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Antihyperglycemic and Antioxidant Activity of Picralima nitida (Stapf) TH.EH.DUR (Apocynaceae) Fruits Powder Fractions on High Caloric Sugar Diet Induced Type 2 Diabetic Rat

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ABSTRACT

Diabetes mellitus is a chronic metabolic disease characterized by chronic hyperglycemia. This disease occurs when the body becomes unable to effectively use the insulin it produces to regulate blood glucose levels. Many plants are explored for their therapeutic properties.

This study aimed to investigate the protective effect of Picralima nitida against type 2 diabetes in order to validate its antihyperglycemic and antistress efficacy.

Picralima nitida fruit powder fractions were prepared using the Controlled Differential Pulverization and Sieving (CDS) process. The various powder fractions (≤ 50 µm; ≤ 120 µm), as well as the unsieved powder, were administered by gavage to rats on a diabetogenic diet.

The results show that the unsieved powder fraction significantly ($P < 0.05$) reduced the fasting blood glucose level of rats (80.55 ± 6.55 mg/dL) 30 minutes before administration to (56.70 ± 5.75 mg/dL) 1 hour after administration compared to the blood glucose level of the normal control group (86.25 ± 2.25 mg/dL) 30 minutes before administration to (85.00 ± 6.25 mg/dL) 1 hour after. On the lipid profile, the fraction ≤ 50 µm significantly ($P < 0.05$) reduced the total cholesterol (117.87 ± 14.21 mg/dL) and triglyceride (71.60 ± 6.89 mg/dL) level compared to 224.70 ± 80.00 mg/dL and 146.00 ± 3.90 mg/dL respectively for total cholesterol and triglycerides in the negative control group. On oxidative stress, the fraction ≤ 50 µm significantly decreased ($P < 0.001$) the level of hepatic MDA (117.85 ± 5.99 µmol /g) compared to 183.69 ± 7.23 µmol/g in the negative control group.

This study attests to the antihyperglycemic effects of Picralima nitida powders and confirms the use of these fruits in traditional medicine to remedy diabetes.

Keywords

Picralima nitida, Antihyperglycemic, Antistress, Powder fractions, Type 2 diabetes.

Introduction

Diabetes mellitus is a serious disorder of sugar, protein, and lipid metabolism, usually described by hyperglycemia [1]. Diabetes mellitus is a disease characterized by inactive insulin production or absence of insulin secretion by pancreatic beta cells and inadequate or defective insulin receptors [2]. There are two types of diabetes, type 1 diabetes manifested by absence of insulin secretion or insufficient production by the body, while type 2 diabetes is an

abnormal or inadequate response of the body's peripheral tissues in recognizing and utilizing insulin [3,4].

The number of diabetic cases continues to increase dramatically every year worldwide and in all age groups [5]. The global report on diabetes mellitus published by the International Diabetes Federation in its 10th IDF Diabetes Atlas report IDF, [6] estimates that 537 million adults (> 20 years) are living with diabetes [7]. The number of people suffering from this disease is expected to reach 643 million or 1 in 9 adults by 2030 and 784 million or 1 in 8 adults by 2045 worldwide. It has also been reported that 81% (4 out of 5) of people with diabetes live in low- and middle-income countries worldwide. It is estimated that 44% of unscreened adults living with diabetes are affected and 90% of these people live in low- and middle-income countries [8]. In view of these figures, diabetes mellitus has become a global public health threat today.

In Cameroon, 2.5 million people were affected by diabetes in 2023, representing a prevalence of 6 to 8% [9]. In view of exponential increase in the number of people with diabetes mellitus worldwide, the need to explore different approaches to prevent or treat this disease remains a major concern. Consequently, the use of oral antidiabetic medications is being seriously considered in pharmacology [10]. However, these drugs have shortcomings that lead to adverse effects on health, and apart from all this, most of these drugs present the risk of severe hypoglycemia for many patients and above all are not as easily available and affordable in developing countries like Cameroon and also in some developed countries [11]. Faced to these shortcomings, much research has focused on suitable alternatives: medicinal plants with hypoglycemic properties that are less toxic, affordable, and easily accessible to all social classes [13]. Medicinal plants contain natural bioactive compounds such as flavonoids, terpenoids, alkaloids, tannins, and carotenoids, which contribute significantly to the treatment of diabetes mellitus in human [14,15]. These natural bioactive compounds are generally more concentrated in the finest powder fractions of the plant and, consequently, exhibit greater therapeutic activity [16,17]. In Cameroon, several plants have been tested and it has been confirmed that they possess hypoglycemic properties in patients with diabetes mellitus induced by a high-calorie diet [18]. Among the most studied plants is *Picralima nitida*. To the best of our knowledge, no scientific work has been conducted on the effect of *Picralima nitida* fruit powder fractions on antihyperglycemic and antioxidant properties in Wistar rats.

The aim of this study was to evaluate the antihyperglycemic and antioxidant effects of the *Picralima nitida* fruit powder fractions on high-calorie diet-induced type 2 diabetes in rats.

Materials and Methods

Chemicals and Drugs

All chemicals used were purchased from Sigma-Aldrich Chimie Gmbh (Munich, Germany); triglycerides and total cholesterol were assessed using diagnostic kits (Fortress, UK). HDL-c was assessed using the MONLAB kit (Barcelona, Spain); metformin, ketamine, diazepam, and dexamethasone were purchased from a local pharmacy.

Experimental Animals

Male Wistar rats, 8 to 10 weeks old and weighing between 150 and 190 g, were used in this study. These animals were purchased from the animal facility of the Faculty of Science, University of Ngaoundéré, Cameroon. These animals were raised in polystyrene cages in an enclosure with room temperature, relative humidity, and a 12-h/12-h light/dark cycle. They were provided with tap water ad libitum and standard chow (normal diet). These manipulations were handled on the rats in strict accordance with the European Union directives for the animals protection (EEC Council 86/609) [19].

