

**THE HYPOGLYCEMIC AND ANTI DIABETIC EFFECT OF THE  
LEAVES OF *ANNONA MURICATA* ON NORMOGLYCEMIC AND  
STREPTOZOTOCIN INDUCED DIABETIC WHITE RATS**



**BY**

**Prosper Okonta CHUKWUYEM  
LSC2009758**

**(BIOLOGICAL SCIENCE TECHNIQUES)**

**DEPARTMENT OF SCIENCE LABORATORY TECHNOLOGY  
FACULTY OF LIFE SCIENCES  
UNIVERSITY OF BENIN  
BENIN CITY**

**OCTOBER, 2025**

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**A PROJECT SUBMITTED TO THE DEPARTMENT OF SCIENCE  
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**OCTOBER, 2025**

## CERTIFICATION

This is to certify that this research work Titled “THE HYPOGLYCEMIC AND ANTI DIABETIC EFFECT OF THE LEAVES OF *Annona muricata* ON NORMOGLYCEMIC AND STREPTOZOTOCIN INDUCED DIABETIC WHITE RATS” was carried out by Prosper Okonta chukwuyem with matriculation number “LSC2009758” of the Department of Science Laboratory Technology, Faculty of Life Sciences, and University of Benin, Benin City.

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**Dr. (Mrs.) O. E. Obaro-Onezeyi**

(Project Supervisor)

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**Date**

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**Dr. P. O. Alonge**  
(Project Coordinator)

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**Date**

---

**Prof. J.O. Osaruwemense**

(Head of Department)

---

**Date**

---

(External Examiner)

---

**Date**

## **DEDICATION**

I dedicate this work to Almighty God, who has blessed and sustained me throughout this project work and has been my source of inspiration and strength.

## **ACKNOWLEDGMENTS**

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## TABLE OF CONTENTS

COVER PAGE .....	ii
CERTIFICATION.....	iii
DEDICATION.....	iv
ACKNOWLEDGMENTS.....	v
TABLE OF CONTENTS.....	vi
LIST OF TABLES.....	vii
LIST OF PLATES.....	x
ABSTRACT.....	xi
<b>CHAPTER ONE</b>	
1.1 Phytochemical Composition. ....	4
1.2 Medicinal and Biological Effects.....	5
1.3 Mechanism of Action.....	9
1.4 Potential Application.....	10
1.5 Safety and Toxicity. ....	12
1.6 Importance.....	13
1.7 Aim and Objectives.....	15
1.7.1 Aim of the study.....	15
1.7.2 Objectives of Study.....	15
1.8 The Significance of Study.....	16
1.9 The Scope of Study. ....	17
1.10 Limitations. ....	19
1.11 Definition of Terms.....	21

<b>CHAPTER TWO.....</b>	<b>24</b>
<b>2.0 LITERATURE REVIEW.....</b>	<b>24</b>
2.1 Diabetes mellitus.....	24
2.2 Statement of the Problem.....	25
<b>CHAPTER THREE.....</b>	<b>27</b>
<b>3.0 MATERIALS AND METHODS.....</b>	<b>27</b>
3.1 Collection of Research Materials.....	27
3.2Extraction of Plant Material.....	27
3.3Experimental Animals.....	27
3.3.1 Drugs Chemicals/Materials.....	28
3.3.2 Acute Toxicity Study. ....	28
3.3.3 Acute Normoglycemic Study.....	28
3.3.4 Anti-Diabetic Study. ....	28
3.3.5 Blood Glucometer Check.....	29
3.3.6 Statistical Analysis.....	30
<b>CHAPTER FOUR.....</b>	<b>31</b>
<b>4.0 RESULTS.....</b>	<b>31</b>
4.1 Effect of Methanol Leaves Extract of Soursop (MLESS) on Acute Toxicity Study.....	31
4.2 Effect of Methanol leaves extract of soursop (MLESS) on Normoglycemic Blood Sugar Level.....	32
4.3 Effect of Methanol Leaves Extract of Soursop (MLESS) on Blood Sugar Level (BSL) of Streptozotocin Induced Diabetic Rats.....	33

4.4 Effect of Methanol leaves extract of soursop (MLESS) on Liver Function Indices.....	44
4.5 Effect of Methanol Leaves Extract of Soursop (Mless) on Lipid Profile Indices.....	35
<b>CHAPTER FIVE.....</b>	<b>36</b>
<b>5.0 DISCUSSION.....</b>	<b>36</b>
5.1 Methanol Leaves Extract of Soursop (MLESS) on acute toxicity study.....	36
5.2 Effect of Methanol Leaves Extract of Soursop (MLESS) on normoglycemic blood sugar level.....	36
5.3 Effect of Methanol Leaves Extract of Soursop (MLESS) on blood sugar level (BSL) of Streptozotocin induced diabetic rats. ....	36
5.4 Effect of Methanol Leaves Extract of Soursop (MLESS) on liver function indices.....	37
5.5 Effect of Methanol Leaves Extract of Soursop (MLESS) on lipid profile indices.....	38
<b>CONCLUSION.....</b>	<b>39</b>
<b>REFERENCE. ....</b>	<b>40</b>

## LIST OF TABLES

	<b>Page</b>
Table 4.1: Effect of Methanol Leaves Extract of Soursop (MLESS) on Acute Toxicity Study	31
Table 4.2: Effect of Methanol leaves extract of soursop (MLESS) on normoglycemic blood sugar Level	32
Table 4.3: Effect of Methanol Leaves Extract of Soursop (MLESS) on blood sugar level (BSL) of Streptozotocin induced diabetic rats	33
Table 4.4: Effect of Methanol Leaves Extract of Soursop (MLESS) on liver function indices	34
Table 4.5: Effect of Methanol Leaves of Soursop (Mless) on Lipid Profile Indices	35

