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Effects of *Physalis peruviana* L. (leaf crude extracts) on blood glucose and functional biomarkers in streptozotocin-nicotinamide-induced diabetic rats

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Promoting antidiabetic phytomedicines necessitates evidence-based preclinical investigations, particularly in animal models. The present study investigated the validity of using the streptozotocin-nicotinamide-induced type 2 diabetic (STZ/NA-induced T2DM) model to evaluate the effects of *Physalis peruviana* leaf crude extracts on controlling blood glucose levels and regulating physiological biomarkers in rats. Aqueous and methanol extracts dissolved in carboxymethylcellulose 1% (100, 200, mg/kg/day) were administered orally to STZ/NA-induced T2DM rats alongside glibenclamide (5 mg/kg) as the standard drug for four weeks. Blood samples were collected in fasting rats on days 1, 7, 14, 21, and 28 to measure glucose concentration, lipoprotein-cholesterol, and common serum biomarkers. Nutrition characteristics were also monitored, as well as the pancreas histology. Administration of STZ/NA in Wistar rats induced the T2DM significantly lower than did STZ alone (glycaemia 200 vs 400 mg/dL). The significant effects observed with plant extracts compared to untreated diabetic rats were blood glucose reduction (28-52 %), HDL-C increase, LDL-C decrease, ALAT increase, WBC increase, body weight gain (24%), and pancreas protection. The findings confirm the antidiabetic effect of *P. peruviana* in T2DM animal model.

1. Introduction

In the year just gone, diabetes mellitus (DM) and its associated complications ranked among the highest leading causes of mortality, accounting for approximately 6.5 million deaths worldwide (Ogurtsova et al. 2022). As per the International Diabetes Federation (IDF) reports, there is an expected increase in the prevalence of DM, which will result in 645 million (11.3%) people being affected by 2030 and, further to 783 million (12.2%) by 2045 (Bellido and Pérez 2021; Al-Khafaf et al. 2022).

Recently, high mortality has also been attributed to the severity of DM induced by coronavirus-19 (COVID-19) infection (Bellido and Pérez 2021). Low- and middle-income countries experienced a higher prevalence rate than high-income countries (Ogurtsova et al. 2022), currently affecting nearly 8.2% of their inhabitants (Zheng et al. 2018). Those people primarily use local herbal medications because of low accessibility to modern therapies.

Physalis peruviana L (Solanaceae) is used locally in different countries to manage several veterinary and human diseases, including diabetes, cancer, malaria, sexual problems, conjunctivitis, cataract, splenomegaly, gastritis, inflammation, jaundice, gout, glaucoma, gastro-intestinal disorders, diverse infections, pains, HIV~AIDS, etc. (Farnsworth et al. 1985; Witika et al. 2020; Kasali et al. 2021, 2022). This plant is a semi-upright herbaceous or perennial shrub, producing branched stems, native to the Andean region, and widely known and cultivated worldwide (Farnsworth et al. 1985). The health benefits of its berries are well documented; they impart various biological activities due to their rich phytochemicals and volatile oils that give off specific flavors (Witika et al. 2020).

The aqueous leaf extract is used orally in non-conventional medicine to manage DM in the Democratic Republic of Congo (Katemo et al. 2012). In previous studies, we have reported the anti-hyperglycemic effect of aqueous leaf extract in guinea pigs using Oral Glucose Tolerance Test (OGTT) and alloxan-induced diabetic models. Also, we explored the antidiabetic effect of the leaf hydroalcoholic extract and its fractions in streptozotocin-induced diabetic rats (Kasali et al. 2013, 2016; Kadima et al. 2016). Studies also reported that using the streptozotocin-nicotinamide (STZ/NA) model presents some characteristics related to T2DM in humans and has the advantage of attenuating diabetic complications and amplifying the chance of survival of the animals involved in the study (Cruz et al. 2021). Therefore, the current study aimed to expand our study series with this experimental STZ/NA model and to highlight the differences to the STZ model.

