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GLUCOREGULATORY EFFECT OF METHANOLIC EXTRACT OF *PICRALIMA NITIDA* SEEDS IN RATS MADE DIABETIC BY ALLOXANE

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Keywords:

Picralima nitida, Diabetes, Glibenclamide®, Glycemia, Insulinemia

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ABSTRACT: Diabetes is a chronic disease characterized by fasting blood glucose levels above 1.26 g/L. The aim of the present study was to evaluate the effect of the methanolic extract of *Picralima nitida* seeds on insulin and blood glucose levels in diabetic rats. Diabetes was induced in normoglycemic rats by injection of 1 mL alloxane at a dose of 125 mg/kg bw for three consecutive days. Blood samples were taken every other day to determine insulin and blood glucose levels. Diabetic rats were then treated for 14 days with 10, 20 and 50 mg/kg bw of *P. nitida* seed extract and 5 mg/kg bw of Glibenclamide®. At the end of treatment, the rats' blood was collected again for determination of insulin and blood glucose *P. nitida* levels. The results obtained show that initial insulinemia, which was 16 ± 0.12 µU/mL, fell in diabetic rats (7 ± 0.004 µU/mL) before significantly increasing to 15 ± 0.3 µU/mL and 17 µU/mL ± 0.02 after treatment with *P. nitida* extract and Glibenclamide®. In addition, initial blood glucose levels, estimated at 0.76 ± 0.022 g/L, increased in rats following alloxane injection and then significantly fell to 0.65 ± 0.06 g/L and 0.55 ± 0.03 g/L in animals treated with extract and Glibenclamide®. These results indicate that the methanolic extract of *Picralima nitida* seeds, like Glibenclamide®, is capable of regulating blood insulin and glucose levels in diabetic rats.

INTRODUCTION: Diabetes is a chronic, metabolic disease characterized by elevated levels of blood glucose. It results from an absolute insufficiency in the secretion of insulin, the hormone that promotes glucose metabolism, or resistance to the biological action of this hormone [1].

This insulin-related deficiency causes chronic hyperglycemia in the victim, associated in the long term with organ dysfunction, particularly of the eyes, kidneys, nerves and cardiovascular system [2]. Alteration in the body's functioning promotes the occurrence of several other pathologies.

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Diabetes is responsible for numerous cases of strokes, lipid disorders, myocardial infarctions and is the main cause of kidney failure, blindness, arteriopathy of the lower limbs and several amputations [3, 4]. These few figures make diabetes one of the world's leading causes of death[5], and therefore a real public health problem. To overcome this pathology, oral antidiabetics and daily injections of insulin, a hypoglycemic hormone, are used for the therapeutic management of patients [6, 7]. But, despite the deployment of these therapeutic solutions, diabetes and its complications remain a major problem for patients. Indeed, the high cost of anti-diabetic drugs puts these remedies beyond the reach of many people, especially the vulnerable. To alleviate this health problem, diabetic patients use medicinal plants, which today occupy a prominent place in primary health care. Our team is working to shed scientific light on the use of plants such as *Picralima nitida*, whose fruit seeds are used to treat diabetes. The present study aims to assess the effect of *Picralima nitida* seed extract on insulin and glucose levels during experimental alloxane-induced diabetes in rats.

MATERIALS AND METHODS:

Plant Material: The plant material consisted of seeds from *Picralima nitida*. The fruits of the plant containing the seeds were harvested in the southern forest region of Côte d'Ivoire, in the Sassandra Region. The plant was authenticated at the National Floristic Center of Félix Houphouët-Boigny University of Abidjan, where a specimen was deposited.

Animals: The study was carried out using Wistar rats of the species *Rattus norvegicus*, aged 2 months, with an average weight of 100 g and provided by the breeding farms of the Pasteur Institute of Côte d'Ivoire. These animals were kept in standard polypropylene cages containing wood chip bedding, where they were acclimatized and fed pellets with free access to water. For the duration of the experiment, the rats were maintained under standard laboratory conditions (12 h light-dark cycle, temperature 20 ± 2°C), while the wet bedding was renewed to avoid stress.

