



Phytochemistry, *In vivo* Hypoglycaemic and Anti-diabetic Potentials of Crude Ethanol root extract of *Leptadenia hastata* in Normal and Diabetic Albino Rats

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ABSTRACT

This study investigated the hypoglycemic and anti-diabetic potentials of *Leptadenia hastata* crude ethanol root extracts in normal and diabetic albino rats. The hypoglycemic study consisted of twenty-five (25) rats assigned to five (5) groups of five (5) rats each. Group A (control), Groups B to E were administered 200, 400, 600 and 800 mg/kg of the extract respectively, orally. Blood- glucose levels were monitored on Days 0, 7, 14, 21, and 28. The anti-diabetic study consisted of Thirty-five (35) albino rats assigned to seven (7) groups of five (5) rats each. Diabetes was induced using a single intra-peritoneal administration of alloxan monohydrate at a dose of 160 mg/kg. Group A was administered distilled water, while Group B was administered Insulin at 0.1µg/kg, Groups C, D and E were administered 200, 400, 600, and 800 mg/kg of the extract (orally), respectively. Diabetes was induced in rats in group F while Group G comprised normal control rats. Blood glucose levels were monitored at 0, 1, 3, 6, 12, and 18 hours post treatment. Phytochemical analysis identified flavonoids, tannins, alkaloids, terpenoids, and varying quantities of micro and macro elements in the LHERE. The extract exhibited a dose-dependent effect on blood glucose levels in diabetic rats, with the highest dose (800 mg/kg) showed a consistent reduction in blood glucose levels compared to the standard drug (insulin). Furthermore, the extract had a hypoglycemic effect on normocemic rats, significantly reducing blood glucose over time. In conclusion, the crude ethanol root extract of *Leptadenia hastata* demonstrated significant anti-diabetic and hypoglycemic effects in rat models. The results obtained in the present study support the traditional use of *Leptadenia hastata* extracts, and its therapeutic potential for developing novel anti-diabetic agents.

Keywords: Albino, antidiabetic, hypoglycaemic, *Leptadenia hastata*, therapeutic

INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disorder manifesting elevation in blood glucose level (BGL), primarily due to defective insulin function or secretion from the islet of Langerhans cell, during glucose uptake in target tissues (Shyam and Kadalmani, 2014; Alema *et al.*, 2020; Melesie *et al.*, 2020). Sustained hyperglycaemic state is often associated with microvascular and macrovascular syndromes that include retinopathy, neuropathy, nephropathy, coronary and peripheral arterial diseases, and stroke. These complications mostly result in irreversible damage in various organs that can result in life threatening conditions (Pari and Saravanan, 2004; Soumya and Srilatha, 2011; Meresa *et al.*, 2017).

Currently, Diabetes mellitus is one of the leading metabolic disorders of public health importance and the cause of morbidity and death globally (Ogurtsova *et al.*, 2015;

Hosseini *et al.*, 2015; Issa and Hussen Bule, 2015; Alema *et al.*, 2020; Melesie *et al.*, 2020). The estimated prevalence of diabetes in adults (20 to 79 years) has more than tripled since the year 2000, rising from an estimated 151 million (4.6% of the world's population at the time) to 537.5 million (10.5%) of the world's population today. The prevalence rate will be higher than 12.8% by 2045 (Kumar *et al.*, 2024).

Management of diabetes mellitus relies solely on keeping blood glucose levels within normal limits between 3.5–5.5 mmol/L (Güemes *et al.*, 2016) by administration of medications and lifestyle modifications (Dinku *et al.*, 2010; Alema *et al.*, 2020). To date, readily available medicines for diabetes comprise various preparations of insulin and oral antihyperglycemic agents (Holstein *et al.*, 2011; Nabi *et al.*, 2013; Pearson, 2016; Connelly *et al.*, 2016; Hammesso *et al.*, 2019). The older oral hypoglycaemic's are sulphonyl urea's, alpha-glucosidase inhibitors, thiazolidinediones, and

biguanides (Tsegaye *et al.*, 2008; Nabi *et al.*, 2013), while the newer classes include insulin-based therapies, sodium-glucose cotransporter 2 (SGLT-2) inhibitors, glucokinase activators, and injectable glucagon-like peptide (GLP-1) agonists (Ohki *et al.*, 2016). These drugs are used either as monotherapy or in combinations to achieve a more potent synergistic outcome (Nabi *et al.*, 2013).

The commonly used antidiabetic agents have several limitations, and successful treatment of diabetes has become a global challenge requiring urgent investigations. These medications have been often linked with several drug reactions or side effects, that includes hepatocellular injury, renal diseases, blood dyscrasias, gastrointestinal irregularities, hypoglycemic hypersensitivity reactions, weight gains, and lactic acidosis, which decrease their effectiveness and/or compliance rates (Rajalakshmi *et al.*, 2009; Nabi *et al.*, 2013; Soumya and Srilatha, 2011; Ramya *et al.*, 2021). The complications resulting from most antidiabetic agents, have defined a clear need for the search for newer antidiabetic drugs, and medicinal plant sources have become the research interest of most scientific communities. Globally, Medicinal Plants (MPs) have been used as sources of medicines, and more than 80% of people depend on them, utilizing their extracts for their primary health care desires (Begashaw *et al.*, 2017; Muthu *et al.*, 2006). Plant-based formulations have become the key players of most available treatments, particularly in rural parts of the world, affordability, due to their accessibility, affordability, and minimum adverse effects (Nabi *et al.*, 2013; Salehi, *et al.*, 2019).