2. Investigations and results

2.1. Effect of treatment on blood glucose levels

Figure 1 shows the evolution of blood glucose concentrations in the current study using the STZ-NA model compared with our previous study using the STZ model. For STZ model: Control received vehicle alone (1% Tween 20, 1 ml orally); reference 6.5 mg/kg glibenclamide, HAC100:100 mg/kg of hydro-alcoholic extract, HEX100: 100 mg/kg of hexane fraction, EA100:100 mg/kg of ethyl acetate fraction, RF100: 100 mg/kg of residue fraction (Kasali et al. 2016).

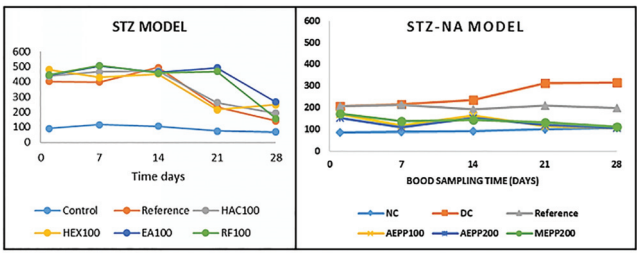

Fig. 1: Mean glycaemia in STZ and STZ/NA diabetic rats treated with *P. peruviana* leaf extracts.

In both STZ-NA and STZ models, the initial basal glycaemia in normal control groups was close to 100 mg/dL (85.9-104 mg/dL) and remained almost unchanged during the 4 weeks. Induction of diabetes raised glycaemia to 150-300 mg/dl in the STZ-NA compared with 400-500mg/dL in STZ model (showing a significant difference, $p< 0.0001$). In the STZ-NA diabetic rats not treated DC, the FBGL increased from 204.8±4.47 to 316.2±3.18 mg/dL. The extracts AEPP100, AEPP200, and MEPP200 significantly reduced the FBGL close to the control value of 104 mg/dL on day 28. Treatment with glibenclamide, at the given dose, reduced slightly FBGL from 205.1±3.46 to 197.8±5.07. In the STZ model, the FBGL had remained above 400 mg/dL for two weeks and declined significantly in the last week.

2.2. *Effect of treatment on hematological counts and functional biomarkers levels*

Comparing NC and DC groups, almost all values varied slightly, some increased, others decreased; only ALAT and BA were significantly increased. However, the plant extracts significantly reduced LDL-cholesterol (% 78.4 - 81.8) and PLT (60%). They increased TG (% 65.9 - 123.1), ALAT (% 22.0 - 106.7), VLDLC (% 89.0 - 165.8), HDLC (% 15.1- 36.1), bilirubin T (% 15.6- 77.1), and creatinine. ALAT levels remained high in all groups. Glibenclamide also increased TG, VLDL, HDL, creatinine, and ALAT.
The mean basal levels of biomarkers measured in normal control NC group; all normal healthy rats' basal values were in the normal human ranges, except ALAT, VLDL, and HDL are shown in Table 1.

Table 1: Mean basal levels of biomarkers measured in normal control NC group.

Parameter	Unit	Mean (n=3)
ALAT	ALAT(U/L)	0.17±1.32
ASAT	ASAT (U/L)	25.3±13.3
Basophiles	BA (10^3/µL)	0.193±0.05
Bilirubin total	Bilirubin T(mg/dL)	0.353±0.05
Creatinine	Creatinine (mg/dL)	0.513±0.01
Eosinophils	EO (10^3/µL)	0.432±0.09
Hematocrit (HCT),	HCT (%)	39.33±0.92
Hemoglobin (HGB),	HGB (g/L)	3.62±0.34
High-density lipoprotein (HDL),	HDLC (mg/dL)	9.68±1.71
Low-density lipoprotein (LDL),	LDLC (mg/dL)	42.65±11.2
Lymphocytes (LY),	LY (10^3/µL)	6.863±0.54
Mean cell hemoglobin (MCH),	MCH (pg)	8.70±0.12
Mean cell hemoglobin concentration (MCHC),	MCHC (g/dL)	34.62±0.18
Mean cell volume (MCV),	MCV (fL)	54.00±0.57
Mean platelet volume (MPV),	MPV (fL)	6.017±0.06
Monocytes (MO),	MO (10^3/µL)	3.167±0.16
Neutrophils (NE),	NE (10^3/µL)	1.077±0.16
Platelet (PLT),	PLT (10^3/µL)	533.2± 6.5
Red blood cell (RBC),	RBC (10^6/µL)	7.285±0.19
Red cell distribution width (RDW),	RDW (%)	10.03±0.22
Total cholesterol (TC),	TC (mg/dL)	57.83±5.08
Triglycerides (tgs),	TG (mg/dL)	71.83±7.17
Urea	Urea (mg/dL)	35.92±2.20
Very low-density lipoprotein (VLDL).	VLDLC (mg/dL)	14.37±1.43
White blood cell (WBC).	WBC (10^3/µL)	11.72±0.59