Chemicals: Alloxane monohydrate was obtained from Pharmacia, St. Quentin en Yvelines (France). Folin-Ciocalteu reagent, sodium carbonate, aluminum trichloride, gallic acid, quercetin, atropine, Dragendorff reagent, sodium sulfate, thio-urea were supplied by Sigma Chemical Co (St. Louis, USA).

Preparation of Methanolic Extract from *Picralima nitida* Seeds: Harvested *Picralima nitida* fruits were washed, split, and the seeds extracted from the pulp. The seeds were then fermented and shade-dried at room temperature for two weeks, before being ground to a powder. One hundred grams (100 g) of the powder was dissolved in one liter (1 L) of methanol, then homogenized using a blender. After several homogenization cycles, the resulting homogenates were successively filtered, twice on hydrophilic cotton and once on Whatman filter paper. The filtrates were then oven-dried at 50°C for two days [8]. The brown evaporate obtained constituted the methanolic extract of *Picralima nitida* seeds coded EX and used for the experiment.

Determination of Total Phenols: Total phenol content of *P. nitida* seed extract was determined using Folin-Ciocalteu method [9]. To this end, 200 µL of the extract (1 mg/mL) was added to 1 mL of Folin-Ciocalteu reagent in three test tubes. After 5 min incubation at room temperature, 800 µL of aqueous sodium carbonate solution (7.5%) was added to the tubes. The mixtures were homogenized and incubated in a water bath for 10 min. Absorbance was read at 765 nm against a blank using a Roche Hitachi 902 spectrophotometer (Germany). A calibration curve was run in parallel under the same operating conditions, using gallic acid as standard, at different concentrations (10; 20; 30; 40; 50; 60; 70; 80 and 100 µg/mL). The concentration of total phenols was expressed as milligram equivalent of gallic acid per gram of extract (mg EGA/g extract).

Determination of Total Flavonoids: Total flavonoid content of *P. nitida* seed extract was determined by the aluminum trichloride ($AlCl_3$) method [10]. A 1 mL volume of the extract (1 mg/mL) was put into three test tubes, then 1 mL of 1% (w/v) $AlCl_3$ was added to each. The mixtures were homogenized and incubated at room temperature for 10 min, then the absorbance was read on a Roche Hitachi 902 spectrophotometer

(Germany) at 760 nm. Flavonoid content was determined from the regression equation of the quercetin calibration line established with the concentration range 10; 20; 30; 40; 50; 60; 70 and 80 µg/mL. This flavonoid content was expressed as milligram equivalent of quercetin per gram of extract (mg EQ/g extract).

Alkaloid Assay: Alkaloids were determined from *P. nitida* seed extract using the spectrophotometric method described by Sreevidya and Mehrotra [11]. For this test, 5 mL of the extract was placed in a tube and 2 mL of Dragendorff's reagent was added. The precipitate formed was centrifuged for 30 min and decanted. The residue was then washed in alcohol and dissolved in 2 mL sodium sulfate solution. After centrifugation at 3000 rpm for 30 min, 2 mL of concentrated nitric acid was added to the brownish-black precipitate formed, before centrifugation again at 3000 rpm for 30 min. At the end of this step, 2 drops of sodium sulfate were added to the centrifugeate and the resulting precipitate was homogenized for 30 min. The resulting homogenate was heated in a hot bath for 10 min, then 10 mL distilled water was added. After 5 min of homogenization, 1 mL of the solution was added to 5 mL of thio-urea, and the absorbance was measured on a Roche Hitachi 902 spectrophotometer (Germany) at 435 nm against a white tube. The calibration curve was based on a 10 mg/L stock solution of atropine, with a concentration range from 10 to 80 µg/mL. The alkaloid content of the extract was expressed as milligram equivalents of atropine per gram of extract (mg EA/g extract).