Leptadenia histata, a herbaceous herb, is widely used in tropical Africa as vegetable (Burkill, 1995), this plant is often used locally for the treatment of many ailments including diabetes amongst local communities in the north eastern part of Nigeria (Burkill, 1995; Bello *et al.*, 2011). Its folkloric use in controlling blood glucose has prompted researchers to investigate its anti-diabetic and hypoglycemic potential in different animal models. Several studies have highlighted the anti-diabetic properties of different plant extracts, emphasizing their ability to modulate glucose homeostasis and improve insulin sensitivity. This study aims to contribute valuable insights into phytochemistry, in vivo hypoglycemic and anti-diabetic potentials of the crude ethanol root extracts of *Leptadenia hastata* in normal and alloxan-induced diabetic rat model.

MATERIAL AND METHODS

SAMPLE COLLECTION AND IDENTIFICATION.

Fresh sample of the root of *Leptadenia histata* was collected within University of Maiduguri campus botanical garden in

Borno State, Nigeria. The plant specimen was identified and authenticated by a plant taxonomist, Prof. S. S. Sanusi at the Department of Biological Sciences University of Maiduguri, Borno State. The herbarium specimen with a voucher number UM/VET/011 was deposited at the Post Graduate Research Laboratory, Department of Chemistry. The root of the plant was washed with clean water and air-dried under shade and pulverized into powder and then coded "*plant material*".

EXTRACTION OF PLANT MATERIAL

The air-dried powdered plant material (11.2 kg) was extracted exhaustively with 85 % ethanol using a Soxhlet apparatus. The sample was placed inside a thimble which was loaded into the main chamber of the Soxhlet extractor was placed into a flask containing the extraction solvent (ethanol). The solvent was heated to reflux the solvent vapour which travelled up a distillation arm and flooded into the chamber housing the thimble with the solid. The condenser ensured that the solvent vapour did not escape but cooled and dripped back down into the chamber housing the solid material (Usman *et al.*, 2007). The chamber containing the solid material was slowly filled with warm solvent and some of the desired compounds dissolved in the warm solvent. When the Soxhlet chamber was almost full, the chamber was automatically equipped with a siphon side arm, with the solvent running back down to the distillation flask. The thimble ensure that the rapid motion of the solvent did not transport any solid material to the still pot. The cycle was allowed to repeat many times, over 48 hours until the extraction was exhaustively done. The titrate was removed and dried at room temperature. The filtrate was concentrated at low pressure to obtain a mass which was coded (LHERE) – *Leptadenia hastata* ethanolic root extract, which served as the working sample for both the acute toxicity determination as well as anti-diabetic activity study (Wu *et al.*, 2005).

ASHING AND DIGESTION OF SAMPLE

Wu *et al.* (2005) laboratory procedure for the preparation and determination of both macro and micronutrients of LHERE was adopted, using the Perkin-Elmer Analysis 300 single beam Atomic Spectrometry. The data were obtained in parts per million (ppm), which were then converted to mg/g. The calibration curve was established using working standard for each element.

PHYTOCHEMICAL SCREENING

Two (2) grams each of the LHERE, were subjected to qualitative phytochemical screening to test for the presence of secondary plant metabolites: alkaloids, anthraquinones, carbohydrates, flavonoids, saponins, tannins, glycosides

(cardiac, steroidal), terpenes/terpenoids as described by Trease & Evans, (2009).

EXPERIMENTAL ANIMALS

Sixty (60) albino rats of both sexes weighing $200\text{g} \pm 30\text{g}$ were used for the study. The rats were purchased from the Department of Veterinary Physiology, Pharmacology and Biochemistry Laboratory, University of Maiduguri, and kept in a well-ventilated plastic cage in the Laboratory. They were allowed feeding *ad-libitum* with commercial Grower's Mash (Livestock Feed[®], Nigeria Ltd.) and provided with fresh tap water on daily basis for 2 weeks before the commencement of the research.

All the rats were handled according to the International Guiding Principles for Biomedical Research Involving animals, Council for International Organization for Medical Science, and International Council for Laboratory Animal Science (CIOMS & ICLAS, 2012) as certified by the faculty of Veterinary medicine, University of Maiduguri.

EVALUATION OF HYPOGLYCAEMIC ACTIVITY OF LHERE IN NORMAL RATS

Twenty-five (25) albino rats were used for the study. They were assigned to five (5) groups of five (5) rats each labelled A to E. Group A were administered 0.25ml of distilled water (control). Groups B to E were orally administered 200, 400, 600 and 800 mg/kg body weight of the LHERE, respectively. The fasting blood glucose levels were tested for on Days 0, 7, 14, 21 and 28.