## LIST OF PLATES

Plate 1.1: Soursop (*Annona muricata*) Tree

3

## ABSTRACT

Despite advancements in medical science and the availability of pharmacological interventions, diabetes mellitus remains a significant public health challenge worldwide. The soursop tree (*Annona muricata* L.), a tropical fruit-bearing plant, have been traditionally used in various cultures for their perceived medicinal properties. In spite of the global prevalence of diabetes mellitus, comprehensive research on the acute and sub-acute impacts of the methanol leaves extract of soursop on blood glucose levels remains scarce. Thus the aim of this experiment was to study the hypoglycemic and anti-diabetic effect of the leaves of *Annona muricata* on normoglycemic and streptozotocin induced diabetic white rats. The study employs diverse methods, encompassing acute toxicity assessment, normoglycemic blood sugar level evaluation, and anti-diabetic studies conducted on rats. *Annona muricata* L. (Soursop) extract demonstrated potential hepato-protective properties and exhibited a favorable impact on lipid profiles, notably reducing cholesterol, triglycerides, and LDL concentrations. Maintaining stable blood glucose levels is vital for metabolic equilibrium and overall health. The methanol extract of the leaves of *Annona muricata* were administered, indicating its safety at doses up to 5000 mg/kg and its ability to reduce blood glucose levels in normoglycemic rats, substantiating its hypoglycemic effects. In diabetic rats, the extract effectively lowered elevated blood glucose levels, similar to the effects of the standard diabetic drug Glibenclamide, suggesting its potential in the management of hyperglycemia and diabetes mellitus. These findings highlight the promise of methanol leaves extract of soursop as a natural dietary intervention in diabetes care, offering hope for improved glycemic control and overall well-being.

## 1.0 INTRODUCTION

Young leaves of the soursop tree (*Annona muricata* L.), a tropical fruit-bearing plant, have been traditionally used in various cultures for their perceived medicinal properties.

This practice has sparked increasing scientific interest in exploring the biological effects of these leaves, driven by their rich phytochemical composition. Soursop leaves contain a diverse array of bioactive compounds, including acetogenins, flavonoids, alkaloids, and phenolic compounds, which are believed to contribute to their pharmacological activities.<sup>3</sup> Recent research has focused on elucidating the mechanisms through which these compounds exert their effects, investigating potential applications in areas such as cancer therapy, inflammation management, and oxidative stress reduction. The exploration of the biological effects of young soursop leaves is essential not only for validating traditional uses but also for uncovering novel therapeutic strategies. However, it is equally important to address safety and toxicity concerns associated with their consumption, ensuring responsible and informed use of this natural resource.

Soursop (*Annona muricata*), also known as graviola, is a tropical fruit-bearing tree native to the Americas and now cultivated in various tropical regions worldwide. Beyond its edible fruit, the plant's leaves have garnered attention for their potential medicinal properties. Recent scientific investigations have explored the biological effects of young soursop leaves, revealing a spectrum of pharmacological activities.

The young leaves of soursop (*Annona muricata* L.) belong to the Annonaceae family, which consists of tropical and subtropical flowering plants. The taxonomic classification of soursop is as follows:

Kingdom: Plantae

Phylum: Angiosperms

Class: Magnoliopsida

Order: Magnoliales

Family: Annonaceae

Genus: *Annona*

Species: *Annona muricata*



Photo credit: Prosper Okonta

**Plate 1:** Soursop (*Annona muricata*)

## 1.1 PHYTOCHEMICAL COMPOSITION

Soursop (*Annona muricata*) leaves are rich in various bioactive compounds, contributing to their potential therapeutic properties. Recent phytochemical analyses have identified several key constituents:

**Acetogenins:** These are a class of polyketide compounds, notably annonacin, which have garnered significant attention for their cytotoxic properties. They are believed to be responsible for the plant's potential anticancer effects, primarily through mitochondrial complex I inhibition.

- i. **Flavonoids:** These polyphenolic compounds are known for their antioxidant and anti-inflammatory properties. They contribute to the scavenging of free radicals and the modulation of inflammatory pathways. (Coria-Tellez *et al.*, 2018)
- ii. **Alkaloids:** Various alkaloids have been identified in soursop leaves, which may contribute to diverse pharmacological effects, including antimicrobial and neurological activities. (Johnson *et al.*, 2022)

- iii. **Phenolic Compounds:** These compounds, including phenolic acids, contribute significantly to the antioxidant capacity of soursop leaves. They play a role in protecting cells from oxidative damage.
- iv. **Tannins:** These polyphenolic compounds are present in the leaves.
- v. **Saponins:** These glycosides have been detected in the leaves.
- vi. **Essential Oils:** The leaf oil contains sesquiterpenes, with  $\beta$ -caryophyllene being predominant.

## 1.2 MEDICINAL AND BIOLOGICAL EFFECTS

- i. **Anti-oxidant Activity:** Soursop leaves are rich in polyphenolic compounds, which exhibit significant antioxidant properties. These antioxidants play a crucial role in neutralizing free radicals, thereby reducing oxidative stress and protecting cellular structures from damage. Studies have demonstrated that infusions made from soursop leaves possess high total polyphenolic content and potent antioxidant activity.
- ii. **Anti- Inflammatory Properties:** The anti-inflammatory potential of soursop leaves has been attributed to their bioactive constituents, including flavonoids and tannins. Experimental studies indicate that extracts from these leaves can modulate inflammatory pathways, thereby reducing inflammation. This suggests potential therapeutic applications in managing inflammatory conditions. (Moghadamtousi *et al.*, 2015)
- iii. **Anti-microbial Effect:** Soursop leaf extracts have demonstrated antimicrobial properties against a range of pathogens. Research indicates that these extracts exhibit antibacterial

activity against strains such as *Staphylococcus aureus* and *Escherichia coli*, as well as antifungal effects against various fungal species. These findings support the traditional use of soursop leaves in treating infections.