Assessment of Glucoregulatory Effect:

Diabetes Induction: Diabetes was induced according to the method of Dunn and Mcletchie [12]. After fasting for 15 h, rats received freshly prepared alloxane monohydrate (125 mg/kg) intraperitoneally in physiological solution (NaCl 0.9%) for three consecutive days. Blood samples were taken before alloxane injection (D0) to measure insulin and blood glucose, and every two days after induction to confirm the onset of diabetes. Their body weight was also recorded before (D0) and every two days after the start of diabetes induction. Rats declared diabetic were then divided into different groups for treatment with the methanolic extract of *Picralima nitida* seeds and Glibenclamide®, a reference antidiabetic.

Treatment of Animals: Twenty-four (24) rats, including 20 diabetic rats, were divided into 6 groups of 4 animals each and treated for 14 days as follows:

Group 1: normoglycemic control rats given distilled water (NC);

Group 2: untreated diabetic rats given distilled water (NTD);

Group 3: diabetic rats treated with Glibenclamide® 5 mg/kg (Gbl5);

Group 4: diabetic rats treated with *P. nitida* aqueous extract at 10 mg/kg bw (EX10);

Group 5: diabetic rats treated with aqueous extract of *P. nitida* at 20 mg/kg bw (EX20);

Group 6: diabetic rats treated with *P. nitida* aqueous extract at 50 mg/kg bw (EX50);

Treatments were carried out daily, with each rat receiving 1 mL of product via an esophageal tube. At the end of the treatment, the animals were weighed and their blood was collected in tubes for insulin and blood glucose determination.

Insulin Assay: Insulin assay was performed using the slightly modified solid-phase immunoassay method [13]. The solid phase consists of a 12-well microplate, each adsorbed with an insulin antibody. For the test, 80 µL of rat blood serum was added to the wells. The insulin antigens contained in the serum bind to the immobilized insulin antibodies. After incubation for 60 min at 37°C, unbound antigens were removed by washing the wells with tris-phosphate buffer. In the next phase, 80 µL of a solution containing horseradish peroxidase (HRP)-conjugated insulin antibodies were added to the wells to bind to the antigens present. After 15 min incubation and washing of the microplates, 80 µL of 3,3′,5,5′-Tetramethylbenzidine (TMB), substrate for the conjugated enzyme, was added to each well. The enzymatic reaction was stopped by adding 10 µL of acid solution after transformation of the substrate, expressed as a blue coloration. The absorbances of the yellow product obtained were then measured at 450 nm after 30 min incubation.

Insulin concentration was determined under the same conditions using a range of insulin concentrations of 0, 4, 8, 12, 16, 20 and 24 µU/mL.

Blood Glucose Determination: Blood glucose levels were determined by the enzymatic method described by McMillin [14]. This method involves the oxidation of glucose by glucose oxidase with the production of gluconicdiacid and hydrogen peroxide (H_2O_2). The latter reacts with phenol and díamino-4-antipyrine in the presence of peroxidase to form quinone imine and water. The optical density of quinone imine at 500 nm is proportional to the concentration of glucose present in the sample. For this test, 10 µL of the sample was added to tubes containing 1 mL of enzyme solution (glucose oxidase and peroxidase). After stirring for 10 s by hand, absorbances were read on a spectrophotometer at 500 nm.

Statistical Analysis: Graph Pad software (Microsoft, San Diego California, USA) was used to analyze the data. Statistical processing was carried out using the Graph Pad Inst at program. Values are expressed as means plus standard error of the mean (M ± SEM). Analysis of variance (Anova) and the Tukey-Kramer multiple comparison test were used to assess the significance of observed differences. If the statistical value $P< 0.05$, the difference between means is considered significant. Graphical representations were made using the Graph Pad Prism 4 program.