EVALUATION OF ANTI-DIABETIC ACTIVITY OF LHERE IN DIABETIC RATS.

A total of thirty-five (35) albino rats of both sexes weighing between 200 and 250 g were used for the study. Thirty (30) of these rats were induced by single intra-peritoneal administration of alloxan monohydrate (Sigma Chemical Co., St. Louis, U.S.A.) at a dose of 160 mg/kg body weight dissolved in 0.1M freshly prepared cold citrate buffer of pH 4.5 as described by Al-Shamoany *et al.*, (1994), while the remaining five (5) rats served as control. Baseline blood glucose values were determined prior to administration of alloxan and on the third day, the glucose level was monitored for increase from the initial value. Stable hyperglycaemia was confirmed on the fifth day post induction when the fasting blood glucose levels of the rats were found to be greater than 180 mg/dl. These diabetic rats were then allotted to six (6) groups of five (5) rats each. Group A were administered distilled water and served as negative control while Group B received insulin at 0.1µg/kg body weight (positive control) and Groups C, D, E and F were administered orally 200, 400, 600, and 800 mg/kg body weight of the LHERE extract, respectively.

BLOOD COLLECTION AND GLUCOSE-LEVEL DETERMINATION

Blood samples were collected from the tail vein by snipping the tail with a pair of scissors. Blood glucose was determined by glucose oxidase method using One Torch Basic Glucose monitoring system (LifeScan Inc. Milpitas, California, USA) at 0 hour and at 1, 3, 6, 12 and 18 hours, in all rat groups.

DATA ANALYSIS

Data obtained from the study were analysed using one way analysis of variance (ANOVA). The Bonferroni post-hoc test was used to determine the relationship between the variables means. The results were expressed as Mean \pm Standard Error of the Mean (SEM) in tables. Statistical Package for Social Sciences (SPSS) version 16 software was used for the analysis. Significance was accepted at $p < 0.05$.

RESULTS

ESTIMATION OF THE ELEMENTAL CONTENT OF CRUDE ETHANOL EXTRACT OF *LEPTADENIA HASTATA*

The macro- and microelements concentrations in the root of *L. hastata* are presented in Table I. The macroelements present in the extract were calcium, magnesium, potassium, and sodium. The result also revealed that calcium had the highest concentration and sodium had the lowest concentration in the sample. The levels of microelements in the sample were shown on I, with iron (Fe) having the highest concentration, while cadmium was the lowest, and the concentration of cobalt (Co) was not detected.

QUALITATIVE PHYTOCHEMICAL CONSTITUENTS OF CRUDE ETHANOL ROOT EXTRACT OF *L. HASTATA*

The qualitative phytochemical screening of the LHERE is shown in Table II. The result showed the presence of alkaloids, carbohydrates, cardenolides, cardiac glycosides, flavonoids, saponins and terpenoids in the ethanol root extract.

ANTI-DIABETIC AND HYPOGLYCAEMIC ACTIVITY OF THE ETHANOL CRUDE OF *L. HASTATA* ROOT EXTRACT

The effect of crude ethanol root extract of *Leptadenia hastata* on mean blood glucose levels of diabetic rats is presented in Table III. After 1 hour of extract administration the blood glucose level of rats treated with 200 mg/kg body weight of the extract showed no statistically significant decrease compared to zero-hour blood glucose value. The glucose level significantly ($p < 0.05$) decreased at 12 and 18 hours post extract administration.

The groups treated with 400 mg/kg body weight of LHERE had a decrease in blood glucose at 18 hours post extract administration was observed. The blood glucose levels of rats administered with 600 mg/kg of LHERE did not show any significant change. In the group treated with 800 mg/kg body weight of LHERE, the glucose kept on decreasing ($p < 0.05$) at 1, 3, 6, 12 and 18 hours post extract administration. The insulin (standard drug) treated group had their blood glucose level significantly ($p < 0.05$) decreased, when compared with control at 1, 3, 6, 8, 12 and 18 hour(s), post-treatment. The diabetic untreated group had their blood glucose levels increased significantly ($p < 0.05$) from 0 up to 18 hours of the experiment. The glucose level in normal control group did not significantly change.

Table I. Macro and micro elements content of *Leptadenia hastata* Root

| Macro elements | Micro elements | Concentration (mg/g) | RDA (mg/g/day) |
|----------------|----------------|----------------------|----------------|
| Ca | | 184.33 | 34.80 |
| Mg | | 31.46 | 41.16 |
| K | | 4.10 | 7.34 |
| Na | | 1.50 | 17.8 |
| | Cd | 0.01 | ND |
| | Cr | 0.35 | 0.2 |
| | Cu | 0.10 | 1-3 |
| | Fe | 3.88 | 33.3 |
| | Ni | 0.08 | ND |
| | Zn | 0.14 | 87.27 |
| | Co | 0.00 | ND |

ND: Not Detected, RDA; Required Dietary Allowance for macro and micro Minerals in *L. hastata*

EFFECT OF ETHANOL CRUDE EXTRACT OF *LEPTADENIA HASTATA* ROOT ON MEAN BLOOD GLUCOSE LEVELS OF NORMAL ALBINO RATS

The effect of ethanol crude extract of *Leptadenia hastata* root on blood glucose level of normal albino rats is presented in Table IV. After day 7 as well as day 14 post-extract administration, the group treated with 400mg/kg body weight of the extract showed no significant decrease in blood glucose level compared with that of day zero. However, between day 14-28 there was significant ($p < 0.05$) reduction in blood glucose level up to day 28 of treatment. In the

groups treated with 600 and 800 mg/kg of LHERE, there were significant ($p < 0.05$) reductions in blood glucose levels at days 7,14, 21 and 28 of the treatment.