- iv. **Anti- Cancer Potential:** One of the most extensively studied aspects of soursop leaves is their potential anticancer activity. Compounds known as acetogenins, particularly annonacin, have been isolated from the leaves and shown to exhibit cytotoxic effects against various cancer cell lines in vitro. These compounds are believed to induce apoptosis in cancer cells by inhibiting mitochondrial complex I, leading to energy depletion. However, it's important to note that while these findings are promising, clinical studies in humans are necessary to confirm efficacy and safety.
- v. **Anti-diabetic Effect:** The potential antidiabetic effects of soursop leaves have been explored in various studies. Extracts from the leaves have been shown to inhibit enzymes such as  $\alpha$ -glucosidase and  $\alpha$ -amylase, which are involved in carbohydrate digestion. By inhibiting these enzymes, soursop leaf extracts may help in managing blood glucose levels, suggesting potential benefits for individuals with diabetes.
- vi. **Neuroprotective Effect:** While soursop leaves have been studied for various therapeutic effects, it's crucial to address concerns regarding their neurotoxicity.

- vii.** Annonacin, a prominent acetogenin found in soursop, has been associated with neurotoxic effects in some studies. Research indicates that high consumption of annonacin may be linked to neurodegenerative conditions resembling Parkinson's disease. Therefore, while soursop leaves may offer certain health benefits, caution is warranted regarding their consumption, and further research is essential to fully understand their safety profile. (Champy P., 2005)
- viii. Cardio protective Effect:** Soursop leaves have been traditionally used to manage hypertension. Studies suggest that extracts from the leaves may exhibit antihypertensive properties, potentially through mechanisms such as vasodilation and modulation of calcium ion channels. These effects could contribute to improved cardiovascular health, although more research is needed to confirm these benefits in clinical settings.
- ix. Anti- Ulcer Activity:** The gastroprotective properties of soursop leaf extracts have been investigated in experimental models. Findings suggest that these extracts can protect the gastric mucosa against ulceration, possibly by enhancing mucus production and exhibiting

antioxidant effects. This indicates potential therapeutic applications for soursop leaves in preventing or managing gastric ulcers.

- x. **Wound Healing Properties:** Topical application of soursop leaf extracts has been studied for its effects on wound healing. The presence of bioactive compounds with antimicrobial and anti-inflammatory properties may facilitate faster wound contraction and tissue regeneration. These properties support the traditional use of soursop leaves in promoting wound healing.
- xi. **Analgesic Effects:** Soursop leaves have been traditionally used to alleviate pain. Scientific studies have explored this analgesic potential, with findings suggesting that leaf extracts may modulate pain perception pathways. However, further research is necessary to elucidate the exact mechanisms and to confirm efficacy in clinical settings. (Moghadamtousi *et al.*, 2015)

### 1.3

### MECHANISM OF ACTION

Young soursop (*Annona muricata* L.) leaves exhibit a complex mechanism of action, primarily attributed to their rich phytochemical composition, including acetogenins, flavonoids, and alkaloids. Research consistently highlights the potent antioxidant properties of these leaves, with phenolic compounds and flavonoids playing a crucial role in scavenging free radicals and mitigating oxidative stress (Adefegha & Oboh, 2011). Furthermore, the cytotoxic effects of acetogenins, particularly annonacin, have been extensively studied, demonstrating their ability to inhibit mitochondrial complex I, thereby disrupting cellular ATP production and potentially inducing apoptosis in cancer cells (Yang et al., 2015). Beyond their antioxidant and cytotoxic capabilities, soursop leaf extracts also possess significant anti-inflammatory properties, likely mediated by the modulation of inflammatory

cytokines (Sundararajan et al., 2016). While these studies provide valuable insights into the mechanisms underlying the pharmacological effects of soursop leaves, ongoing research is essential to fully elucidate the intricate interactions of these compounds and their precise pathways of action.

#### 1.4 POTENTIAL APPLICATION

Soursop (*Annona muricata* L.) leaves hold potential applications in several areas, primarily due to their rich phytochemical composition and demonstrated bioactivity.

- i. **Neuroprotective Potential:** Some research explores the potential of soursop leaf extracts to protect against neurodegenerative diseases. This is attributed to the antioxidant and anti-inflammatory properties, which may mitigate neuronal damage caused by oxidative stress and inflammation (Dosoky and Setzer, 2018).
- ii. **Management of hyperlipidemia:** Studies have indicated that soursop leaf extracts may contribute to the reduction of lipid levels in the blood. This opens the possibility of using it as a natural remedy for hyperlipidemia, a risk factor for cardiovascular diseases.
- iii. **Anti-microbial Application:** Soursop leaves have shown promise in inhibiting the growth of various bacteria and fungi. This suggests potential applications in developing natural

antimicrobial agents, which could be useful in food preservation or as topical treatments for infections. (Gavamukulya *et al.*, 2017)

- iv. **Potential Anti-Cancer Agent:** The presence of acetogenins, particularly annonacin, suggests a potential role in cancer therapy. Studies have indicated that these compounds can induce apoptosis in cancer cells by inhibiting mitochondrial complex I, disrupting cellular energy production. Therefore, soursop leaf extracts could be explored as a complementary or alternative cancer treatment (Yang *et al.*, 2015).
  
- v. **Antioxidant and Anti-Inflammatory Application:** The abundance of phenolic compounds and flavonoids provides potent antioxidant and anti-inflammatory properties. These properties suggest potential applications in managing chronic diseases associated with oxidative stress and inflammation, such as arthritis and cardiovascular diseases. Furthermore, they may be useful in topical applications for skin conditions (Adefegha and Oboh, 2011; Sundararajan *et al.*, 2016).
  
- vi. **Potential use in Diabetes management:** Some studies indicate that soursop leaves may have a positive effect on blood glucose levels. Additional studies are needed.

## 1.5 SAFETY AND TOXICITY

While young soursop leaves offer potential health benefits, it's crucial to acknowledge safety and toxicity concerns:

- i. **Potential Neurotoxicity:** The presence of annonacin, an acetogenin, raises concerns about potential neurotoxicity. Studies have linked annonacin consumption to atypical Parkinsonism, particularly in regions where soursop consumption is high. This highlights the importance of cautious consumption, especially with long-term usage.
- ii. **Drug Interactions:** Soursop leaves may interact with certain medications, particularly those for diabetes and hypertension, potentially altering their efficacy. Therefore, individuals taking these medications should consult their healthcare provider before using soursop leaf products.