RESULTS:

Contents of Targeted Secondary Metabolites in the Methanolic Extract of *Picralima nitida*: Quantitative analysis determined the total phenol, flavonoid and alkaloid contents of *Picralima nitida* methanolic extract **Table 1**. The linear regression equation (Y= 0.0183X-0.108) of the Gallic acid calibration curve yielded a total phenol content of 183.2 ± 0.05 mg equivalent of Gallic acid/g (mg EGA/g)of extract. Similarly, the Y= 0.0104X-0.0003 equation for quercetin gave a flavonoid content of 215.6 ± 0.65 mg equivalent of quercetin/g (mg EQ/g) of extract. On the other hand, the alkaloid content obtained from the regression equation Y= 0.0136X-0.0007 of the atropine calibration curve is 418.1 mg equivalent of atropine/g (mg EA/g) of extract.

TABLE 1: CONTENTS OF SECONDARY METABOLITES ASSAYED IN *P. NITIDA* METHANOLIC EXTRACT

Extract Concentration	10 mg/mL		
Metabolites	**Alkaloids**	**Total phenols**	**Flavonoids**
Contents	418.1± 0.03 mg EA/g extract	183,2 ± 0,05 mg EGA/g extract	215,60± 0,25 mg EQ/g extract

Animal Body Weights during Diabetes Induction: The evolution of rat body weights after alloxane injection is shown in **Fig. 1**. The results indicate that the initial weight of the animals (121.7 ± 0.88 g) progressively increased to 126.3 ± 1.33 g, 133.3 ± 0.88 g and 141 ± 0.58 g respectively on days 2, 4 and 6 after the start of diabetes induction. On days 8, 10, 12 and 14, the animals' weights significantly decreased to 115.7 ± 0.67 g, 99.05 ± 0.58 g, 87.12 ± 0.58 g and 80.75 ± 0.25 g, i.e. reduction rates of 4.93%, 18.08%, 28.41% and 33.65% respectively.

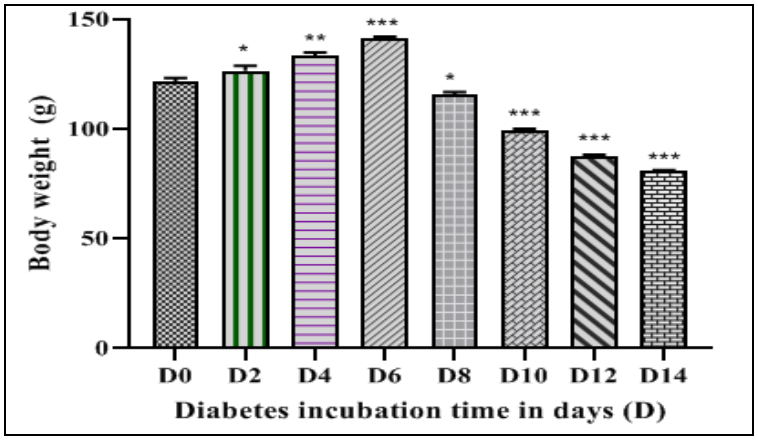

FIG. 1: CHANGES IN RAT BODY WEIGHT DURING DIABETES INCUBATION. Each bar represents the mean ± SEM. The symbol (*) represents statistical significance. *P<0.05; **P<0.01; ***P<0.001: significant difference compared with D0.

Insulin and Blood Glucose Levels during Diabetes Induction in Rats: Insulin and blood glucose values recorded in rats during diabetes induction are shown in **Fig. 2** and **3**.

The results reveal that the initial value of insulinemia (16 ± 0.12 µU/mL) significantly increased to 22 ± 0.23; 28 ± 0.12 and 37 ± 0.45 µU/mL respectively on days 2, 4 and 6 of diabetes induction. From day 8 after the start of alloxane injection, insulin levels (15 ± 0.56 µU/mL) began to decrease. At days 10, 12 and 14, this decrease was significant compared to the initial insulin level (16 ± 0.12 µU/mL), with recorded values of 12 ± 0.65, 9 ± 0.12 and 7 ± 0.004 µU/mL respectively **Fig. 2**.