The effect of plant extracts on the level values of hematological, hepatic, renal, and lipid parameters profile is provided in Fig. 2.

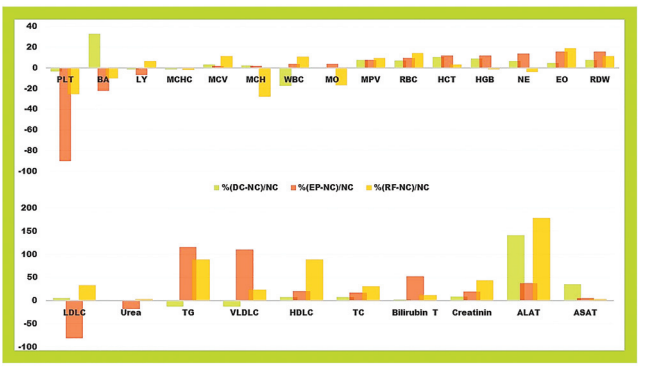

Fig. 2: Biomarkers levels in different treatment groups compared with typical basal values.

2.3. *Effect of treatment on rat body parameters*

As demonstrated in Fig. 3, in all experimental groups, the weight remained between 210-300 g, with a ratio week 4/week 1 between the minimal 1.04 for the DC group to the maximal 1.26 for AEPP100, meaning a weight gain of 4 to 26%.
Compared to the NC group, the weight was lost in DC and reference groups, not changed in other groups but increased in the AEPP100. The higher the blood sugar, the greater the amount of water consumed, the reverse for food and body weight. No objective relation appeared between body and organ weights, except for the pancreas.

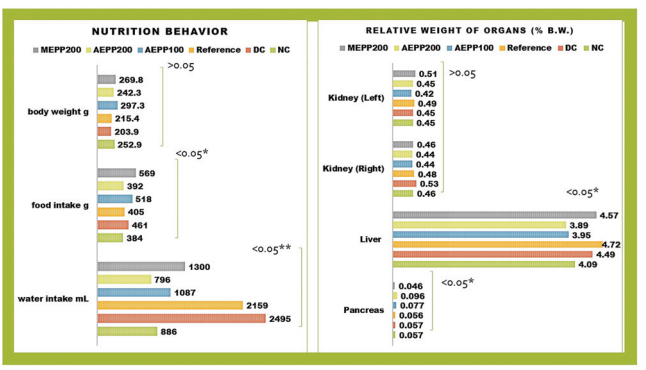

Fig. 3: Effect of *Physalis* extracts on zootechnical parameters in STZ/NA-induced T2DM Wistar rats.

2.4. *Effect of treatments on the pancreas injury*

The histopathological sections of the pancreas for different treatment groups are depicted in Fig. 4.

In the NC group, few beta cells have vacuoles in the cytoplasm. For the DC group, vacuolisation of the beta cells indicated acute injury. In the glibenclamide-treated group, fewer islets appeared with micro and macrovesicles in the beta cells. The AEPP100-treated group showed marked vacuolisation and enlargement of beta cells. The AEPP200-treated group presented marked vacuolisation of pancreatic islets. The AEPP400-treated group also showed vacuolisation of the beta cells of islets of Langerhans.

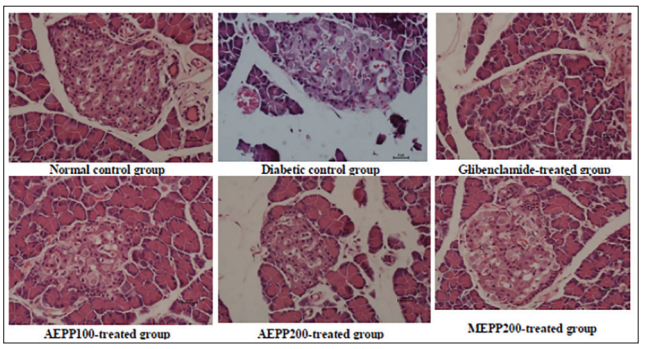

Fig. 4: Photomicrograph of pancreas sections of rats on different treatments. H&E 100X.