Plant Material

The plant material used in this study consisted of mature *Picralima nitida* fruits. These fruits were harvested in February 2024 in Bamena, West Region of Cameroon. After harvest, the fruits were identified at the Biodiversity and Sustainable Development Laboratory of the Department of Biological Sciences at the University of Ngaoundéré by Professor Pierre-Marie Mapongmetsem, a botanist at the Department of Biological Sciences, Biodiversity and Sustainable Development Laboratory, University of Ngaoundéré. This identification was subsequently authenticated at the National Herbarium of Cameroon (HNC) in Yaoundé, Cameroon, under number 55727/HNC, with the name *Picralima nitida* (Stapf) TH.EH.DUR, (Appocinaceae).

Preparation of Powder Fractions from *Picralima nitida* Fruits

Harvested mature fruits were washed with tap water, then cut into small pieces using a machete and dried in the laboratory at room temperature in the shade for 6 weeks. After drying, 1350 g of minced fruit was pounded in a mortar to facilitate passage through a hammer mill (Biobase Disintegrator Model MPD-102) to reduce it to a very fine powder. The resulting powders were then divided into two equal parts. One half was sieved through an ENDECOTTS sieve column (Minnor 1332-06) to obtain the different powder fractions of varying particle sizes using the method described by Deli et al. [17].

To do this, 30 g of powder from the fruits of *Picralima nitida* were placed at the top of a sieve column comprising sieves of decreasing mesh size (300-350 µm; 120-140 µm; 50-60 µm and 10 µm) and mounted on a platform directly connected to the motor shaft of the sieve. Connecting the platform to a power outlet induced a continuous vertical vibratory movement to all the sieves for 10 minutes. The powder fraction remaining in each sieve was recovered and then weighed. We were thus able to obtain from this process, five powder fractions of sizes (≤ 10 µm; ≤ 50 µm; ≤ 120 µm; 300-350 µm and > 350 µm) and a sample of unsieved powder fraction. All different fractions of *Picralima nitida* fruit powder were stored at – 4°C in glass bottles for further use.

To perform the antihyperglycemic and antioxidant tests, only the finer powder fractions (≤ 125 µm; 125-200 µm) were used for the

simple reason that they are richer in bioactive compounds [16,17]. The unsieved powder fraction used was used for comparison with the finer powder fractions. The unsieved powder fraction used alone was to test the hypoglycemic effect of the plant fruits. To administer the different powder fractions of the plant to the different groups of animals, 300 mg/kg of each of the powder fractions (≤ 125 µm; 125-200 µm) as well as the unsieved powder of the fruits of *Picralima nitida* were dissolved separately in distilled water and administered respectively by gavage using a gavage tube.

Induction and Treatment of Type 2 Diabetes

Diabetes was induced using a high-calorie diet (Figure 1) following the model described by Kamgang et al. [18], modified by an additional intraperitoneal injection of dexamethasone (NDC 57319–519-05, Phoenix) at 20 mg/kg body weight and D-glucose at 4 mg/kg body weight orally [20].

Table 1: Composition of the sugary high-calorie diet and the normal diet [18].

Ingredients	ND (g/kg)	HSD (g/kg)
Corn	615	360
Wheat	50	250
Soy	100	100
Fish powder	120	30
Sugar	-	80
Palm oil	-	100
Bone powder	50	35
Palm kernel meals	50	-
Cassava	-	30
Salt	05	05
Vitamin mix	10	10
Energy kcal/kg	**3540**	**4390**

ND: Normal Diet HSD: High-calorie sugar diet

Dexamethasone was administered once weekly from the second week until the end of the seventh week. Animal treatment consisted of either metformin (the reference drug for diabetes treatment) or particle size fractions (≤ 50 µm, ≤ 120 µm) and unsifted powder of *Picralima nitida* fruit.

Thirty (30) male rats were divided into six (06) groups of five (05) rats each and treated daily for 7 weeks as follows:

- Group 1: normal control (NC) which received a normal diet and distilled water (10 mL/kg) per os;
- Group 2: diabetic control (DC) which received a high-caloric diet, D-glucose (4 mg/kg bw) per os, and distilled water (10 mL/kg) per os;
- Group 3: positive control (PC) which received a high-caloric diet, D-glucose (4 mg/kg bw) per os and Metformin Hydrochloride (NDC 0378–6001-91, Mylan Pharmaceuticals Inc.) (20 mg/kg bw);
- Group 4: fractions-treated (PNPF≤ 50 µm) which received a high-caloric diet, D-glucose (4 mg/kg bw) per os and 300 mg/kg of the fraction (≤ 50 µm) of *P. nitida* fruit per os;
- Group 5: fractions-treated (PNPF ≤ 120 µm) which received a high-caloric diet, D-glucose (4 mg/kg bw) per os and 300 mg/kg of the fraction (≤ 120 µm) of *P. nitida* fruit per os;
- Group 6: Unsieved powder-treated which received a high-caloric diet, D-glucose (4 mg/kg bw) per os and 300 mg/kg of unsieved powdered *P. nitida* fruit per os [21].

From the beginning of the second week until the end of the seventh week, dexamethasone (0.2 mg/kg body weight) was administered intraperitoneally to all animals except those in the normal control group, which received saline (5 ml/kg) intraperitoneally. At the end of the seventh week, an oral glucose tolerance test (OGTT) was performed to confirm the presence of type 2 diabetes. The test involved measuring fasting blood glucose using a One Touch glucometer, followed by a single gavage administration of D-glucose solution (4 mg/kg body weight) to each animal. Blood glucose levels were measured at 30, 60, 90, and 120 minutes after D-glucose administration in the five rats in each group [22]. At the end of the treatment, the 5 rats in each group were fasted for 16 hours and anesthetized by intraperitoneal injection of a diazepam (10 mg/kg)/ketamine (50 mg/kg) mixture [23]. After anesthesia, the rats were sacrificed, and blood was collected by incision of the jugular vein in the neck into dry tubes for analysis of the lipid profile, blood transaminases, and oxidative stress parameters.

A buffer was used for the liver and kidney homogenates (20%). Each homogenate was centrifuged at 3000 g for 15 min, and the collected supernatant was stored at −20 °C for the evaluation of oxidative stress parameters.

