standard errors (M ± SEM) were used to express all experimental outcomes. The significance between the two averages was confirmed using the Bonferroni test after one-way ANOVA, or analysis of variance in one direction. The statistical application Origin 9.1 was used to carry out the Bonferroni test and variance analysis. A difference was deemed significant when the p-value was less than 0.05.

4. Findings and Conversation

The experiment was carried out to ascertain the relative efficacy. Synthetic Glibenclamide, Bitter melon extract, Banana extract and a mixture of Rats with streptozotocin-induced diabetes were given bitter melon and banana extract to control body weight, blood glucose, and blood pressure.

Table1: The outcome of the diabetic rats' blood pressure, weight increase, and blood glucose level

Parameter		No STZ -ve Control	STZ Not Treated	STZ Gilb	STZ BM Treated	STZ Ban Ext	STZ Mixture
Fasting Glucose (mg/dL)	Initial	87.39±0.13	346.01±0.17	348.30±0.12	347.34±0.06	352.43±0.10	350.43±0.14
	Final	91.34±1.70	409.41±26.06	287.64±24.06	292.23±24.53	300.39±21.02	291.59±23.26
Systolic Bld Pressure (mmHg)	Initial	121.05	153.05	146.08	142.17	129.19	149.80
	Final	120.50	129.25	130.75	127.20	129.58	127.92
DiastolicBld Pressure (mmHg)	Initial	99.23	129.25	130.75	127.20	129.58	127.92
	Final	99.17	102.33	99.83	99.58	98.06	91.25
Weight Gain(g)	Initial	250±05	248±02	249±11	250±32	250±79	250±04
	Final	322±70	297±71	311±42	319±90	319±89	324±81

Key: Group I: Control (1 ml/kg of normal saline) Group II = Diabetic Control (STZ + distil water (0.5ml)
Group III = STZ + Banana (200mg/kg) (0.5ml) Group IV = STZ + Glibenclamide (2mg/kg) (0.5ml)
Group V = STZ + Bitter Melon (300mg/kg) (0.5ml) Group V1 = STZ + Mixture (200mg + 300mg) (0.5ml)