3. Discussion

The present study aimed to expand knowledge on the antidiabetic effect and safety of *P. peruviana* using an experimental STZ/NA-induced T2DM model and to highlight the differences with the single STZ model. It has been argued that a single high-dose STZ-induced DM in rodents arises from irreversible destruction of the β-islet cells of the pancreas, causing degranulation, reduction of insulin secretion, and decrease in body weight (Pushparaj et al. 2001). Nicotinamide has been attributed to neuroprotective and antioxidant functions that partially protect the pancreatic β-cells. It modulates the occurrence of T1DM via its cytoprotective action against the toxic effect of STZ at a particular dose, limiting the events to T2DM (Cruz et al. 2021). The severity of diabetes in experimental rats strongly depends on the doses of STZ and NA given to these animals. STZ is known to cause pancreatic B-cell damage, whereas NA is administered to partially protect insulin-secreting cells against STZ (Saisho 2016). STZ is transported into B-cells via the glucose transporter GLUT2 and causes DNA damage leading to increased activity of poly(ADP-ribose) polymerase (PARP-1) to repair DNA. However, the exaggerated activity of this enzyme results in the depletion of intracellular NADþ and ATP, and the insulin-secreting cells undergo necrosis. The protective action of NA is due to the inhibition of PARP-1 activity, and NA inhibits this enzyme, preventing depletion of NADþ and ATP in cells exposed to STZ. Moreover, NA serves as a NADþ precursor, thereby increasing intracellular NADþ levels (Cruz et al. 2021).

In the present study, the glycaemia level was significantly ($p< 0.0001$) increased between 160 and 230 mg/dL after a 5-days administration of a single dose of streptozotocin-nicotinamide. Also, STZ/NA decreased by <10% WBC, VLDL-C, and TG and increased by >20% ASAT and ALAT. The pancreas was slightly injured. However, In the STZ model, the glycaemia could reach ≥ 400 mg/dL. Also, the findings revealed no significant change in body weight between different treated groups on day 28. However, low doses produced more weight gain than high doses. In a previous study (Fokunang et al. 2017), the administration of *P. peruviana* extracts from the leaf and fruit had shown a significant decrease in weight body compared to standard control in STZ-diabetic rats.

In our study‘s context, the protective effect of nicotinamide is perceived to have played an essential role in preventing the degeneration of protein structures, which positively impacts weight loss and is similar to results obtained in previous studies (Szkudelski, 2012; Fukaya et al. 2013; Szkudelska, Nogowski and Szkudelski, 2014; Cruz et al. 2021). Moreover, the weight and growth rate change were higher in plant extracts-treated groups than in controls and glibenclamide-treated groups. This observation supports the cytoprotective effect of nicotinamide.

Regarding the antidiabetic effect and safety of *P. peruviana* leaves, the extracts AEPP100, AEPP200, and MEPP200 decreased hyperglycemia significantly ($p<0.0001$) on the 4th week of treatment compared to the untreated DC group. The reduction was 51.8% (AEPP100), 48.9% (AEPP200), 43.9% (AEPP400), 33.3% (MEPP200), and 10.7% (MEPP400). A previous study, based on an intraperitoneal glucose tolerance test, had shown that different doses (100, 200, and 400 mg/kg) of leaf methanolic extracts reduced hyperglycemia by 54.55%, 46.50%, and 39.78%, respectively. Moreover, a 400 mg/kg dose of aqueous extract lowered hyperglycemia by 39.44% (Kasali et al. 2022). One surprisingly observes that low amounts produce higher efficacy, meaning a reduction of not dose-dependent type. The reason is not known if an experimental error is ruled out. Doses > 200 mg/kg b.w. should be avoided.