In parallel with the change in insulinemia, blood glucose levels in alloxane-treated rats significantly decreased compared to the initial value (0.76 ± 0.022 g/L), giving values of 0.72 ± 0.01; 0.72 ± 0.005 and 0.65± 0.012 g/L on days 2, 4 and 6 respectively. Hyperglycemia began to set in from day 8 with a value of 0.99 ± 0.015 g/L, progressing to values of 1.28 ± 0.025 g/L at day 10; 1.55 ± 0.011 g/L at day 12 and 1.80 ± 0.027 g/L at day 14 **Fig. 3**.

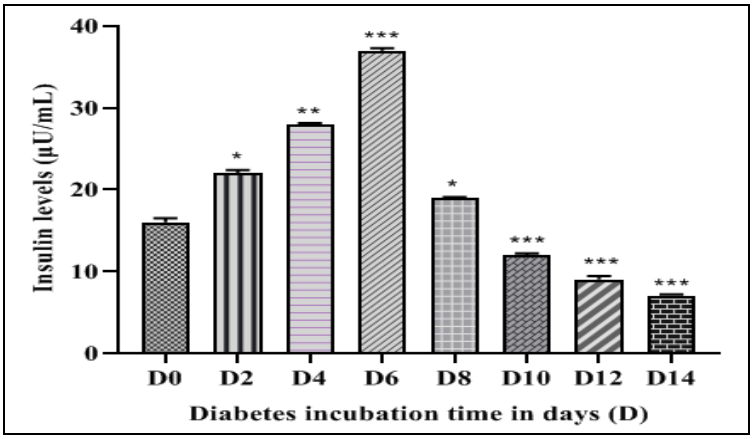

FIG. 2: CHANGES IN INSULIN LEVELS IN RATS DURING THE INCUBATION PERIOD FOR DIABETES. Each bar represents the mean ± SEM. The symbol (*) represents statistical significance. *P<0.05; **P<0.01; ***P<0.001: significant difference compared with D0.

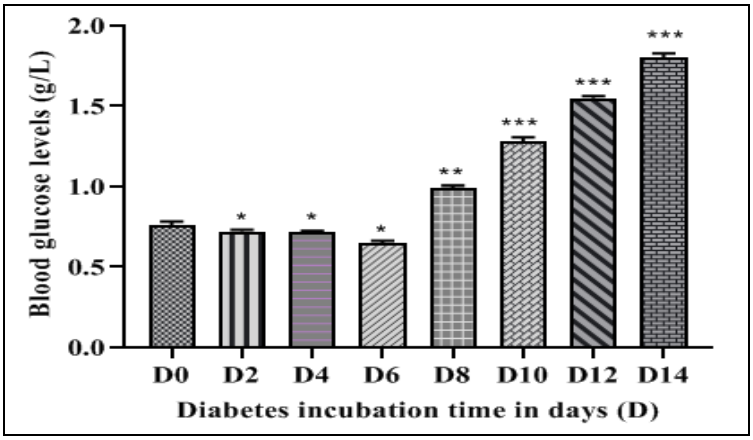

FIG. 3: CHANGES IN BLOOD GLUCOSE LEVELS IN RATS DURING THE INCUBATION PERIOD FOR DIABETES. Each bar represents the mean ± SEM. The symbol (*) represents statistical significance. *P<0.05; **P<0.01; ***P<0.001: significant difference compared with D0.