Biochemical Analysis

For lipid profile analysis, total cholesterol (TC), HDL cholesterol, and triglyceride (TG) concentrations were determined using Fortress Diagnostics kits (BXC0317A, UK) following the manufacturer's protocols. LDL cholesterol concentration was calculated from total cholesterol (TC), triglyceride (TG), and HDL cholesterol values using the formula [24]:

$$[\text{LDL} - \text{cholesterol}] = [\text{TC}] - [\text{HDL} - \text{chol}] - \frac{[\text{TG}]}{5} \quad (1)$$

The activities of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were evaluated using Fortress diagnostic kits (BXC0202A and BXC0212A respectively) following the manufacturer's protocols.

Serum creatinine was evaluated using the kinetic method described by Bartels and Cikes [25]. According to this method, 100 µL of standard creatinine, 100 µL of distilled water, and 100 µL of sample were successively added to the standard tube; then to each of the control and test tubes, each containing 500 µL of reaction medium. The mixture in each tube was homogenized, and the absorbance for each of the standard and test tubes were read at 500 nm relative to the blank at 30 and 90 s. The serum creatinine concentration of each sample was calculated using the formula:

where [Crea]: creatinine concentration (mg/dL); A.Sample: absorbance of the sample; A.Std: absorbance of the standard; Conc.Std: standard concentration (200 mg/dL).

$$[\text{Crea}] = \frac{\text{A.Sample}}{\text{A.Std}} * \text{conc std} \quad (2)$$

For the determination of malondialdehyde (MDA), the following mixtures were prepared: 250 µL of thiobarbituric acid (TBA, 0.67%) and 125 µL of trichloroacetic acid (TCA, 20%) were introduced into test tubes containing 250 µL of Tris-HCl buffer (50 mM, pH 7.4) or homogenate. The tubes were then stoppered with glass beads and heated in a water bath at 90 °C for 10 minutes. The tubes were subsequently cooled with tap water to stop the reaction and centrifuged at 3000 g at room temperature for 10 minutes. The supernatant was pipetted, and the absorbance was read by spectrophotometer at 530 nm against a blank [26]. The MDA concentration of the different samples was calculated using the following formula:

$$[\text{MDA}] = \frac{\Delta DO}{\varepsilon * L * m} \quad (3)$$

where [MDA]: MDA concentration (mol/g of organs); ΔDO: optical density of the assay — optical density of the blank; L, optical path length (1 cm); ε, molar extinction coefficient (13,600 mol−1. cm−1); m, organ mass (g).

To quantify superoxide dismutase (SOD), 1666 µL of carbonate buffer (0.05 M, pH 10.2) and 200 µL of adrenaline (0.3 mM) were mixed into test tubes containing 134 µL of sample. In blank tubes, 1800 µL of carbonate buffer (0.05 M, pH 10.2) was mixed with 200 µL of adrenaline (0.3 mM). After homogenization of the different tubes, the absorbance of the various test tubes were compared to that of the blank tube, read by spectrophotometer at 480 nm at 20 and 80 s [26]. The activity of SOD was determined using the following formula:

$$\%\text{inhibition} = 100 - \frac{(A20s - A80s)\ \text{test}}{(A20s - A80s)\text{blank}} * 100 \quad (4)$$

where A20s: Absorbance measured at 20 s; A80s: Absorbance measured at 80 s.

To quantify catalase (CAT), 187.5 µL of phosphate buffer (0.1 mM; pH 7.5) was mixed with 12.5 µL of homogenate for the test tubes and with 12.5 µL of distilled water for the control tube. 50 µL of hydrogen peroxide (50 mM) was added to each tube and incubated for 1 minute at room temperature. Subsequently, 500 µL of potassium dichromate/glacial acetic acid (5%) was added to all tubes, and the mixture was heated to boiling for 10 minutes. After the tubes cooled, the absorbance was read by spectrophotometer at 570 nm relative to the control tube [26]. The specific activity of catalase was calculated using the following formula:

$$\text{Act CAT} = \frac{\text{A.test} - \text{A.blank}}{a * t * m} \quad (5)$$

where ActCAT: catalase activity (mM H2O2/min/g organs); A.test: absorbance of the test tubes; A.blank: absorbance of the blank tube; a: slope of the calibration curve; t: reaction time (1 min); m, organ mass (g).

Statistical analysis

Data are presented as mean ± standard deviation, with five animals per sample group. All data were statistically analyzed using one-way analysis of variance (ANOVA) followed by a post-hoc test (Student-Newman-Keuls) using Graph Pad Prism software version 5.03. A p-value <0.05 was considered statistically significant.

Results

Evaluation of the antihyperglycemic effect of *Picralima nitida* fruit powder fractions

Effect of *Picralima nitida* fruit powder fractions on fasting blood glucose in rats

This study consisted of administering to the different groups of animals the sugary high-calorie diet associated with dexamethasone (i.p) and coupled with a treatment either with the distilled water, metformin, fraction ≤ 50 µm, fraction ≤ 120 µm or the unsieved powder of *Picralima nitida* fruits for 7 weeks. It appears from this study that on day 0 (before administration of treatments), the fasting blood glucose of all animals showed no significant difference (P ≥ 0.05) with a mean value of 82.88 ± 2.21 mg/dl.

From the 1st to the 4th week of treatment, no significant difference (P ≥ 0.05) was observed in the variation of fasting blood glucose levels in animals of all groups. The mean blood glucose values were 80.93 ± 4.26 mg/dl for the 1st week; 81.90 ± 4.35 mg/dl for the 2nd week; 83.79 ± 4.92 mg/dl for the 3rd week and 85.16 ± 3.15 mg/dl for the 4th week.

From the 5th to the 7th week of treatment of the animals, the fasting blood glucose levels of the animals in the negative control group significantly increased (P < 0.001) compared to those of the animals in the other groups that received either the fractions or the reference drug (metformin). Blood glucose values increased from 118.65 ± 2.08 mg/dl in the 5th week to 152.10 ± 8.77 mg/dl in the 7th week for the animals in the negative control group compared to 75.15 ± 3.84 mg/dl in the 5th week to 87.33 ± 3.87 mg/dl in the 7th week for the animals treated with the fraction ≤ 50 µm; 83.70 ± 2.60 mg/dl the 5th week to 94.43 ± 5.00 mg/dl the 7th week for animals treated with the fraction ≤ 120 µm; 88.65 ± 4.67 mg/dl the 5th week to 101.70 ± 4.69 mg/dl the 7th week for animals treated with the unsieved mother powder; 82.80 ± 2.64 mg/dl the 5th week to 90.52 ± 4.31 mg/dl the 7th week for animals treated with metformin and 92.25 ± 2.37 mg/dl the 5th week to 97.65 ± 4.18 mg/dl the 7th week for animals in the normal control group.