- iii. **Pregnancy and Lactation:** Due to limited safety data, pregnant and breastfeeding women should avoid consuming soursop leaf products.
- iv. **Variability in Phytochemical Content:** The concentration of bioactive compounds in soursop leaves can vary depending on factors such as geographical location, growing conditions, and preparation methods. This variability can affect both efficacy and safety.
- v. **Kidney and liver toxicity:** Some studies have shown potential kidney and liver toxicity with high doses of soursop.

## 1.6 Importance

The investigation of the polyherbal combination of garlic, ginger, and turmeric in the context of diabetes mellitus holds significant importance for several reasons:

1. **Alternative Therapeutic Options:** Diabetes mellitus presents a formidable health challenge globally, and current pharmacological interventions have limitations such as side effects, cost, and accessibility. Exploring alternative and complementary therapies,

particularly those derived from traditional medicinal plants like garlic, ginger, and turmeric, offers new avenues for diabetes management.

2. Traditional Wisdom and Scientific Validation: Garlic, ginger, and turmeric have been used for centuries in traditional medicine systems for their purported health benefits. By subjecting these botanical remedies to rigorous scientific investigation, we can validate their therapeutic potential and bridge the gap between traditional knowledge and modern evidence-based medicine.

3. Multi-Targeted Approach: Diabetes mellitus is a complex metabolic disorder characterized by dysregulation in glucose metabolism, lipid metabolism, inflammation, and oxidative stress. The polyherbal combination of garlic, ginger, and turmeric, with their diverse bioactive compounds, has the potential to target multiple pathways involved in the pathogenesis and progression of diabetes mellitus, offering a comprehensive therapeutic approach.

4. Synergistic Interactions: Studies have suggested that the combination of garlic, ginger, and turmeric may exhibit synergistic interactions, enhancing their individual therapeutic effects. Understanding the mechanisms underlying these synergies can lead to the development of optimized polyherbal formulations with enhanced efficacy and bioavailability.

5. Cost-Effective and Accessible Interventions: Traditional medicinal plants are often more affordable and accessible than conventional medications, particularly in resource-limited settings. If proven effective, the polyherbal combination could serve as a cost-effective and sustainable adjunctive therapy for individuals with diabetes mellitus, contributing to improved health outcomes and reduced healthcare costs.

6. Prevention of Complications: Diabetes mellitus is associated with various complications, including cardiovascular disease, neuropathy, nephropathy, and retinopathy, which significantly impact quality of life and increase healthcare burden. Effective management of diabetes through interventions such as the polyherbal combination may help prevent or mitigate the progression of these complications, thereby improving overall health outcomes and reducing morbidity and mortality rates.

7. Global Health Impact: Diabetes mellitus affects millions of people worldwide and imposes a substantial socioeconomic burden on individuals, families, healthcare systems, and economies. By exploring novel therapeutic options such as the polyherbal combination, we can address the unmet needs of diverse populations and contribute to the global effort to combat the diabetes epidemic.

In summary, the investigation of the polyherbal combination of garlic, ginger, and turmeric in diabetes mellitus is not only scientifically intriguing but also holds great promise for improving therapeutic options, promoting health equity, and alleviating the burden of diabetes-related complications on individuals and societies worldwide.

### **1.7 Objectives of Study**

The objectives of the study are outlined as follows:

Investigate the effects of the polyherbal combination of garlic, ginger, and turmeric on blood glucose levels in diabetic albino rats. Assess the impact of the polyherbal combination on lipid profile parameters, including total cholesterol, triglycerides, LDL (low-density lipoprotein), and

HDL (high-density lipoprotein), in diabetic albino rats. Evaluate the potential anti-inflammatory effects of the polyherbal combination by assessing inflammatory markers such as TNF-alpha (tumor necrosis factor-alpha), IL-6 (interleukin-6), and CRP (C-reactive protein) in diabetic albino rats. Determine the antioxidant activity of the polyherbal combination by measuring oxidative stress markers such as superoxide dismutase (SOD), catalase, and malondialdehyde (MDA) levels in diabetic albino rats. Explore the histopathological changes in pancreatic tissue, liver, kidney, and adipose tissue following treatment with the polyherbal combination, aiming to elucidate its potential protective effects against diabetic complications. Investigate the dose-response relationship of the polyherbal combination and determine the optimal dosage regimen for achieving maximal therapeutic efficacy in diabetic albino rats. Elucidate the underlying mechanisms of action of the polyherbal combination in diabetes management, including its effects on insulin sensitivity, glucose uptake, pancreatic beta-cell function, and cellular signaling pathways involved in glucose and lipid metabolism. Compare the efficacy of the polyherbal combination with standard anti-diabetic medications or monotherapies commonly used in clinical practice, providing insights into its potential as an alternative or adjunctive therapy for diabetes mellitus.

By addressing these objectives, the study aims to contribute to the existing body of knowledge on the therapeutic potential of the polyherbal combination of garlic, ginger, and turmeric in diabetes management, providing valuable insights for the development of novel therapeutic interventions and informing evidence-based healthcare practices.

## **1.5 The Significance of Study**

The significance of the study lies in its potential to advance our understanding of alternative and complementary therapies for diabetes mellitus and its implications for healthcare practices. The study holds significance in the following ways:

**Novel Therapeutic Approach:** Investigating the polyherbal combination of garlic, ginger, and turmeric represents a novel therapeutic approach to managing diabetes mellitus. Traditional medicinal plants have long been used in various cultures for their purported health benefits, and exploring their therapeutic potential in diabetes management offers new avenues for treatment.

**Diverse Bioactive Compounds:** Garlic, ginger, and turmeric contain a plethora of bioactive compounds with diverse pharmacological properties, including anti-inflammatory, antioxidant, and hypoglycemic effects. Understanding how these compounds interact and exert their effects in combination can provide valuable insights into their synergistic mechanisms of action and enhance our understanding of polyherbal formulations.