Effect of *Picralima nitida* Extract and Glibenclamide® on Body Weight in Diabetic Rats: The evolution of body weight in diabetic animals after treatment with *Picralima nitida* extract and Glibenclamide® is shown in **Fig. 4**. The initial weight of healthy animals (NC), which was 121.7 g, decreased to 80.75 g after the onset of diabetes at Day 14. Treatment of diabetic rats with *P. nitida* extract at doses of 10, 20 and 50 mg/kg bw for 14 days resulted in an increase in body weight (80.75 g) to 93, 120 and 160 g respectively, i.e. increases of 15.17, 48.61 and 98.14%.

Glibenclamide®, at a dose of 5 g/kg bw, increased the body weight of diabetic animals from 80.75 to 135 g, i.e. an increase of 67.18%. On the other hand, the weight of untreated diabetic animals (NTD) decreased from 80.75 g to 40 g, i.e. a reduction of 50.46%.

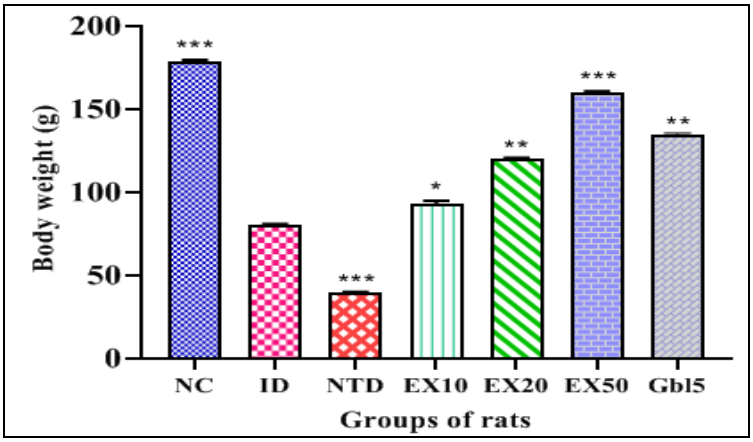

FIG. 4: EFFECT OF *P. NITIDA* EXTRACT AND GLIBENCLAMIDE® ON DIABETIC RATS BODY WEIGHT. NC: normal control group; **ID:** initial diabetic group; **NTD:** untreated diabetic group; **EX10, EX20** and **EX50:** diabetic groupsrespectively treated with P. nitida extract at 10, 20 and 50 mg/kg bw; **Gbl5:** diabetic group treated with Glibenclamide® at 5 mg/kg bw. Each bar represents the mean ± SEM. The symbol (*) represents statistical significance. *P<0.05; **P<0.01; ***P<0.001: significant difference compared with the initial diabetic group (ID).

Effect of *Picralimanitida* Extract and Glibenclamide® on Insulin and Blood Glucose Levels in Diabetic Rats: The effect of methanolic extract of *Picralima nitida* and Glibenclamide® on insulin and blood glucose levels in diabetic rats is shown in **Fig. 5** and **6**. The results indicate a dose-response decrease in blood glucose correlated with an increase in insulinemia. Indeed, treatment of diabetic rats with methanolic extract of *P. nitida* at doses of 10, 20 and 50 mg/kg bw and glibenclamide (5 mg/kg bw) resulted in a significant increase in insulinemia, from 7 ± 0.004 µU/mL to 10 ± 0.3, 12 ± 0.1, 15 ± 0.3 and 17 ± 0.02 µU/mL respectively, i.e. increases of 42.86, 71.43, 114.29 and 142.86% **Fig. 5**. At the same time, hyperglycemia significantly decreased from 1.80 g/L to 1.35 ±0.02, 1.27±0.02, 0.85 ± 0.06 and 0.55 ± 0.03 g/L in diabetic rats treated with methanolic extract of *P. nitida* at doses of 10, 20 and 50 mg/kg bw and glibenclamide at 5 mg/kg bw respectively **Fig. 6**. These values correspond to reductions in hyperglycemia of 25, 33.33, 52.78 and 69.44%. For diabetic animals not treated (NTD) for 14 days, insulinemia fell from 7 ± 0.004 to 3 ± 0.02 µU/mL, resulting in hyperglycemia of 2.80 ± 0.2 g/mL.