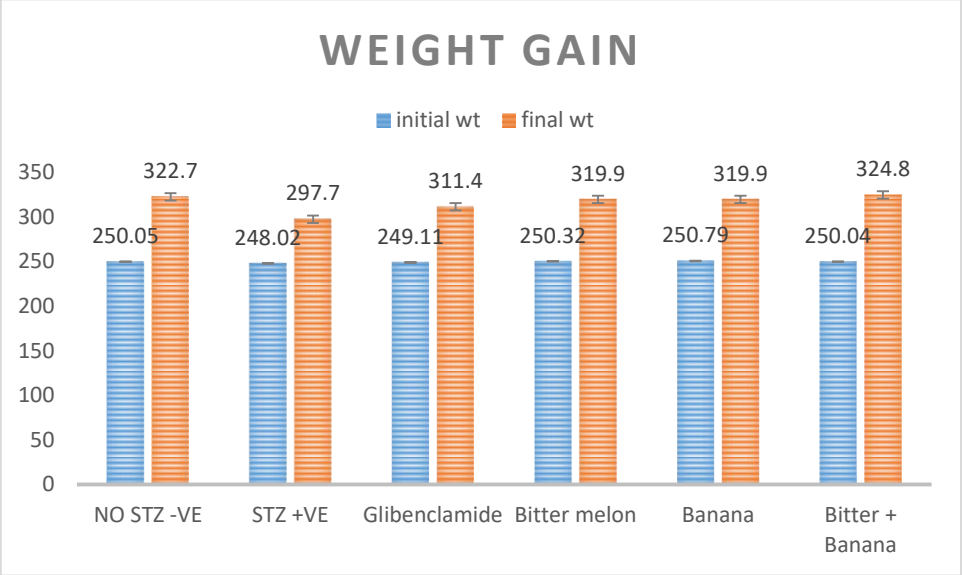

Figure 1: The effect of the combined effort of two remedial plant extracts

The body weight of this research indicated that the final weight of diabetes-induced rats untreated was significantly low (297.7±7.64) compared with other diabetes-induced rats treated in other groups with values of (311.4±1.39, 319.89±2.76, 319.90±4.29 and 324.81±5.32). The final body weight of diabetes-induced rats treated with commercial medication (Glibenclamide) positive control was reduced compared with the negative control without diabetes-induced. After the trial, the body weight of bitter melon and banana treated with a medicinal plant extract does not change due to diabetes. No discernible change has occurred. ($P<0.05$) between the diabetic rats administered with a combination of bitter melon and banana extracts (324.81±5.32) and the negative control (322.70±3.95). According to [22], there was no significant difference observed at ($P<0.05$) between the treatments of bitter melon and banana extracts (319.89±2.76) and (319.90±4.29), respectively. However, all groups experienced a significant increase in body weight, ranging from 20.03% to 29.90%. The findings were corroborated by [22], who observed that the diabetes control group's body weight was 25% higher and the rats' body weight was 30% higher after receiving Momordica charantia extract. The results of [22] showed that an aqueous extract of Momordica charantia considerably decreased body weight (303±7.03 vs 253.72±7.8gm), which was in contrast to the current findings. The current study shows diabetic rats' body weights increased slightly after receiving banana and bitter melon treatments. The results of this study were in line with those of [21,22] who found that giving diabetic rats cinnamon considerably boosted their body weight. These results [21,22] are not consistent. The potential of combo extract to lower hyperglycemia may account for its beneficial effect on weight reduction. Here, in treated diabetic rats, the bioactive components in cinnamon may help suppress the free radicals produced and regulate muscle wastage brought on by glycemic management, ultimately resulting in a return to normal body weight. This study's results also agreed with those of Shahadat and his colleagues. (2019), who found that diabetic groups received daily treatment with a 200 mg/kg body weight supplement containing an ethanol extract from the plants swertiachirata and rographispaniculata. After the treatment, the animal's body weight had increased much more than that of the diabetic groups. The current findings corroborated the findings of [21,22] who found that even though diabetic rats consumed more food,

anabolism of protein and lipids could contribute to a drop in body weight caused by alloxan induction.

4.1. Blood Glucose

Table 2 displays the blood glucose level variation throughout the 4-week investigation. Despite being hyperglycemia rats, the bitter melon treatment group and mixture had the lowest blood glucose levels, with baseline and final blood glucose levels of 352.56±0.10 to 300.39±21.04 and 350.43±0.14 to 291.59±23.26, respectively. Compared to the standard group, the average blood glucose level is lower (Table 2). The group with hyperglycemia was fed a regular meal but had elevated blood glucose levels, with a rise of 18.32%. Fig. 2 displays the initial and ultimate blood glucose increases.

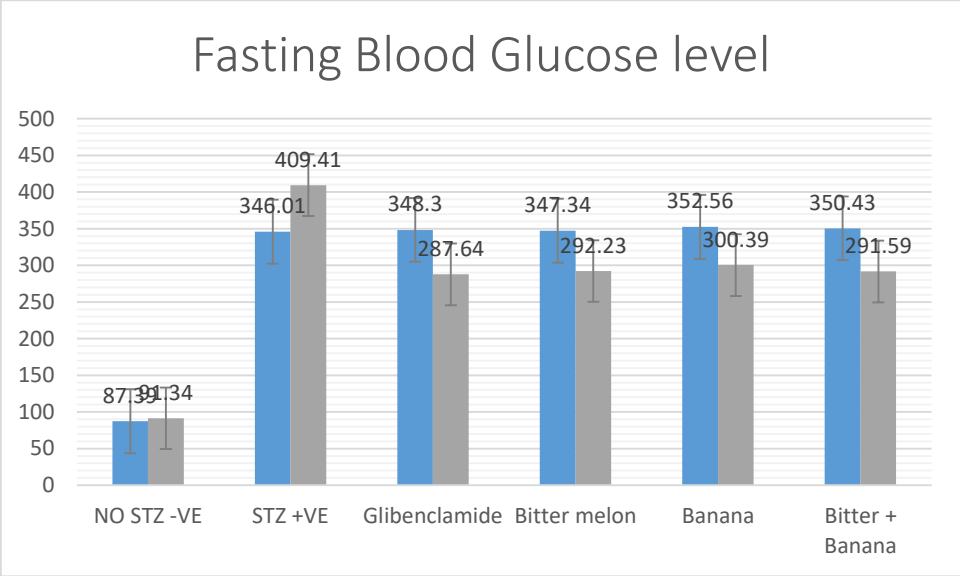

Figure 2: The synergetic effect of two remedial plants against medicinal drug

Following pancreatic injury caused by STZ, elevated blood glucose levels were noted.

Rat models of diabetes were compared to the control group (>346.01 ± 0.17 vs. 87.39 ± 0.13 mg/dL). Blood glucose levels were significantly lower than the STZ control following four weeks of recurrent administration of Glibenclamide, bananas and bitter melon extracts, and the combination cocktail ($p < 0.05$), as illustrated in Figure 2 and Table 2. Positive management When left untreated, STZ's blood sugar level is higher than that of the other group that received a medicinal plant extract. The groups that received both the single and mixed extract of bitter melon experienced the most significant drop in blood sugar, with a level of 16.80%.

Bitter melon's capacity to lower blood sugar levels results from its bioactive compounds, essential for numerous physiological, pharmacological, and biochemical functions [23] The possible mechanisms by which eating bitter melon lowers blood sugar levels include stimulating the skeletal and peripheral muscles to improve glucose utilisation [23] blocking the intestinal uptake of glucose [23,24,25] preserving the enzymatic activities linked to glucose metabolism [26]; and stabilising and enhancing the functionality of pancreatic β-cells [23,26] Because bitter melon includes both vicine and charantin, which are potentially antidiabetic substances, combining these

two compounds has been proven to be more helpful in managing diabetes. Charantin is a typical cucurbitane-type triterpenoid found in M. charantia. Charantin may be used in place of other medications to treat diabetes. According to (Nimule Shahadat and his colleagues, 2019) it is a blend of sitosterol glucoside and stigmasterol glucoside.