DISCUSSION

Medicinal plants have an invaluable role in the management of diabetes mellitus and other related ailments especially in developing countries where resources are scarce, and a major part of the population mostly affected do not have access to or cannot afford the synthetic drug. Management of diabetes relies mostly on the maintenance of lower blood glucose levels with long-term treatment rather than the acute hypoglycaemic effect after a single administration. In this study, it was found that repeated administration of LHERE consistently decreased blood glucose levels in diabetic albino rats after induction of hyperglycaemia by a single intra-peritoneal administration of alloxan monohydrate at a dose of 160 mg/kg body weight (Rahman *et al.*,2017). The present study confirms the folkloric use of *L. hastata* in the treatment of diabetes mellitus and agrees with the findings of Sanda *et al.*, (2013) who reported the antidiabetic and hypoglycemic effects of *L. hastata* aqueous root extracts in albino rats. The qualitative phytochemical screening of ethanol root extract of *L. hastata* revealed the presence of some macro and microelements, and the presence of phytometabolites such as flavonoids, tannins, alkaloids, and terpenoids that were detected and are known to have antidiabetic effect (Choudhury *et al.*, 2024).

The effect of the ethanol root extract of *Leptadenia hastata* root on mean blood glucose levels of diabetic rats as shown in Table 3. revealed that 1 hour of post-extract administration, the blood glucose level of rats treated with 200 mg/kg body weight of the extract showed no significant decrease compared to zero-hour blood glucose value. The glucose level significantly ($P \leq 0.05$) decreased at 3, 6, 8, 12, and 18 hours post extract administration, respectively. Administration of 400 mg/kg body weight decreased blood glucose at 18 hours post-extract administration. The blood glucose levels of rats administered with 600 mg/kg did not show any significant change. Furthermore, at 800 mg/kg body weight, the glucose level continuously decreased ($P \leq 0.05$) at 1, 3-, 6-, 12-, and 18-hours post-extract administration, respectively, while the insulin (standard drug) treated group had their blood glucose level significantly ($P \leq 0.05$) decreased at 1, 3, 6, 8, 12 and 18 hour(s) respectively. The diabetic untreated group had their blood glucose levels increased significantly ($P \leq 0.05$) from 0 up to the 18 hours of the experiment. The glucose level in the normal control group did not significantly change.

The ethanol root extracts of *L. hastata* had significant effect on blood glucose levels in both diabetic and normal

Table II. Qualitative Phytochemical Constituents of Crude Ethanol and Fractionated Portion of the Root Extract of *L. hastata*

| S/No. | Constituents | Methods Adapted | Results |
|-------|---------------------------|--------------------------|---------|
| | | | Crude |
| 1. | Alkaloids | Dragendorff's Mayer's | + + |
| 2. | Antraquinones | | |
| | Combined antraquinones | Borntrager's | - |
| 3. | Carbohydrates | | |
| | General test | Molisch's | + |
| | Monosaccharide | Barfoed's | - |
| | Free reducing sugar | Fehling's | + |
| | Combined reducing sugar | Fehling's | + |
| | Ketoses | Salivanoff's | + |
| | Pentoses | | - |
| 4. | Cardenolides | Keller-Kiliani's | + |
| 5. | Cardiac glycosides | | |
| | Salkowski's | L-Buchard's | + |
| | Lieberman-Buchard's | L-Buchard's | + |
| 6. | Flavonoids | | |
| | | Shinoda's | + |
| | | Ferric chloride | + |
| | | Lead acetate | - |
| | | NaOH | + |
| 7. | Phlobatannins | | - |
| 8. | Saponins | Frothing's | + |
| 9. | Soluble starch | | - |
| 10. | Tannins | | |
| | | Ferric chloride | - |
| | | Lead acetate | - |
| 11. | Terpenoids | | + |

Key: + = Present, - = Absent.