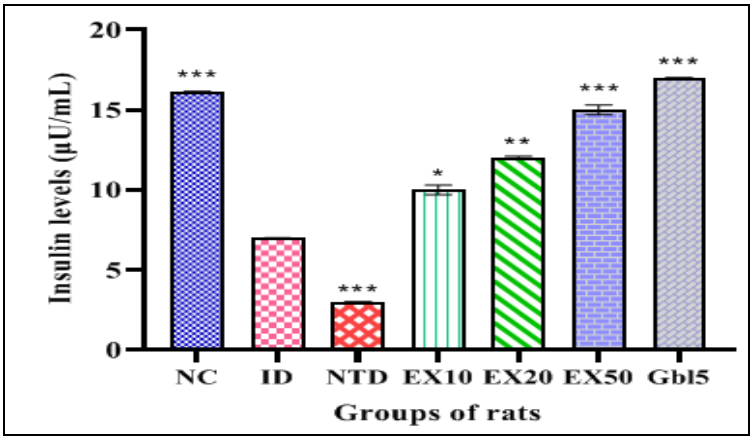

FIG. 5: EFFECT OF *P. NITIDA* EXTRACT AND GLIBENCLAMIDE® ON INSULIN LEVELS IN DIABETIC RATS. NC: normal control group; **ID:** initial diabetic group; **NTD:** untreated diabetic group; **EX10, EX20** and **EX50:** diabetic groups respectively treated with P. nitida extract at 10, 20 and 50 mg/kg bw; **Gbl5:** diabetic group treated with Glibenclamide® at 5 mg/kg bw. Each bar represents the mean ± SEM. The symbol (*) represents statistical significance. *P<0.05; **P<0.01; ***P<0.001: significant difference compared with the initial diabetic group (ID).

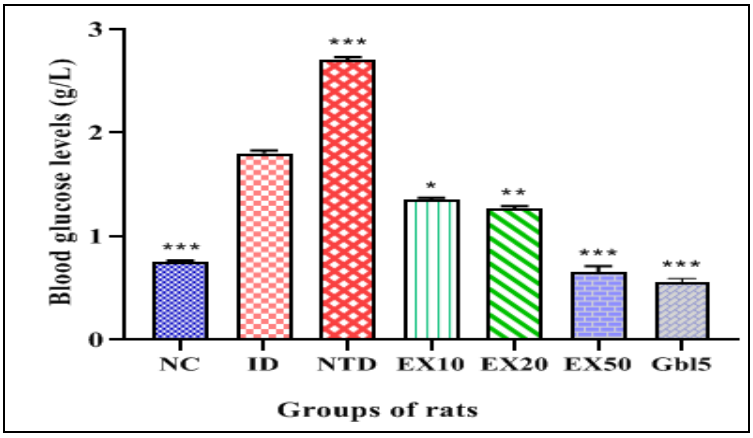

FIG. 6: EFFECT OF *P. NITIDA* EXTRACT AND GLIBENCLAMIDE® ON BLOOD GLUCOSE LEVELS IN DIABETIC RATS. NC: normal control group; **ID:** initial diabetic group; **NTD:** untreated diabetic group; **EX10, EX20** and **EX50:** diabetic groups respectively treated with P. nitida extract at 10, 20 and 50 mg/kg bw; **Gbl5:** diabetic group treated with Glibenclamide® at 5 mg/kg bw. Each bar represents the mean ± SEM. The symbol (*) represents statistical significance. *P<0.05; **P<0.01; ***P<0.001: significant difference compared with the initial diabetic group (ID).