At the 7th week of this antihyperglycemic test, only animals in the negative control group showed a significant increase (p<0.001) in

fasting blood glucose to the point of exceeding the threshold value of hyperglycemia recognized by the World Health Organization (WHO) (the value 152.10 ± 8.77 mg/dl ≥ 126 mg/dl recognized by the WHO). Animals in the normal control group, which received only distilled water, showed a fasting blood glucose level that remained normal (< 120 mg/dl according to the WHO). As for animals treated either with the fraction ≤ 50 µm; ≤ 120 µm, the unsieved mother powder of the fruits of *Picralima. nitida* or with metformin, the increase in their blood glucose was prevented and stabilized at a glycemic value statistically identical to that of animals in the normal control group. It is found from this study that the ≤ 50 µm fraction of *Picralima nitida* fruits had a better antihyperglycemic effect followed by metformin, the ≤ 120 µm fraction and the unsieved mother powder of *Picralima nitida* fruits (Figure 2).

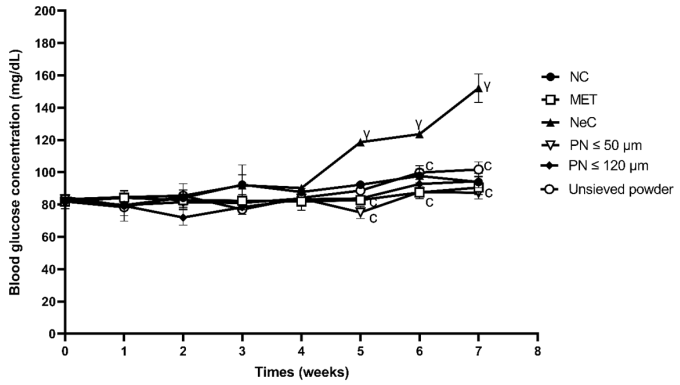

Figure 2: Effect of *Picralima nitida* fruit powder fractions on fasting blood glucose in High-calorie sugar diet induced diabetic rats.

Each value represents the mean ± MSE of the group, n= 4; $^{\gamma}p<0.001$ significant difference compared to normal control; $^{c}p<0.001$ significant difference compared to negative control; NC : Normal Control; MET : Metformin (20 mg/kg); NeC : Negative Control; PN ≤ 50 µm : Fraction ≤ 50 µm of *Picralima nitida* fruits (600 mg/kg); PN ≤ 120 µm : Fraction ≤ 120 µm of *Picralima nitida* fruits (600 mg/kg); Unsieved powder of *Picralima nitida* fruits (600 mg/kg).

Effect of *Picralima nitida* fruit powder fractions on the oral glucose tolerance test (OGTT)

In order to confirm the onset of diabetes mellitus in animals in the negative control group (diabetic control) compared to other groups of animals (normal control, positive control and test controls), it appears from this study that at time t = 0 min (before administration of D-glucose), the blood glucose level of animals in the diabetic control group was 152.10 ± 8.77 mg/dl, while that of animals in the other groups was 106.20 ± 3.67 mg/dL for the normal control, 78.03 ± 5.72 mg/dL for the positive control, 75.08 ± 2.87 mg/dL for the fraction ≤ 50 µm, 94.43 ± 5.00 mg/dL for the fraction ≤ 120 µm and 101.70 ± 4.69 mg/dL for the unsieved powder. 30 minutes after administration of D-glucose, a significant increase (P < 0.05) in blood glucose levels was observed, which increased to 125.87 ± 0.68 mg/dL for the normal control, 120.87 ± 2.08 mg/dL for the positive control, 167.4 ± 11.71 mg/dL for the diabetic control, 121.73 ± 1.30 mg/dL for the group treated with the fraction ≤ 50 µm, 121.60 ± 2.08 mg/dL for the group treated with the fraction ≤ 120 µm and 124.87 ± 2.16 mg/dL for the group treated with the unsieved powder of *Picralima nitida* fruits. From the 30th to the 120th min after administration of D-glucose, there was a significant decrease (P < 0.001) in the blood glucose level of animals treated with the fraction ≤ 50 µm, going from 121.73 ± 1.30 mg/dL at the 30th min to 73.53 ± 2.40 mg/dL at the 120th min. For animals treated with the fraction ≤ 120 µm, the blood glucose levels of the animals decreased from 121.60 ± 2.08 mg/dL at the 30th min to 78.27 ± 1.77 mg/dL at the 120th min. For animals treated with the unsieved powder of *Picralima nitida* fruits, the blood glucose levels of the animals decreased from 124.87 ± 2.16 mg/dL at the 30th min to 83.27 ± 3.71 mg/dL at the 120th min. For the group of animals treated with metformin, the blood glucose levels of the animals decreased from 120.87 ± 2.08 mg/dL at the 30th min to 75.93 ± 3.27 mg/dL at the 120th min. The blood sugar of the animals in the normal control group went from 125.87 ± 0.68 mg/dL at the 30th min to 95.07 ± 4.69 mg/dL (120th min). In the animals in the diabetic control group, on the other hand, the blood sugar of the animals went from 167.40 ± 11.71 mg/dL at the 30th min to 143.40 ± 3.28 mg/dL at the 120th min. Only the animals in the diabetic control group showed blood sugar that remained above the hyperglycemia threshold value recognized by the WHO (≥ 126 mg/dl) while the blood sugar of the animals in the other groups dropped considerably to stabilize slightly below the value of the animals in the normal group recognized by the WHO (< 120 mg/dl). This test shows that the animals in the negative control group are diabetic while animals in other groups are not (Figure 3).