Table III: Mean Blood Glucose Level \pm SEM of Diabetic Albino Rats treated with crude ethanol root extract of *L. hastata*

| Groups | Dosage (mg/kg) | Time (hrs) | | | | | | |
|--------|---------------------|------------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|
| | | 0hr | 1hr | 3hrs | 6hrs | 8hrs | 12hrs | 18hrs |
| A | Insulin | 437.0 \pm 42.2 | 119.5 \pm 3.96 ^b | 80.5 \pm 3.96 ^b | 79.0 \pm 8.34 ^b | 112.3 \pm 12.9 ^b | 190.5 \pm 18.2 ^b | 196.8 \pm 63.0 ^b |
| B | 200 | 318.0 \pm 55.2 | 271.0 \pm 58.5 | 225.8 \pm 37.8 | 220.0 \pm 37.3 | 203.0 \pm 32.9 | 187.0 \pm 29.6 ^b | 163.0 \pm 37.1 ^b |
| C | 400 | 377.5 \pm 45.1 | 427.8 \pm 16.4 ^a | 394.8 \pm 19.7 ^a | 338.3 \pm 17.7 | 324.5 \pm 24.6 | 298.8 \pm 28.7 ^b | 273.0 \pm 29.7 ^b |
| D | 600 | 375.0 \pm 47.4 | 395.5 \pm 60.2 ^a | 354.8 \pm 53.3 ^a | 304.0 \pm 57.5 ^b | 289.0 \pm 74.0 ^b | 222.5 \pm 48.6 ^b | 185.8 \pm 33.6 ^b |
| E | 800 | 505.0 \pm 53.7 | 412.5 \pm 14.8 ^b | 363.8 \pm 20.9 ^b | 363.5 \pm 24.9 ^b | 327.0 \pm 30.0 ^b | 273.0 \pm 37.3 ^b | 264.3 \pm 37.1 ^b |
| F | Untreated | 344.8 \pm 75.5 | 358.0 \pm 58.8 ^a | 369.3 \pm 57.8 ^a | 379.3 \pm 54.5 ^a | 399.0 \pm 58.6 ^a | 412.0 \pm 41.6 ^a | 449.3 \pm 28.8 ^a |
| G | Normal control rats | 131.5 \pm 3.9 | 142.5 \pm 4.3 | 127.0 \pm 1.7 | 125.0 \pm 1.87 | 136.0 \pm 2.6 | 131.0 \pm 2.6 | 129.8 \pm 4.0 |

Values with superscripta within a group along the row is significantly ($P < 0.05$) higher than zero hour blood glucose value.

Values with superscriptb within groups along the row are significantly ($P < 0.05$) lower than zero hour blood glucose value.

Table IV: Mean Blood Glucose levels of Normal rats treated with LHERE.

| Groups | Dosage (mg/kg) | Day 0 | Day 7 | Day 14 | Day 21 | Day 28 |
|--------|---------------------|--------------|-------------------------|--------------------------|--------------------------|--------------------------|
| A | 200 | 119.6±0.57 | 119.4±0.45 ^b | 114.8±14.08 ^a | 118.5±0.85 ^b | 120.2±13.81 ^b |
| B | 400 | 118.4±1.68 | 115.7±2.74 ^b | 120.8±12.16 ^b | 102.6±13.22 ^a | 101.0±1.67 ^a |
| C | 600 | 121.1±0.48 | 116.7±0.93 ^b | 112.1±0.02 ^a | 110.7±0.29 ^a | 105.5±0.19 ^a |
| D | 800 | 127.4±2.67 | 115.3±2.67 ^b | 113.1±2.84 ^a | 103.7±2.14 ^a | 102.0±3.42 ^a |
| E | Normal control rats | 120.6 ± 2.56 | 110.8±2.97 | 116.3±0.28 | 117.0 ±0.05 | 116.4±1.66 |

Mean values with the same Superscript within groups along the row are significantly ($P<0.05$) lower than zero-hour blood glucose value. Mean values with different Superscript between groups along the column have statistical significantly ($p>0.05$) when compared to value in the control group.

this may be attributed to the phytometabolites detected such as flavonoids and associated polyphenols that elicit their blood glucose lowering effects by enhancing the expression and translocation of GLUT-2 (Belayneh *et al.*, 2019; Khalid AL-Ishaq *et al.*, 2019; Melaku and Getnet, 2020), and GLUT-4 (Moradi *et al.*, 2018; Salehi *et al.*, 2019; Shewasinad *et al.*, 2019; Khalid AL-Ishaq *et al.*, 2019; Chadt and Al-Hasani, 2020) in pancreatic β -cells that will ultimately facilitate glucose uptake by the liver, muscles and adipose tissue (Moradi *et al.*, 2018; Chadt and Al-Hasani, 2020), and facilitating insulin release (Moradi *et al.*, 2018; Salehi *et al.*, 2019; Shewasinad *et al.*, 2019; Khalid AL-Ishaq *et al.*, 2019; Chadt and Al-Hasani, 2020).

Flavonoids have regenerative potentials on pancreatic beta cells (Shewamene *et al.*, 2015; Kifle & Enyew *et al.*, 2020, Melaku & Getnet, 2020), inhibit the activity of aldose reductase, improve calcium ion uptake, slow gastric emptying, and inhibit α -glycosidase (Shewasinad *et al.*, 2019; Khalid AL-Ishaq *et al.*, 2019; Gebremeskel *et al.*, 2020). They also have potent antiapoptotic properties (Salehi *et al.*, 2019).