Concerning the effect of the plant extracts on body functional indices, the findings showed significant ($p< 0.05$) variations in STZ and STZ/NA models. The administration of STZ (Mohamed 2018) decreased MCH and MCHC levels indicating abnormal hemoglobin synthesis, failure of blood osmoregulation, and plasma osmolarity. The reduction of hematological parameters in diabetic animals may also be attributed to a fall in the body‘s iron content resulting from oxidative stress associated with T2DM. The administration of SZT/NA reduced WBC, MO, LY, MCHC, and HCT slightly but increased RBC and other indices. In the glibenclamide treated group, WBC (-16.7), MCHC (-4.2%), and MO (-2.1%) decreased, while all other parameters increased. Even in humans, DM reduces WBC, affecting the distribution of lymphocytes and monocytes without effect on basophils and neutrophils. Metformin also may reduce WBC counts.

The results of the biochemical markers assessment showed that treatment with different doses (100, 200, and 400 mg/kg) of the aqueous and methanolic extract significantly increased ALAT and ASAT enzymes. For lipids, only LDL-C decreased, while other lipids (HDL-C, VLDL-C, TGs) increased. Abnormal plasma lipids in diabetic rats, including elevated triglyceride and VLDL levels, are associated with obesity and precede the onset of diabetes. This happens because decreased insulin levels increase hormone-sensitive lipase activity (Udayakumar et al. 2009; Fuente et al. 2020). In general, withdrawing exceptional cases, the treatment with plant extracts significantly increased all biomarkers but reduced LDL-C. Finally, the administration of aqueous and methanolic extracts of *P. peruviana* resulted in a significant restoration of the pancreas histology, which was much affected by the action of STZ.

In conclusion, the findings with STZ/NA-induced diabetes model confirmed the antidiabetic effect in the leaves of *P. peruviana* as it has been with a single STZ-induced model. In general, withdrawing exceptional cases, the treatment with plant extracts significantly increased all biomarkers but reduced LDL-C. The indices of T2DM were mitigated by nicotinamide. The relative limitations can be expressed regarding experimental design and animal inter-individual differences. Close attention should be paid to eliminating outliers in the validation of data.

4. Experimental

4.1. *Plant material*

Fresh leaves, collected between April and October 2019 in Lwiro (2°14‘24 „S, 28°47‘50 „E), 50 km away from Bukavu, were identified by the botanist Mr. Gentil Iragi at the Center for Research in Natural Sciences/Lwiro, where the voucher specimen number LWI113898883 was deposed. Then, the fresh plant material was air-dried and ground to a fine powder to prepare water infusion (250 g/L) and methanol maceration (250 g/L).

The mixtures were subsequently filtered through cotton wool and concentrated to dryness under reduced pressure at 40 °C with IKA® RV 10 rotary evaporator (Staufen, Germany), then frozen at -80 °C and lyophilized with FD-ICL Benchtop Freeze Dryer (Tokyo, Japan) (Senhaji et al. 2020).

4.2. Animal material

We used healthy male Wistar rats aged three months with an average weight of 187.45±14.82 g, housed at the Animal Research Facility of the Department of Pharmacology, Faculty of Medicine, Mbarara University of Science and Technology, under standardized conditions (temperature 23.8±1.9 °C, relative humidity 63.6±6.6%, 12 h daylight/dark cycles, with free access to pelleted animal food and drinking water *ad libitum*).

4.3. Experimental procedure

Before the manipulation, the rats were acclimated in the experimental room for at least seven days. Each rat received intraperitoneal injection daily for 5 days, first 120 mg/kg nicotinamide (Sigma-Aldrich, Germany) single dose dissolved in saline solution (NaCl 0.9%), and 15 min later 60 mg/kg single dose of Streptozotocin (Sigma-Aldrich, Germany) dissolved in 0.1 M of cold citrate buffer (pH 4.5) (Dreanca et al. 2018). Each day, fasting blood glucose (FBG) level was measured. Any animal presenting with FBG above 126 mg/dL (7 mmol/L) was declared diabetic and submitted to the treatment phase (Peter et al. 2021).
In total, 48 animals were randomly divided into six groups of six animals each. A technician unaware of the type of intervention used the Experimental Design Assistant (EDA) Tool to generate a randomization amplification and assign animals to each group as follows:
(1) NC: Normal control group received 1 mL/100g b.w of carboxymethylcellulose 1%;
(2) DC: Diabetic control group untreated received STZ/NA in CMC1%;
(3) RF: Reference group received glibenclamide 5 mg/kg b.w dissolved in CMC1%,
(4) AEPP100: received aqueous extract 100 mg/kg b.w dissolved in CMC1%;
(5) AEPP200: received aqueous extract 200 mg/kg b.w in CMC1%;
(6) MEPP200: received methanol extract 200 mg/kg b.w in CMC1%.
Each dose was administered every morning (8:00 am) through oral gavage using a cannula. The dosage was adjusted daily according to any change in body weight using an electronic balance scale (Kern PRS 6200-2) to maintain an equivalent dose per kg of body weight of rats over the 28 days of study.