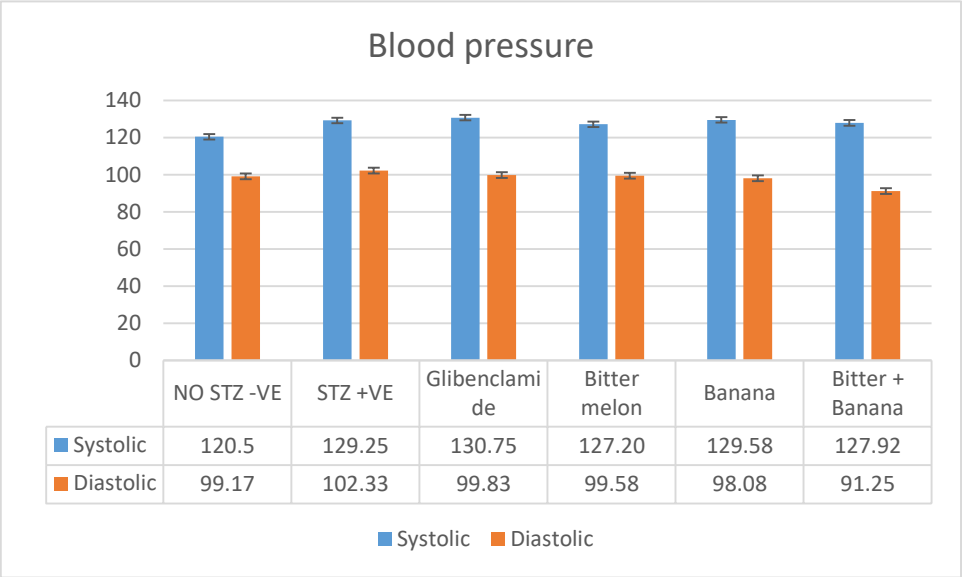

Figure 3: The synergetic effect of two remedial plants on Blood pressure against medicinal drug

This study investigated the combined effect of banana and bitter melon extracts in diabetes treatment, revealing a noteworthy synergistic effect. The findings demonstrated that the combined extract effectively regulated blood pressure, with systolic and diastolic values measured at 127.92 mmHg and 91 mmHg, respectively. This result is in tandem with[27]. This indicates that the combination falls within the normal range of 125- 129 mmHg for blood pressure, highlighting its potential as a comprehensive approach to diabetes management [28].

The research compared the combined extract to individual banana and bitter melon extracts; all three demonstrated the ability to maintain systolic blood pressure within the normal range129.58, 127.20 and 127.92mmHg, respectively, which conformed with the findings. [29] As suggested by (Parasuraman & Raveendran, 2012 Toral and his colleagues, 2019), the diastolic values for each extract were higher than the normal range indicated by (Huang and his colleagues, 2020). Interestingly, glibenclamide, a commonly prescribed medication for diabetes, also exhibited normal systolic but elevated diastolic blood pressure levels, which confirms the side effects of the drug.[29,30]. This makes the drug not suitable for diabetes treatment.

Specifically, bitter melon extract, banana extract, and glibenclamide individually showed systolic values within the normal range, indicating their efficacy in controlling this aspect of blood pressure. However, the elevated diastolic values suggest a potential need for complementary interventions or careful monitoring to address this aspect of cardiovascular health in diabetes patients [31].

Both negative and positive controls were included to validate the study's findings. The negative control, which

received no treatment, maintained blood pressure within the normal range, establishing a baseline for comparison. In contrast, the positive control, which received a placebo or inactive substance, exhibited very high blood pressure levels. This stark contrast emphasises the efficacy of the combined banana and bitter melon extracts in maintaining blood pressure within the normal range compared to the placebo[32].

5. Conclusion

Ultimately, the study's findings unequivocally demonstrate that a combination's cooperative effect of bitter melon and banana extract exhibits a remarkable hypoglycemic impact on diabetic-induced rats, surpassing the efficacy of the commercial medicinal drug glibenclamide. It does not affect the weight gain of the rats negatively; the result shows the increase in growth of the animal alongside the increase in their age, which is also commensurate with the feeding supply. Notably, the combined plant extract shows superiority in mitigating diabetic conditions without any discernible complications, in stark contrast to the therapeutic drug, which induces an undesirable increase in blood pressure. Furthermore, the cost-effectiveness of the locally available plant extract stands out prominently, offering a more economical alternative to the expensive commercial medication. Notably, the simplicity of processing the remedial plant extract underscores its practicality and accessibility. Considering these compelling results, it is evident that the synergistic effect of the bitter melon and banana extract combination surpasses both individual plant extracts and commercial medications, presenting a promising avenue for developing cost-effective and safer alternatives in diabetes management.

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