**Comprehensive Evaluation:** The study aims to conduct a comprehensive evaluation of the polyherbal combination's effects on various aspects of diabetes mellitus, including blood glucose levels, lipid profile, inflammatory markers, oxidative stress, and histopathological changes. This multidimensional approach allows for a thorough assessment of the formulation's potential therapeutic benefits and safety profile.

**Potential for Adjunctive Therapy:** If proven effective, the polyherbal combination could serve as a cost-effective and accessible adjunctive therapy for individuals with diabetes mellitus, particularly in regions where conventional medications may be less accessible or affordable. This

could contribute to improved glycemic control, reduced risk of complications, and enhanced overall quality of life for patients with diabetes.

**Integration of Traditional and Modern Medicine:** By bridging the gap between traditional medicinal knowledge and modern evidence-based medicine, the study promotes the integration of traditional botanical remedies into mainstream healthcare practices. This integration not only preserves cultural heritage but also enriches therapeutic options for individuals with diabetes mellitus.

**Potential for Global Health Impact:** Diabetes mellitus is a global health concern with significant socioeconomic implications. Investigating alternative and complementary therapies such as the polyherbal combination has the potential to address the unmet needs of diverse populations and contribute to the global effort to combat the diabetes epidemic.

**Stimulating Further Research:** The findings of this study may stimulate further research into the therapeutic potential of polyherbal formulations and encourage exploration of other traditional medicinal plants for diabetes management. This can lead to the development of new therapeutic interventions and personalized treatment strategies tailored to individual patient needs.

## **1.6 The Scope of Study**

The scope of the study encompasses several key aspects related to investigating the effects of the polyherbal combination of garlic, ginger, and turmeric on diabetic albino rats. The study will focus on:

1. **Animal Model:** The research will be conducted using diabetic albino rats as the experimental model. This choice allows for the investigation of the polyherbal combination's effects in a controlled laboratory setting while providing insights into its potential therapeutic mechanisms and safety profile.
2. **Biochemical Assessment:** The study will involve the measurement of blood glucose levels to evaluate the polyherbal combination's impact on glycemic control. Additionally, lipid profile parameters such as total cholesterol, triglycerides, LDL (low-density lipoprotein), and HDL (high-density lipoprotein) will be assessed to examine its effects on lipid metabolism.
3. **Inflammatory Markers:** The study will assess inflammatory markers such as TNF-alpha (tumor necrosis factor-alpha), IL-6 (interleukin-6), and CRP (C-reactive protein) to evaluate the polyherbal combination's potential anti-inflammatory effects in diabetic conditions.
4. **Oxidative Stress Markers:** The evaluation of oxidative stress markers, including superoxide dismutase (SOD), catalase, and malondialdehyde (MDA) levels, will provide insights into the polyherbal combination's antioxidant activity and its ability to mitigate oxidative damage associated with diabetes mellitus.
5. **Histopathological Analysis:** Histopathological examination of pancreatic tissue, liver, kidney, and adipose tissue will be conducted to elucidate any structural changes or protective effects induced by the polyherbal combination against diabetic complications.
6. **Dose-Response Relationship:** The study will explore the dose-response relationship of the polyherbal combination to determine the optimal dosage regimen for achieving maximal therapeutic efficacy while minimizing potential adverse effects.

7. Mechanisms of Action: Investigating the underlying mechanisms of action of the polyherbal combination will be a key focus of the study. This will involve assessing its effects on insulin sensitivity, glucose uptake, pancreatic beta-cell function, and cellular signaling pathways involved in glucose and lipid metabolism.
8. Comparison with Standard Therapies: The study may compare the efficacy of the polyherbal combination with standard anti-diabetic medications or monotherapies commonly used in clinical practice, providing insights into its potential as an alternative or adjunctive therapy for diabetes mellitus.

It's important to note that while the study aims to provide comprehensive insights into the effects of the polyherbal combination on diabetes mellitus, certain limitations may exist. These limitations could include variations in individual responses, the specificity of the animal model to human diabetes, and potential confounding factors that may influence the study outcomes.

Overall, the scope of the study encompasses a multidimensional evaluation of the polyherbal combination's effects on diabetes mellitus, aiming to contribute to our understanding of alternative therapeutic options and inform evidence-based healthcare practices for individuals with diabetes mellitus.

### **1.7 Limitations**

While the study aims to provide valuable insights into the effects of the polyherbal combination of garlic, ginger, and turmeric on diabetic albino rats, several limitations should be considered:

1. Animal Model: The use of diabetic albino rats as an animal model may not fully replicate the complexity of human diabetes mellitus. While animal models provide valuable

insights into disease mechanisms and treatment efficacy, the findings may not always translate directly to human physiology and pathology.

2. Efficacy, the findings may not always translate directly to human physiology and pathology.
3. Generalizability: Findings from animal studies may have limited generalizability to human populations. Factors such as species differences, genetic variability, and environmental influences may affect the interpretation and extrapolation of results to clinical settings.
4. Short-Term Study: The duration of the study may be limited, and therefore, long-term effects of the polyherbal combination on diabetes mellitus and its complications may not be fully elucidated. Longitudinal studies with extended follow-up periods would provide more comprehensive insights into the sustained effects and safety profile of the polyherbal combination.
5. Dose and Formulation: Variability in the composition and dosage regimen of the polyherbal combination may affect the study outcomes. Standardization of the formulation and dosing protocols is essential to ensure consistency and reproducibility across experimental groups.
6. Interactions with Diet and Environment: Factors such as diet composition, environmental conditions, and housing facilities may influence the study outcomes. Standardization of these factors and careful consideration of potential confounders are crucial to minimize variability and enhance the validity of the results.
7. Mechanistic Understanding: While the study aims to explore the mechanisms of action underlying the polyherbal combination's effects on diabetes mellitus, the precise

molecular pathways involved may not be fully elucidated. Further mechanistic studies, including molecular and cellular investigations, may be necessary to unravel the underlying mechanisms comprehensively.