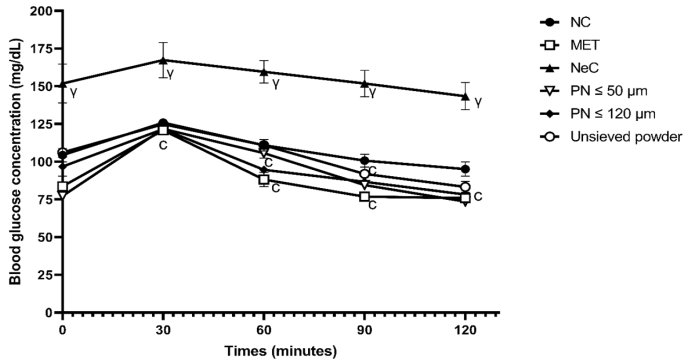

Figure 3: Effect of *Picralima nitida* fruit powder fractions on the oral glucose tolerance test (OGTT) in High-calorie sugar diet induced diabetic rats.

Each value represents the mean ± MSE of the group, n= 4 ; $^{\gamma}p<0.001$ significant difference compared to normal control ; $^{c}p<0.001$ significant difference compared to negative control ; NC : Normal Control ; MET : Metformin (20 mg/kg) ; NeC : Negative Control ; PN ≤ 50 µm : Fraction ≤ 50 µm of *Picralima nitida* fruits (600 mg/kg) ; PN ≤ 120 µm : Fraction ≤ 120 µm of *Picralima nitida* fruits (600 mg/kg) ; Unsieved powder of *Picralima nitida* fruits (600 mg/kg).

Effects of *Picralima nitida* fruit powder fractions on animal body weight

This study showed that there was no significant variation ($P \geq 0.05$) in body mass between animals in different groups from day 0 to the end of the 4th week. The mean body mass values of the animals ranged from 166.08 ± 4.18 g for day 0; 176.71 ± 6.80 g at the end of the 1st week; 187.04 ± 6.19 g at the end of the 2nd week; 185.58 ± 6.19 g at the end of the 3rd week and 186.13 ± 4.39 g at the end of the 4th week.

From the 5th to the 7th week, there was a significant increase ($P < 0.001$) in the body mass of animals in the normal control group compared to that of animals in the other groups. The mean values are as follows: 234.25 ± 16.32 g and 232.50 ± 8.39 g respectively at the 5th and 7th week for animals in the normal control group; 171.50 ± 3.12 g and 163.75 ± 6.14 g respectively at the 5th and 7th week for animals treated with fractions ≤ 50 µm; compared to 159.75 ± 3.35 g and 126.25 ± 15.94 g respectively at the 5th and 7th week for animals in the negative control group. From the 6th and 7th week of treatment, there was a significant decrease ($P < 0.05$) in body mass of animals in the negative control group compared to animals in the groups treated with fractions ≤ 50 µm; ≤ 120 µm, with the reference drug (metformin) and with the unsieved powder. Only animals in the normal control group showed a significant increase in body mass compared to that of animals in the negative control group (Figure 4).

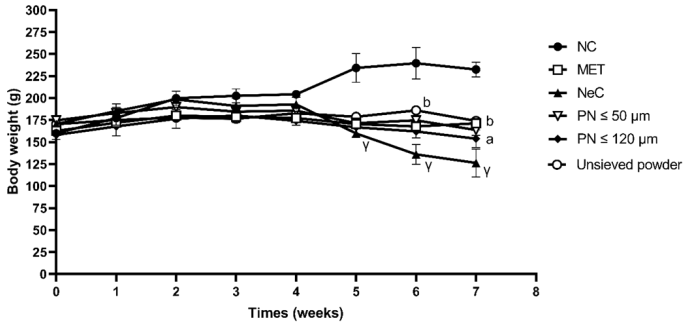

Figure 4: Effects of *Picralima nitida* fruit powder fractions on animal body weight in High-calorie sugar diet induced diabetic rats.

Each value represents the mean ± MSE of the group, n= 4; $^{\gamma}p<0.001$ significant difference compared to normal control; $^{a}p<0.05$, $^{b}p<0.01$ significant difference compared to negative control; NC : Normal Control; MET : Metformin (20 mg/kg); NeC : Negative Control; PN ≤ 50 µm : Fraction ≤ 50 µm of *Picralima nitida* fruits (600 mg/kg); PN ≤ 120 µm : Fraction ≤ 120 µm of *Picralima nitida* fruits (600 mg/kg); Unsieved powder of *Picralima nitida* fruits (600 mg/kg).

Effect of *Picralima nitida* fruit powder fractions on biochemical parameters of rats

From this lipid profile study, it was found that total cholesterol (TC), triglyceride (TG) and LDL cholesterol levels were significantly higher ($P < 0.05$) in animals in the diabetic control group (224.70 ± 80.00 mg/dL for TC; 146.00 ± 3.90 mg/dL for TG and 132.57 ± 81.14 mg/dL for LDL), compared to animals treated with the ≤ 50 µm fraction (117.87 ± 14.21 mg/dL for TC, 71.60 ± 6.89 mg/dL for TG and 43.31 ± 14.97 mg/dL for LDL). For animals treated with the fraction ≤ 120 µm, the values of these parameters were (157.43 ± 18.39 mg/dL for CT; 66.40 ± 8.98 mg/dL for TG and 83.15 ± 18.31 mg/dL for LDL) and those of animals treated with the unsieved powder (170.37 ± 6.89 mg/dL for CT; 72.37 ± 11.75 mg/dL for TG and 95.18 ± 22.62 mg/dL for LDL). The animals treated with metformin showed the values (173.87 ± 17.21 mg/dL for CT, 74.80 ± 10.77 mg/dL for TG and 99.64 ± 22.85 mg/dL for LDL). The values obtained for the animals of the normal control group are (114.73 ± 17.21 mg/dL for CT; 52.37 ± 7.00 mg/dL for TG and 44.56 ± 19.93 mg/dL for LDL).

Regarding the variation of HDL cholesterol level, no significant variation ($P \geq 0.05$) between animals of different groups of animals was observed and the mean value for this parameter was 60.64 ± 1.68 mg/dL. The fraction ≤ 50 µm showed the lowest total cholesterol and LDL levels followed by the fraction ≤ 120 µm and then the unsieved powder (Figure 5).