4.4. Laboratory measurements

Blood glucose levels (BGL) (mg/dL) were determined using an Accu-Chek® glucometer (Roche Diabetes Care, Inc, Johannesburg, South Africa) and tips by the enzymatic glucose oxidase method applied to blood. The blood samples were collected from the end of the tail. All rats were fasted for 6 h (8:00 am to 2:00 pm) before determining BGL but were allowed free access to water *ad libitum*. Blood samples were withdrawn on days 1, 7, 14, and 28 to evaluate biochemical markers via cardiac puncture without or with EDTA for serum separation or plasma.
A blood sample aliquot was centrifuged at 3,000 rpm for 20 min for biochemical analysis, using an automatic biochemical analyzer (AU480, Backman coulter® Mishima KK) to separate the serum that was then analyzed for the levels of different markers. A blood sample for hematological investigation was collected in the pre-calibrated tubes containing EDTA. An automated hematological analyzer (Beckman Coulter AC-T 5diff CP, Kraemer Blvd, Brea, USA) was used to determine the hematological parameters.
On the 28th day, all animals were fasted and then anesthetized using 25 mL of diethyl ether (Loba Chemie, India), and blood and organs were collected for various estimations (Palsamy, Sivakumar and Subramanian, 2010). The pancreas was harvested from the rats and weighed appropriately before being stored in 10% formalin (Sigma-Aldrich) for the histological exam. Organ sections (5-µm thickness) were cut, stained (hematoxylin and eosin dye), and examined under a light microscope (Weng et al. 2014).
The samples were rinsed with xylene and embedded in paraffin. The pancreas was fixed in 10% formalin (Sigma-Aldrich) solution at ambient temperature and then dehydrated by successively passing through an ethyl alcohol and water mixture gradient.

4.5. Nutrition status measurements

Rats' body weights were documented before (day 0) and during treatment (7, 14, 21, and 28). After the experiment, animals were sacrificed after using anesthesia, and organs were removed and weighed (Ojuade et al. 2021). An electronic balance scale (Kern PRS 6200-2) determined the experimental rat's body weight.

4.6. Statistical analysis

Data were statistically performed by one-way analysis of variance (ANOVA) followed by Tukey's multiple comparison tests using version 8.0.1 GraphPad Prism (GraphPad Holdings LLC, La Jolla, California, United States of America). Values were represented as mean±standard error of the mean of six experiments, and the $p \leq 0.05$ was used as a criterion of statistical significance.

4.7. Ethics statement

All experiments operations were performed following the standard ethical guidelines related to the protection of animals to use for scientific research as described in the policies of the European Community; EEC Directive 2010/63/EU in revising Directive form 86/609/EEC, adopted on 22 September 2010 (European Commission, 2010). The research protocol was initially submitted and then approved by the Research Ethical Committee of MUST with registration number MUST-REC 25/01-19 and then at the Uganda National Council for Science and Technology with the number of registration NS440ES.

Author Contributions: FMK conceived and designed the study. FMK, JTK, and AGA contributed to the acquisition of data, analysis, and interpretation of data. FMK, JT, and BAW drafted or revised the work critically for important intellectual content. FMK, JNK, AGA, JT, JBS, and BAW analyzed the data and revised the article. All authors approved the manuscript and contributed significantly.

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Data Availability Statement: The data used in this study are provided and included within the article and can be available from the corresponding author (FMK) upon reasonable request.

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Conflicts of Interest: The authors declare no conflict of interest.

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