DISCUSSION: The glucoregulatory effect of the methanolic extract of *Picralima nitida* seeds was assessed in diabetic rats by determining blood glucose and insulin levels. Insulin is a hormone secreted by the β-cells of the islets of Langerhans in the pancreas, whose role is to regulate blood glucose levels in the body. Deficiency in its production results in hyperglycemia, which can lead to diabetic pathology. Experimental diabetes was induced in rats by injection of alloxane, in order to observe the evolution of insulin and blood glucose levels in the presence of the methanolic extract of *Picralima nitida* seeds. The results showed strong insulin secretion within six days of the onset of diabetes induction. This is due to the fact that the destruction of pancreatic β-cells activates the establishment of precursor cells that are converted into β-cells [15]. Similarly Guo *et al.* [16] were able to demonstrate the spontaneous ability of α cells to be activated and reprogrammed into β cells upon their destruction. All these neo-formed and initial β cells would therefore be responsible for the high insulin secretion observed in the first six days of β-cell destruction.

On the 8th day after the start of alloxane injection, progressive hyperglycemia set in, correlating with a decrease in insulinemia, associated with weight loss in the rats. The rats were declared diabetic on day 14, with a fasting blood glucose level of 1.80 g/L and an insulin level of 7 ± 0.004 µU/mL. These observations could be explained by a general loss of β-cell regeneration mechanisms[17] and the total destruction of the initial β-cells. In addition, the body feels unable to use the large amount of glucose during diabetes to produce the energy it needs to function properly. Thus, cells try to survive using other, poor-quality fuels, which they make from proteins and fats explaining the weight loss observed [18].

Treatment of diabetic animals with the methanolic extract of *Picralima nitida* seeds and Glibenclamide®, the reference anti-diabetic molecule, resulted in a decrease in blood glucose levels and an increase in insulin levels to values close to those of normal control rats. These results corroborate those of Jaiswal *et al.*[19], who studied the effect of *Anacardium occidental* leaves on rats made diabetic by n-streptozotocin. Rammal *et al.* [20] also demonstrated that the aqueous extract of fresh *Momordica charantia* fruits normalized blood glucose levels in diabetic rats. These results are also similar to those of Chabane *et al.* [21], who revealed that the aqueous extract of *Ajugaiva* L. schreber has a regulatory effect on blood glucose and insulin levels during experimental alloxane-induced diabetes.

Glibenclamide® activates the closure of ß-pancreatic cell potassium channels and the opening of voltage-dependent calcium channels, with consequent calcium entry and insulin release. The methanolic extract of *Picralima nitida* seeds, regulating insulin secretion and blood glucose levels in diabetic rats to values close to those of normal rats, may have the same mechanism as Glibenclamide®. This effect could be attributed to

the phenolic compounds in this extract, in particular flavonoids, whose content was estimated at 215.60 ± 0.25 mg EQ/g extract. Indeed, flavonoids could activate a rise in cytosolic calcium responsible for an increase in insulin secretion by non-destroyed β-cells, and hence a reduction in blood glucose levels [22]. In addition, polyphenols and flavonoids inhibit glucosidase or glucose transporters at the intestinal barrier, thus limiting intestinal glucose absorption [23]. Unabsorbed, glucose is therefore assimilated by muscle cells or adipocytes, leading to its depletion in the blood.

The reduction in hyperglycemia in diabetic rats treated with *Picralima nitida* extract may also be due to the alkaloids, estimated at 418.1 ± 0.03 mg EA/g extract. Indeed, according to Pamplona[24], alkaloids have a discrete hypoglycemic effect, lowering blood glucose levels which in turn reduces glycosuria. The weight gain observed during treatment of diabetic rats reflects the regulation of blood glucose levels and its use by cells for energy production [18].

CONCLUSION: The results of the present study show that the methanolic extract of *Picralima nitida* seeds is capable of regulating insulin secretion and consequently blood glucose levels in diabetes. This extract could act via the same mechanism as Glibenclamide® in insulin secretion. The synergistic action of its metabolites, in particular flavonoids and alkaloids, gives it the anti-diabetic potential that justifies its use in traditional medicine.

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CONFLICTS OF INTEREST: Nil

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