In order to evaluate the effect of the different treatments on the organs of the animals, the activities of ALAT and ASAT were measured. This study showed that the level of ALAT and ASAT was significantly higher ($P< 0.01$) in the animals of the diabetic control group (94.93 ± 3.44 U/L for ALAT and 151.35 ± 4.87 U/L for ASAT) compared to the animals treated with the fraction ≤ 50 µm (46.25 ± 7.02 U/L for ALAT and 99.58 ± 0.78 U/L for ASAT). For animals treated with the fraction ≤ 120 µm (48.83 ± 3.29 U/L for ALAT and 107.83 ± 7.86 U/L for ASAT) and those treated with the unsieved mother powder (52.70 ± 14.43 U/L for ALAT and 107.70 ± 6.17 U/L for ASAT). The animals in the normal control group, on the other hand, gave the values (37.53 ± 2.47 U/L for ALAT and 97.93 ± 6.57 U/L for ASAT). The fractions ≤ 50 µm and ≤ 120 µm as well as the unsieved powder of *Picralima nitida* fruits showed lower ALAT and ASAT levels than the reference drug. Metformin, on the other hand, showed ALAT and ASAT levels that were close to those of the negative control batch. Thus, the powder fractions of *Picralima nitida* fruits were found to be hepatoprotective and the ≤ 50 µm fraction of *Picralima nitida* powder was more hepatoprotective than all other treatments (Figure 6).

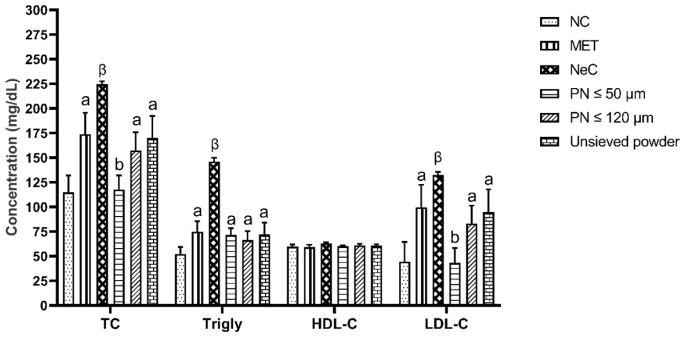

Figure 5: Effect of *Picralima nitida* fruit powder fractions on lipid

parameters in High-calorie sugar diet induced diabetic rats.

Each value represents the mean ± MSE of the group, n= 3; $^{\beta}p<0.001$ significant difference compared to normal control; $^{a}p<0.05$, $^{b}p<0.01$ significant difference compared to negative control; NC : Normal Control; MET : Metformin (20 mg/kg); NeC : Negative Control; PN ≤ 50 µm : Fraction ≤ 50 µm of *Picralima nitida* fruits (600 mg/kg); PN ≤ 120 µm : Fraction ≤ 120 µm of *Picralima nitida* fruits (600 mg/kg); Unsieved powder of *Picralima nitida* fruits (600 mg/kg).

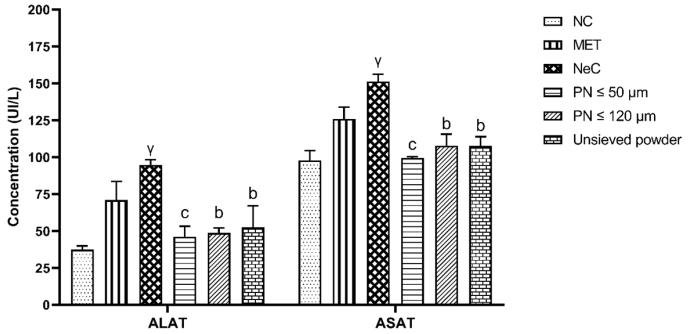

Figure 6: Effect of *Picralima nitida* fruit powder fractions on transaminases parameters in High-calorie sugar diet induced diabetic rats. Each value represents the mean ± MSE of the group, n= 3; $^{\gamma}p<0.001$ significant difference compared to normal control; $^{b}p<0.01$, $^{c}p<0.001$ significant difference compared to negative control; NC : Normal Control; MET : Metformin (20 mg/kg); NeC : Negative Control; PN ≤ 50 µm : Fraction ≤ 50 µm of *Picralima nitida* fruits (600 mg/kg) ; PN ≤ 120 µm : Fraction ≤ 120 µm of *Picralima nitida* fruits (600 mg/kg) ; Unsieved powder of *Picralima nitida* fruits (600 mg/kg).

Effects of *Picralima nitida* fruit powder fractions on oxidative stress parameters in rats

This study on the effect of *Picralima nitida* powder fractions on oxidative stress shows that a significant decrease (P < 0.001) in the hepatic MDA level is observed in animals treated with the fraction ≤ 50 µm (117.85 ± 5.99 µmol/g), with the fraction ≤ 120 µm (138.84 ± 2.04 µmol/g), with the unsieved powder (138.15 ± 7.49 µmol/g) and for metformin (137.30 ± 15.59 µmol/g) compared to diabetic control animals (183.69 ± 7.23 µmol/g). In this study, the ≤50 µm fraction showed a greater decrease in hepatic MDA level followed by metformin, unsieved powder and the ≤120 µm fraction.

The effect of *Picralima nitida* fruit fractions on catalase activity shows that animals treated with either fractions ≤ 50 µm, ≤ 120 µm, and unsieved powder or metformin had a significant increase (P < 0.05) in the liver compared to that of animals in the negative control group. The values of this activity are 199.88 ± 14.65 mM/min/g, 189.40 ± 38.15 mM/min/g, 173.69 ± 5.38 mM/min/g and 179.88 ± 8.49 mM/min/g against 91.31 ± 13.00 mM/min/g respectively for the fraction ≤ 50 µm; the fraction ≤ 120 µm, for the unsieved powder and for metformin. At the serum level, no significant variation in catalase activity was noted between animals in the different groups. The fraction ≤ 50 µm further increased catalase activity followed by the fraction ≤ 120 µm, the unsieved powder and metformin.