Tannins contribute to blood glucose lowering activities due to their ability to stimulate insulin secretion or have insulin-like effects, reduce carbohydrate absorption by inhibiting activities of α -glucosidase and α -amylases, enhance β -cell propagation and restoration, and prevent β -cell impairment through their antioxidant effects (Ifesan *et al.*, 2013; Oboh & Rocha, 2013; Melaku & Getnet, 2020).

Alkaloids have received increased attention in recent years due to their potential role in the treatment of diabetes by the inhibition of α -glucosidase, α -amylase, dipeptidyl peptidase -4 (DPP-4), as well as their potent protein tyrosine

phosphatase 1B (PTP1B) inhibitory effects (Bhaskaran *et al.*, 2019; Kumar *et al.*, 2019). Additionally, alkaloids help in pancreatic regeneration and insulin secretion, and have protective effect against oxidative tissue damage due to reactive oxygen species (Erejuwa *et al.*, 2012; Kumar *et al.*, 2019).

Terpenoids exhibit their anti-diabetic activities by inhibiting the activities of α -glucosidase, α -amylase (Bhaskaran *et al.*, 2019), aldose reductase, and hepatic glycogen phosphorylase (Nazaruk & Borzym-Kluczyk, 2015; Bhaskaran *et al.*, 2019). They also possess G-protein-coupled receptor (TGR5) agonistic characteristics. Additionally, they reduce oxidative stress and body weight while preventing pancreatic β -cell dysfunction and increasing insulin-stimulated GLUT-4 translocation, inhibit the production of advanced glycation end products (AGEs), thus, making them prospective candidates in drug formulation for the prevention and treatment of diabetes (Nazaruk & Borzym-Kluczyk, 2015).

CONCLUSION

In this current research the crude ethanol root extract of *Leptadenia histata* demonstrated significant anti-diabetic, and hypoglycaemic effects in both normal and diabetic rat models. These results support its traditional use for treating diabetes mellitus.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

REFERENCES

- 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*, 61-71.
- Al-Ishaq, R. K., Abotaleb, M., Kubatka, P., Kajo, K., & Büsselberg, D. (2019). Flavonoids and their anti-