8. **Ethical Considerations:** Ethical considerations related to animal welfare and experimentation should be carefully addressed throughout the study. Measures to minimize animal discomfort and suffering, adherence to ethical guidelines, and appropriate oversight by institutional review boards are essential to uphold ethical standards in research involving animal subjects.
9. **Potential Confounding Factors:** Despite efforts to control for confounding variables, unanticipated factors or biases may influence the study outcomes. Robust study design, randomization, blinding, and statistical analysis techniques are essential to minimize the impact of confounding factors and enhance the reliability of the results.

Acknowledging these limitations is critical for interpreting the findings of the study accurately and contextualizing their implications for clinical practice and future research endeavors. While the study contributes valuable insights into the therapeutic potential of the polyherbal combination for diabetes mellitus, further research is warranted to address these limitations and advance our understanding of alternative therapeutic options for diabetes management.

## **1.8 Definition of Terms**

1. **Diabetes Mellitus:** A chronic metabolic disorder characterized by elevated blood glucose levels resulting from defects in insulin secretion, insulin action, or both. Diabetes mellitus may lead to various complications, including cardiovascular disease, neuropathy, nephropathy, and retinopathy.

2. **Polyherbal Combination:** A formulation containing a combination of multiple herbs or botanical extracts with the intention of producing synergistic therapeutic effects. In the context of this study, the polyherbal combination refers to the mixture of garlic (*Allium sativum*), ginger (*Zingiber officinale*), and turmeric (*Curcuma longa*) used for investigating its effects on diabetic albino rats.
3. **Albino Rats:** Laboratory rats with a genetic condition resulting in a lack of pigmentation, characterized by white fur and pink eyes. Albino rats are commonly used as experimental models in scientific research due to their ease of handling, availability, and physiological similarities to humans.
4. **Hypoglycemic:** Having the property or ability to lower blood glucose levels. Hypoglycemic agents or compounds are used in the treatment of diabetes mellitus to reduce hyperglycemia and maintain blood glucose within a normal range.
5. **Antioxidant:** A substance that inhibits oxidative stress and protects cells from damage caused by free radicals. Antioxidants play a crucial role in reducing oxidative damage and inflammation associated with various chronic diseases, including diabetes mellitus.
6. **Inflammatory Markers:** Biomolecules or proteins produced by the body in response to inflammation. Common inflammatory markers include tumor necrosis factor-alpha (TNF-alpha), interleukin-6 (IL-6), and C-reactive protein (CRP). Elevated levels of inflammatory markers are associated with chronic inflammation, which is implicated in the pathogenesis of diabetes mellitus and its complications.
7. **Oxidative Stress:** An imbalance between the production of reactive oxygen species (ROS) and the body's ability to detoxify or neutralize their harmful effects through antioxidants.

Oxidative stress contributes to cellular damage, inflammation, and dysfunction of various organs and tissues, including those affected by diabetes mellitus.

8. **Histopathological Analysis:** The microscopic examination of tissue specimens to evaluate their structural and cellular characteristics. Histopathological analysis involves staining tissue sections with dyes and examining them under a microscope to identify abnormalities, assess tissue damage, and elucidate disease processes.
9. **Dose-Response Relationship:** The relationship between the dose or concentration of a drug, intervention, or substance and its biological or physiological effects. Understanding the dose-response relationship is essential for determining the optimal dosage regimen that achieves the desired therapeutic effects while minimizing adverse reactions or toxicity.
10. **Mechanisms of Action:** The specific biochemical, cellular, and physiological processes through which a drug or intervention exerts its therapeutic effects. Understanding the mechanisms of action helps elucidate the pharmacological properties, target pathways, and potential side effects of the intervention, facilitating rational drug design and clinical use.

These definitions provide a foundational understanding of key terms relevant to the investigation of the polyherbal combination's effects on diabetes mellitus and its associated parameters in experimental models. Clarifying these terms enhances communication, facilitates interpretation of study findings, and promotes scientific understanding in the field of diabetes research and therapeutics.

## **CHAPTER ONE**

### **INTRODUCTION**

#### **1.1 Diabetes mellitus**

The prevalence of diabetes mellitus has reached epidemic proportions worldwide, constituting a significant public health challenge. Diabetes mellitus, characterized by chronic hyperglycemia resulting from defects in insulin secretion, action, or both, presents a multifaceted burden that extends beyond individual health to societal and economic domains. Despite advances in medical science and the availability of pharmacological interventions, the management of diabetes remains complex and often inadequate, with a substantial proportion of patients experiencing complications and suboptimal glycemic control.

In light of the limitations and challenges associated with conventional therapies, there has been a growing interest in exploring alternative and complementary approaches to diabetes management. Traditional medicinal plants, rich in bioactive compounds with diverse pharmacological properties, have emerged as promising candidates for adjunctive or alternative therapeutic

strategies. Among the plethora of botanical remedies, the polyherbal combination comprising garlic (*Allium sativum*), ginger (*Zingiber officinale*), and turmeric (*Curcuma longa*) has garnered attention for its potential anti-diabetic effects.

Garlic, ginger, and turmeric, commonly used as culinary ingredients and traditional medicines in various cultures, have been attributed with a myriad of health benefits. These botanicals are renowned for their anti-inflammatory, antioxidant, and hypoglycemic properties, making them attractive candidates for combating the pathophysiological mechanisms underlying diabetes mellitus. While individual components of the polyherbal combination have been investigated for their anti-diabetic effects in experimental and clinical studies, the collective impact of garlic, ginger, and turmeric on diabetes management remains relatively underexplored.

This study seeks to address this gap in knowledge by elucidating the effects of the polyherbal combination on diabetic albino rats, serving as a preclinical model for investigating the therapeutic potential of herbal interventions in diabetes. Through a comprehensive examination of biochemical, hematological, and histopathological parameters, this research aims to provide insights into the efficacy and mechanisms of action underlying the polyherbal formulation's anti-diabetic effects.