On the activity of superoxide dismutase, it appears from this study that the animals which received either the different fractions of the fruits of *Picralima nitida* or metformin the activity of hepatic SOD significantly increased (P < 0.001) compared to the animals of the diabetic control group. The values are as follows: 868.42 ± 40.19 U/g for the fraction ≤ 50 µm; 789.43 ± 26.32 U/g for the fraction ≤ 120 µm; 807.02 ± 38.24 U/g for the unsieved powder; 736.85 ± 105.26 U/g for positive control animals and 557.89 ± 23.73 U/g for normal control animals versus 357.89 ± 23.73 U/g for diabetic control animals (negative control). Unsieved powder of *Picralima nitida* fruits increased hepatic SOD levels the most, followed by fraction ≤ 50 µm, fraction ≤ 120 µm and metformin (Table 2).

Each value represents the mean ± MSE of the group, n= 3; $^{\alpha}p<0.05$, $^{\beta}p<0.01$, $^{\gamma}p<0.001$ significant difference compared to normal control; $^{a}p<0.05$, $^{b}p<0.01$, $^{c}p<0.001$ significant difference

Table 2: Effect of *Picralima nitida* fruit powder fractions on oxidative stress parameters in High-calorie sugar diet induced diabetic rats

	MDA (µmol/g)		CAT (mM/min/g)		SOD (U/g)	
	liver	serum	liver	serum	liver	serum
NC	128.54 ± 15.59	6.69 ± 0.26	166.79 ± 42.31	46.45 ± 10.95	557.89 ± 23.73	173.68 ± 15.19
MET	137.30 ± 15.59^{c}	11.37 ± 3.50	179.88 ± 8.49^{a}	47.88 ± 13.59	736.85 ± 105.26^{c}	163.16 ± 3.04
NeC	183.69 ± 7.23$^{\gamma}$	21.78 ± 2.66	91.31 ± 13.00$^{\alpha}$	32.40 ± 3.09	357.89 ± 23.73$^{\beta}$	157.89 ± 3.04
PN ≤ 50 µm	117.85 ± 5.99^{c}	5.91 ± 0.48	199.88 ± 13.00^{b}	56.93 ± 16.37	868.42 ± 40.20^{c}	164.91 ± 6.33
PN ≤ 120 µm	138.84 ± 2.04^{c}	8.02 ± 1.26	189.40 ± 38.15^{b}	47.40 ± 2.42	789.47 ± 26.32^{c}	156.14 ± 1.75
UP	138.15 ± 7.49^{c}	6.73 ± 0.90	173.69 ± 5.38^{a}	46.22 ± 13.45	807.02 ± 38.24^{c}	168.42 ± 13.24

compared to negative control; NC: Normal Control; MET: Metformin (20 mg/kg); NeC: Negative Control; PN ≤ 50 µm: Fraction ≤ 50 µm of *Picralima nitida* fruits (600 mg/kg); PN ≤ 120 µm : Fraction ≤ 120 µm of *Picralima nitida* fruits (600 mg/kg); UP : Unsieved powder of *Picralima nitida* fruits (600 mg/kg).

Discussion

A phytochemical screening of the fruits of *P. nitida* has revealed the presence of numerous bioactive compounds such as Saponins, Alkaloids, Tannins, Terpenoids, Phenols, Flavonoids, Glycosides, Steroids and Phytosterols [14].

The seed extract contains many bioactive components that may explain their efficacy in the treatment of several metabolic disorders. Polyphenols, flavonoids, tannins, saponins, and terpenoids identified in the seed extract belong to families of hypoglycemic and hypolipidemic compounds fully investigated in the literature [27].

For decades, researchers have devoted much of their time to the search for medicinal plants with antidiabetic properties, because medicinal plants offer several therapeutic effects linked to a number of bioactive compounds, including those mentioned above. These statements are consistent with research by Ngounou Deutchoua et al. [28], which clearly demonstrate that antidiabetic medicinal plants significantly prevent the rise in blood glucose levels in diabetic rats induced by a high-calorie sugar diet.

This study was conducted to evaluate the antidiabetic and antistress effects of *Picralima nitida* fruits against diabetes induced by a high-calorie sugar diet combined with dexamethasone (glucocorticoid) in rats.

Dexamethasone is one of the chemicals commonly used in the laboratory to induce type 2 diabetes in rats [29,30]. Dexamethasone is a molecule that has the ability to increase insulin resistance through biological corticosteroid receptors to inhibit the production and expression of the secretin gene [31]. Dexamethasone in the body increases the secretion and expression of the resistin gene, reduces the number and activity of glucose transporters by stimulating gluconeogenesis from amino acids derived from protein breakdown, and ultimately promotes the development of insulin resistance in cells [32]. Combining dexamethasone with a high-calorie sugar diet in rats aims to induce type 2 diabetes in these animals, similar to that observed in humans, and in a very short time [29].

Body weight loss is one of the signs of diabetes mellitus manifested by a deterioration in glycemic control [29,33]. It has been established that significant weight loss is a symptom of untreated diabetes in rats which could lead to the death of the animal if not properly treated. Body weight decreases significantly in rats in the diabetic control group induced by a high-calorie sugar diet associated with dexamethasone, this is linked to several responsible factors including: acute fluid loss, lipolysis, proteolysis which finally leads to muscle atrophy [34]. In the present study, the decrease in body weight observed in the diabetic control group would be due to a hydrolysis of protein and lipid reserves in muscle tissues to produce energy, due to the inability of these tissues to metabolize blood glucose [35]. On the other hand, the extract prevented a significant loss of body weight in rats, which testifies to its effect against muscle atrophy.

Metformin are known to prevent and lower blood sugar levels, through an antihyperglycemic action before and after meals by reducing hepatic glucose production, reducing insulin resistance and especially by delaying intestinal glucose absorption [30].

Picralima nitida powder fractions prevented a significant increase in blood glucose in animals receiving a high-calorie sugar diet and dexamethasone injection. These results may be attributable to the bioactive compounds (flavonoids, phenols, and glycosides) present in the powder fractions, which are known for their multiple hypoglycemic effects by increasing the number and activity of glucose transporters and inhibiting gluconeogenesis, thus preventing the development of insulin resistance in cells [27,36].