- diabetic effects: Cellular mechanisms and effects to improve blood sugar levels. *Biomolecules*, 9(9), 430.
- Begashaw, B., Mishra, B., Tsegaw, A., & Shewamene, Z. (2017). Methanol leaves extract *Hibiscus micranthus* Linn exhibited antibacterial and wound healing activities. *BMC Complementary and Alternative Medicine*, 17, 1-11.
- Belayneh, Y. M., Birru, E. M., & Ambikar, D. (2019). Evaluation of hypoglycemic, antihyperglycemic and antihyperlipidemic activities of 80% methanolic seed extract of *Calpurnia aurea* (Ait.) Benth.(Fabaceae) in mice. *Journal of Experimental Pharmacology*, 73-83.
- Bello, A., Aliero, A. A., Saidu, Y., & Muhammad, S. (2011). Hypoglycaemic and hypolipidaemic effects of *Leptadenia hastata* (Pers.) Decne in alloxan induced diabetic rats. *Nigerian Journal of Basic and Applied Sciences*, 19(2).
- Bhaskaran, M., Mruthunjaya, K., Manjula, S. N., & Rajan, D. (2019). Evaluation of anti-diabetic activity of leaves of *Actinodaphne hookeri* Meissn. *International Journal of Pharmaceutical Sciences and Research*, 10(1), 83-96.
- Burkill, H. M. (1995). The useful plants of west tropical Africa, Vols. 1-3. *The useful plants of west tropical Africa, Vols. 1-3.*, (2. ed.).
- Chadt, A., & Al-Hasani, H. (2020). Glucose transporters in adipose tissue, liver, and skeletal muscle in metabolic health and disease. *Pflügers Archiv-European Journal of Physiology*, 472(9), 1273-1298.
- Cherie, M. B., & Amare, G. G. (2020). Evaluation of antidiabetic and antioxidant potential of hydromethanolic seed extract of *Datura stramonium* Linn (Solanaceae). *Journal of Experimental Pharmacology*, 181-189
- Choudhury, S., Majgaonkar, A., Bhatia, M., Sinha, D., Datta, S., Banerjee, S., & Seal, S. (2024). Molecular Mechanisms of Action of Antidiabetic Phytochemicals. *Advances in Pharmacognosy and Phytochemistry of Diabetes*, 147.
- Connelly, M. A., Gruppen, E. G., Wolak-Dinsmore, J., Matyus, S. P., Riphagen, I. J., Shalaurova, I., & Dullaart, R. P. (2016). GlycA, a marker of acute phase glycoproteins, and the risk of incident type 2 diabetes mellitus: PREVENT study. *Clinica Chimica Acta*, 452, 10-17.
- Dinku, T. T., S., & Asres, K. (2010). Antidiabetic activity of the leaf extracts of *Pentas schimperiana* subsp. *schimperiana* (A. Rich) Vatke on alloxan induced diabetic mice. *Ethiopian Pharmaceutical Journal*, 28, 22-26.
- Erejuwa, O. O. (2012). Oxidative stress in diabetes mellitus :is there a role for hypoglycemic drugs and/or antioxidants. *Oxidative stress and diseases*, 217, 246.
- Evans, W. C. (2009). *Trease and Evans' pharmacognosy*. Elsevier Health Sciences.
- Gebremeskel, L., Beshir Tuem, K., & Teklu, T. (2020). Evaluation of antidiabetic effect of ethanolic leaves extract of *Becium grandiflorum* Lam.(Lamiaceae) in streptozotocin-induced diabetic mice. *Diabetes, Metabolic Syndrome and Obesity*, 1481-1489
- Güemes, M., Rahman, S. A., & Hussain, K. (2016). What is a normal blood glucose?. *Archives of disease in childhood*, 101(6), 569-574.
- Hammesso, W. W., Emiru, Y. K., Ayalew Getahun, K., & Kahaliw, W. (2019). Antidiabetic and antihyperlipidemic activities of the leaf latex extract of *Aloe megalacantha* baker (Aloaceae) in streptozotocin-induced diabetic model. *Evidence-Based Complementary and Alternative Medicine*, 2019.
- Holstein, A., Hahn, M., Körner, A., Stumvoll, M., & Kovacs, P. (2011). TCF7L2 and therapeutic response to sulfonylureas in patients with type 2 diabetes. *BMC medical genetics*, 12, 1-5.
- Hosseini, S. M., Boright, A. P., Sun, L., Canty, A. J., Bull, S. B., Klein, B. E., & Paterson, A. D. (2015). The association of previously reported polymorphisms for microvascular complications in a meta-analysis of diabetic retinopathy. *Human genetics*, 134, 247-257.
- Ifesan, B. O. T., Fashakin, J. F., Ebosele, F., & Oyerinde, A. S. (2013). Antioxidant and antimicrobial properties of selected plant leaves. *European Journal of Medicinal Plants*, 3(3), 465-473.
- Issa, I. A., & Hussen Bule, M. (2015). Hypoglycemic effect of aqueous and methanolic extract of *Artemisia afra* on alloxan induced diabetic Swiss albino mice. *Evidence-based complementary and alternative medicine*, 2015.
- Kifle, Z. D., & Enyew, E. F. (2020). Evaluation of in vivo antidiabetic, in vitro α -amylase inhibitory, and in vitro antioxidant activity of leaves crude extract and solvent fractions of *Bersama abyssinica* fresen (melianthaceae). *Journal of Evidence-Based Integrative Medicine*, 25, 2515690X20935827.
- Kumar, A., Aswal, S., Semwal, R. B., Chauhan, A., Joshi, S. K., & Semwal, D. K. (2019). Role of plant-derived alkaloids against diabetes and diabetes-related complications: a mechanism-based approach. *Phytochemistry Reviews*, 18, 1277-1298.
- Kumar, A., Gangwar, R., Ahmad Zargar, A., Kumar, R., & Sharma, A. (2024). Prevalence of diabetes in India: A review of IDF diabetes atlas 10th edition. *Current diabetes reviews*, 20(1), 105-114.
- Melesie T, G., Bose, L., Beressa, T. B., Tefera, G. M., Mosisa, B., Dinsa, H., & Umata, G. (2020). COVID-19 knowledge, attitudes, and prevention practices among people with hypertension and diabetes mellitus attending public health facilities in Ambo, Ethiopia. *Infection and drug resistance*, 4203-4214.
- Meresa, A., Gemechu, W., Basha, H., Fekadu, N., Teka, F., Ashebir, R., & Tadele, A. (2017). Herbal medicines for the management of diabetic mellitus in Ethiopia and Eritria including their phytochemical