By elucidating the pharmacological properties and therapeutic efficacy of the polyherbal combination, this study endeavors to contribute to the growing body of evidence supporting the integration of traditional botanical remedies into mainstream diabetes

## **1.1 Statement of the Problem**

Despite advancements in medical science and the availability of pharmacological interventions, diabetes mellitus remains a significant public health challenge worldwide. Characterized by chronic hyperglycemia and associated with a myriad of complications, diabetes exerts a substantial burden on individuals, healthcare systems, and society as a whole. The current therapeutic armamentarium for diabetes management, although effective to some extent, is often limited by factors such as cost, adverse effects, and inadequate glycemic control.

In light of these challenges, there is a growing interest in exploring alternative and complementary therapies, including traditional medicinal plants, as adjunctive or alternative approaches to diabetes management. Among these botanical remedies, the polyherbal combination comprising garlic (*Allium sativum*), ginger (*Zingiber officinale*), and turmeric (*Curcuma longa*) has garnered attention for its potential anti-diabetic effects.

While individual components of the polyherbal combination have been studied for their therapeutic properties, the collective impact of garlic, ginger, and turmeric on diabetes management remains relatively underexplored, particularly in preclinical models. Consequently, there exists a significant gap in knowledge regarding the specific effects and mechanisms of action of the polyherbal formulation in mitigating diabetes-associated pathophysiological processes.

Therefore, the overarching problem addressed by this study is the lack of comprehensive understanding regarding the efficacy, safety, and mechanisms of action underlying the polyherbal combination's effects on diabetes mellitus. Specifically, there is a need to elucidate the impact of the polyherbal formulation on glycemic control, lipid metabolism, inflammatory markers, and oxidative stress in diabetic conditions. Additionally, the potential synergistic

interactions among the bioactive compounds present in garlic, ginger, and turmeric warrant investigation to ascertain the optimal composition and dosage regimen for therapeutic efficacy.

Addressing these knowledge gaps is essential for advancing our understanding of alternative and complementary approaches to diabetes care and informing evidence-based healthcare practices. Furthermore, elucidating the therapeutic potential of the polyherbal combination may pave the way for the development of novel therapeutic interventions that are accessible, cost-effective, and conducive to improved outcomes for individuals with diabetes mellitus.

## **CHAPTER THREE**

### **MATERIALS AND METHODS**

#### **3.1 COLLECTION OF RESEARCH MATERIALS**

The Fruits of *Pentaclethra macrophylla* were purchased from of Oba market in Benin City, Edo State, Nigeria. They were cleaned and air dried at room temperature for 2 weeks and transferred to an oven to completely dry for 24 hours at 45<sup>0</sup>C after which they were weighed and pulverised into powdery form and stored in air tight container respectively (Obaro *et al.*, 2024).

### **3.2 EXTRACTION OF PLANT MATERIAL**

The powdered sample was extracted by method of cold maceration. 200 g of the powdered samples were soaked in 1000 ml of methanol solvent and scooped vigorously in an air tight jar and wrapped with black cloth which was kept in a cupboard and monitored regularly and scooped for 72 hours. After 72 hours, cheese cloth was used to separate the plant fiber from the concentrate and transferred to the oven to dry for seven (7) days at a controlled temperature of 45<sup>0</sup>C. The dried sample was weighed and the yield was calculated.

### **3.3 EXPERIMENTAL ANIMALS**

Albino mice weighing 25 to 30 g and rats weighing 200 to 250 g were purchased from the Animal House of the Department of Anatomy, School of Basic Medicine, University of Benin.

#### **3.3.1 DRUGS /CHEMICALS/MATERIALS**

Streptozotocin, Glibenclamide, distilled water, rat restrainer, pelletized feed, cotton wool, methylated spirit, pocket P<sup>H</sup> meter, glass slide, cover slips, microscope, centrifuge, hand gloves, plastic cages, syringe, oral gavage, glucometer.

#### **3.3.2 ACUTE TOXICITY STUDY**

Acute toxicity study was carried out by methods of (OECD, 2018) Organization of economic cooperation development guidelines.

Three (3) male mice and 3 female mice each were administered 5000 mg/kg of the aqueous extract of unripe plantain peel respectively and observed for 72 hours for possible signs of toxicity, mortality or morbidity.

### **3.3.3 ACUTE NORMOGLYCEMIC STUDY**

Study Design Before the induction of diabetes, six normoglycemic rats were administered single of 1000 mg/kg of the Methanol fruit extract of *Pentaclethra macrophylla* (MFEPM) orally and the blood sugar level were evaluated using blood samples obtained from tail vein.

### **3.3.4 ANTI-DIABETIC STUDY**

Control Group: Rats of this group were administered distilled water (2 ml/kg/body weight) for 14 days.

Diabetic Group: In this group, rats were induced to become diabetic through a single intramuscular injection of STZ at a dose of 40 mg/kg of body weight. These diabetic rats received oral administration of distilled water for 14 days at a dose of 1 mL/kg/d body weight.

MFEPM Treated Diabetic Group: Diabetic rats in this group were treated with methanol fruit extract of *Pentaclethra macrophylla* (MFEPM) at doses of 100 and 250 mg/kg of body weight/d for 14 days while in a fasting state.

Glibenclamide Treated Diabetic Group: Rats in this group, which were also diabetic, received treatment with glibenclamide at a dose of 20 mg/kg of body weight/d for 14 days.

A single dose of Methanol fruit extract of *Pentaclethra macrophylla* (MFEPM) was administered orally every day in the morning (at 10.00 AM) using an orogastric gavage for a duration of 14 days. After 14 days of extract treatment animals were left untreated for 7 days (24<sup>th</sup> day of STZ-

injection), blood glucose levels were measured, and all animals were euthanized using chloroform anesthesia. Blood was subsequently drawn, and serum was separated by centrifugation at 3000 rpm for 10 minutes to perform serum biochemical and lipid profile tests. The right kidney were dissected out from each group and fixed in 10% formalin for histological studies.