Diabetes is associated with hyperlipidemia, which results in an abnormal increase in cholesterol, lipoproteins and triglycerides. An abnormal elevation in serum lipid levels observed in rats in the normal control group (diabetic control group) generally results in a considerable mobilization of free fatty acids followed by a deposition of peripheral fats and in which insulin in this case has an antilipolytic action which results in an inhibition of hormone-sensitive lipase [37]. By administering different fractions of *Picralima nitida* powders to rats which received simultaneously a sugary high-calorie diet coupled with dexamethasone intraperitoneally would have improved the lipid profile of these animals by preventing an abnormal elevation in serum lipid levels observed rather in rats in the diabetic control group, by mimicking either the action of insulin or also by stimulating the biosynthesis of this hormone. *Picralima nitida* powder fractions have also been reported to delay the diffusion rate at the intestinal mucosa, which significantly reduces the absorption of triglycerides and cholesterol [38]. In summary, many authors have reported that many secondary metabolites such as phenolic compounds, flavonoids and saponins possess hypolipidemic properties in the body [39]. According to Olumese et al. [14], *Picralima nitida* fruits are rich in phenolic compounds, flavonoids and saponins and therefore, the hypolipidemia observed in this study would be related to the effects of these different groups of bioactive compounds present in *Picralima nitida* powder fractions.

In this study, a significant increase in serum levels of liver biomarkers (ASAT and ALAT) was observed in animals in the negative control group (diabetic control) compared to serum levels in animals in the normal control group as well as in animals in the groups treated with *Picralima nitida* powder fractions. This increase in ASAT and ALAT levels reflects compromised liver function, attributed to hepatocellular necrosis. Administration of *Picralima nitida* powder fractions in combination with a high-calorie sugar diet coupled with intraperitoneal injection of

dexamethasone effectively inhibited the activity of ASAT and ALAT enzymes in liver function. This result suggests that elevated serum transferase activities are commonly seen in liver diseases prevalent in diabetic conditions and was confirmed by Akah et al., Soliman, [40,41].

Elevated levels of ASAT and ALAT in the blood indicate hepatocellular damage resulting from dexamethasone toxicity, which causes leakage of these enzymes from the liver cytosol into the bloodstream. Moreover, Ghosh and Suryawanshi [42], Joseph et al. [43] stated that complications of diabetes, such as increased ketogenesis and gluconeogenesis, may be related to increased transaminase activity. The prevention of the increase in these biomarker enzymes during treatment of animals with *Picralima nitida* powder fractions explains a reduction in diabetic conditions in animals receiving the powder fractions along with the reference drug (metformin). The beneficial effects of *Picralima nitida* powder fractions on liver biomarkers highlight its therapeutic potential to alleviate liver damage associated with diabetes.

The high presence of oxidative stress in diabetic subjects led us to evaluate the antioxidant properties of *Picralima nitida* fruits different fractions of powders. The measurement of MDA (end product of lipid peroxidation) explains the degree of oxidative stress in the body [44]. A reduction in the level of MDA in an organism testifies to the decrease in lipid peroxidation which results in an increased production of antioxidant enzymes. In the present work, the different fractions of powders of *Picralima nitida* fruits (fractions ≤ 50 µm; ≤ 120 µm as well as the unsieved powder) prevented an increase in the level of MDA levels in subjects who were subjected to a diabetogenic diet, and thus prevented the onset of diabetes in these subjects. In short, these different fractions of powders of *Picralima nitida* have a good capacity to prevent lipid peroxidation and therefore to strengthen the antioxidant defense system. Indeed, induced hyperlipidemia leads to an increase in the production of oxygenated free radicals, thus causing lipid peroxidation [45].

Superoxide dismutase (SOD) is an enzyme that exerts a significant influence on the biological defense mechanism by dismutating endogenous cytotoxic superoxide radicals into hydrogen peroxide (H_2O_2) [46]. In this study, SOD activity was decreased in rats in the negative control group (diabetic controls). In contrast, the reference drug as well as the various fractions and unsieved powder of *Picralima nitida* fruits caused an increase in hepatic SOD activity.

The fractions of *Picralima nitida* powders therefore have a significant effect on the body's oxidative defense mechanism.

Catalase (CAT) is a tetrameric enzyme that efficiently converts H_2O_2 into oxygen and water. Unlike glutathione, catalase's affinity for hydrogen peroxide increases with high H_2O_2 concentrations [47].

Abundantly present in organisms living in the presence of oxygen, CAT protects the cell from oxidative damage caused by reactive oxygen species (ROS) [48]. In the present study, the increase in catalase activity observed with *Picralima nitida* extract would therefore reflect a decrease in ROS concentrations in the cell.

Furthermore, phenols and flavonoids have been shown to be substances with antioxidant activity. However, some plant extracts contain antioxidant molecules that lower blood sugar by capturing free radicals to isolate their electrons and transform them into stable molecules or ions [49]. This could also represent a possible mechanism of action of *Picralima nitida* on blood sugar and the body's antioxidant defenses.

Conclusion

The objective of this work was to evaluate the antidiabetic and antioxidant effects of powder fractions of *Picralima nitida* fruits on diabetes mellitus induced by a high-calorie diet associated with dexamethasone in rats. The fruits of this plant showed antihyperglycemic properties in hyperglycemic rats, hypolipidemic activity and antioxidant activity. This study on *Picralima nitida* attests to the properties of *Picralima nitida* fruits against type 2 diabetes and offers arguments in favor of its use in traditional medicine in the treatment of diabetes. In order to better understand the mechanisms of action of *Picralima nitida* fruit powder fractions in the treatment of diabetes mellitus, it will be important in the future to test the effect of the different bioactive compounds contained in the different powder fractions on the β cells of the islets of Langerhans of the pancreas, on the inhibition of α-glucosidases and especially on the inhibition of intestinal glucose absorption, as well as the potential toxic effects of this plant. Once these mechanisms are elucidated, *Picralima nitida* fruit powder could be used as a dietary supplement in diabetic patients.

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