- constituents. *American Journal of Advance Drug Delivery*, 5(1), 40-58.
- Moradi, B., Abbaszadeh, S., Shahsavari, S., Alizadeh, M., & Beyranvand, F. (2018). The most useful medicinal herbs to treat diabetes. *Biomedical research and therapy*, 5(8), 2538-2551.
- Muthu, C., Ayyanar, M., Raja, N., & Ignacimuthu, S. (2006). Medicinal plants used by traditional healers in Kancheepuram District of Tamil Nadu, India. *Journal of Ethnobiology and ethnomedicine*, 2, 1-10.
- Nabi, S. A., Kasetti, R. B., Sirasanagandla, S., Tilak, T. K., Kumar, M. V. J., & Rao, C. A. (2013). Antidiabetic and antihyperlipidemic activity of *Piper longum* root aqueous extract in STZ induced diabetic rats. *BMC complementary and alternative medicine*, 13, 1-9.
- Nazaruk, J., and Borzym-Kluczyk, M. (2015). The role of triterpenes in the management of diabetes mellitus and its complications. *Phytochemistry Reviews*, 14, 675-690.
- Oboh, G., & Rocha, J. B. T. (2007). Polyphenols in red pepper [(*Capsicum annum* var. *aviculare* (Tepin)] and their protective effect on some pro-oxidants induced lipid peroxidation in brain and liver. *European Food Research and Technology*, 225, 239-247.
- Ogurtsova, K., da Rocha Fernandes, J. D., Huang, Y., Linnenkamp, U., Guariguata, L., Cho, N. H., & Makaroff, L. E. (2017). IDF Diabetes Atlas: Global estimates for the prevalence of diabetes for 2015 and 2040. *Diabetes research and clinical practice*, 128, 40-50.
- Ohki, T., Isogawa, A., Toda, N., & Tagawa, K. (2016). Effectiveness of ipragliflozin, a sodium-glucose co-transporter 2 inhibitor, as a second-line treatment for non-alcoholic fatty liver disease patients with type 2 diabetes mellitus who do not respond to incretin-based therapies including glucagon-like peptide-1 analogs and dipeptidyl peptidase-4 inhibitors. *Clinical drug investigation*, 36, 313-319.
- Pari, L., & Saravanan, R. (2004). Antidiabetic effect of diasulin, a herbal drug, on blood glucose, plasma insulin and hepatic enzymes of glucose metabolism in hyperglycaemic rats. *Diabetes, Obesity and Metabolism*, 6(4), 286-292.
- Pearson-Stuttard, J., Blundell, S., Harris, T., Cook, D. G., & Critchley, J. (2016). Diabetes and infection: assessing the association with glycaemic control in population-based studies. *The lancet Diabetes and endocrinology*, 4(2), 148-158.
- Rahman, S. S., Yasmin, N., Rahman, A. T. M. M., Zaman, A., Rahman, M. H., & Rouf, S. M. A. (2017). Evaluation and optimization of effective-dose of alloxan for inducing type-2 diabetes mellitus in long evans rat. *Indian J Pharmaceutical Education and Research*, 51(4), 661-6.
- Rajalakshmi, M., Eliza, J., Priya, C. E., Nirmala, A., & Daisy, P. (2009). Anti-diabetic properties of *Tinospora cordifolia* stem extracts on streptozotocin-induced diabetic rats. *African Journal of Pharmacology*, 3(5), 171-180.
- Ramya, V., Madhu-Bala, V., Prakash-Shyam, K., Gowdhami, B., Sathiya-Priya, K., Vignesh, K., & Kadalmani, B. (2021). Cytotoxic activity of *Indigofera aspalathoides* (Vahl.) extracts in cervical cancer (HeLa) cells: Ascorbic acid adjuvant treatment enhances the activity. *Phytomedicine Plus*, 1(4), 100142.
- Salehi, B., Ata, A., V. Anil Kumar, N., Sharopov, F., Ramírez-Alarcón, K., Ruiz-Ortega, A., & Sharifi-Rad, J. (2019). Antidiabetic potential of medicinal plants and their active components. *Biomolecules*, 9(10), 551.
- Salehi, B., Venditti, A., Sharifi-Rad, M., Kregiel, D., Sharifi-Rad, J., Durazzo, A., & Martins, N. (2019). The therapeutic potential of apigenin. *International journal of molecular sciences*, 20(6), 1305.
- Sanda, K. A., Sandabe, U. K., Auwal, M. S., Bulama, I., Bashir, T. M., Sanda, F. A., & Mairiga, A. (2013). Hypoglycemic and antidiabetic profile of the aqueous root extracts of *Leptadenia hastata* in albino rats. *Pakistan Journal of Biological Sciences: PJBS*, 16(4), 190-194.
- Shewamene, Z., Abdelwuhab, M., & Birhanu, Z. (2015). Methanolic leaf extract of *Otostegia integrifolia* Benth reduces blood glucose levels in diabetic, glucose loaded and normal rodents. *BMC Complementary and Alternative Medicine*, 15, 1-7.
- Shewasinad, A., Bhoumik, D., Zero, H. M., & Masresha, B. (2018). Antidiabetic activity of methanol extract and fractions of *Thymus schimperii ronniger* leaves in normal and streptozotocin induce diabetic mice. *Iranian Journal of Pharmacology and Therapeutics*, 16(1), 1-8.
- Shyam, K., & Kadalmani, B. (2014). Antidiabetic activity of *Bruguiera cylindrica* (Linn.) leaf in Alloxan induced diabetic rats. *International Journal of Current Research in Biosciences Plant Biology*, 1, 56-60.
- Soumya, D., & Srilatha, B. (2011). Late stage complications of diabetes and insulin resistance. *Journal of Diabetes and Metabolism*, 2(9), 1000167.
- Tsegaye, W., Urga, K., & Asres, K. (2008). Antidiabetic activity of *samma* (*Urtica simensis* hochst. Ex. A. Rich.) in streptozotocin-induced diabetic mice. *Ethiopian Pharmaceutical Journal*, 27, 75-82.
- Usman, H., Abdulrahman, F. I., & Ladan, A. H. (2007). Phytochemical and antimicrobial evaluation of *Tribulus terrestris* L. (*Zygophyllaceae*). Growing in Nigeria. *Research. Journal of Biological Science. Medwell Journals*, 2(3), 244-247.
- Wu, W., Zhu, Y., Zhang, L., Yang, R., & Zhou, Y. (2012). Extraction, preliminary structural characterization, and antioxidant activities of polysaccharides from *Salvia miltiorrhiza* Bunge. *Carbohydrate Polymers*, 87(2), 1348-1353.