While administering glibenclamide treatment, the FBG levels in all the test rats were assessed after 7 and 14 days of treatment through blood samples obtained from the tail vein were analyzed using an AccuCheck glucometer.

### **3.3.5 BLOOD GLUCOMETER CHECK**

Accucheck active glucometer and blood glucose test strips, manufactured by Roche Diagnostic GmbH in Mannheim, Germany, were employed to measure fasting blood glucose levels.

### **3.3.6 HISTOLOGICAL STUDY**

Wistar rats used for the anti-diabetic studies were anesthetized and had their Kidneys excised. The excised organs were histologically prepared for further microscopic study.

### **3.3.7 STATISTICAL ANALYSIS**

The results from the studies were expressed as mean  $\pm$  SEM. Statistical analysis were carried out using graph pad prism 8 version software (UK). Comparisms between the control and treated groups were analysed using one-way ANOVA and, Dunnett's multiple comparisms test a and d =  $P \leq 0.05$ , and 0.0001 was regarded as indicating significant difference.

## **3.4 Experimental Grouping**

Group 1 (G1) Control group

Group 2 (G2) the rats were given

Group 3 (G3) the rats were given

### **3.5 Experimental design**

The albino rats were housed in wooden cages. The rabbits were fed 10% body weight with their respective food twice daily.

Group 1 rabbits were fed with commercial growers mash (10 am and 6 pm), Group 2 rabbits were fed with ripe plantain peel (10 am and 6 pm) while Group 3 rabbits were fed with unripe plantain peel (10 am and 6 pm). Cleaning and changing of the rabbit's beddings and enclosures was done twice daily at 10 hours (10 am and 6pm) in order to keep the environment clean for the rabbits to prevent infections and out breaks. Regular feed of the rabbits and cleaning of utensils as well as routine management practices was ensured.

### **3.6 Data collection**

Data was collected at the beginning of the experiment regarded as day zero (1) and subsequently on weekly basis by taking measurements body weight. The body weight was measured using a Meteller electronic scale to the nearest 1000 g, while hematological parameters were measured using capillary tube and hematocrit reader. The average weekly weight gain was determined by the mean weight gains or loss. Twenty four (24) hours after the last feeding blood was drawn from the vein in the ear for Haematology and biochemical tests.

### **3.7 Statistical analysis**

Every value was represented as Mean  $\pm$  Standard Error of Mean (SEM). Using the UK's Graph Pad Prism 8.2 software, oneway ANOVA was used to analyze the data.  $P \leq 0.05$  was used to define significance for differences.

## **CHAPTER FOUR**

### **RESULTS**

#### **4.1 EFFECT OF N-HEXANE EXTRACT OF POLY HERBAL MIXTURE (NHEPHM) ON ACUTE TOXICITY STUDY**

Administration of a single dose of 1000, 2000 and 5000 mg/kg of N-Hexane extract of poly herbal mixture (NHEPHM) to mice resulted in no signs of toxicity such as: Grooming, nausea and writhing.

#### **TABLE 4.1: EFFECT OF N-HEXANE EXTRACT OF POLY HERBAL MIXTURE (NHEPHM) ON ACUTE TOXICITY STUDY**

#### **4.2 EFFECT OF N-HEXANE EXTRACT OF POLY HERBAL MIXTURE (NHEPHM) ON NORMOGLYCEMIC BLOOD SUGAR LEVEL**

#### **TABLE 4.2: EFFECT OF N-HEXANE EXTRACT OF POLY HERBAL MIXTURE (NHEPHM) ON NORMOGLYCEMIC BLOOD SUGAR LEVEL**

#### **4.3 EFFECT OF N-HEXANE EXTRACT OF POLY HERBAL MIXTURE (NHEPHM) ON BLOOD SUGAR LEVEL (BSL) OF STREPTOZOTOCIN INDUCED DIABETIC RATS.**

#### **TABLE 4.3: EFFECT OF N-HEXANE EXTRACT OF POLY HERBAL MIXTURE (NHEPHM) ON BLOOD SUGAR LEVEL (BSL) OF STREPTOZOTOCIN INDUCED DIABETIC RATS.**

#### **4.4 EFFECT OF N-HEXANE EXTRACT OF POLY HERBAL MIXTURE (NHEPHM) ON LIVER FUNCTION INDICES**

**TABLE 4.4: EFFECT OF N-HEXANE EXTRACT OF POLY HERBAL MIXTURE (NHEPHM) ON LIVER FUNCTION INDICES**

**4.5 EFFECT OF N-HEXANE EXTRACT OF POLY HERBAL MIXTURE (NHEPHM) ON LIPID PROFILE INDICES**

**Table 4.5 Effect of N-Hexane extract of poly herbal mixture (NHEPHM) on Lipid profile indices**

## **CHAPTER FIVE**

### **DISCUSSION**

**5.1 N-HEXANE EXTRACT OF POLY HERBAL MIXTURE (NHEPHM) ON ACUTE TOXICITY STUDY**

**5.2 EFFECT OF N-HEXANE EXTRACT OF POLY HERBAL MIXTURE (NHEPHM) ON NORMOGLYCEMIC BLOOD SUGAR LEVEL**

**5.3 EFFECT OF N-HEXANE EXTRACT OF POLY HERBAL MIXTURE (NHEPHM) ON BLOOD SUGAR LEVEL (BSL) OF STREPTOZOTOCIN INDUCED DIABETIC RATS.**

**5.4 EFFECT OF N-HEXANE EXTRACT OF POLY HERBAL MIXTURE (NHEPHM) ON LIVER FUNCTION INDICES**

**5.5 EFFECT OF N-HEXANE EXTRACT OF POLY HERBAL MIXTURE (NHEPHM) ON LIPID PROFILE INDICES**

**5.6 EFFECT OF N-HEXANE EXTRACT OF POLY HERBAL MIXTURE (NHEPHM) ON THE HISTOLOGY OF THE KIDNEY**

## CONCLUSION

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